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# ATEZO-BRAIN STUDY

**"Phase II non-randomized study of atezolizumab (mpdl3280a) in combination with carboplatin plus pemetrexed in patients who are chemotherapy-naïve and have stage IV non-squamous non-small cell lung cancer with untreated brain metastasis" (GECP 17/05- ML40238)**

## CLINICAL STUDY REPORT: FINAL REPORT SUMMARY

**Sponsor: Fundación GECP**

Trial Coordinator in Spain (SLCG): Dr. Ernest Nadal

# INDEX

1. TITLE PAGE

**TITLE:** "Phase II non-randomized study of atezolizumab (mpdl3280a) in combination with carboplatin plus pemetrexed in patients who are chemotherapy-naïve and have stage IV non-squamous non-small cell lung cancer with untreated brain metastasis"

2. SYNOPSIS

This is a multicenter, national, nonrandomized, phase II trial in subjects with nonsquamous NSCLC patients that have untreated BM. A pre-screening period using brain MRI for patients diagnosed with advanced non-squamous NSCLC EGFR/ALK wild type and ECOG PS 0-1 will be crucial to identify patients with untreated BM. Forty patients will be recruited. Atezolizumab will be administered intravenously (iv) at a dose of 1200 mg over 60 minutes on day 1 of each cycle. The subsequent cycles of atezolizumab can be administered over 30 minutes, if there were no infusion-related toxicities. Pemetrexed will be administered at a dose of 500 mg/m2 iv over 15 minutes on day 1 of each cycle. In addition, folic acid, vitamin B12, and dexamethasone 4mg bid will be administered one day before and after pemetrexed treatment. Carboplatin will be administered at a dose with an area under the curve of 5 over 30 minutes on day 1 of each cycle approximately 30 minutes after the end of the pemetrexed infusion. After completing 4 to 6 cycles of carboplatin plus pemetrexed and atezolizumab, patients will continue with pemetrexed in combination with atezolizumab until unacceptable toxicity, disease progression, patient/physician decision or completion of 2 years of therapy.

Tumor measurements by CT scan (systemic response) and brain MRI (intracranial response) will be performed every 6 weeks until the 12th week and thereafter every 9 weeks until disease progression. In case of brain progression, rescue with brain radiotherapy should be considered. In case of exclusive brain progression, patients are allowed to receive brain radiotherapy (WBRT or SRS) and then continue with study therapy if the patients maintain clinical benefit and appropriate performance status (ECOG PS≤2).Immunotherapy should be started no later than 4 weeks after completing radiation therapy (brain radiotherapy 2 weeks + 4 weeks of recovery from potential acute toxicity). In case of systemic progression without brain progression, a novel line of systemic treatment should be considered. Patients experiencing systemic progression and/or brain progression will be followed and two post-progression visits will be performed at 30 and 90 days.

Response will be assessed independently in the brain and systemically: systemic response will be evaluated according to RECIST v1.1 and brain response according to the RANO response assessment criteria for BM (RANO-BM). Adverse events will be assessed throughout and assessed using the CTCAE version 4.03. EORTC quality of life questionnaire EORTC C30 and the submodules QLQ-LC13 and BN20 will be assessed in the ITT population at baseline, cycle 5 (week 12),cycle 8 (week 21), at end of study treatment (30 and 90 days) and/or at disease progression. Periodic evaluations of the trial data will be conducted by an independent DMC to ensure subject safety and to evaluate the efficacy at the interim analyses.

Neurocognitive assessment including the standardized neuropsychological tests: Hopkins Verbal Learning Test (HVLT), Trail Making Test (TMT), Rey–Osterrieth complex figure test (ROCF) and Controlled Oral Word Association Test (COWA) will be assessed at baseline cycle 5 (week 12),cycle 8 (week 21), at end of study treatment (30 and 90 days) and/or at disease progression.

## 3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

Please refer to page 2, to the index of this report.

## 4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation or special term | Explanation |
|---|---|
| ADA | Anti-drug antibody |
| BM | Brain metastases |
| CBDCA | Carboplatin |
| CRO | Contract research organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | Data Monitoring Committee |
| EC | Ethics Committee |
| eCRF | electronic Case Report Form |
| EDC | Electronic data capture |
| FDA | Food and Drug Administration |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICH | International Council for Harmonisation |
| IMP | Investigational medicinal product |
| IND | Investigational New Drug (Application) |
| IRB | Institutional Review Board |
| LPLV | Last patient, last visit |
| NCI | National Cancer Institute |
| NSCLC | Non-small cell lung cancer |
| OS | Overall survival |
| PRO | Patient-reported outcome |
| PFS | Progression-free survival |
| PS | Performance status |
| ULN | Upper limit of normal |

## 5. ETHICS

### 5.1. INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

| **IEC Hospital Universitari de Bellvitge (CEIm)** |
|---|
| IEC Hospital Universitari Germans Trias i Pujol |
| IEC Hospital General de Valencia |
| IEC Hospital de la Santa Creu i Sant Pau |
| IEC Hospital Fundación Jiménez Díaz |
| IEC Hospital Universitario de A Coruña |
| IEC Hospital General Universitario de Elche |
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| IEC Hospital Universitario Vall d'Hebron |
| IEC Hospital La Paz |
| IEC ICO Girona – Hospital Dr. Josep Trueta |

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|---|
| IEC Hospital Clínico Universitario de Valladolid |
| IEC Hospital Universitario La Fe de Valencia |
| IEC Complexo Hospitalario Universitario de Vigo |

### 5.2. ETHICAL CONDUCT OF THE STUDY

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Subject data protection.

### 5.3. PATIENT INFORMATION AND CONSENT

Last version of the PIS-IC: v.2.1_20.Sep.2019 + Addendum 1_26.Apr.2021

Last version of the pregnancy PIS-IC: v.2.0_24.Oct.2018

## 6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

| | |
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| Hospital Universitari de Bellvitge (CEIm) | Dr. Nadal |
| Hospital Universitari Germans Trias i Pujol | Dr. Carcereny |
| Hospital General de Valencia | Dr. Blasco |
| Hospital de la Santa Creu i Sant Pau | Dr. Sullivan |
| Hospital Fundación Jiménez Díaz | Dr. Domine |
| Hospital Universitario de A Coruña | Dr. García Campelo |
| Hospital General Universitario de Elche | Dr. Guirado |
| Hospital General de Alicante | Dr. Massuti |
| Hospital Insular de Gran Canaria | Dr. Rodríguez Abreu |
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| Hospital La Paz | Dr. De Castro |
| ICO Girona – Hospital Dr. Josep Trueta | Dr. Bosch |
| Hospital Clínico Universitario de Valladolid | Dr. López |
| Hospital Universitario La Fe de Valencia | Dr. Juan |
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This study is managed from the Sponsor headquarters, Fundación GECP (Av. Meridiana 358, 6$^{th}$ Floor, 08027, Barcelona)

## 7. INTRODUCTION

**BACKGROUND**

**Background on brain metastases in advanced NSCLC patients**

Lung cancer is the leading cause of cancer-related death in industrialized countries (1). Non-small cell lung cancer (NSCLC) accounts for 85% of cases of lung cancer and is categorized into a variety of histological subtypes being non-squamous tumors the most common subtype (2). Patients with lung

cancer present initially with brain metastases in about 10-25% of cases, with up to 50% of patients developing brain metastases throughout their disease course (3).

Brain metastases represent a significant healthcare problem and have not only an adverse impact on patient morbidity and quality of life, but also are associated with dismal prognosis (4). Although effective treatments in patients with brain metastases are urgently needed, those patients have been generally excluded from clinical trials (5,6). Asymptomatic brain metastases are a rising challenge for clinicians since their incidence is growing due to broad access to more sensitive brain imaging and routine imaging as a screening procedure before entry into a clinical trial and due to improvement of systemic therapies that control more effectively the extracranial disease.

Whole brain radiotherapy (WBRT) has been considered the standard of care for patients with brain metastases in spite of the lack of randomized studies compared to best supportive care especially in patients with poor performance status. According to the results of the RTOG 9508 trial of WBRT with or without radiosurgery (SRS), first-line WBRT without SRS yielded a median overall survival (OS) of only 4 months (7). In the QUARTZ clinical trial, optimal supportive care (OSC) including dexamethasone plus WBRT was compared with OSC (including dexamethasone) in patients with advanced NSCLC with brain metastases (8). Most patients included in this study had uncontrolled thoracic disease or extracranial metastases and about a third were classified as RPA class 3. The primary endpoint was quality of life-adjusted life-years (QUALY) and overall survival (OS) was a secondary endpoint. The study did not show a difference in OS (HR= 1.06; 95% CI 0.90-1.26), overall quality of life, or dexamethasone use between the two groups.

Systemic therapies might be an alternative approach to WBRT, since blood-brain barrier is frequently disrupted by the presence of BM. The timing of WBRT with respect of platinum-based chemotherapy in patients with NSCLC and synchronic brain metastases was studied in the 95-1 GFPC trial (9). All patients received cisplatin and vinorelbine and were randomized to receive delayed WBRT for patients who did not respond to chemotherapy or concurrent WBRT during the first cycle of chemotherapy. The study did not find differences in intracranial overall response and OS, supporting the efficacy of chemotherapy in brain metastases of NSCLC patients and suggesting that delaying WBRT was not deleterious. A latter study (GFPC 07-01) investigated the efficacy of chemotherapy based on cisplatin 75mg/m2 plus pemetrexed 500mg/m2 in the setting of multiple asymptomatic BM from NSCLC. This treatment was well tolerated and achieved an encouraging cerebral and overall response rate (RR) of 42% and 35% respectively (10).

The immune microenvironment in brain metastases is active with a high density of tumor-infiltrating lymphocytes (TIL) in certain patients which might therefore be a potential target (11). TIL density was not associated with corticosteroid treatment, but density of CD8+ TILs was positively correlated with the extent of peritumoral edema seen on pre-operative magnetic resonance imaging (12). In addition, the density of CD3+, CD8+ and CD45RO+ TILs was associated with longer overall survival.

Although clinical data about efficacy of immune checkpoint inhibitors in brain metastases are limited, as most clinical trials evaluating immunotherapy excluded patients with active brain metastases. In a non-randomized phase 2 clinical trial, 36 patients with untreated or progressive brain metastases (18 with melanoma, 18 with NSCLC) without neurological symptoms or the need for corticosteroids received pembrolizumab 10mg/kg every 2 weeks until progression (13). The primary endpoint was brain metastasis response that was achieved in in four (22%) of 18 patients with melanoma and six (33%) of 18 patients with NSCLC. Responses were durable and treatment-related adverse events in NSCLC cohort were grade 3 colitis (n=1 [6%]), grade 3 pneumonitis (n=1 [6%]), grade 3 fatigue (n=1 [6%]), grade 4 hyperkalemia (n=1 [6%]), and grade 2 acute kidney injury (n=1 [6%]) in the NSCLC cohort.

In the Italian nivolumab Expanded Access Program (EAP) for patients with advanced non-squamous NSCLC, 409 patients (26%) out of 1588 had asymptomatic and controlled brain metastases. Patients received a median number of 7 doses (1-45) and the disease control rate was 40%, including 3 pts with a complete response, 65 pts with a partial response and 96 with stable disease. Among these patients, 118 were receiving steroid therapy at baseline and 74 received concomitant radiotherapy. The median overall survival of this subpopulation was 8.1 months (6.2-10.1). Overall, among patients with brain metastasis, 337 discontinued treatment for any reason, but only 23 (7%) patients discontinued treatment due to adverse events.

*First-line treatment for advanced NSCLC without an EGFR mutation or ALK rearrangement*

Patients with previously untreated NSCLC that does not harbor a driver mutation that confers sensitivity to a targeted agent are typically treated with chemotherapy. The first evidence that chemotherapy produced a significant survival benefit in patients with advanced NSCLC came in 1995; a meta-analysis showed that platinum-based doublet chemotherapy conferred a 2-month improvement in median survival over best supportive care (BSC) (14). More recently, the European Big Lung Trial demonstrated the potential benefits of chemotherapy. In this study, 725 patients with advanced NSCLC were randomly assigned to BSC plus cisplatin-based chemotherapy or BSC alone (15). Patients who were allocated to chemotherapy had a significantly longer median survival than did those who were managed with BSC (8 vs. 5.7 months; hazard ratio [HR] = 0.77, 95% CI: 0.66, 0.89).

The benefit conferred by platinum-based chemotherapy regimens appears to have reached a plateau in ORR (approximately 15%–22%) and median survival (7–10 months). More recently, the addition of bevacizumab to carboplatin and paclitaxel resulted in an increase in response rate from 15% to 35% and an increase in median overall survival (OS) from 10 to 12 months (16).

Despite the limited survival benefit conferred by cytotoxic chemotherapy, platinum-based regimens remain the standard first-line option for most patients with locally advanced and metastatic NSCLC that was not harboring an activating EGFR mutation or ALK gene rearrangement. In particular, for newly diagnosed advanced stage non-squamous NSCLC, the standard of care is a platinum doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. However, these regimens are associated with substantial toxicities (such as febrile neutropenia, myelosuppression, nausea, alopecia, nephropathy, and neuropathy) and are generally poorly tolerated by elderly and poor-performance-status patients. Therefore, novel therapies that deliver an improved therapeutic index are urgently needed for non-squamous NSCLC.

*Platinum-based regiment for First-Line NSCLC*

Several meta-analyses have compared the use of cisplatin and carboplatin as treatments for NSCLC. In general, although the ORR was higher in patients treated with cisplatin than in those treated with carboplatin, the 1-year and OS rates were comparable. When given in combination with a third-generation chemotherapy, cisplatin may result in longer survival than carboplatin (overall response of 30% vs. 24% respectively; (17), but overall benefit was quite marginal, and subgroup analyses including additional, more recent studies indicate that there may be no difference between the two agents (18,19). As to safety, cisplatin-based chemotherapy has been associated with more severe nausea and vomiting and nephrotoxicity, while severe thrombocytopenia has been more frequent during carboplatin-based chemotherapy. The risk of treatment-related deaths was greater in the cisplatin arm, but this increase was not statistically significant (18).

Currently, the standard of care for newly diagnosed advanced stage non-squamous NSCLC is a platinum doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. In particular, the combination of platinum doublet with pemetrexed has been used more widely because of a better tolerability and safety profile.

*Pemetrexed*

Pemetrexed disodium (ALIMTA®, pemetrexed) is a novel pyrrolo[2,3 d]pyrimidine–based folic acid analogue. In vitro studies, pemetrexed inhibited multiple folate-dependent enzymes (thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl-transferase) crucial in the de novo biosynthesis of thymidine and purine nucleotides (20).

*Pemetrexed plus Platinum compounds in First-line NSCLC*

Two Phase II studies demonstrated that the combination of pemetrexed and carboplatin is tolerable and that its activity in first-line treatment of advanced-stage NSCLC is comparable with other standard platinum doublets commonly used in clinical practice. The toxicity profile of the pemetrexed/carboplatin combination appears to be more favorable than that seen with other standard regimens in first-line NSCLC.

A Phase III non-inferiority study comparing the efficacy of cisplatin/pemetrexed (n = 862) versus cisplatin/gemcitabine (n = 863) in patients with incurable Stage IIIB or IV NSCLC who had received no prior chemotherapy. Median OS, PFS, and time to progression were comparable between the two treatment groups. However, among patients who had adenocarcinoma or large-cell carcinoma, patients treated with cisplatin/pemetrexed had significantly better median OS than patients treated with cisplatin/gemcitabine (12.6 vs. 10.9 months for adenocarcinoma [HR = 0.84; 95% CI: 0.71, 0.99; p = 0.03]); 10.4 vs. 6.7 months for large-cell carcinoma [HR = 0.67; 95% CI: 0.48, 0.96; p = 0.03]). In addition, cisplatin/pemetrexed was associated with better tolerability and safety and necessitated less supportive care (21).

Additionally, a supportive study named PRONOUNCE was designed to assess the efficacy and safety of pemetrexed + carboplatin (Pem + Cb) followed by pemetrexed maintenance versus paclitaxel + carboplatin+bevacizumab (Pac + Cb + Bev) followed by bevacizumab maintenance (Pac + Cb + Bev) in patients with advanced non-squamous NSCLC (22). The median PFS was 4.44 months for Pem + Cb versus 5.49 months for Pac + Cb + Bev (HR = 1.06; 95% CI: 0.84, 1.35; p = 0.610). The median OS for Pem + Cb was 10.5 months versus 11.7 months for Pac + Cb + Bev (HR = 1.07; 95% CI: 0.83, 1.36; p = 0.615). One- and 2-year survival rates were not significantly different between the arms and were 43.7% and 18.0% for Pem + Cb and 48.8% and 17.6% for Pac + Cb + Bev. Response rate and disease control rate (DCR) were 23.6% and 59.9% for Pem + Cb and 27.4% and 57.0% for Pac + Cb + Bev (p = 0.414 and 0.575, respectively).

*Pemetrexed maintenance Therapy in NSCLC*

A Phase III, randomized, double-blind, placebo-controlled, study that explored the use of pemetrexed as switch maintenance in first-line patients with NSCLC after four cycles of induction therapy using one of six standard platinum doublets (gemcitabine, paclitaxel, or docetaxel with either carboplatin or cisplatin). Patients who achieved a complete response (CR), partial response (PR), or stable disease

were then randomized to maintenance therapy with pemetrexed plus BSC or placebo plus BSC until progression (23). A significant improvement in PFS was reported for patients who received pemetrexed maintenance therapy compared with those who received placebo (4.04 vs. 1.97 months; unadjusted HR 0.50; 95% CI: 0.42, 0.61; $p < 0.00001$). In patients with non-squamous histology, the median PFS for patients receiving pemetrexed versus placebo was 4.5 months versus 2.6 months (unadjusted HR 0.44; 95% CI: 0.36, 0.55; $p < 0.00001$). The median follow-up for OS was 11.2 months for patients in the pemetrexed group and 10.2 months for those receiving placebo. The median OS following induction chemotherapy in the overall study population was 13.4 months with pemetrexed and 10.6 months with placebo (unadjusted HR 0.798; 95% CI: 0.65, 0.95; $p = 0.012$). In the non-squamous population, the median OS was 15.5 months for pemetrexed-treated patients and 10.3 months for patients on placebo (unadjusted HR 0.70; 95% CI: 0.56 to 0.88; $p = 0.002$).

A second study also explored the value of pemetrexed in the continuous maintenance setting. In this study, patients who had not received prior treatment for lung cancer received four cycles of pemetrexed + cisplatin (24,25). Maintenance therapy was continued if stable disease, a PR, or a CR was documented. Patients were then randomized in a 2:1 fashion to either pemetrexed + BSC or placebo + BSC. The median PFS in patients who received pemetrexed was 4.1 months (range 3.2–4.6 months) compared with the median PFS of 2.8 months (range 2.6–3.1 months) in patients who received placebo. The HR for PFS as assessed by the investigator was 0.62 (95% CI: 0.49, 0.79; $p = 0.00006$). The PFS benefit was internally consistent, and benefit was seen across all clinically important subgroups. OS data from this study are pending.

**Background on atezolizumab**

Atezolizumab (MPDL3280A) is a humanized immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution on position 298 of the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans.

Atezolizumab blocks the interaction between Programmed death-ligand 1 (PD-L1 or B7-H1) and Programmed death-1 (PD-1) and B7.1 (CD80), both of which are negative regulators of T-lymphocyte activation (26). Binding of PD-L1 to its receptors suppresses T-cell migration, proliferation and secretion of cytotoxic mediators and restricts tumor cell killing. Blocking PD-L1 enhances anticancer immunity by restoring antitumor T-cell activity and T-cell priming.

*Clinical Pharmacokinetics and Immunogenicity*

On the basis of available preliminary PL data (0.03-20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥ 1mg/kg. For the 1-mg/kg and 20-mg/kg dose groups, the mean apparent clearance and the mean volume of distribution under steady-state conditions had a range of 3.11 to 4.14 mL/kg and 48.1 to 67.0 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

The development of anti-therapeutic antibodies (ATAs) has been observed in patients in all dose cohorts and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses from 10 to 20 mg/kg. Patients dosed at the 10-, 15- and 20-mg/kg dose levels have maintained the expected target trough levels of drug despite detection of ATAs. To date, no clear relationship among ATAs detection and adverse events or infusion reactions or efficacy has been observed.

*Summary of Nonclinical Studies*

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to demonstrate an acceptable safety profile and to identify a Phase I starting dose. The safety, pharmacokinetics and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in defining the appropriate starting dose in humans. The nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies and were consistent with the anticipated pharmacologic activity of down-modulating the PD-L1/PD-1 pathway.

*Summary of Clinical Studies*

Safety and efficacy data are summarized below from the following studies:

- Study PCD4989g: A Phase Ia, multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, PK, exploratory pharmacodynamics and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion every 3 weeks (q3w) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.
- Study GO28753 (POPLAR): A randomized, Phase II, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in PD-L1 unselected patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen.
- Study OAK: A randomized, Phase III, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in PD-L1 unselected patients with previously treated advanced NSCLC that has progressed during or following treatment with a platinum-containing regimen.
- Study GP28328: A Phase Ib study of the safety and pharmacology of atezolizumab administered with bevacizumab and/or with chemotherapy in patients with advanced solid tumors.

When the protocol was designed atezolizumab is approved by FDA and EMA in patients with advanced NSCLC who progressed to previous therapies including platinum-based chemotherapy.

At the date of this report in metastatic NSCLC there are currently these EMA and FDA approved indications:

- Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies
- Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC.
- Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC.
- Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving Tecentriq.

*Atezolizumab Single-Agent Safety Data on Patients with Advanced NSCLC*

In the Phase I PCD4989g, in which atezolizumab was used as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies no maximum tolerated (MTD), no dose-limiting toxicities (DLTs) and no clear dose-related trends in the incidence of adverse events was determined. In this study, 520 out of 558 (93%) safety-evaluable patients experienced at least one adverse event, including 376 (67%) patients who experienced one treatment-related adverse event. Commonly reported events (≥10% of all patients) included fatigue, decreased appetite, nausea, pyrexia, constipation and cough. Grade 3-4 adverse events based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 [NCI CTCAE v4.0] were reported in 239 (43%) patients, of which 66 (12%) were considered related. Grade 3 and 4 adverse events considered related by the investigator included dyspnea, pneumonitis, increased ALT, increase AST, increased GGT, lymphocyte count decreased, cardiac tamponade, asthenia, autoimmune hepatitis, pneumonia, influenza and hypoxia.

In the randomized Phase II POPLAR Study (GO28753), the frequency of patients who reported any adverse events regardless of attribution was 96% for both arms (27). A higher number of Grade ≥ 3 adverse events were observed in the docetaxel arm (53% vs 40%), explained mainly by the difference in adverse events due to bone marrow suppression. This difference was more evident in Grade 3-4 treatment-related adverse events (39% vs 11%). The most common atezolizumab Grade 3 adverse events were pneumonia (2%) and increased AST (2%). No atezolizumab-related Grade 4 adverse events were reported. Immune-related adverse events of any grade with atezolizumab were increased AST (4%), increased ALT (4%), pneumonitis (3%), colitis (1%) and hepatitis (1%). Fewer patients discontinued treatment with atezolizumab than with docetaxel (8% vs 22% respectively). There were six (4%) Grade 5 adverse events in atezolizumab were cardiac failure, pneumonia, ulcer hemorrhage, pneumothorax, pulmonary embolism and embolism.

In the randomized Phase III OAK Study, the frequency of patients who reported any adverse event regardless of attribution was similar in both arms: 94% in atezolizumab arm and 96% in docetaxel arm (28). A higher number of Grade ≥ 3 adverse events were observed in the docetaxel arm (54%) compared with atezolizumab arm (37%). This difference was greater in Grade 3-4 treatment-related adverse events (43% vs 15%). The most common atezolizumab-related adverse events were fatigue (14%), nausea (9%), decreased appetite (9%) and asthenia (8%). Immune-related adverse events reported with atezolizumab included pneumonitis (1%), hepatitis (<1%) and colitis (<1%).

A pooled safety analysis conducted in 843 patients who received atezolizumab in 4 studies (PCD4989g [N = 76]; BIRCH [N = 520]; FIR [N = 105]; POPLAR [N = 142]) (Lukas et al. WCLC 2016). Twenty-seven (3%) of 843 patients had asymptomatic untreated brain metastases or stable previously treated brain metastases at baseline. The incidence of treatment-related neurological AEs was 4 (15%) in patients with baseline brain metastases, including the most common treatment-related AE of headache in 2 (7%) and 27 (3%) patients, respectively. The most common all-cause AEs in patients with baseline brain metastases were fatigue, nausea, and vomiting (7 [26%] each). No treatment discontinuations occurred due to AEs.

*Atezolizumab in Combination with Platinum-Based Chemotherapy Safety Data on patients with Advanced NSCLC*

The Study GP28328 is a Phase Ib study of atezolizumab in combination with bevacizumab or cytotoxic chemotherapy in patients with multiple tumor types including NSCLC, triple-negative breast cancer and colorectal cancer. Patients with advanced NSCLC were included in the following arms: Arm C (atezolizumab + carboplatin + paclitaxel), Arm E (atezolizumab + carboplatin + pemetrexed) and Arm E (atezolizumab + carboplatin + nab-paclitaxel). These combinations have been generally well tolereated and no DLTs have been reported during the dose-escalation stage in any study arm. A total of 141 of 144 (98%) patients reported at least one adverse event while receiving study drug. Most of these events were Grade 2 and 3 in severity. The five most commonly adverse events across the study arms (≥10%) included fatigue, nausea, diarrhea, decreased appetite and pyrexia. The adverse events were consistent with the known safety profile of each agent and no additive effects were observed when atezolizumab was administered with chemotherapy.

*Atezolizumab Single-Agent Efficacy Data on Patients with Advanced NSCLC*

In the Phase I PCD4989g Study, the efficacy evaluable population included 88 patients with locally advanced or metastatic NSCLC and represented a heavily pre-treated patient population (97% of the patients had received ≥ 2 prior systemic therapies and 77% had received ≥ 4 prior systemic therapies). Overall, responses were observed in 20 out of 88 (23%) patients with NSCLC and included responses in patients with squamous and non-squamous NSCLC (4 in 21 and 16 in 67 patients respectively).

In the POPLAR Study, the primary OS analysis was conducted when 173 deaths had occurred. Most patients had received one prior therapy (65%), had non-squamous histology (66%) and ECOG performance status of 1 (68%). Atezolizumab showed significant improvement in OS compared with docetaxel (12.6 vs 9.7 months; HR = 0.73, 95% CI 0.53-0.99; p = 0.04). OS benefit was associated with tumor PD-L1 overexpression. PFS was similar among both arms (2.7 vs 3 months respectively) and

objective responses with atezolizumab were durable, with a median duration of 14.3 months compared with 7.2 months for docetaxel.

In the OAK Study, the primary efficacy analysis population comprised the first 850 patients. Most patients had received one prior therapy (75%), had non-squamous histology (74%) and ECOG performance status of 1 (63%). Atezolizumab showed significant improvement in OS compared with docetaxel (13.8 vs 9.6 months; HR = 0.73, 95% CI 0.62-0.87; p = 0.003). Based on the last data cutoff with a minimum follow-up of 26 months, the 2-year OS rate in patients who received atezolizumab was 31% versus 21% in patients treated with docetaxel (Satouchi et al. WCLC 2017). Although the benefit in terms of OS was associated with tumor PD-L1 overexpression, patients with low or undetectable PD-L1 expression (IC0/TC0) also had improved OS with atezolizumab. A post-hoc subgroup analysis showed that patients with stable previously treated BM also had significant benefit in OS and PFS from atezolizumab (Gadgeel et al. WCLC 2016).

*Atezolizumab in Combination with Platinum-Based Chemotherapy Efficacy Data on patients with Advanced NSCLC*

In the Study GP28328, patients with advanced NSCLC received atezolizumab q3w in combination with platinum-based chemotherapy: carboplatin + paclitaxel (Arm C), carboplatin + pemetrexed (Arm D) and carboplatin + nab-paclitaxel (Arm E). All patients had histologically or cytologically documented Stage IIIB or IV or recurrent NSCLC and had not received prior chemotherapy for advanced disease. The median age was 65 years and 79% had non-squamous histology. In the first data cutoff (February 10th 2015), 41 patients were evaluable for efficacy and the ORR in all three arms was 63%. In the last update of the study, 76 patients were evaluable for efficacy and the ORR according to the three arms was: Arm C (n=25) 46%; Arm D (n=25) 68%; Arm E (n=26) 36% (Liu et al. ASCO 2017). For patients treated with carboplatin + pemetrexed (Arm D), median PFS was 8.4 months (4.7-11) and OS rate at 12 months was 68%.

Refer to the local prescribing information for additional details on nonclinical and clinical studies.

**Study rationale and benefit-risk assessment**

*Rationale for combining Inmune-checkpoint inhibitors with chemotherapy*

Platinum-based regimen has been considered the standard first-line option for patients with locally advanced or metastatic NSCLC not harboring EGFR mutations or ALK gene rearrangements. However, the survival benefit conferred by cytotoxic chemotherapy reached a plateau with overall response

rates of approximately 20% and 1-year survival ranging from 31% to 36%, leaving considerable room for improvement in outcomes (29). Monotherapy with pembrolizumab, an anti-PD-1 antibody, has demonstrated OS benefit in the first line setting compared with platinum-based chemotherapy for advanced NSCLC with PD-L1 expression ≥ 50% (30). However first-line nivolumab, an anti-PD-1 antibody, was not associated with significantly longer OS than platinum-based chemotherapy among patients with advanced NSCLC with a PD-L1 expression level of ≥ 5% (31).

Cytotoxic chemotherapy may induce a favorable environment by inducing rapid tumor shrinkage, immunogenic death, exposition of tumor antigens, promoting antigen-presentation and depleting immunosuppressive cells, allowing immune-based therapies to elicit long lasting memory immune responses capable of controlling relapse due to drug-resistant disease and metastatic spreading (32). The combination of front-line platinum-based chemotherapy with immune-checkpoint inhibitors was explored in the cohort G of the KEYNOTE-021 study, a randomized Phase II trial that compared pembrolizumab (an anti-PD-1 therapy) plus carboplatin + pemetrexed with carboplatin + pemetrexed alone in 60 patients with previously untreated advanced non-squamous NSCLC (33). In the primary analysis (median follow-up of 10.6 months), patients receiving pembrolizumab plus chemotherapy had significantly longer median PFS (13 months) compared with chemotherapy alone (8.9 months; HR = 0.53, 95% CI 0.31 – 0.91, p=0.010). Overall response rate was significantly higher in patients receiving pembrolizumab plus chemotherapy (55% vs 29%, p=0.0016), regardless of tumor PD-L1 expression. In an updated analysis (median follow-up of 18.7 months), patients receiving pembrolizumab plus chemotherapy achieved a median PFS of 19 months compared to 8.9 months with chemotherapy (HR = 0.54, 95% CI 0.33-0.88, p=0.0067). A trend towards longer OS was observed in patients treated with pembrolizumab plus chemotherapy (HR=0.59, 95% CI 0.34-1.05, p=0.025) (Borghaei et al. WCLC 2017).

*Rationale for combining atezolizumab with chemotherapy in First-line*

The combination of platinum-based double chemotherapy and atezolizumab in advanced NSCLC has been evaluated in the Phase Ib study GP28328 (see previous section). Atezolizumab was well tolerated when combined various platinum-doublet chemotherapy regimens and promising clinical activity was observed in terms of ORR and PFS, especially for patients receiving atezolizumab in combination with carboplatin + pemetrexed. Adverse events and immune-related adverse events were consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis and colitis which were manageable with appropriate treatment.

Based on these results, several randomized Phase III trials (IMpower 130, 131, 132, 150) have been developed to assess whether combining in the first-line setting atezolizumab with platinum-based doublet chemotherapy would translate into clinically relevant improvement in PFS and OS. The accrual of these studies has been completed and data analysis is ongoing. However, in these clinical trials patients with untreated BM have been systematically excluded and therefore this therapeutic combination has not been tested yet in the setting of clinically stable or asymptomatic untreated BM.

*In summary, front-line treatment with atezolizumab in addition to chemotherapy based on carboplatin plus pemetrexed offers the potential for clinical benefit in advanced non-squamous NSCLC with untreated brain metastases.*

## 8. STUDY OBJECTIVES

This study will evaluate the efficacy and safety of atezolizumab combined with CBDCA and pemetrexed in patients with NSCLC and untreated brain metastases. Specific objectives and corresponding endpoints for the study are outlined below.

**Table 1. Objectives and corresponding Endpoints**

| Primary Efficacy Objective | Corresponding Endpoint |
|---|---|
| • To evaluate the efficacy of atezolizumab combined with CBDCA and pemetrexed in patients with NSCLC and untreated BM | • PFS after enrollment defined as the time from enrollment to the first occurrence of disease progression (intracranial or systemic) or death from any cause whichever occurs first as determined by the investigator according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively |
| • To evaluate the safety of atezolizumab combined with CBDCA and pemetrexed in patients with NSCLC and untreated BM | • Occurrence and severity of adverse events, with severity determined according to NCI CTCAE v4.0 criteria<br>• Change from baseline in targeted vital signs<br>• Change from baseline in targeted clinical laboratory test results |
| **Secondary Efficacy Objective** | **Corresponding Endpoints** |
| • To evaluate the efficacy of atezolizumab combined with carboplatin and pemetrexed in patients with NSCLC and untreated BM | • Objective response, defined as a complete response or partial response on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively<br>• DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause whichever occurs first, as determined by the investigator according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively<br>• OS after enrollment defined as the time from enrollment to death from any cause |
| **Exploratory Objectives** | **Corresponding Endpoints** |

| | |
|---|---|
| • To assess the neurocognitive function | • Change from baseline in the following standardized neuropsychological tests: Hopkins Verbal Learning Test (HVLT), Trail Making Test (TMT), Rey–Osterrieth complex figure test (ROCF) and Controlled Oral Word Association Test (COWA) at baseline, cycle 5 (week 12), cycle 8 (week 21), at end of study treatment (30 and 90 days) and/or at disease progression. |
| • To determine the time to neurological deterioration and to record the number of patients requiring an increase steroid dose for ≥96h to control neurologic symptoms. | • Neurological deterioration from baseline will be determined using the NANO scale at baseline, cycle 5 (week 12), cycle 8 (week 21), at end of study treatment (30 and 90 days) and/or at disease progression. Increase in the steroid use for ≥96h will be recorded in the database. |
| • To determine the time to need for salvage therapy during the study | • Defined by the median time to brain radiotherapy (WBRT or SRS) |
| • To determine the quality of life (QoL). | • Change from baseline in HRQol, as assessed through use of the EORTC C30 and submodules LC13 BN20 at baseline, at week 12 (cycle 5), week 21 (cycle 8), and at the end of study treatment (30 and 90 days) and/or at progression |
| **Exploratory Biomarker Objective** | **Corresponding Endpoint** |
| • To identify biomarkers that are predictive of response to treatment<br>• To identify neuroimaging markers (MRI) in that are predictive of intracranial response to systemic treatment<br>• To identify radiomic neuroimaging markers (MRI) that are predictive of intracranial response to systemic treatment (ICIs plus chemotherapy). | • Relationship between PD-L1 expression by 22C3 DAKO in tumor tissue (listed in Section 4.5) and efficacy endpoints<br>• Changes in volumetric brain morphometry (voxel-based morphometry) and blood brain barrier disruption from baseline to week 12 and at progression or end of study<br>• Radiomic analysis of baseline and early magnetic resonance images (MRIs) (MRI corresponding to cycle 5 of systemic treatment or if the last one is not available, corresponding to cycle 3) |

*HRQol = health-related quality of life.*

# 9. INVESTIGATIONAL PLAN

## 9.1. OVERALL STUDY DESIGN AND PLAN – DESCRIPTION

**DESCRIPTION OF THE STUDY**

This is a non-randomized, Phase II, multicenter, open-label study designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + pemetrexed in patients who are chemotherapy naïve and have Stage IV non-squamous NSCLC with untreated brain metastases. Figure 1 presents an overview of the study design. A schedule of activities is provided in **Appendix 1.**

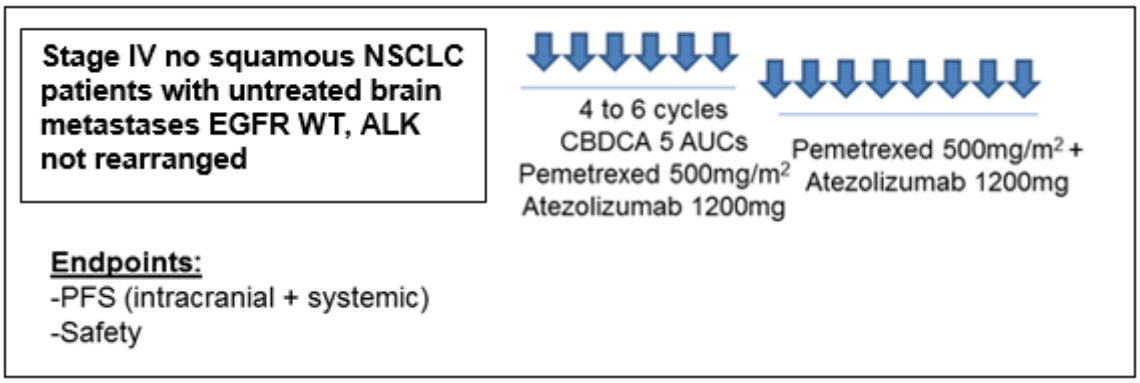



**Figure 1. Study Schema**

Eligible patients will be registered and will receive the following treatment regimen:

| Induction (four or six 21-day cycles) | Maintenance (21-day cycles) |
|---|---|
| Atezolizumab 1200 mg/iv + carboplatin 5 AUCs + pemetrexed 500mg/m$^2$ | Atezolizumab 1200mg/iv + pemetrexed 500 mg/m$^2$ |

The number of cycles of induction treatment (four or six) will be at the discretion of the investigator and will be determined and documented prior to enrollment. Induction treatment will be administered on a 21-day (+/- 3 days) cycles until the following occurs (whichever occurs first): 1) administration of 4 or 6 cycles, 2) unacceptable toxicity, or 3) documented disease progression. Following the induction phase, patients who have not experienced disease progression or unacceptable toxicity will continue treatment with maintenance therapy.

Response will be assessed independently in the brain and systemically: systemic response will be evaluated according to RECIST v1.1 and brain response according to the RANO response assessment criteria for BM (RANO-BM). PFS event will be possible based on three potential clinical scenarios due to the dual component of the PFS endpoint:

| CNS (RANO-BM) | Non-CNS (RECIST 1.1.) | PFS event | Note |
|---|---|---|---|
| CR, PR or SD | Progressive disease | Yes | Log as non-CNS progressive disease |
| Progressive disease | CR, PR or SD | | Log as CNS progressive disease |
| Progressive disease | Progressive disease | | Log as both non-CNS and CNS progressive disease |

CR: complete response; PR: partial response; SD: stable disease.

Patients will undergo tumor assessments (body CT scan and brain MRI) at baseline every 6 weeks for the first 12 weeks following Cycle 1, Day 1, regardless of dose delays and thereafter tumor assessments will be performed every 9 weeks until disease progression or loss of clinical benefit (for atezolizumab-treated only patients who continue treatment beyond radiographic disease progression), withdrawal of consent, study termination by Sponsor or death, whichever occurs first.

During induction or maintenance treatment, treatment with chemotherapy should be discontinued in all patients who exhibit evidence of progressive disease. Atezolizumab administration may continue beyond progressive disease in case they have clinical benefit as assessed by the investigator as described below:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- ***In case of brain progression according to RANO-BM criteria (Appendix 3), rescue with brain radiotherapy should be considered. In case of exclusive brain progression, patients are allowed to receive brain radiotherapy (WBRT or SRS) and then continue with atezolizumab if the patients maintain clinical benefit and appropriate performance status (ECOG PS≤1) and can start immunotherapy not later than 4 weeks after completing radiation therapy (brain radiotherapy 2 weeks + 4 weeks of recovery from potential acute toxicity). In case of systemic progression by RECIST v1.1 without brain progression, a novel line of systemic treatment should be considered but patients should follow brain radiographic assessments to document the CNS disease progression.***

Patients who discontinue study treatment for reasons other than radiographic disease progression (e.g. toxicity) will continue scheduled tumor assessments until disease progression of loss of clinical benefit (for atezolizumab-treated only patients who continue treatment beyond radiographic disease progression), withdrawal of consent, study termination by Sponsor or death, whichever occurs first.

Secondary endpoints are investigator-assessed CNS and non-CNS or systemic response rate (RR) based on RANO-BM criteria and RECIST v1.1 criteria respectively, time to need for salvage therapy defined as the time from enrollment to the time of brain radiotherapy and landmark OS analysis at 6, 12 and 18 months. Exploratory endpoints are duration of response of brain metastases, the assessment of neurocognitive function, progression-free to neurological deterioration and quality of life. Additionally, several neuroimaging markers will be assessed in the baseline MRI to predict response to systemic therapy.

This study will initially enroll 40 patients across all sites.

**END OF STUDY AND LENGTH OF STUDY**

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient whichever occurs later. The end of the study is expected to occur 18 months after the last patient is enrolled. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3 years. In addition, the Sponsor may decide to terminate the study at any time.

## 9.2. DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

**RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE**

The fixed dose of 1200 mg (equivalent to an average body weight-base dose of 15mg/kg) intravenously was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g. The target exposure for atezolizumab was projected on the basis of nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, the observed atezolizumab interim pharmacokinetics and other factors.

Antitumor activity has been observed across doses from 1 mg/kg to 20 mg/kg. The MTD of atezolizumab was not reached and DLTs have been observed at any dose in Study PCD4989g. Currently available PK and ATA data suggest that the 15-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent) for Phase II and Phase III studies would be sufficient to both maintain Ctrough ≥ 6 µg/mL and further safeguard against both interpatient variability and the potential effect of ATAs that may lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab q3w regimen.

In this trial, atezolizumab will be given as an intravenous fixed dose of 1200 mg every 3 weeks (+/- 3 days) (q3w) until unacceptable toxicity or disease progression, as assessed by the investigator. Atezolizumab treatment could continue beyond disease progression if the investigator deems the patient to have clinical benefit.

**RATIONALE FOR USING PFS AND SAFETY AS PRIMARY ENDPOINTS**

In patients with brain metastases, either brain metastases or extracranial disease may have a major impact on survival as it has been shown in several clinical trials (34). Although response to systemic therapies may differ among intracranial and extracranial disease due to limited capacity to penetrate into the blood-brain barrier or molecular heterogeneity between tumor and metastases, the Response Assessment Neuro-Oncology Brain Metastases (RANO-BM) Working Group considers that PFS at 12 weeks is a reasonable endpoint for Phase II trials in patients with brain metastasis (35). Indeed, tumor volume in the enclosed space of the skull may have significant clinical impact. Patient-reported outcomes (PROs), cognitive and neurological status assessments and health-related QoL tests are deemed relevant endpoints in this clinical setting as they can capture the impact of treatment and progressive disease on neurological symptoms, cognitive function or patient's quality of life.

Cancer immunotherapy based on atezolizumab in second or third line setting of treatment of advanced NSCLC demonstrated a positive impact on OS that was not captured by PFS (27,28). However positive clinical trials based on cancer immunotherapy in the first line setting of treatment for advanced NSCLC demonstrated a positive impact on PFS as well as OS (30,33). Although PFS has been considered a challenging endpoint for immunotherapy clinical trials, we consider that this is an appropriate endpoint in this clinical setting.

This clinical trial incorporates safety as co-primary endpoint in order to minimize any potential deleterious effect of this treatment on patient's outcome. Rescue with brain radiotherapy (WBRT or SRS) will be considered in case of brain progression. In case of exclusive brain progression, patients are allowed to continue with study therapy after completing brain radiotherapy if the patients maintain clinical benefit and appropriate performance status (ECOG PS≤2).

**RATIONALE FOR ATEZOLIZUMAB TREATMENT BEYOND PROGRESSION (TBP)**

Cancer immunotherapy in second- or third-line setting of treatment can have a positive impact on OS that exceeds response rate or PFS effects, termed post progression prolongation of survival (PPPS). This effect can also result from unconventional response due to tumor immune infiltration or delayed response, reducing reliability of RECIST v1.1 (RECIST) progression as an indicator of treatment failure. A posthoc analysis evaluated clinical benefit from TBP, defined by post PD tumor regression, OS and safety (Gandara et al. ASCO 2017). Among 332 patients who received atezolizumab and experienced progression, 51% (n = 168) continued atezolizumab TBP; 7% (12/168) achieved subsequent response in target lesions and 49% (83/168) had stable target. Median OS was 12.7 months (95% CI 9.3 - 14.9) post PD for pts on atezolizumab TBP. TBP with atezolizumab was not associated with increased safety risk.

In this clinical trial, patients will be fully informed of the risk of continuing study treatment in spite of apparent radiographic progression when they maintain clinical benefit, and investigators should make a careful assessment of the potential benefit of doing so, considering radiographic data, biopsy results and the clinical status of the patient.

**RATIONALE FOR PATIENT POPULATION**

This study focuses on advanced NSCLC patients with untreated brain metastases, because this patient population has been underrepresented in most clinical trials and data from two previous studies demonstrated that systemic therapy is safe in this clinical setting and that delaying brain radiotherapy

is not deleterious (9,10). Addition of immunotherapy to conventional platinum-based chemotherapy may increase intracranial tumor response and provide clinically relevant benefit in terms of PFS, OS and quality of life to the patients with asymptomatic brain metastases.

**RATIONALE FOR BIOMARKER ASSESSMENT**

PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors PD-1 and B7.1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer. Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen-presenting cells can mediate downregulation of immune responses, including inhibition of T-cell activation and cytokine production.

Overexpression of PD-L1 on tumor cells (TCs) has been reported to impede anti-tumor immunity, resulting in immune evasion. Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity. PD-L1 expression is prevalent in many human tumors, and elevated PD-L1 expression is associated with a poor prognosis in patients with NSCLC.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies and who have failed standard of care therapies. Study PCD4989g, a Phase Ia dose-escalation and expansion study of patients treated with atezolizumab as a single agent had the following clinical activity: 345 evaluable patients were dosed by 21 October 2013 (data cutoff date as of 21 April 2014) with a minimum of 6 months of follow-up; 62 patients experienced objective responses per RECIST v1.1 with an ORR of 18.0% (95% CI: 14.1%, 22.3%). Objective responses were observed across a broad range of malignancies, including NSCLC, RCC, melanoma, and UBC.

In addition, as explained above, the POPLAR study key efficacy results for the ITT population and the PD-L1–selected subgroup categories indicate that an OS benefit in the atezolizumab arm was observed, with a stratified HR of 0.78 (95% CI: 0.59, 1.03) even though PFS and ORR for the atezolizumab arm were similar to those for the docetaxel arm.

### 9.3. SELECTION OF STUDY POPULATION

Forty patients who are chemotherapy naïve and have Stage IV non-squamous NSCLC with untreated brain metastases will be enrolled in this study.

#### 9.3.1. Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- ECOG Performance Status (PS) of 0 to 1

- Histologically or cytologically confirmed, Stage IV non-squamous NSCLC; patients with mixed non-small cell histology (i.e. squamous and non-squamous) are eligible whether the major component appears to be non-squamous
- No prior treatment or Stage IV non-squamous NSCLC
    - Patients with a sensitizing mutation in EGFR gene are excluded given that EGFR TKIs are the appropriate front-line treatment for those patients
    - Patients with an ALK fusion are excluded given that ALK TKIs are the appropriate front-line treatment for those patients
    - Patients with unknown EGFR and ALK status require test results at screening, they can be assessed at a local or central laboratory
- Patients who received prior neo-adjuvant, adjuvant chemotherapy or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months since the last dose of chemotherapy and/or radiotherapy
- Asymptomatic or oligosymptomatic* (considered to have alterations in the neurological examination, whether or not they are noted in the anamnesis, that do not prevent appropriate functioning according to the patients' basal state, or that disappear with medical treatment (corticosteroids, analgesics, anticonvulsants) )untreated brain metastases. *olygosymptomatic cases must be consulted with Trial Chair prior to patient enrollment
- Steroids treatment (dexamethasone) is allowed and patients that remained oligosymptomatic or asymptomatic for 2 weeks on steroids will be eligible when they were receiving ≤ 4mg dexamethasone once a day.
- Systemic measurable disease by computed tomography (CT) per response evaluation criteria in solid tumors version (RECIST) 1.1 criteria AND brain measurable disease by magnetic resonance imaging (MRI) per RANO-BM criteria
- Availability of a formalin-fixed paraffin-embedded block (cell blocks will be accepted if tumor biopsy is not available) containing tumor tissue or 10 unstained slides.
- Adequate hematopoietic, hepatic and renal function:
    - ANC ≥ 1,500 cells/µL
    - Lymphocyte count ≥ 500 cells/µL
    - Platelet count ≥ 100,000 cells µL
    - Hemoglobin ≥ 9.0 g/dL (transfusion is allowed)
    - INR or aPTT ≤ 1.5 x upper limit of normal (ULN); patients receiving therapeutic anticoagulation should be on a stable dose
    - ALT, AST and/or alkaline phosphatase ≤ 2.5 x ULN, with the following exceptions:

      -patients with known liver metastasis: ALT and/or AST ≤ 5 x ULN
      -patients with known bone metastasis: alkaline phosphatase ≤ 5 x ULN

- Serum bilirubin ≤ 1.5 x ULN; patients with known Gilbert disease who have serum bilirubin ≤ 3 x ULN may be recruited)
- Calculated creatinine clearance (CRCL) ≥ 45 mL/min (based on the standard Cockcroft and Gault formula)

- For women of childbearing potential: agreement to remain abstinent or use contraceptive non-hormonal methods with a failure rate of < 1% per year during the treatment period and for 3 months after the last dose of study treatment. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization and copper intrauterine devices.
- For men: agreement to remain abstinent or use a condom, and agreement to refrain from donating sperm. With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 3 months after the last dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

#### 9.3.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of other malignancy within 3 years* prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer *less than 3 years cases can be consulted with trial chair
- Patients harboring an EGFR mutation or an ALK fusion will be excluded
- Leptomeningeal carcinomatosis or metastases in the brain stem, mid-brain, pons, medulla or lesions causing obstructive hydrocephalus
- Patients with neurological symptoms, including those receiving > 4mg of dexamethasone will not be eligible for this study
- Spinal or hemorrhagic metastases will be excluded
- Prior surgical resection of brain or spinal lesions in the prior 14 days
- Previous systemic treatment or neo-adjuvant or adjuvant chemotherapy less than 6 months before enrollment
- Clinical significant comorbidities that impaired administration of platinum-based chemotherapy
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis or glomerulonephritis

- Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone are eligible for this study
- Patients with controlled Type 1 diabetes mellitus on a stable dose of insulin are eligible for this study
- Patients with eczema, psoriasis, lichen simplex chronicus or vitiligo with dermatologic manifestations only (e.g. patients with psoriasic arthritis would be excluded) are permitted provided that they meet the following conditions: rash covers less than 10% of body surface area, disease is well controlled at baseline and only requires low-potency topical steroids, no acute exacerbations during the last 12 months

- History of idiopathic pulmonary fibrosis, drug-induced pneumonitis or active radiation pneumonitis out of the radiation field
- Previous treatment with immune checkpoint inhibitors or CD137 and OX-40 agonists
- Treatment with investigational therapy within 28 days prior to initiation of study drug
- Positive for hepatitis C virus (HCV) antibody or for hepatitis B surface antigen (HBsAg) at screening. Patients with past or resolved hepatitis B virus (HBV) infection (HBcAb positive with absence of HBsAg) would be eligible whether they are negative for HBV DNA. Patients positive for HCV antibody would be eligible whether they are negative for HCV RNA
- Active tuberculosis or HIV infection
- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study.

#### 9.3.3. Removal of Patients from Therapy or Assessment

**Study treatment discontinuation**

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy
- Use of an anti-cancer therapy not required per protocol
- Symptomatic deterioration attributed to disease progression
- Disease progression per investigator assessment according to ***RECIST v1.1 criteria*** and loss of clinical benefit
- Disease progression in the CNS per investigator assessment according to ***RANO criteria*** and loss of clinical benefit. In patients who may benefit from brain radiotherapy and maintain clinical benefit and ECOG PS≤ 2, treatment with atezolizumab can be considered

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit 30 days (± 7) days after the last dose of study drug (see Appendix 1 for additional details).

**Patient discontinuation from study**

Patients will return to the clinic for a study completion. Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

**Study discontinuation**

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

**Site discontinuation**

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

## 9.4. TREATMENTS

### 9.4.1. Treatments Administered

The investigational medicinal product (IMP) for this study is Atezolizumab.

### 9.4.2. Identity of Investigational Product(s)

**Atezolizumab**

The atezolizumab (MPDL3280A) drug product is provided as a sterile liquid in 20-mL glass vials. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. For further details on the formulation and handling of atezolizumab, see the Pharmacy Manual and Investigator's Brochure.

**Carboplatin + Pemetrexed**

Each study drug will be used in the commercially available formulation (with the exception of atezolizumab) that will be provided by the Sponsor.. (For information on the formulation, packaging, and handling of carboplatin, and pemetrexed, see the local prescribing information for each drug)

### 9.4.3. Method of Assigning Patients to Treatment Groups

This is an open-label study. After written informed consent has been obtained and eligibility has been established, the study site will register the patient in the electronic Case Report Form (eCRF). For patients who are eligible for enrollment, the study site will obtain the patient's inclusion number. The number of cycles of induction treatment (four or six) will be determined by the investigator and documented prior to randomization.
Patients should receive their first dose of study drug on the day of enrollment if possible. If this is not possible, the first dose should occur within 5 business days after enrollment.

### 9.4.4. Selection of Doses in the Study

**Atezolizumab**

Patients will receive 1200 mg of atezolizumab administered by IV infusion every 21 days (+/- 3 days) in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. Dose modifications to atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided in Section **¡Error! No se e ncuentra el origen de la referencia.**. Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.
Atezolizumab infusions will be administered per the instructions outlined in **¡Error! No se encuentra el origen de la referencia.**.

**Pemetrexed**

Institutions should follow their standard administration procedures for pemetrexed. The premedication doses administered should be in compliance with the prescribing information. All patients eligible for pemetrexed therapy should avoid taking non-steroidal anti-

inflammatory drugs with long elimination half-lives for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration.

**Carboplatin**

Carboplatin should be administered 30 minutes after completion of pemetrexed administration by IV infusion over 30–60 minutes to achieve an initial target area under the concentration–time curve (AUC) of 5 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines.

The carboplatin dose of AUC 5 will be calculated using the Calvert formula (Calvert et al. 1989):

Calvert Formula

Total dose (mg) = (target AUC) × (glomerular filtration rate [GFR] + 25)

**NOTE**: The GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min.

For the purposes of this protocol, the GFR is considered to be equivalent to the CRCL.The CRCL is calculated by institutional guidelines or by the method of Cockcroft and Gault (1976) using the following formula:

$$\text{CRCL} = \frac{(140 - \text{age})\,(\text{weight})}{72 \times \text{Scr}} \quad (\times 0.85 \text{ if female})$$

Where: CRCL = creatinine clearance in mL/min; age = patient's age in years;
weight = patient's weight in kg; Scr = serum creatinine in mg/dL

**NOTE**: For patients with an abnormally low serum creatinine level, estimate the GFR through use of a minimum creatinine level of 0.8 mg/dL or cap the estimated GFR at 125 mL/min.

If a patient's GFR is estimated based on serum creatinine measurements by the isotope dilution mass spectroscopy method, the U.S. Food and Drug Administration (FDA) recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. Based on the Calvert formula described in the carboplatin label, the maximum doses can be calculated as follows:

Maximum carboplatin dose (mg) = target AUC (mg • min/mL) × (GFR + 25 mL/min)

The maximum dose is based on a GFR estimate that is capped at 150 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC = 5, the maximum dose is 5 × 150 = 750 mg.
For a target AUC = 4, the maximum dose is 4 × 150 = 600 mg.

9.4.5. Selection and Timing of Dose for each Patient

The induction phase of the study will consist of four or six cycles of chemotherapy, each cycle being 21 days (+-/ 3 days) in duration. On Day 1 of each cycle, all eligible patients will receive drug infusions in the following order:

Atezolizumab → [carboplatin + pemetrexed]

During the induction phase, a chemotherapy cycle counts toward the pre-specified number of induction chemotherapy cycles (4 or 6) as long as at least one chemotherapy component has been administered at least once during a 21-day cycle (+/- 3 days). Cycles in which no chemotherapy component is given do not count toward the total number of induction chemotherapy cycles.

Patients who experience no further clinical benefit or disease progression at any time during the induction phase will discontinue all study treatment. In the absence of the above criteria, after the 4 or 6-cycle induction phase, patients will begin maintenance therapy (atezolizumab +□ pemetrexed). During treatment (induction or maintenance), patients who show evidence of clinical benefit will be permitted to continue atezolizumab after RECIST v1.1 for progressive disease are met if they meet all criteria listed in Section **¡Error! No se encuentra el origen de la referencia.**. However, treatment with chemotherapy should be discontinued.

In case of willing to continue the maintenance phase only with Atezolizumab due to toxicity or any other reason, it has to be consulted to the Trial Chair.

Patients should receive anti-emetics and IV hydration for platinum-pemetrexed treatments according to the local standard of care and manufacturer's instruction. However, due to their immunomodulatory effects, premedication with steroids should be limited when clinically feasible. Additionally, in the event of pemetrexed related skin rash, topical steroid use is recommended as front-line treatment whenever is clinically feasible. **¡Error! No se encuentra el origen de la referencia.** lists the premedication for pemetrexed. Table 1 lists the suggested infusion times for treatment administration for pemetrexed + platinum during the induction and maintenance phases.

**Table 1 Treatment Regimen for Pemetrexed + Platinum-Based Chemotherapy**

| Study Drug | Dose/Route | Induction Period (Four or Six Cycles) | Maintenance Period (Until PD) |
|---|---|---|---|
| Pemetrexed | 500 mg/m$^2$ IV | Over approximately10 minutes on Day 1 q3w | Over approximately 10 minutes on Day 1 q3w |
| Carboplatin | AUC 5 IV | Over approximately 30–60 minutes on Day 1 q3W | Not applicable |

AUC = area under the concentration–time curve; IV = intravenous; PD = progressive disease; q3w = every 3 weeks.

Guidelines for dose modification and treatment interruption or discontinuation for carboplatin or cisplatin and pemetrexed are provided in Sections

Prior and Concomitant Therapy

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the

study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

#### 9.4.6. Treatment Compliance

The investigational medicinal product for this study is atezolizumab. Pemetrexed and Carboplatin are considered non−investigational medicinal product (NIMP). The study site will acknowledge receipt of the IMPs to confirm shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor or designee with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

### 9.5. EFFICACY AND SAFETY VARIABLES

#### 9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

Patients will be closely monitored for safety and tolerability throughout the study. All activities must be performed and documented for each patient. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

INFORMED CONSENT FORMS AND SCREENING LOG

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

MEDICAL HISTORY, CONCOMITANT MEDICATION, AND DEMOGRAPHIC DATA

Demographic data including age and gender and medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history and all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

NSCLC cancer history will include prior cancer therapies (surgery, chemoradiation, SBRT, palliative radiotherapy) and results of tumor mutational status (e.g., sensitizing EGFR mutation, ALK fusion

status). For patients not previously tested for tumor mutational status, testing will be required at screening. For these patients, testing can either be performed locally or submitted for central evaluation during the screening period to Department of pathology at the Hospital Universitari de Bellvitge (L'Hospitalet, Barcelona). If EGFR mutations or ALK status testing is not performed locally, additional tumor sections may be required for central evaluation of the mutational status of these genes.

PHYSICAL EXAMINATIONS

A complete physical examination, performed at screening and other specified visits, should include ECOG, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

VITAL SIGNS

Vital signs will include measurements of temperature, pulse rate, oxygen saturation by pulse oximetry, and systolic and diastolic blood pressures while the patient is in a seated position.

TUMOR AND RESPONSE EVALUATIONS

Screening assessments must include CT scans (with oral/IV contrast unless contraindicated) of the chest and abdomen. A CT scan of the pelvis or the neck should be included if clinically indicated at subsequent response evaluations. Bone scans should also be performed if clinically indicated.

An MRI scan of the brain is required to confirm the diagnosis of CNS metastases at baseline. At the investigator's discretion, CT scans or brain MRI may be repeated at any time if progressive disease is suspected, however a brain MRI must be performed to confirm progression.

Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1, may be used rather than repeating tests if the following scans are going to be performed using the same radiographic procedure and device. All known sites of disease must be documented at screening and re assessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Systemic response will be assessed by the investigator using RECIST v1.1 (see **¡Error! No se encuentra el origen de la referencia.**) and CNS response w ill be assessed using RANO criteria (see Appendix 3).. Assessments should be performed

by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

Tumor assessments should occur every 6 weeks (± 7 days) for 12 weeks following Cycle 1, Day 1 and then every 9 weeks (± 7 days) thereafter, after the completion of the Week 12 tumor assessment, regardless of treatment delays, until radiographic disease progression per RECIST v1.1 or RANO criteria (loss of clinical benefit for atezolizumab-treated patients who continue treatment beyond disease progression), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Patients who are treated with atezolizumab who continue to experience clinical benefit, despite evidence of radiographic progression, will continue tumor assessments as per the schedule listed above.

LABORATORY AND BLOOD SAMPLES

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, total or direct bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, uric acid, and albumin, amylase, lipase)
- Coagulation (TP, aPTT or INR, or ratio PT/aPTT)
- Serum pregnancy test for women of childbearing potential, including women who have had a tubal ligation; urine pregnancy tests will be performed at Day 1 of each cycle during treatment prior to administration of study treatment. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

Childbearing potential is defined as not having undergone surgical sterilization, hysterectomy, and/or bilateral oophorectomy or not being postmenopausal (≥12 months of amenorrhea).

- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria); dipstick permitted
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3 and/or free T4)

*Total T3 (instead of free T3) will be tested only at sites where free T3 testing cannot be performed.*

- HBV serology: hepatitis B surface antigen (HBsAg), *antibodies against HbsAg (HBsAb or anti-HBs), and* hepatitis B core antibody (HBcAb).

*If the patient has a negative serology for HbsAg and a positive serology for HBcAb, an HBV DNA test must be obtained prior to randomization and must be negative.*

- HCV serology: HCV antibody (anti-HCV)

*If the patient tests positive for anti-HCV, an HCV RNA must be obtained prior to randomization and be negative.*

- HIV testing

All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical study.

- Biomarker assays in blood samples. One 9-10 ml EDTA tube and one 8.5 ml serum separator tube (SST) will be collected for obtaining plasma and serum respectively. After 20-30 minutes at room temperature, a clot will appear in the SST tube and then this tube will be spinned at 1,600G for 10 minutes at room temperature. The supernatant will be recovered and collected in cryotubes and will be frozen at -80ºC. Plasma from EDTA tube will be recovered and collected in cryotubes and will be frozen at -80ºC.

Blood samples will be obtained for biomarker evaluation (including, but not limited to, biomarkers that are related to NSCLC or tumor immune biology) from all eligible patients according to the schedule in Appendix 1. Samples will be processed to obtain EDTA plasma and serum for the determination of changes in blood-based biomarkers (e.g., ctDNA, cytokines). Exploratory biomarker research may include extraction of ctDNA to assess blood tumor mutational burden.

TUMOR TISSUE SAMPLES AT SCREENING

A pre-treatment tumor tissue (archival or freshly obtained) sample (if available) should be submitted before or 4 weeks after enrollment. This specimen must be accompanied by the associated pathology report. Although any available tumor tissue sample can be submitted, it is strongly encouraged that the sites submit representative tumor specimens in paraffin blocks (preferred) or 10 (or more) serial, freshly cut, unstained slides exploratory biomarker analysis (including, but not limited to, markers related to immune or NSCLC biology, such as T-cell markers or non-inherited biomarkers identified through NGS on extracted DNA).

The preferred sample types include: resections, core needle, excisional, incisional, punch, or forceps biopsies. If specimens described above are not available, any type of specimens (including fine-needle aspiration, cell pellet specimens e.g., from pleural effusion, and lavage samples) are also acceptable. Tumor tissue should be of good quality based on total and viable tumor content. Tumor tissue from bone metastases that is subject to decalcification is not advisable. If tumor tissue is not available, the patient is still eligible.

For archival samples, the remaining tumor tissue block for all patients enrolled will be returned to the site upon request or 18 months after final closure of the study database, whichever is sooner. Tissue samples from patients who are deemed ineligible to enroll in the study will be returned no later than 6 weeks after eligibility determination.

Exploratory biomarker research may include, but will not be limited to, tumor PD-L1 expression and CD8 lymphocyte infiltration expression assessed by immunohistochemistry and may involve extraction of DNA to assess somatic mutations by using a targeted sequencing panel.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed, or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

ELECTROCARDIOGRAMS

A 12-lead ECG is required at screening and as clinically indicated. ECGs should be obtained on the same machine whenever possible. Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine position for at least 10 minutes. For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

CLINICIAN-REPORTED OUTCOMES (CLINRO), HEALTH-RELATED QUALITY OF LIFE (HRQOL) AND NEUROCOGNITIVE ASSESSMENT

The ClinRO data will include the Neurologic Assessment in Neuro-Oncology (NANO) scale (36). The NANO scale is an objective clinician-reported outcome of neurologic function with high inter-observer agreement quantifiable evaluation of 9 relevant neurologic domains (gait, strength, ataxia, sensation, visual fields, facial strength, language, level of consciousness and behavior) with a median assessment time of 4 minutes. It is designed to combine with radiographic assessment to provide an overall assessment of outcome for neuro-oncology patients in clinical trials and in daily practice. Furthermore, it complements existing cognition testing to combine for a global clinical outcome assessment of well-being brain tumor patients. The clinRO will be completed at baseline, at cycle 5 (week 12), cycle 8 (week 21), at end of study treatment (30 and 90 days) and/or at disease progression. To ensure instrument validity and that data standards meet health authority requirements, the NANO scale will be administered before the patient receives any information on disease status, prior to the performance of HRQol and neurocognitive assessments, and prior to the administration of study treatment, unless otherwise specified.

Health-related Quality of Life (HRQol) questionnaires will include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 y QLQ-LC13) and EORTC QLQ-BN20 (specifically for brain tumor patients). They are validated self-report health status questionnaire that is has been widely used in neuro-oncology trials. QLQ tests allow to capture the patient's' own perception about their physical, mental, and social functions, as well as other related symptoms frequently suffered by cancer patients in general (C30), and especially in patients with brain cancer (BN20).The QLQ-C30 is composed of multi-item scales and isolated measurements. It consists of 5 functional scales, which address questions about patient activities, one on

the overall health status and 3 scales plus 6 isolated questions from symptoms and the perception of the illness consequences reported by the patient's. The functional scales are: scale of social function (questions 26,27), cognitive (questions 20, 25), emotional (questions 21-24), daily activity (questions 6 and 7) and physical condition (questions 1 - 5). The overall health status scale is evaluated by questions 29 and 30. The measured symptoms are: fatigue (questions 10,12,18), nausea and vomiting (questions 14 and 15), pain (questions 9 and 19), dyspnoea (question 8), insomnia (question 11), anorexia (question 13), constipation (question 16), diarrhea (question 17), and financial difficulties (question 28). The highest score achieved in the functional scales and overall health status means higher functional level and quality of life; but a higher punctuation in the questions about symptoms means worst intensity of the symptoms.

The BN-20 module is a complementary test to QLQ-C30, specifically aimed at assessing aspects of the quality of life of patients with brain tumors. This test consists in 20 questions that are organized on 4 scales and 7 isolated items. The scales are: uncertainty for the future (questions 1,2,3,5), visual disturbances (questions 6,7,8), motor alterations (questions 10,15,19) and communication deficits (questions 11,12,13). The isolated items are: headache (question 4), seizures (question 9), gait sensation (question 14), alopecia (question 16), itching (question 17), legs weakness (question 18), and sphincter control (question 20). Published weighting systems allow for creation of a single composite score of the patient's health status. The questionnaires, translated into the local language as appropriate, will be completed in their entirety at baseline, at cycle 5 (week 12),cycle 8 (week 21), at end of study treatment (30 and 90 days) and/or at disease progression. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered or interviewer-administered (as appropriate) before the patient receives any information on disease status, following the performance of clin-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

**Neurocognitive Assessment** include the following standardized neuropsychological tests: Hopkins Verbal Learning Test revised (HVLT-R), Trail Making Test (TMT), Rey–Osterrieth complex figure test (ROCF) and Controlled Oral Word Association Test (COWA). These tests have been selected based on the International Cognition and Cancer Task Force (ICCTF) recommendations to harmonize studies of cognitive function in patients with cancer and different versions at the different time points have been used in clinical trials: RTOG 0212, RTOG 0214, RTOG 0424, RTOG 0525, RTOG 0933, ACOSOG Z0933, NCCTG N0574, NCCTG N0577, RTOG 0825, ECOG E3F05, NCCTG N0874/ABTC 090 y N107C (37). HVLT test has been validated in previous phase III clinical trials in metastatic brain patients (38,39). It consists of a 12-item list repeated 3 times consecutively (immediate recall and verbal learning) and a free-recall after 20 minutes (delayed recall). The HVLT-R has adequate psychometric properties, six alternate forms, and has been translated into several languages (40). The TMT consists of two parts (A and B) in which the subject is instructed to connect a set of 25 dots as quickly as possible while still maintaining accuracy. It has

adequate psychometric properties, is not language dependent, and the instruction set has been translated into several languages. The test measures psychomotor speed and aspects of executive function. The Rey–Osterrieth complex figure test (ROCF) is a neuropsychological assessment in which examinees are asked to reproduce a complicated line drawing, first by copying it freehand (recognition), and then drawing from memory (recall). Many different cognitive abilities are needed for a correct performance, and the test therefore permits the evaluation of different functions, such as visuospatial abilities, visual memory, attention, planning, and working memory (executive functions). The COWA testing is a measure of speeded lexical fluency, which requires aspects of executive function; it has adequate psychometric properties and has one alternate form. A similar word-frequency approach has been taken to choose letter stimuli for several other languages, making this measure adaptable to multinational studies. The questionnaires, translated into the local language as appropriate, will be completed in their entirety at baseline, cycle 5 (week 12), cycle 8 (week 21), at end of study treatment (30 and 90 days) and/or at disease progression. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be administered by trained, neuro-oncologist or oncologists before the patient receives any information on disease status, following the performance of clinPRO and HRQol) questionnaires, and prior to the administration of study treatment, unless otherwise specified.

TRANSLATIONAL MRI EXPLORATORY STUDY

As an exploratory neuroimaging biomarker, all patients recruited in ICO L'Hospitalet and selected sites will undergo in addition to the conventional Brain Magnetic Resonance Imaging (MRI), a three dimensional T1-weighted imaging and a DCE-MRI (dynamic contrast enhanced) sequences, to study volumetric brain morphometry changes (voxel-based morphometry or VBM) and blood brain barrier disruption, respectively (41,42). The addition of these 2 MRI sequences will add to the conventional MRI a 20 min extra duration in the procedure.

TRANSLATIONAL MRI RADIOMIC EXPLORATORY STUDY

Patients with non-small cell lung cancer (NSCLC) and synchronous brain metastases historically had dismal prognosis, but recent advances in immune checkpoint inhibitors (ICIs) have been associated with intracranial responses and improved outcomes in some patients. However, while a subset of patients may respond to treatment with ICI and achieve long-term remission, there persists a subset of patients who do not respond and have poor survival as a direct result of intracranial progression. There is an unmet clinical need to discriminate which patients should receive upfront immunotherapy. Given the heterogeneity in the response to ICIs and the variation in the management of these patients, there is an increasing need for biomarkers able to predict therapeutic response and outcomes. There are no validated imaging biomarkers associated with clinical outcome in patients with NSCLC and synchronous brain metastases who are treated with ICI in combination with chemotherapy.

We hypothesized that radiomic analysis of baseline or early magnetic resonance images (MRIs) could identify higher-order features associated with long-term survival and/or response to systemic treatment (ICIs plus chemotherapy).

Exploratory Biomarker Objective: To identify radiomic neuroimaging markers (MRI) that are predictive of intracranial response to systemic treatment by analyzing baseline MRI and early MRI (MRI corresponding to cycle 5 of systemic treatment or if the last one is not available, corresponding to cycle 3).

**Methods**

As an exploratory neuroimaging biomarker, we will retrospectively analyze 40 NSCLC patients enrolled in the phase 2 clinical trial of atezolizumab plus platinum-based chemotherapy for untreated brain metastases (NCT03526900). Baseline and post-cycle 5 (or post-cycle 3) MRIs data will be included in this sub-analysis. Image registration will be performed using ANTs. Binary brain masks from T1 gadolinium were co—registered to other imaging volumes (FLAIR) for each patient. These images will be registered to the brain using Affine registration. To normalize image intensity, we will use the WhiteStripe R package and a N4-bias field correction. Tumor segmentation will be performed semi-automatically using a region-growing segmentation algorithm implemented in ITK-SNAP. The radiomic feature extraction will be performed with PyRadiomics pipeline. This allowed us to extract a large number of radiomics features: i) first-order features, ii) shape and volume features and iii) texture features. Volume and shape features depend on the binary information of the segmentation mask only, while first-order (i.e. mean, standard deviation, kurtosis, skewness, uniformity, energy and entropy) and texture features (i.e.grey-level co-occurrence matrices, GLCM, including Haralick features, gray-level run-length matrix, GLRLM, among others) reflect the intensity of normalized imaging sequences and the wavelet transformations.

CNS progression was determined using Response Assessment in Neuro-Oncology (RANO) Brain Metastases. To assess the multivariate performance of radiomic features we will build a signature. We selected the 100 most stable features, determined by averaging the stability ranks of the radiomics features. Next, we will compute the performance data set of each of the selected 100 features using the concordance index (CI) using 10-fold cross-validations. This measure is comparable with the area under the curve but can also be used for Cox regression analysis.

To assess the complementary effect of the signature with clinical parameters, we will build a new model with the prediction of the signature as one input and the clinical parameter and we will compare the performance of the different models according to the CI.

**Information management**

Anonymous MRIs imaging will be obtained and codified for each patient. Only the Steering Committee will have access to these codes, according the Spanish laws LOPD 3/2018 and the RD 1720/2007. These anonymized images will be delivered and processed centrally in

collaboration with the Pitié-Salpêtrière Hospital. Only the clinical data about RANO radiological response status achieved at first assessment will be associated to these images. Any other complementary analysis related with the radiomic signature will be performed at the Steering Committee members center.

**ASSESSMENT OF SAFETY**

Atezolizumab has been approved by the European Medicine Agency (EMA) for the treatment of locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy or who are considered cisplatin ineligible and for the treatment of locally-advanced or metastatic NSCLC after prior chemotherapy. Human experience is still limited, and the entire safety profile is not known at this time. The safety plan for patients in this study is based on clinical experience with atezolizumab in completed and ongoing studies. The anticipated important safety risks for atezolizumab are outlined below. Please refer to the atezolizumab Investigator's Brochure for a complete summary of safety information.

**Safety plan**

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo close safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. All serious adverse events and adverse events of special interest will be recorded during the study and for up to 90 days after the last dose of study treatment or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. All other adverse events will be recorded during the study and for up to 30 days after the last dose of study treatment or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study. The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

*Risk associated with atezolizumab*

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events (ir-AE), specifically the induction or enhancement of autoimmune conditions. Adverse events with potentially immune-mediated causes, including rash, hypothyroidism, hepatitis/transaminitis, colitis,

pneumonitis, myositis, and myasthenia gravis, have been observed in the Phase Ia study PCD4989g. For further details regarding clinical safety, including a detailed description of the anticipated safety risks for atezolizumab, see the Atezolizumab Investigator's Brochure.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested workup and management guidelines procedures for suspected immune-mediated adverse events are provided in the Atezolizumab Investigator's Brochure.

*Risk associated with pemetrexed administration*

The most common side effects of pemetrexed include gastrointestinal symptoms (nausea, vomiting, diarrhea, or constipation), myelosuppression, infection, fatigue, stomatitis, loss of appetite, edema and rash. For more details regarding the safety profile of pemetrexed, see the prescribing information for pemetrexed.

*Risk associated with carboplatin*

Carboplatin is known to cause bone marrow suppression including myelosuppression, anemia, and thrombocytopenia. Carboplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for carboplatin-related adverse events. For more details regarding the safety profile of carboplatin, refer to the prescribing information for carboplatin.

*General plan to manage safety concerns: Monitoring*

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events defined and graded according to NCI CTCAE v4.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1.. Laboratory values must be reviewed prior to each infusion.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts During the study, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

All serious adverse events and protocol-defined events of special interest will be reported in an expedited fashion (see Section 0). Patients will be followed for serious adverse events and adverse events of special interest for 90 days after their last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. For all other adverse events, patients will be followed for 30 days after their last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study.

Patients who have an ongoing study treatment–related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

*Potential overlapping toxicities*

To date, on the basis of safety data from Study GP28328, the risk of overlapping toxicities between atezolizumab, carboplatin or cisplatin, and pemetrexed is thought to be minimal. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hepatotoxicity, skin, and gastrointestinal toxicity) may not be unambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with these chemotherapeutic agents (e.g., hepatotoxicity) could be exacerbated by the immunostimulatory activity of atezolizumab.

Toxicities should initially be managed according to the recommendations with dose holds and modifications (if applicable) applied to the component of the study drug judged to be the primary cause. For severe (Grade 3) or persistent Grade 1 or 2 diarrhea, an endoscopic evaluation should be considered. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology for adverse events listed above. If, in the opinion of the investigator, atezolizumab is a potential inciting factor, the dose of atezolizumab may be withheld for a maximum of 105 days beyond when the next dose should have been given Prompt symptomatic management is `appropriate for mild immune-mediated adverse events. In severe cases, immune-mediated toxicities may be acutely managed with systemic corticosteroids or TNF-$\alpha$ inhibitors. These cases should be discussed with the Medical Monitor.

SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious and non-serious adverse events, and adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

**Adverse events**

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical

product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 0
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

**Serious adverse events (inmediately reportable to the sponsor)**

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death). This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.4.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.2; the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and

seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 0 for reporting instructions).

**Adverse events of special interest (inmediately reportable to the sponsor)**

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 0 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade $\geq 2$ cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia

- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

**Infusion-Related reactions**

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g. "infusion-related reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.2.2 and 5.2.3..

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity and causality (see Section 5.3.2 and 5.3.3)

**Adverse Event reporting period**

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF. After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 0 for instructions for reporting serious adverse events).

After initiation of study drug, all serious adverse events and adverse events of special interest, regardless of relationship to study drug will be reported until 90 days after the last dose of study drug or initiation of non-protocol systemic anti-cancer therapy, after the last dose of study treatment whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy after the last dose of study treatment, whichever occurs first. Investigators are instructed to report all serious adverse events and adverse events of special interest considered to be related to study treatment regardless of time after study (see Section 5.2.3).

**Assessment of Severity of Adverse Events**

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity.

**Assessment of Causality of Adverse Events**

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

**Procedures for Recording Adverse Events**

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

*Diagnosis versus signs and symptoms*

For all adverse events, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the Adverse Event eCRF (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

*Adverse Events that are Secondary to Other Events*

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is

separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example: If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF. If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

*Persistent or Recurrent Adverse Events*

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme intensity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 0 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

*Abnormal Laboratory Values*

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event. If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin $5 \times$ ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor

indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

*Abnormal Vital Sign Values*

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

*Abnormal Liver Function Tests*

The finding of an elevated ALT or AST ($> 3 \times$ baseline value) in combination with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 0).

*Deaths*

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of NSCLC should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 0). The iDMC will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "**sudden death**" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "**Death due to Unknown Cause**" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), the event should be replaced by the established cause of death.

During survival follow-up, deaths attributed to progression of NSCLC should be recorded only on the Study Completion/Early Discontinuation eCRF.

*Preexisting Medical Conditions*

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

*Worsening of NSCLC*

Events that are clearly consistent with the expected pattern of progression of the NSCLC should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST. In rare cases, the determination of clinical progression will be based on

symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

*Hospitalization or Prolonged Hospitalization*

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2 except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or to perform an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

The following hospitalization scenario is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

*Adverse Events Associated with an Overdose or Error in Drug Administration*

Study overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded in the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 0).

*Clinical-Reported Outcome Data*

Adverse event reports will not be derived from clinPRO data, and safety analyses will not be performed using clinPRO data. However, if any clinPRO responses suggestive of a possible adverse event are identified during site review of the clinPRO data, the

investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

**Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest**

*Events That Occur prior to Study Drug Initiation*

After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

*Events That Occur after Study Drug Initiation*

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until

30 days after the last dose of study treatment or initiation of new anti-cancer therapy after the last dose of study treatment, whichever occurs first.

Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.5.3.

**Reporting Requirements for Pregnancies**

*Pregnancies in Female Patients*

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study, within 5 months after the last dose of atezolizumab, or within 6 months after the last dose of cisplatin. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to the Sponsor. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, a paper Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed to the sponsor that will send immediately to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

*Pregnancies in Female Partners of Male Patients*

Atezolizumab is not expected to be genotoxic. In addition, the anticipated concentrations of atezolizumab in seminal fluid as well as the potential risk to the developing conceptus is low following seminal transfer of atezolizumab to a female partner.

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the chemotherapy treatment period or within 6 months after the last dose of chemotherapy. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus to support an informed decision in cooperation with the treating physician and/or obstetrician.

*Abortions*

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 0).

*Congenital anomalies/Birth defects*

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 0).

FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

**Investigator Follow-up**

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

**Sponsor Follow-up**

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

**Post-Study Adverse Events**

Investigators are instructed to report all serious adverse events or adverse events of special interest that occur after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug for adverse events and 90 days after the last dose of study drug for serious adverse events and adverse events of special interest or initiation of new systemic anti-cancer therapy after the last dose of study treatment , whichever occurs first), if the event is believed to be related to prior study drug treatment, regardless of time after study.

The investigator should report these events directly to the Sponsor, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special InteresReporting Form with use of the fax number or email address provided to investig

## 9.6. ATA QUALITY ASSURANCE

This report has been carried out in accordance with GCP guidelines, the developer's SOPs and current legislation.

## 9.7. STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

### 9.7.1. Statistical and Analytical Plans

Three populations will be considered for different analyses:

- **Per protocol population (PP):** Per protocol population will consider patients that will receive a minimum of two cycles of atezolizumab, pemetrexed and carboplatin (whichever dose will be received) that have a 12-weeks tumor response evaluation. Patients without any radiological evaluation who may die during the first 12 weeks will also be considered PP population. Patients without 12 weeks tumor evaluation but with a progression disease at 6 weeks will also be considered into PP population. A patient without radiological evaluations at 6 weeks and at 12 weeks but alive at 12 weeks will be replaced by another patient with these evaluations available.
- **Intention to treat analysis (ITT):** Intention to treat analysis will include all patients that will be registered into the clinical trial.
- **Safety population (SFP):** Safety population will include all patients that will be exposed to study treatment (atezolizumab), whatever will be the quantity received.

Efficacy endpoints will be evaluated mainly per protocol population (PP) since this is an early phase II clinical trial. Decisions about continuing to phase III clinical trial will be made based upon PP population. Efficacy analysis will be also conducted with ITT population but only as a measure of sensitivity. Safety endpoints will be assessed using SF population. A patient with missing information about efficacy will be replaced for PP population, but never for SF if fulfills SFP population definition.

This is sequential clinical trial with two stopping rules for efficacy and toxicity and with a maximum sample size of 40 patients. These rules will be calculated in each interim analysis and recruitment will be stopped if any of these were achieved.

The efficacy will be evaluated as PFS at 12 weeks and toxicity will be monitored simultaneously in a cohort of 40 patients using the Bayesian approach of Thall, Simon and Estey and further developed by Thall and Sung (43–45). Toxicity is defined as appearance of a severe toxicity consisting of grade 3-4 treatment-related toxicity that impedes to continue with the treatment or intracranial complications such a tumor bleeding or significant increase of oedema during the first 9 weeks of treatment. Historical data on similar patients showed a 12-weeks PFS rate

of 40% with platinum and pemetrexed (10) and toxicity rate of 35% (phase Ib GP28328 study). This information was given an Effective Sample Size of 40 patients. Independence was assumed between efficacy and toxicity. It is expected for the current trial that atezolizumab in combination with Pemetrexed and Carboplatin will improve the PFS at 12 weeks to 50% while the treatment-related grade 3-4 toxicity will remain at 35% or below. The probabilities of efficacy and toxicity for the historical data are modeled by beta distributions (Beta(14,26) and Beta(9,16), respectively). The prior probabilities of PFS rate at 12 weeks and toxicity for the experimental regimen were also modeled by beta distributions (Beta(0.4,0.6) and Beta(0.35,0.65), respectively), which have the same means as the corresponding beta distributions for the historical data, and an Effective Sample Size of 1.

DETERMINATION OF SAMPLE SIZE

A maximum sample size of 40 patients ensures that, if the trial is not terminated early, a posterior 90% credibility interval for overall response rate will have width of 0.257 at most, under the assumption of 50 % of PFS at 12 weeks. Denoting the historical probabilities of overall response rate and toxicity rate by {p(PFS12W,H) , p(TOX,H)}, the following decision criteria will be applied:

- Let E correspond to the experimental treatment, stop if
- Prob{p(PFS12W,H) + $\delta_{PFS}$**12W P** > p(PFS12W,E) | data} > 0.95, where **δPFS12W** =0.15*
- Stop if Prob{p(TOX,H) + $\delta_{TOX}$ < p(TOX,E)| data}>0.95, where ***δTOX*** =0

It is expected that approximately the 10% of the patients initially enrolled should be discarded be-cause they do not meet the inclusion criteria; so that in order to reach the proposed sample size, if a patient initially enrolled in the study does not fulfil the inclusion criteria, it will be replaced by a new subject that fulfil them, this replacement will ensure that the sample size will be the one calculated initially.

Patients will be monitored according to the following stopping boundaries for efficacy:

**Model Parameters and Stopping Criteria:**

- Standard PFS rate at 12 weeks Beta a = 14
- Standard PFS rate at 12 weeks Beta b = 26
- Experimental PFS rate at 12 weeks Prior Beta a = 0.4
- Experimental PFS rate at 12 weeks Prior Beta b = 0.6
- Maximum sample size = 40
- Minimum sample size = 5
- Cohort size = 5
- Bayesian statistical significance level for efficacy Pi^* = 0.95

- Expected difference between historical and experimental efficacy rate: Delta_R = 0.15
- Standard Toxicity Beta a = 9
- Standard Toxicity Beta b = 16
- Experimental Toxicity Prior Beta a = 0.35
- Experimental Toxicity Prior Beta b = 0.65
- Bayesian statistical significance level for toxicity Pi_* = 0.95
- Expected difference between historical and experimental toxicity rate: Delta_T = 0

**PFS rate at 12 weeks Stopping Boundaries**

Full PFS rate at 12 weeks PFS Stopping Boundaries are shown in the following table:

| # Patients (in complete cohorts of 5 ) (inclusive) | Stop the trial boudaries |
|---|---|
| | \| # Progression-free at 12 weeks (FOP12W) patients (inclusive). Stop if # patients FOP12W less or equal to |
| 5 | 0 |
| 10 | 2 |
| 15 | 3 |
| 20 | 5 |
| 25 | 7 |
| 30 | 9 |
| 35 | 11 |
| 40 | Always stop with this many patients |

**Toxicity stopping boundaries**

Full Toxicity Stopping Boundaries are shown in the following table:

| # Patients (in complete cohorts of 5 ) (inclusive) | Stop the trial if there are this many toxicities total |
|---|---|
| | # Toxicities. Stop if # patients with unacceptable toxicity equal or higher than |
| 5 | 5 |
| 10 | 7 |
| 15 | 10 |
| 20 | 13 |
| 25 | 15 |

| | |
|---|---|
| 30 | 18 |
| 35 | 21 |
| 40 | Always stop with this many patients |

SUMMARIES OF CONDUCT OF STUDY

The number of patients who will be enrolled, discontinued, or completed the study will be summarized. A frequency table with patients with inclusion-exclusion criteria not met, patients with tumor evaluations at 12 weeks available, number of cycles with full dose and dose modifications will be performed. Reasons for premature study withdrawal will be listed and summarized.

SUMMARIES OF TREATMENT GROUP COMPARABILITY AND PATIENT'S CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, primary tumor status (controlled or not), histology, tumor affected sites (other than NCS), Performance status, EGFR status, ALK status, Steroid levels) will be summarized using means, standard deviations, medians and ranges for continuous variables and proportion for categorical variables, as appropriate.

EFFICACY ANALYSES

To evaluate the efficacy of atezolizumab combined with CBDCA and pemetrexed in patients with NSCLC and asymptomatic BM three endpoints will be used: PFS rate at 12 weeks, PFS estimation, objective response, duration of overall response and overall survival estimation.

**Primary Efficacy Endpoint**

Rate of PFS at 12 weeks after enrollment defined as the rate of patients free of disease progression (intracranial or systemic) or death from any cause whichever occurs first at 12 weeks as determined by the investigator according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively.

The prior probabilities of PFS rate at 12 weeks for the experimental regimen are also modeled by beta distributions (Beta(0.4,0.6), respectively), which have the same means as the corresponding beta distributions for the historical data, and an Effective Sample Size of 1. Posterior distribution for rate of PFS at 12 weeks will be calculated (including expected value) through beta-binomial model. A sample size of 40 patients ensures that, if the trial is not terminated early, a posterior 90% credibility interval for rate of PFS at 12 weeks rate will have width of 0.257 at most, under the assumption of 50 % of PFS at 12 weeks.

- **Also** Prob{p(PFS12W,H) + $\delta_{PFS}$**12W P** > p(PFS12W,E) | data} > 0.95, where **δPFS12W** =0.15* will be calculated.

**Secondary Efficacy Endpoint**

*Progression-free survival (PFS)*

PFS after enrollment defined as the time from enrollment to the first occurrence of disease progression (intracranial or systemic) or death from any cause whichever occurs first as determined by the investigator according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively.

Kaplan-Meyer survival estimation with 95 % confidence interval (95% CI), mean with 95% CI, median with 95% CI and restricted mean with 95% CI. Based on non-informative priors, several parametric survival models (exponential with prior gamma, Weibull with prior gamma-normal, extreme-value with gamma-normal, log-normal with priors normal and gamma with priors gamma-normal) will be obtained and the best will be selected using Bayes factors. Expected value and 95% credibility intervals for mean survival, median survival and restricted mean survival will be obtained for the best model.

*Objective response rate (ORR)*

Objective response defined as a complete response or partial response on two consecutive evaluations 6 weeks apart, as determined by the investigator according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively.

Conjugated beta-binomial distribution will be performed using a prior distribution of beta (0.5,0.5) to calculate objective response rate. Posterior distribution with expected posterior and credibility interval value will be provided.

*Duration of overall response (DoR)*

Duration of response defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause whichever occurs first, as determined by the investigator according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively.

Kaplan-Meyer survival estimation with 95 % confidence interval (95% CI), mean with 95% CI, median with 95% CI and restricted mean with 95 % CI.

Based on non-informative priors, several parametric survival models (exponential with prior gamma, Weibull with prior gamma-normal, extreme-value with gamma-normal, log-normal with priors normal and gamma with priors gamma-normal) will be obtained and the best will be selected using Bayes factors. Expected value and 95% credibility intervals for mean survival, median survival and restricted mean survival will be obtained for the best model.

**Exploratory Efficacy Endpoint**

*Neurocognitive function assessment*

Change from baseline in the following standardized neuropsychological tests will be study: Hopkins Verbal Learning Test (HVLT), Trail Making Test (TMT), Rey–Osterrieth complex figure test (ROCF) and Controlled Oral Word Association Test (COWA) at week 12 (cycle 5), week 21 (cycle 8), and at the end of study treatment (30 and 90 days) and/or at progression Numeric and graphical descriptive analysis will be performed for each sample. A paired three sample test comparing mean of scores using Bayesian normal model will be adjusted.

*Time to neurological deterioration*

The aim of this study is to determine the time to neurological deterioration and to record the number of patients requiring an increase steroid dose for ≥96h to control neurologic symptoms. Neurological deterioration from baseline will be determined using the NANO scale at week 12 (cycle 5), week 21 (cycle 8), and at the end of study treatment (30 and 90 days) and/or at progression. Increase in the steroid use for ≥96h will be recorded in the database. Numeric and graphical descriptive analysis will be performed for each sample. A paired three sample test comparing mean of scores using Bayesian normal model will be adjusted.

*Time to need of savage therapy*

Time to need for salvage therapy during the study is also a relevant efficacy measure. Ti is defined as median time to brain radiotherapy (WBRT or SRS).

Kaplan-Meyer survival estimation with 95 % confidence interval (95% CI), mean with 95% CI, median with 95% CI and restricted mean with 95% CI. Based on non-informative priors, several parametric survival models (exponential with prior gamma, Weibull with prior gamma-normal, extreme-value with gamma-normal, log-normal with priors normal and gamma with priors gamma-normal) will be obtained and the best will be selected using Bayes factors. Expected value and 95% credibility intervals for mean survival, median survival and restricted mean survival will be obtained.

*Quality of life*

Quality of life study consist of assessing changes from baseline in HRQol, as assessed through use of the EORTC C30 and submodule BN20 at week 12 (cycle 5), week 21 (cycle 8), and at the end of study treatment (30 and 90 days) and/or at progression. Numeric and graphical descriptive analysis will be performed for each sample. A paired five sample test comparing mean of scores using Bayesian normal model will be adjusted.

SAFETY ANALYSES

The safety analysis population will include all patient patients who received at least one dose of study drug. All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to **NCI CTCAE v4.0**.

UNACCEPTABLE TOXICITY RATE

A co-primary endpoint is to calculate the rate of unacceptable toxicity and depending on the rate recruitment could be stopped (see toxicity stopping boundaries). Specifically, the definition of unacceptable toxicity is the appearance of a severe toxicity consisting of grade 3-4 treatment-related toxicity that impedes to pursue with the treatment or intracranial complications such a tumor bleeding or significant increase of edema during the first 9 weeks of treatment.

Patients will be classified as having (or not having) unacceptable toxicity if they suffer the appearance (or not) of at minimum one severe toxicity during the 12 first weeks.

The prior probabilities of toxicity rate for the experimental regimen are also modeled by beta distributions (Beta(0.35,0.65), respectively), which have the same means as the corresponding beta distributions for the historical data, and an Effective Sample Size of 1. Posterior distribution for toxicity rate will be calculated including expected posterior value. A sample size of 40 patients ensures that, if the trial is not terminated early, a posterior 90% credibility interval for toxicity rate will have width of 0.257 at most, under the assumption of 50 % of toxicity rate.

***Also,*** *Prob{p(TOX,H) +* $\delta_{TOX}$ *< p(TOX,E)| data}>0.95, where* $\delta$TOX *=0* will be calculated.

**<u>Frequency of adverse events (AE)</u>**

Occurrence and severity of adverse events, with severity determined according to NCI CTCAE v4.0 criteria will be reported. See adverse events section to know the period which will be reported on eCRF. Specifically:

- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test
- Grade, severity, duration and relation of all other adverse events that could occur during the specified period

A frequency table with grade, severity, relationship, action taken regarding to study medication, duration and causality will be performed.

BIOMARKER ANALYSES

The aim of biomarker analysis is to identify biomarkers that are predictive of response to treatment. Specifically consist in study the relationship between PD-L1 expression by 22C3 DAKO in tumor tissue (listed in Section 4.5) and efficacy endpoints. PD-L1 staining will be carried out with 22C3 DAKO antibody at Department of Pathology in the Hospital Universitari de Bellvitge (L'Hospitalet, Barcelona). Bayesian hazard ratio for each unit of change of PD-L1 expression and for each unit of change in 22C3 DAKO expression will be obtained.

INTERIM ANALYSES

This is a Bayesian group sequential trial and interim analyses are planned every 5 included patients. Toxicity and efficacy boundaries rules are specified in sample size section. It is necessary for each interim analysis to know the efficacy and toxicity status of each recruited patient (see toxicity and efficacy stopping boundaries sections for the definition). Depending of the number of toxicities and number of patients free of progression at 12 weeks in each section recruitment will continue or interrupted. Since this is a Bayesian design, alpha error adjust is not applicable.

#### 9.7.2 Determination of Sample Size

Please refer to point 9.7.1 of this report.

### 9.8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

There has been no change in the conduct of the trial or in the planned per-protocol analyses.

## 10. STUDY PATIENTS

### 10.1. DISPOSITION OF PATIENTS

| HOSPITAL | INCLUDED PATIENTS |
|---|---|
| ICO-HOSPITALET | 8 |
| H. INSULAR DE GRAN CANARIA | 8 |
| H. GENERAL DE ALICANTE | 6 |
| H.U. DE LA FE | 3 |
| C.H. UNIVERISTARIO DE VIGO | 3 |
| H. CLÍNICO UNIV. VALLADOLID | 2 |
| H.U. LA PAZ | 2 |
| ICO-BADALONA | 2 |
| H. U. A CORUÑA | 2 |
| H. SANT PAU | 1 |
| H.U. VALL D'HEBRON | 1 |
| H.U. GENERAL DE VALENCIA | 1 |
| H.U. DE ELCHE | 1 |
| ICO- GIRONA DR. TRUETA | 0 |
| H. FUNDACIÓN JIMÉNEZ DÍAZ | 0 |

## 11. EFFICACY EVALUATION

### 11.1. DATA SETS ANALYSED

43 patients were enrolled in the study although 3 patients (01000008, 00800011 and 03500023) were finally considered as an inclusion error so it did not enter in the analysis. 40 patients from 13 different sites were considered for the analysis.

### 11.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

**Demographic characteristics**

| Variable | Category | N | Perc | ValidPerc | n |
|---|---|---|---|---|---|
| Sex | Male | 29 | 72,5 | 72,5 | 40 |
| | Female | 11 | 27,5 | 27,5 | |
| Race | Caucasian | 40 | 100 | 100 | 40 |
| | Latin | 0 | 0 | 0 | |
| | Asian | 0 | 0 | 0 | |
| | African | 0 | 0 | 0 | |
| | Other | 0 | 0 | 0 | |

**Clinical factors: General**

| Variable | Category | N | Perc | ValidPerc | n |
|---|---|---|---|---|---|
| PerformanceStatus | 0 | 14 | 35 | 35 | 40 |
| | 1 | 26 | 65 | 65 | |
| CigarretteSmokingHistory | NeverSmoke | 6 | 15 | 15 | 40 |
| | FormerSmoke | 11 | 28 | 28 | |
| | Smoker | 23 | 58 | 58 | |
| | Uk | 0 | 0 | 0 | |

| | N | NA | Min | Q1 | Median | Mean | Q3 | Max | Stdev | Var | IQR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 40 | 0 | 38 | 56,8 | 62,5 | 62,2 | 68,25 | 79 | 9,4 | 88,8 | 11,5 |
| Cigarettes2 | 40 | 13 | 5 | 20 | 20 | 24,1 | 30 | 60 | 12,4 | 154,4 | 10 |
| Weight | 40 | 0 | 47,5 | 59,4 | 66,75 | 68,8 | 77,2 | 113,5 | 14,2 | 201,6 | 17,8 |
| Temperature | 40 | 2 | 35 | 36,0 | 36,2 | 36,3 | 36,6 | 37,6 | 0,5 | 0,2 | 0,6 |

**Cancer diagnosis characteristics**

| Variable | Category | N | Perc | ValidPerc | n |
|---|---|---|---|---|---|
| Histology | Adenocarcinoma | 39 | 97,5 | 97,5 | 40 |
| | Adenosquamous | 0 | 0 | 0 | |
| | Squamous | 0 | 0 | 0 | |
| | LargeCellCarcinoma | 0 | 0 | 0 | |
| | NOS/Undifferentiated | 1 | 2,5 | 2,5 | |
| | Other | 0 | 0 | 0 | |

| Variable | Category | N | Perc | ValidPerc | n |
|---|---|---|---|---|---|
| 1st Diagn. TClinicalStage | Tx | 1 | 2,5 | 2,5 | 40 |
| | T0 | 0 | 0 | 0 | |
| | Tis | 0 | 0 | 0 | |
| | T1a | 3 | 7,5 | 7,5 | |
| | T1b | 2 | 5 | 5 | |
| | T1c | 3 | 7,5 | 7,5 | |
| | T2a | 4 | 10 | 10 | |
| | T2b | 1 | 2,5 | 2,5 | |
| | T3 | 6 | 15 | 15 | |
| | T4 | 20 | 50 | 50 | |
| | NA | 0 | 0 | 0 | |
| 1st Diagn. NClinicalStage | Nx | 1 | 2,5 | 2,5 | 40 |
| | N0 | 5 | 12,5 | 12,5 | |
| | N1 | 2 | 5 | 5 | |
| | N2 | 19 | 47,5 | 47,5 | |
| | N3 | 13 | 32,5 | 32,5 | |
| | NA | 0 | 0 | 0 | |
| 1st Diagn. MClinicalStage | Mx | 0 | 0 | 0 | 40 |
| | M0 | 3 | 7,5 | 7,5 | |
| | M1a | 1 | 2,5 | 2,5 | |
| | M1b | 5 | 12,5 | 12,5 | |
| | M1c | 31 | 77,5 | 77,5 | |
| | NA | 0 | 0 | 0 | |

| Variable | Category | N | Perc | ValidPerc | n |
|---|---|---|---|---|---|
| InclusionTClinicalStage | Tx | 3 | 7,5 | 7,5 | 40 |
| | T0 | 0 | 0 | 0 | |
| | Tis | 0 | 0 | 0 | |
| | T1a | 2 | 5 | 5 | |
| | T1b | 2 | 5 | 5 | |
| | T1c | 2 | 5 | 5 | |
| | T2a | 4 | 10 | 10 | |
| | T2b | 1 | 2,5 | 2,5 | |
| | T3 | 7 | 17,5 | 17,5 | |
| | T4 | 19 | 47,5 | 47,5 | |
| | NA | 0 | 0 | 0 | |
| InclusionNClinicalStage | Nx | 3 | 7,5 | 7,5 | 40 |
| | N0 | 5 | 12,5 | 12,5 | |
| | N1 | 2 | 5 | 5 | |
| | N2 | 17 | 42,5 | 42,5 | |
| | N3 | 13 | 32,5 | 32,5 | |
| | NA | 0 | 0 | 0 | |

| | | | | | |
|---|---|---|---|---|---|
| InclusionMClinicalStage | Mx | 0 | 0 | 0 | 40 |
| | M0 | 0 | 0 | 0 | |
| | M1a | 1 | 2,5 | 2,5 | |
| | M1b | 5 | 12,5 | 12,5 | |
| | M1c | 34 | 85 | 85 | |
| | NA | 0 | 0 | 0 | |

| Variable | Category | N | Perc | ValidPerc | n |
|---|---|---|---|---|---|
| AntineoplasticTmt | No | 36 | 90 | 90 | 40 |
| | Yes | 4 | 10 | 10 | |
| OtherDiagnosesALKResult | No | 40 | 100 | 100 | 40 |
| | Yes | 0 | 0 | 0 | |
| | ND | 0 | 0 | 0 | |
| OtherDiagnosesEGFRResult | No | 40 | 100 | 100 | 40 |
| | Yes | 0 | 0 | 0 | |
| | ND | 0 | 0 | 0 | |
| PDL1P | - | 18 | 45 | 47,4 | 40 |
| | + | 20 | 50 | 52,6 | |
| | NA's | 2 | 5 | 5,3 | |

**Comorbidities**

| Variable | Categoria | N | Perc | ValidPerc | n |
|---|---|---|---|---|---|
| Asthma | No | 40 | 100 | 100 | 40 |
| | Yes | 0 | 0 | 0 | |
| HeartDisease | No | 34 | 85 | 85 | 40 |
| | Yes | 6 | 15 | 15 | |
| MellitusDiabetes | No | 32 | 80 | 80 | 40 |
| | Yes | 8 | 20 | 20 | |
| Dyslipemia | No | 24 | 60 | 60 | 40 |
| | Yes | 16 | 40 | 40 | |
| Alcoholism | No | 35 | 87,5 | 87,5 | 40 |
| | Yes | 5 | 12,5 | 12,5 | |
| Hepatitis | No | 40 | 100 | 100 | 40 |
| | Yes | 0 | 0 | 0 | |
| Hypercholesterolemia | No | 39 | 97,5 | 97,5 | 40 |
| | Yes | 1 | 2,5 | 2,5 | |
| Hypertension | No | 23 | 57,5 | 57,5 | 40 |
| | Yes | 17 | 42,5 | 42,5 | |

| | | | | | |
|---|---|---|---|---|---|
| Nephropathy | No | 38 | 95 | 95 | 40 |
| | Yes | 2 | 5 | 5 | |
| Obesity | No | 39 | 97,5 | 97,5 | 40 |
| | Yes | 1 | 2,5 | 2,5 | |
| DepressiveSyndromeAnxiety | No | 34 | 85 | 85 | 40 |
| | Yes | 6 | 15 | 15 | |

| Variable | Categoria | N | Perc | ValidPerc | n |
|---|---|---|---|---|---|
| Tuberculosis | No | 39 | 97,5 | 97,5 | 40 |
| | Yes | 1 | 2,5 | 2,5 | |
| Vasculopathy | No | 40 | 100 | 100 | 40 |
| | Yes | 0 | 0 | 0 | |
| AutoimmuneDisease | No | 40 | 100 | 100 | 40 |
| | Yes | 0 | 0 | 0 | |
| NeurologicalDisease | No | 40 | 100 | 100 | 40 |
| | Yes | 0 | 0 | 0 | |
| Osteoporosis | No | 38 | 95 | 95 | 40 |
| | Yes | 2 | 5 | 5 | |
| Arthritis | No | 39 | 97,5 | 97,5 | 40 |
| | Yes | 1 | 2,5 | 2,5 | |
| Hyperthyroidism | No | 40 | 100 | 100 | 40 |
| | Yes | 0 | 0 | 0 | |
| Hypothyroidism | No | 38 | 95 | 95 | 40 |
| | Yes | 2 | 5 | 5 | |
| BenignProstaticHypertrophy | No | 38 | 95 | 95 | 40 |
| | Yes | 2 | 5 | 5 | |
| COPD | No | 34 | 85 | 85 | 40 |
| | Yes | 6 | 15 | 15 | |
| Others | No | 16 | 40 | 40 | 40 |
| | Yes | 24 | 60 | 60 | |
| Ncomorb | 0 | 4 | 10 | 10 | 40 |
| | 1 | 8 | 20 | 20 | |
| | 2 | 9 | 22,5 | 22,5 | |
| | 3 | 9 | 22,5 | 22,5 | |
| | 4 | 5 | 12,5 | 12,5 | |
| | 5 | 4 | 10 | 10 | |
| | 7 | 1 | 2,5 | 2,5 | |

**Nano Scale**

| Variable | Category | N | Perc | ValidPerc | n |
|---|---|---|---|---|---|
| NANO Baseline | Yes | 35 | 87,5 | 87,5 | 40 |
| | Uk | 5 | 12,5 | 12,5 | |
| | NA's | 0 | 0 | 0 | |
| NANOGait | 0 | 31 | 77,5 | 88,6 | 40 |
| | 1 | 2 | 5 | 5,7 | |
| | 2 | 1 | 2,5 | 2,9 | |
| | 9995 | 1 | 2,5 | 2,9 | |
| | NA's | 5 | 12,5 | 14,3 | |
| NANOStrength | 0 | 33 | 82,5 | 94,3 | 40 |
| | 1 | 2 | 5 | 5,7 | |
| | NA's | 5 | 12,5 | 14,3 | |
| NANOAtaxia | 0 | 29 | 72,5 | 82,9 | 40 |
| | 1 | 5 | 12,5 | 14,3 | |
| | 9995 | 1 | 2,5 | 2,9 | |
| | NA's | 5 | 12,5 | 14,3 | |
| NANOSensation | 0 | 33 | 82,5 | 94,3 | 40 |
| | 1 | 1 | 2,5 | 2,9 | |
| | 9995 | 1 | 2,5 | 2,9 | |
| | NA's | 5 | 12,5 | 14,3 | |
| NANOVisual | 0 | 30 | 75 | 85,7 | 40 |
| | 1 | 1 | 2,5 | 2,9 | |
| | 3 | 2 | 5 | 5,7 | |
| | 9995 | 2 | 5 | 5,7 | |
| | NA's | 5 | 12,5 | 14,3 | |
| NANOFacial | 0 | 33 | 82,5 | 94,3 | 40 |
| | 9995 | 2 | 5 | 5,7 | |
| | NA's | 5 | 12,5 | 14,3 | |
| NANOLanguage | 0 | 34 | 85 | 97,1 | 40 |
| | 1 | 1 | 2,5 | 2,9 | |
| | NA's | 5 | 12,5 | 14,3 | |
| NANOConsciousness | 0 | 35 | 87,5 | 100 | 40 |
| | NA's | 5 | 12,5 | 14,3 | |
| NANOBehaviour | 0 | 34 | 85 | 97,1 | 40 |
| | 1 | 1 | 2,5 | 2,9 | |
| | NA's | 5 | 12,5 | 14,3 | |
| NANOSum | 0 | 24 | 60 | 68,6 | 40 |
| | 1 | 5 | 12,5 | 14,3 | |
| | 2 | 3 | 7,5 | 8,6 | |
| | 3 | 2 | 5 | 5,7 | |
| | 4 | 1 | 2,5 | 2,9 | |
| | NA's | 5 | 12,5 | 14,3 | |

**Dexamethasone**

| Variable | Categoria | N | Perc | ValidPerc | n |
|---|---|---|---|---|---|
| Steroids Baseline | 0 | 18 | 45 | 46,2 | 40 |
| | 1 | 21 | 52,5 | 53,9 | |
| | NA's | 1 | 2,5 | 2,6 | |
| Steroid Dose (mg) | 0 | 18 | 45 | 46,2 | 40 |
| | 1 | 1 | 2,5 | 2,6 | |
| | 2 | 1 | 2,5 | 2,6 | |
| | 3 | 4 | 10 | 10,3 | |
| | 4 | 15 | 37,5 | 38,5 | |
| | NA's | 1 | 2,5 | 2,6 | |
| Steroid Recode | - | 18 | 45 | 46,2 | 40 |
| | + | 6 | 15 | 15,4 | |
| | ++ | 15 | 37,5 | 38,5 | |
| | NA's | 1 | 2,5 | 2,6 | |

**Systemic treatment**

| | N | Min | Q1 | Median | Mean | Q3 | Max | Stdev | Var | IQR |
|---|---|---|---|---|---|---|---|---|---|---|
| NAtezo | 40 | 2 | 4 | 8,5 | 12,0 | 17,5 | 31 | 10,1 | 101,2 | 13,5 |
| NDaysAtezo | 40 | 21 | 81,8 | 150 | 247,2 | 387,3 | 714 | 226,8 | 51429,9 | 305,5 |
| NPeme | 40 | 2 | 4 | 8,5 | 11,7 | 17 | 31 | 10,0 | 99,8 | 13 |
| NDaysPeme | 40 | 0 | 61,8 | 137 | 233,7 | 300,3 | 714 | 227,5 | 51757,1 | 238,5 |
| NCarbo | 40 | 2 | 4 | 4 | 4,3 | 6 | 7 | 1,5 | 2,1 | 2 |
| NDaysCarbo | 40 | 21 | 61 | 71 | 76,0 | 105 | 139 | 32,3 | 1045,1 | 44 |

| | Eficacia (EVALUACIÓN DURANTE EL TRANSCURSO DEL ENSAYO) | | | | | Toxicidad | | | | | EFICACIA: DEFINITIVA | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Paciente | Completado Seguimiento 12 semanas | Respuesta 6 semanas | Respuesta 12 semanas | Mejor respuesta | Evento eficacia | Completado Seguimiento 9 semanas | AE con Grado>=3? | Descripción AE | Evento toxicidad | PatientNumbe | OverallResponse_1_2 | OverallResponse_1_3 | TumEvent |
| 15700001 | Si | no prog | PROG | | 0 | Si | No | | 0 | 15700001 | SD | PD | PD |
| 5100002 | Si | PROG | | PROG | 0 | Si | No | | 0 | 5100002 | PD | NA | PD |
| 800003 | Si | no prog | no prog | RP | 1 | Si | Si | Anemia | 1 | 800003 | SD | SD | NonPD |
| 3600004 | Si | | | | desc | Si | Si | Urinary Tract infection | 1 | 3600004 | SD | PD | PD |
| 5100005 | Si | | | | desc | Si | No | | 0 | 5100005 | PR | NA | NA |
| 03500006 | Si | EE | EE | EE | 1 | si | No | | 0 | 3500006 | SD | SD | NonPD |
| 00800007 | Si | EE | EE | EE | 1 | Si | Si | Anemia G3 | 1 | 800007 | SD | SD | NonPD |
| 01000008 | No disponible | | | | | Si | si | Exitus infección resp | 1 | | | | |
| 03500009 | sI | EE | RP | RP | 1 | Si | No | | 0 | 3500009 | SD | PR | NonPD |
| 00800010 | Si | EE | EE | EE | 1 | Si | NO | | 0 | 800010 | SD | SD | NonPD |
| 1300012 | Si | RP | RP | RP | 1 | si | NO | | 0 | 1300012 | PR | PR | NonPD |
| 1300013 | Si | PROG | NA | PROG | 0 | si | NO | | 0 | 1300013 | NE | NA | NA |
| 1300014 | Si | EE | RP | RP | 1 | si | NO | | 0 | 1300014 | SD | SD | NonPD |
| 1600015 | Si | EE | EE | EE | 1 | si | NO | | 0 | 1600015 | SD | SD | NonPD |
| 1300016 | Si | EE | EE | EE | 1 | si | NO | | 0 | 1300016 | SD | SD | NonPD |
| 00800017 | si | EE | EE | EE | 1 | SI | NO | | 0 | 800017 | SD | SD | NonPD |
| 15700018 | si | EE | EE | EE | 1 | SI | NO | | 0 | 15700018 | SD | SD | NonPD |
| 00100019 | si | EE | EE | EE | 1 | SI | SI | telet DC, Urin.tr.infecti | 1 | 100019 | SD | SD | NonPD |
| 00100020 | si | PROG | DUDA | | Duda | SI | NO | | 0 | 100020 | PR | PR | NonPD |
| 00100025 | no | EE | No evaluado | | no evaluable | SI | NO | | 0 | 100025 | PR | PR | NonPD |
| 01300021 | sI | EE | EE | EE | 1 | SI | NO | | 0 | 1300021 | SD | PR | NonPD |
| 01300022 | si | PROG | No evaluado | PROG | 0 | NO | si | Hypomagnesemia | 1 | 1300022 | PD | NA | PD |
| 01300024 | No | EE | No evaluado | ee | no evaluable | no | no | | 0 | 1300024 | SD | SD | NonPD |
| 00100026 | Si | EE | RP | RP | 1 | SI | NO | | 0 | 100026 | PR | PR | NonPD |
| 01000027 | SI | EE | EE | EE | 1 | SI | NO | | 0 | 1000027 | SD | NE | NA |
| 01300028 | Si | EE | EE | EE | 1 | SI | NO | | 0 | 1300028 | SD | SD | NonPD |
| 800029 | Si | PROG | NA | PROG | 0 | SI | SI | utrophil count decreas | 1 | 800029 | PD | NA | PD |
| 00800033 | SI | EE | EE | RP | 1 | SI | NO | | 0 | 800033 | SD | SD | NonPD |
| 01500034 | Si | PROG | NA | PROG | 0 | SI | NO | | 0 | 1500034 | PR | NA | NA |
| 00300035 | Si | EE | RP | RP | 1 | SI | SI | hatic system disorders | 1 | 300035 | SD | PR | NonPD |
| 200036 | Si | PROG | NA | PROG | 0 | Si | NO | | 0 | 200036 | SD | SD | NonPD |
| 00100038 | Si | EE | EE | EE | 1 | Si | SI | Hallucinations | 1 | 100038 | SD | SD | NonPD |
| 00800040 | NO | EE | No evaluado | No evaluable | no evaluable | si | NO | | 0 | 800040 | SD | NA | NA |
| 01500041 | NO | EE | No evaluado | No evaluable | no evaluable | sI | SI | Back pain | 1 | 1500041 | PR | PD | PD |
| 00100043 | NO | EE | No evaluado | No evaluable | no evaluable | SI | NO | | 0 | 100043 | PR | PR | NonPD |
| 00200030 | SI | EE | EE | EE | 1 | SI | NO | | 0 | 200030 | SD | PR | NonPD |
| 03600031 | si | rp | rp | rp | 1 | SI | NO | | 0 | 3600031 | SD | PR | NonPD |
| 15700032 | SI | EE | EE | EE | 1 | SI | NO | | 0 | 15700032 | SD | PR | NonPD |
| 02300037 | SI | EE | EE | EE | 1 | SI | NO | | 0 | 2300037 | SD | SD | NonPD |
| 00800042 | no | EE | No evaluado | No evaluable | no evaluable | SI | SI | Upper respiratory infection AND Vascular Disorders | 1 | 800042 | SD | NA | NA |

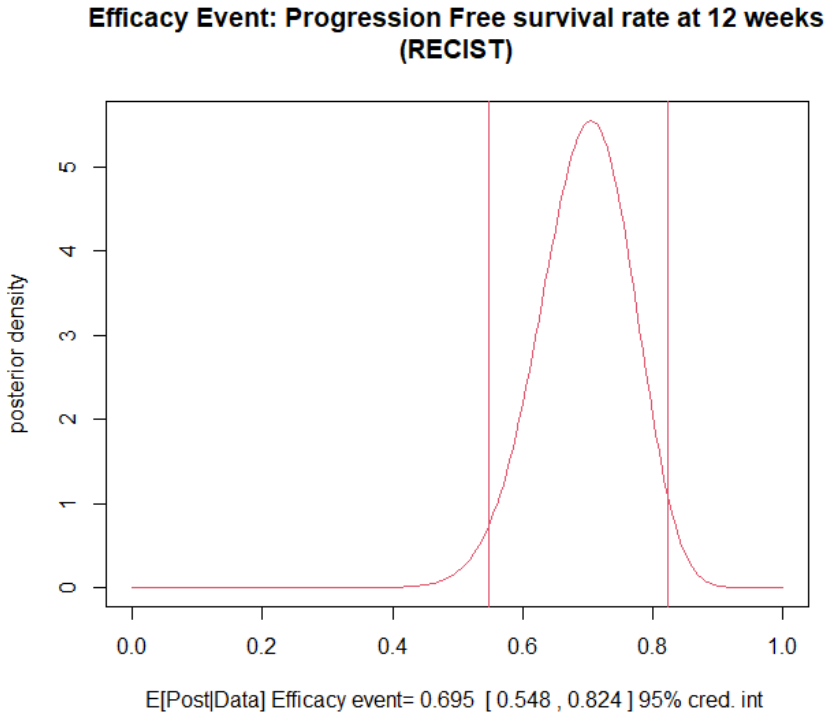
**TREATMENT RESPONSE**

**Description**

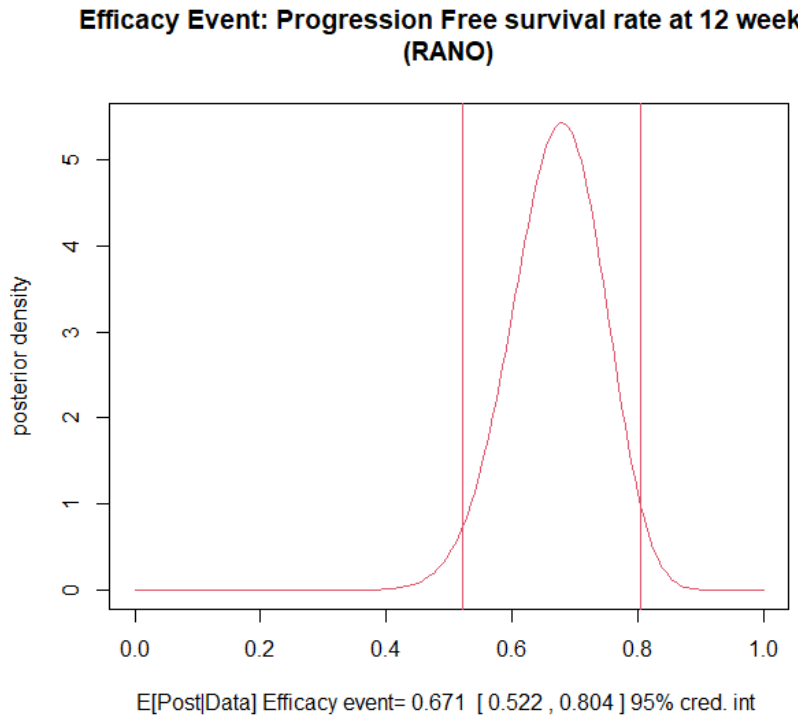
| Variable | Categoriy | N | Perc | ValidPerc | n |
|---|---|---|---|---|---|
| TumEvent | NonPD | 28 | 70 | 70 | 40 |
| | PD | 6 | 15 | 15 | |
| | UK | 6 | 15 | 15 | |
| TumEventRECIST | NonPD | 28 | 70 | 70 | 40 |
| | PD | 6 | 15 | 15 | |
| | UK | 6 | 15 | 15 | |
| TumEventRANO | NonPD | 27 | 68 | 68 | 40 |
| | PD | 8 | 20 | 20 | |
| | UK | 5 | 12,5 | 12,5 | |
| TumEventJOIN | NonPD | 25 | 63 | 63 | 40 |
| | PD | 11 | 28 | 28 | |
| | UK | 4 | 10 | 10 | |
| RECIST Best Response | CR | 1 | 3 | 3 | 40 |
| | PR | 17 | 43 | 44 | |
| | SD | 16 | 40 | 41 | |
| | PD | 4 | 10 | 10 | |
| | NE | 1 | 2,5 | 3 | |
| | NA's | 1 | 2,5 | 3 | |
| RANO Best Response | CR | 5 | 13 | 13 | 40 |
| | PR | 12 | 30 | 31 | |
| | SD | 17 | 43 | 44 | |
| | PD | 5 | 13 | 13 | |
| | NE | 0 | 0 | 0 | |
| | NA's | 1 | 3 | 3 | |
| RECIST Response | No | 20 | 50 | 53 | 40 |
| | Yes | 18 | 45 | 47 | |
| | NA's | 2 | 5 | 5 | |
| RANO Response | No | 22 | 55 | 56 | 40 |
| | Yes | 17 | 43 | 44 | |
| | NA's | 1 | 3 | 3 | |

**Efficacy Event: Disease Free survival rate at 12 weeks**

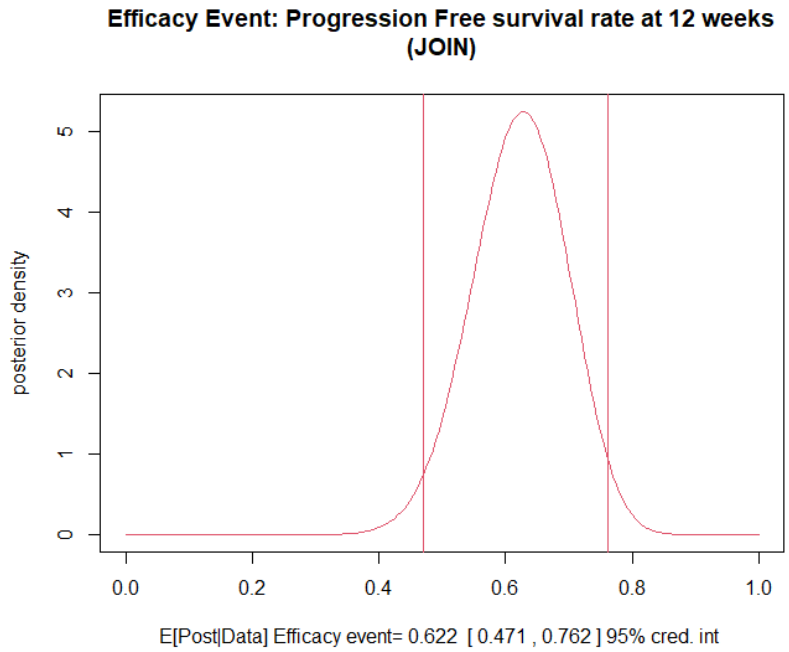
*Disease Free survival rate at 12 weeks By RECIST*




*Disease Free survival rate at 12 weeks By RANO criteria*



*Disease Free survival rate at 12 weeks: Joint RECIST and RANO criteria*

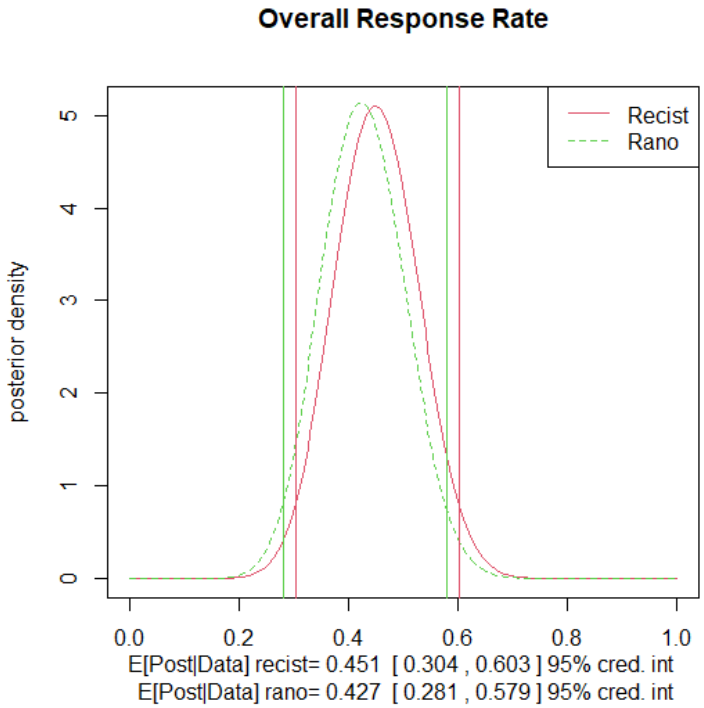


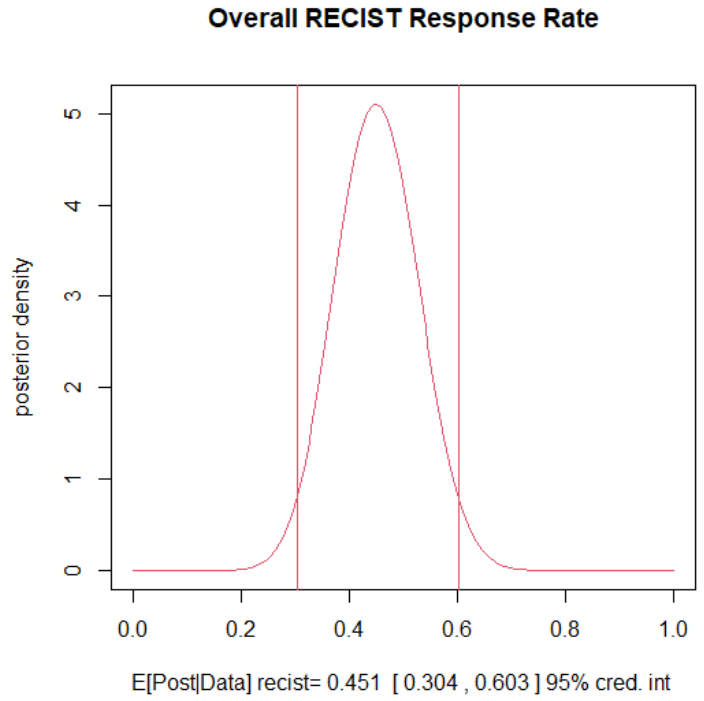

(*) Join: If any of responses are “Progression disease” then Join event is declared as not event (or not progression free). Event is consider for patients that are progression free at 12 weeks for simultaneously both criteria (RECIST and RANO).

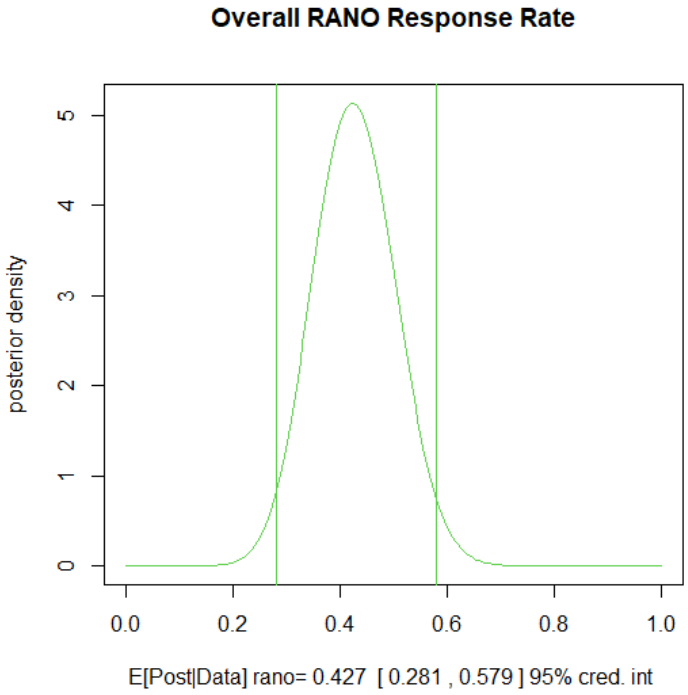
**Response rate estimations: RECIST and RANO relation**

```
   Cell Contents
|-------------------------|
|                       N |
| Chi-square contribution |
|           N / Row Total |
|           N / Col Total |
|         N / Table Total |
|-------------------------|

Total Observations in Table:  39
```

| BestResponse RECIST | BestResponse RANO | | | | |
|---|---|---|---|---|---|
| | CR | PR | SD | PD | Row Total |
| CR | **1** | 0 | 0 | 0 | 1 |
| | **5.928** | 0.308 | 0.436 | 0.128 | |
| | **1.000** | 0.000 | 0.000 | 0.000 | 0.026 |
| | **0.200** | 0.000 | 0.000 | 0.000 | |
| | **0.026** | 0.000 | 0.000 | 0.000 | |
| PR | 3 | **7** | 6 | 1 | 17 |
| | 0.309 | **0.598** | 0.268 | 0.638 | |
| | 0.176 | **0.412** | 0.353 | 0.059 | 0.436 |
| | 0.600 | **0.583** | 0.353 | 0.200 | |
| | 0.077 | **0.179** | 0.154 | 0.026 | |
| SD | 1 | 5 | **8** | 2 | 16 |
| | 0.539 | 0.001 | **0.151** | 0.001 | |
| | 0.062 | 0.312 | **0.500** | 0.125 | 0.410 |
| | 0.200 | 0.417 | **0.471** | 0.400 | |
| | 0.026 | 0.128 | **0.205** | 0.051 | |
| PD | 0 | 0 | 3 | **1** | 4 |
| | 0.513 | 1.231 | 0.905 | **0.463** | |
| | 0.000 | 0.000 | 0.750 | **0.250** | 0.103 |
| | 0.000 | 0.000 | 0.176 | **0.200** | |
| | 0.000 | 0.000 | 0.077 | **0.026** | |
| NE | 0 | 0 | 0 | 1 | 1 |
| | 0.128 | 0.308 | 0.436 | 5.928 | |
| | 0.000 | 0.000 | 0.000 | 1.000 | 0.026 |
| | 0.000 | 0.000 | 0.000 | 0.200 | |
| | 0.000 | 0.000 | 0.000 | 0.026 | |
| Column Total | 5 | 12 | 17 | 5 | 39 |
| | 0.128 | 0.308 | 0.436 | 0.128 | |


Overall Response Rate
Recist
Rano
posterior density
0
1
2
3
4
5
0.0
0.2
0.4
0.6
0.8
1.0
E[Post|Data] recist= 0.451 [ 0.304 , 0.603 ] 95% cred. int
E[Post|Data] rano= 0.427 [ 0.281 , 0.579 ] 95% cred. int


Overall RECIST Response Rate
posterior density
0
1
2
3
4
5
0.0
0.2
0.4
0.6
0.8
1.0
E[Post|Data] recist= 0.451 [ 0.304 , 0.603 ] 95% cred. int


Overall RANO Response Rate
posterior density
0
1
2
3
4
5
0.0
0.2
0.4
0.6
0.8
1.0
E[Post|Data] rano= 0.427 [ 0.281 , 0.579 ] 95% cred. int

**Response by steroids**

*Overall response by RECIST criteria and Steroids*

| | BestResponse RECIST | | | | | |
|---|---|---|---|---|---|---|
| Steroid Baseline | CR | PR | SD | PD | NE | Row Total |
| NO | 0 | 8 | 8 | 2 | 0 | 18 |
| | 0.474 | 0.000 | 0.023 | 0.236 | 0.474 | |
| | 0.000 | 0.444 | 0.444 | 0.111 | 0.000 | 0.474 |
| | 0.000 | 0.471 | 0.500 | 0.667 | 0.000 | |
| | 0.000 | 0.211 | 0.211 | 0.053 | 0.000 | |
| YES | 1 | 9 | 8 | 1 | 1 | 20 |
| | 0.426 | 0.000 | 0.021 | 0.212 | 0.426 | |
| | 0.050 | 0.450 | 0.400 | 0.050 | 0.050 | 0.526 |
| | 1.000 | 0.529 | 0.500 | 0.333 | 1.000 | |
| | 0.026 | 0.237 | 0.211 | 0.026 | 0.026 | |
| Column Total | 1 | 17 | 16 | 3 | 1 | 38 |
| | 0.026 | 0.447 | 0.421 | 0.079 | 0.026 | |

*Best Response ( CR-PR vs SD-Prog) by RECIST criteria and Steroids*

| Cell Contents |
|---|
| N |
| Chi-square contribution |
| N / Row Total |
| N / Col Total |
| N / Table Total |

Total Observations in Table: 37

| | Response | | |
|---|---|---|---|
| Baseline Steroids | SD-Prog | CR-PR | Row Total |
| NO | 10 | 8 | 18 |
| | 0.062 | 0.065 | |
| | 0.556 | 0.444 | 0.486 |
| | 0.526 | 0.444 | |
| | 0.270 | 0.216 | |
| YES | 9 | 10 | 19 |
| | 0.059 | 0.062 | |
| | 0.474 | 0.526 | 0.514 |
| | 0.474 | 0.556 | |
| | 0.243 | 0.270 | |
| Column Total | 19 | 18 | 37 |
| | 0.514 | 0.486 | |

Fisher's Exact Test for Count Data

---

Sample estimate odds ratio: 1.376535 Alternative hypothesis: true odds ratio is not equal to 1

p = 0.7458546 95% confidence interval: 0.3176767 6.129819

Alternative hypothesis: true odds ratio is less than 1

p = 0.7956112 95% confidence interval: 0 4.960872

Alternative hypothesis: true odds ratio is greater than 1

p = 0.4331196 95% confidence interval: 0.389403 Inf

*Best response (PD vs NOPD) by RECIST criteria and Steroids*

| Best response Recist Progression | Baseline Steroids: No | Yes | Row Total |
|---|---|---|---|
| PD | 2 | 1 | 3 |
| | 0.200 | 0.190 | |
| | 0.667 | 0.333 | 0.081 |
| | 0.111 | 0.053 | |
| | 0.054 | 0.027 | |
| NoPD | 16 | 18 | 34 |
| | 0.018 | 0.017 | |
| | 0.471 | 0.529 | 0.919 |
| | 0.889 | 0.947 | |
| | 0.432 | 0.486 | |
| Column Total | 18 | 19 | 37 |
| | 0.486 | 0.514 | |

Cell Contents

| |
|---|
| N |
| Chi-square contribution |
| N / Row Total |
| N / Col Total |
| N / Table Total |

Total Observations in Table: 37

Fisher's Exact Test for Count Data

---

Sample estimate odds ratio: 2.202385

Alternative hypothesis: true odds ratio is not equal to 1

p = 0.603861 95% confidence interval: 0.1052443 139.8631

Alternative hypothesis: true odds ratio is less than 1

p = 0.8949807 95% confidence interval: 0 68.77482

Alternative hypothesis: true odds ratio is greater than 1

p = 0.4791506 95% confidence interval: 0.1589725 Inf

*Overall response by RANO criteria and Steroids*

| BestResponse RANO | | | | | |
|---|---|---|---|---|---|
| Baseline Steroids | CR | PR | SD | PD | Row Total |
| NO | 4 | 3 | 9 | 2 | 18 |
| | 1.124 | 1.268 | 0.266 | 0.057 | |
| | 0.222 | 0.167 | 0.500 | 0.111 | 0.474 |
| | 0.800 | 0.250 | 0.562 | 0.400 | |
| | 0.105 | 0.079 | 0.237 | 0.053 | |
| YES | 1 | 9 | 7 | 3 | 20 |
| | 1.012 | 1.141 | 0.240 | 0.052 | |
| | 0.050 | 0.450 | 0.350 | 0.150 | 0.526 |
| | 0.200 | 0.750 | 0.438 | 0.600 | |
| | 0.026 | 0.237 | 0.184 | 0.079 | |
| Column Total | 5 | 12 | 16 | 5 | 38 |
| | 0.132 | 0.316 | 0.421 | 0.132 | |

Fisher's Exact Test for Count Data

---

Alternative hypothesis: two.sided

p = 0.1717884

*Best Response ( CR-PR vs SD-Prog) by RANO criteria and Steroids*

| Baseline Steroids | Response by RANO: SD-PROG | CR-PR | Row Total |
|---|---|---|---|
| NO | 11 | 7 | 18 |
| | 0.111 | 0.138 | |
| | 0.611 | 0.389 | 0.474 |
| | 0.524 | 0.412 | |
| | 0.289 | 0.184 | |
| YES | 10 | 10 | 20 |
| | 0.100 | 0.124 | |
| | 0.500 | 0.500 | 0.526 |
| | 0.476 | 0.588 | |
| | 0.263 | 0.263 | |
| Column Total | 21 | 17 | 38 |
| | 0.553 | 0.447 | |

Cell Contents

| N |
|---|
| Chi-square contribution |
| N / Row Total |
| N / Col Total |
| N / Table Total |

Total Observations in Table: 38

Fisher's Exact Test for Count Data

Sample estimate odds ratio: 1.552684 Alternative hypothesis: true odds ratio is not equal to 1

p = 0.5318374 95% confidence interval: 0.3622266 6.946378

Alternative hypothesis: true odds ratio is less than 1

p = 0.8447379 95% confidence interval: 0 5.609404

Alternative hypothesis: true odds ratio is greater than 1

p = 0.3595512 95% confidence interval: 0.4429622 Inf

*Best response Response (PD vs NOPD) by RANO criteria and Steroids*

| Baseline Steroids | RESPONSE by RANO: PD | NoPD | Row Total |
|---|---|---|---|
| NO | 2 | 16 | 18 |
| | 0.057 | 0.009 | |
| | 0.111 | 0.889 | 0.474 |
| | 0.400 | 0.485 | |
| | 0.053 | 0.421 | |
| YES | 3 | 17 | 20 |
| | 0.052 | 0.008 | |
| | 0.150 | 0.850 | 0.526 |
| | 0.600 | 0.515 | |
| | 0.079 | 0.447 | |
| Column Total | 5 | 33 | 38 |
| | 0.132 | 0.868 | |

Cell Contents

|---|
| N |
| Chi-square contribution |
| N / Row Total |
| N / Col Total |
| N / Table Total |

Total Observations in Table: 38

Fisher's Exact Test for Count Data

---

Sample estimate odds ratio: 0.7147265 Alternative hypothesis: true odds ratio is not equal to 1

p = 1 95% confidence interval: 0.05315394 7.117247

Alternative hypothesis: true odds ratio is less than 1

p = 0.5521236 95% confidence interval: 0 5.185792

Alternative hypothesis: true odds ratio is greater than 1

p = 0.7953668 95% confidence interval: 0.07940113 Inf

**Response and PD-L1**

*Overall response by RECIST criteria and PD-L1*

Cell Contents

|-------------------------|
| N |
| Chi-square contribution |
| N / Row Total |
| N / Col Total |
| N / Table Total |
|-------------------------|

Total Observations in Table: 37

| | BestResponse | | | | | |
|---|---|---|---|---|---|---|
| PDL1P | CR | PR | SD | PD | NE | Row Total |
| - | 0 | 7 | 9 | 0 | 1 | 17 |
| | 0.459 | 0.017 | 0.370 | 1.378 | 0.636 | |
| | 0.000 | 0.412 | 0.529 | 0.000 | 0.059 | 0.459 |
| | 0.000 | 0.438 | 0.562 | 0.000 | 1.000 | |
| | 0.000 | 0.189 | 0.243 | 0.000 | 0.027 | |
| + | 1 | 9 | 7 | 3 | 0 | 20 |
| | 0.391 | 0.014 | 0.314 | 1.172 | 0.541 | |
| | 0.050 | 0.450 | 0.350 | 0.150 | 0.000 | 0.541 |
| | 1.000 | 0.562 | 0.438 | 1.000 | 0.000 | |
| | 0.027 | 0.243 | 0.189 | 0.081 | 0.000 | |
| Column Total | 1 | 16 | 16 | 3 | 1 | 37 |
| | 0.027 | 0.432 | 0.432 | 0.081 | 0.027 | |

Fisher's Exact Test for Count Data

---

Alternative hypothesis: two.sided

p = 0.2640382

*Best Response ( CR-PR vs SD-Prog) by RECIST criteria and PD-L1*

| PDL1P | Response: SD-PROG | CR-PR | Row Total |
|---|---|---|---|
| - | 9 | 7 | 16 |
| | 0.037 | 0.041 | |
| | 0.562 | 0.438 | 0.444 |
| | 0.474 | 0.412 | |
| | 0.250 | 0.194 | |
| + | 10 | 10 | 20 |
| | 0.029 | 0.033 | |
| | 0.500 | 0.500 | 0.556 |
| | 0.526 | 0.588 | |
| | 0.278 | 0.278 | |
| Column Total | 19 | 17 | 36 |
| | 0.528 | 0.472 | |

Cell Contents

| N |
|---|
| Chi-square contribution |
| N / Row Total |
| N / Col Total |
| N / Table Total |

Total Observations in Table: 36

Fisher's Exact Test for Count Data

---

Sample estimate odds ratio: 1.276743

Alternative hypothesis: true odds ratio is not equal to 1

p = 0.7485727 95% confidence interval: 0.2846671 5.887704

Alternative hypothesis: true odds ratio is less than 1

p = 0.7603963 95% confidence interval: 0 4.741467

Alternative hypothesis: true odds ratio is greater than 1

p = 0.4854437 95% confidence interval: 0.3505753 Inf

*Best response (PD vs NOPD) by RECIST criteria and PD-L1*

| PDL1P | Recist PD | NoPD | Row Total |
|---|---|---|---|
| - | 0 | 16 | 16 |
| | 1.333 | 0.121 | |
| | 0.000 | 1.000 | 0.444 |
| | 0.000 | 0.485 | |
| | 0.000 | 0.444 | |
| + | 3 | 17 | 20 |
| | 1.067 | 0.097 | |
| | 0.150 | 0.850 | 0.556 |
| | 1.000 | 0.515 | |
| | 0.083 | 0.472 | |
| Column Total | 3 | 33 | 36 |
| | 0.083 | 0.917 | |

Cell Contents

| |
|---|
| N |
| Chi-square contribution |
| N / Row Total |
| N / Col Total |
| N / Table Total |

Total Observations in Table: 36

Fisher's Exact Test for Count Data

---

Sample estimate odds ratio: 0

Alternative hypothesis: true odds ratio is not equal to 1

p = 0.2380952 95% confidence interval: 0 2.957257

Alternative hypothesis: true odds ratio is less than 1

p = 0.1596639 95% confidence interval: 0 2.075781

Alternative hypothesis: true odds ratio is greater than 1

p = 1 95% confidence interval: 0 Inf

*Overall best response by RANO criteria and PD-L1*

Cell Contents

|-------------------------|
| N |
| Chi-square contribution |
| N / Row Total |
| N / Col Total |
| N / Table Total |
|-------------------------|

Total Observations in Table: 37

| BestResponse RANO

| PDL1P | CR | PR | SD | PD | Row Total |
|---|---|---|---|---|---|
| - | 0 | 8 | 7 | 2 | 17 |
| | 2.297 | 1.121 | 0.002 | 0.038 | |
| | 0.000 | 0.471 | 0.412 | 0.118 | 0.459 |
| | 0.000 | 0.667 | 0.467 | 0.400 | |
| | 0.000 | 0.216 | 0.189 | 0.054 | |
| + | 5 | 4 | 8 | 3 | 20 |
| | 1.953 | 0.953 | 0.001 | 0.033 | |
| | 0.250 | 0.200 | 0.400 | 0.150 | 0.541 |
| | 1.000 | 0.333 | 0.533 | 0.600 | |
| | 0.135 | 0.108 | 0.216 | 0.081 | |
| Column Total | 5 | 12 | 15 | 5 | 37 |
| | 0.135 | 0.324 | 0.405 | 0.135 | |

Fisher's Exact Test for Count Data

---

Alternative hypothesis: two.sided

p = 0.104064

*Best Response ( CR-PR vs SD-Prog) by RANO criteria and PD-L1*

| PDL1P | Best Response RANO: SD-PD | CR-PR | Row Total |
|---|---|---|---|
| - | 9 | 8 | 17 |
| | 0.004 | 0.005 | |
| | 0.529 | 0.471 | 0.459 |
| | 0.450 | 0.471 | |
| | 0.243 | 0.216 | |
| + | 11 | 9 | 20 |
| | 0.003 | 0.004 | |
| | 0.550 | 0.450 | 0.541 |
| | 0.550 | 0.529 | |
| | 0.297 | 0.243 | |
| Column Total | 20 | 17 | 37 |
| | 0.541 | 0.459 | |

Cell Contents

| |
|---|
| N |
| Chi-square contribution |
| N / Row Total |
| N / Col Total |
| N / Table Total |

Total Observations in Table: 37

Fisher's Exact Test for Count Data

---

Sample estimate odds ratio: 0.9225207

Alternative hypothesis: true odds ratio is not equal to 1

p = 1 95% confidence interval: 0.208828 4.067357

Alternative hypothesis: true odds ratio is less than 1

p = 0.5809996 95% confidence interval: 0 3.303301

Alternative hypothesis: true odds ratio is greater than 1

p = 0.675713 95% confidence interval: 0.2572453 Inf

*Best response (PD vs NOPD) by RANO criteria and PD-L1*

| Progression RANO | | | |
|---|---|---|---|
| PDL1P | PD | NoPD | Row Total |
| - | 2 | 15 | 17 |
| | 0.038 | 0.006 | |
| | 0.118 | 0.882 | 0.459 |
| | 0.400 | 0.469 | |
| | 0.054 | 0.405 | |
| + | 3 | 17 | 20 |
| | 0.033 | 0.005 | |
| | 0.150 | 0.850 | 0.541 |
| | 0.600 | 0.531 | |
| | 0.081 | 0.459 | |
| Column Total | 5 | 32 | 37 |
| | 0.135 | 0.865 | |

Cell Contents

| |
|---|
| N |
| Chi-square contribution |
| N / Row Total |
| N / Col Total |
| N / Table Total |

Total Observations in Table: 37

Fisher's Exact Test for Count Data

---

Sample estimate odds ratio: 0.7612414

Alternative hypothesis: true odds ratio is not equal to 1

p = 1 95% confidence interval: 0.05640047 7.616329

Alternative hypothesis: true odds ratio is less than 1

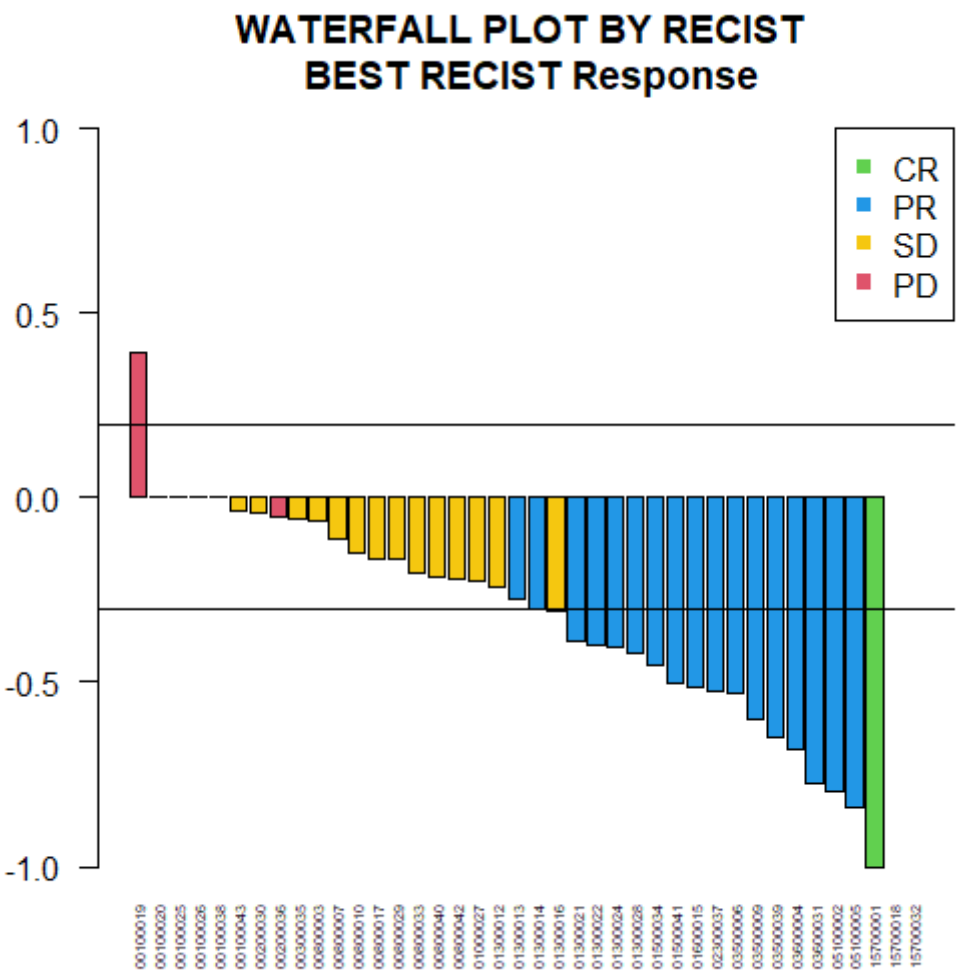
p = 0.5802036 95% confidence interval: 0 5.547201

Alternative hypothesis: true odds ratio is greater than 1

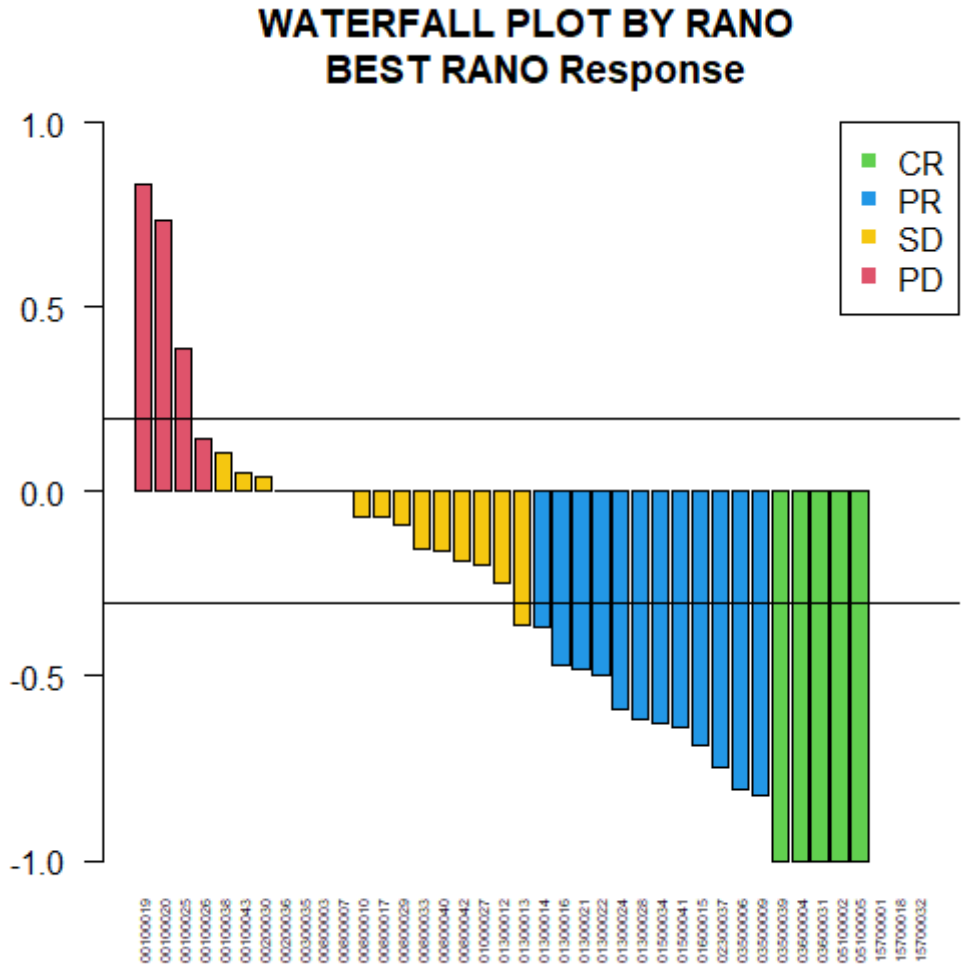
p = 0.7754768 95% confidence interval: 0.08429126 Inf

**Waterfall plots**

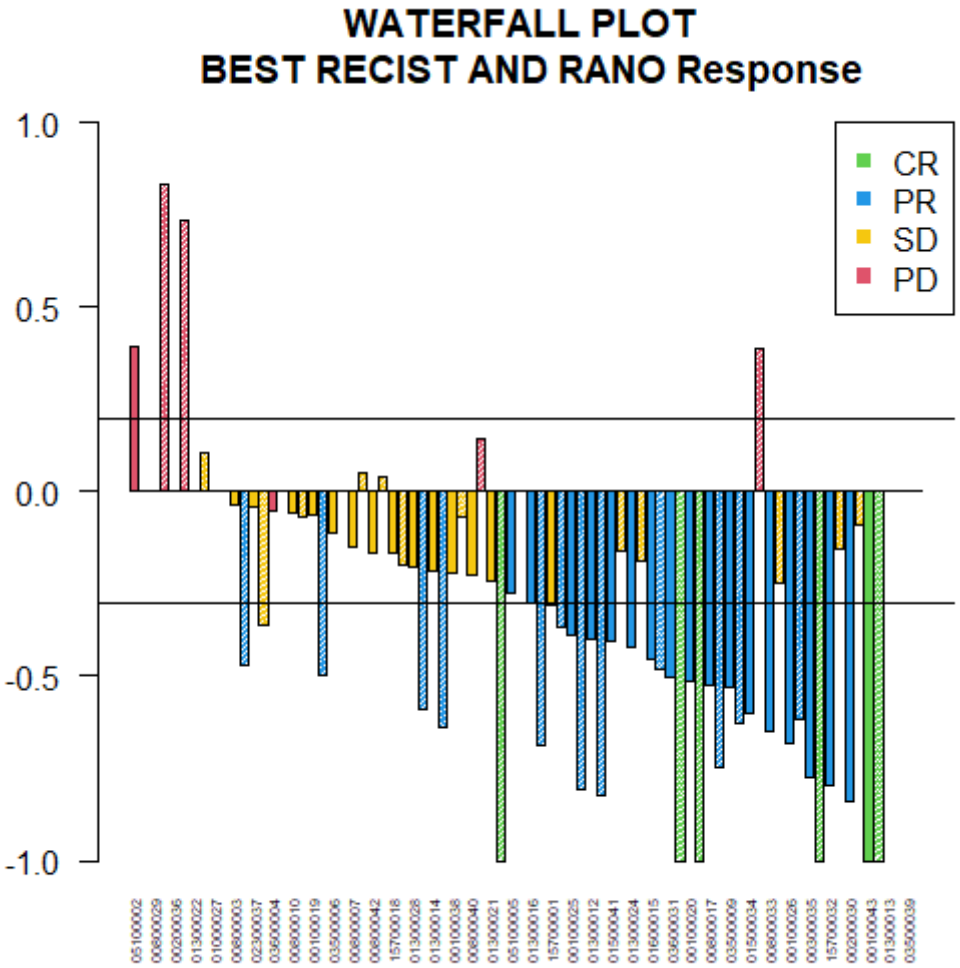
*Waterfall plot RECIST*



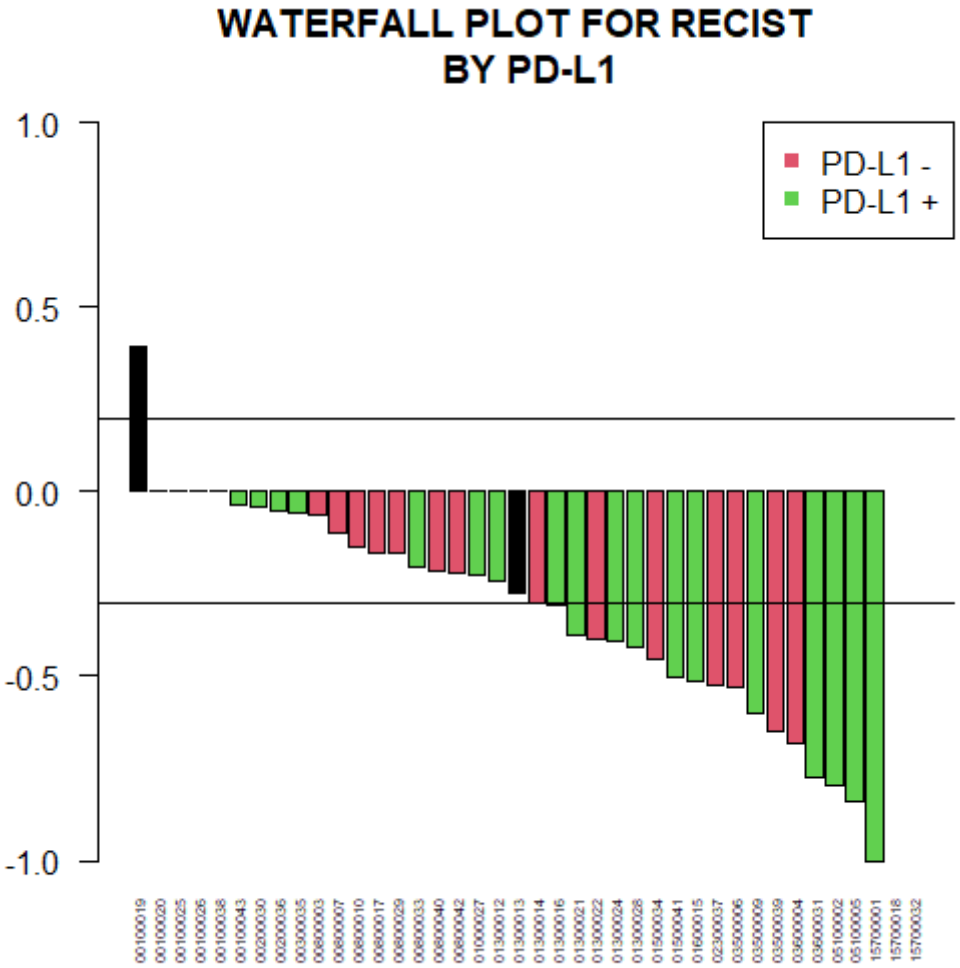
*Waterfall plot RANO*



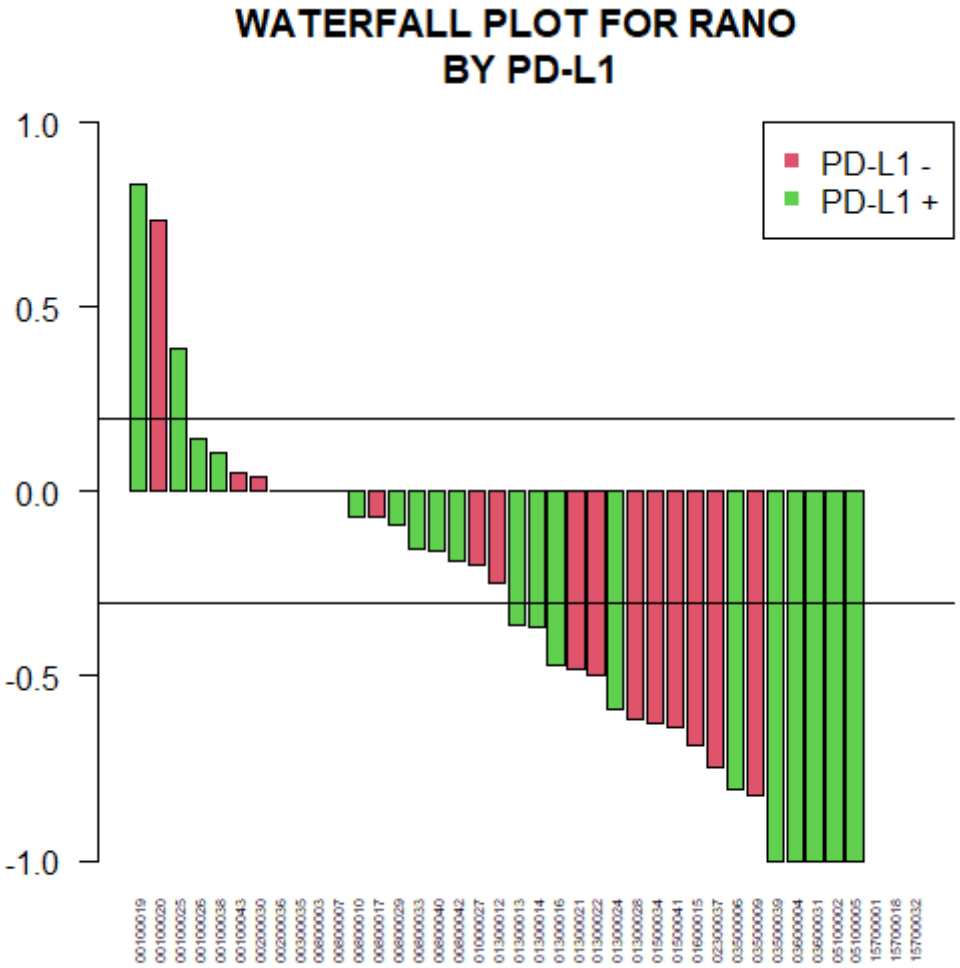
*Waterfall plot combining RECIST & RANO*



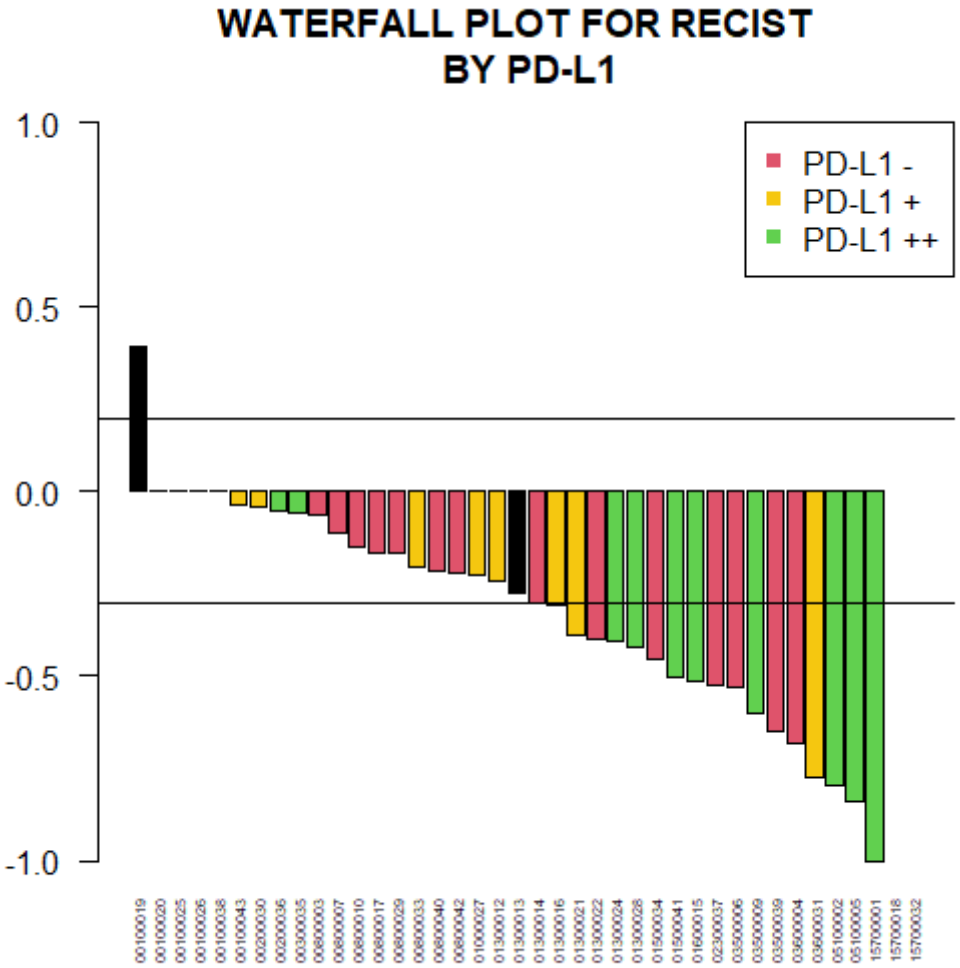
*Waterfall plot for RECIST By PD-L1 (+/-)*



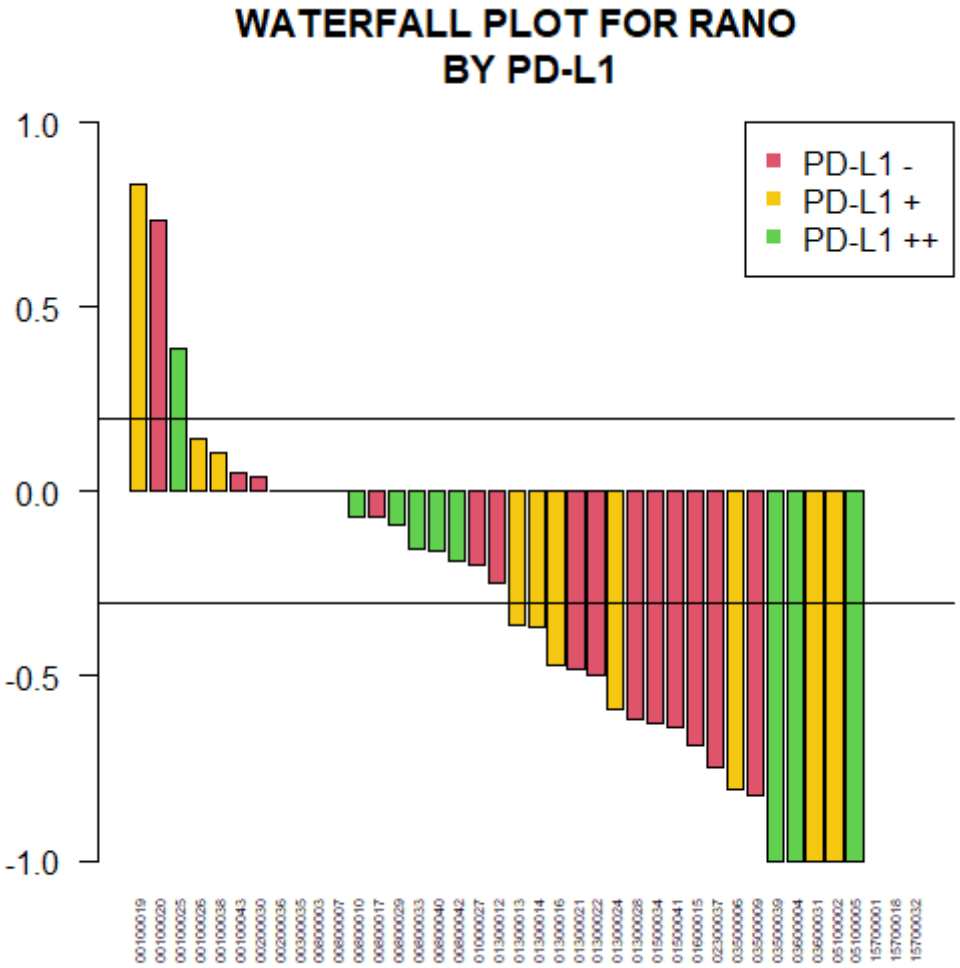
*Waterfall plot for RANO By PD-L1 (+/-)*



*Waterfall plot for RECIST By PD-L1 (-/+/++)*



*Waterfall plot for RANO By PD-L1 (-/+/++)*



**ANTINEOPLASIC TREATMENTS POSTERIOR TO TRIAL'S TREATMENT**

**Radiotherapy schemes**

| Variable | Category | N | Perc | ValidPerc | n |
|---|---|---|---|---|---|
| RT Type | NA | 16 | 40 | 40 | 40 |
| | FocalRT | 8 | 20 | 20 | |
| | WBRT | 16 | 40 | 40 | |
| RTTotalDose | 18 | 1 | 2,5 | 4,35 | 40 |
| | 20 | 4 | 10 | 17,39 | |
| | 27 | 2 | 5 | 8,7 | |
| | 28 | 1 | 2,5 | 4,35 | |
| | 30 | 11 | 27,5 | 47,83 | |
| | 40 | 1 | 2,5 | 4,35 | |
| | 60 | 1 | 2,5 | 4,35 | |
| | 72 | 2 | 5 | 8,7 | |
| | NA's | 17 | 42,5 | 73,91 | |
| RTScheme | 1*18Gy/s=18Gy | 1 | 2,5 | 2,5 | 40 |
| | 1*20Gy/s=20Gy | 1 | 2,5 | 2,5 | |
| | 10*3Gy/s=30Gy | 11 | 27,5 | 27,5 | |
| | 10*4Gy/s=40Gy | 1 | 2,5 | 2,5 | |
| | 14*2Gy/s=28Gy | 1 | 2,5 | 2,5 | |
| | 3*24Gy/s=72Gy | 2 | 5 | 5 | |
| | 3*9Gy/s=27Gy | 2 | 5 | 5 | |
| | 4*5Gy/s=20Gy | 1 | 2,5 | 2,5 | |
| | 5*12Gy/s=60Gy | 1 | 2,5 | 2,5 | |
| | 5*4Gy/s=20Gy | 2 | 5 | 5 | |
| | NoRT | 17 | 42,5 | 42,5 | |

**Exitus previous to Radiotherapy**

| Variable | Categoria | N | Perc | ValidPerc | n |
|---|---|---|---|---|---|
| RT_Exitus | NotYetRT | 3 | 7,5 | 7,5 | 40 |
| | Ex_PrevtoRT | 13 | 32,5 | 32,5 | |
| | RT_Yes | 24 | 60 | 60 | |

## LIST OF PATIENT'S DATA AVAILABILITY

| | Baseline | | Tumour Assessment | | Main analysis | | Overall Survival | | Safety(AE) | |
|---|---|---|---|---|---|---|---|---|---|---|
| PatientNumber | included | info | included | info | included | info | included | info | included | info |
| 15700001 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 5100002 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 800003 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Not Available |
| 3600004 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 5100005 | yes | Available | yes | Available | yes | Not Available | yes | Available | yes | Available |
| 3500006 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 800007 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 3500009 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 800010 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 1300012 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 1300013 | yes | Available | yes | Not Available | yes | Not Available | yes | Available | yes | Available |
| 1300014 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 1600015 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 1300016 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 800017 | yes | Available | yes | Available | yes | Available | yes | Not Available | yes | Available |
| 15700018 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 100019 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 100020 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 1300021 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 1300022 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 1300024 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 100025 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 100026 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 1000027 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 1300028 | yes | Available | yes | Available | yes | Available | yes | Not Available | yes | Not Available |
| 800029 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 200030 | yes | Available | yes | Available | yes | Available | yes | Not Available | yes | Available |
| 3600031 | yes | Available | yes | Available | yes | Available | yes | Not Available | yes | Available |
| 15700032 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 800033 | yes | Available | yes | Available | yes | Available | yes | Not Available | yes | Available |
| 1500034 | yes | Available | yes | Available | yes | Not Available | yes | Available | yes | Available |
| 300035 | yes | Available | yes | Available | yes | Available | yes | Not Available | yes | Available |
| 200036 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 2300037 | yes | Available | yes | Available | yes | Available | yes | Not Available | yes | Available |
| 100038 | yes | Available | yes | Available | yes | Available | yes | Not Available | yes | Available |
| 3500039 | yes | Available | yes | Not Available | yes | Not Available | yes | Not Available | yes | Available |
| 800040 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 1500041 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 800042 | yes | Available | yes | Available | yes | Available | yes | Available | yes | Available |
| 100043 | yes | Available | yes | Available | yes | Available | yes | Not Available | yes | Available |

## 1.1. EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

### 11.4.1 Analysis of Efficacy

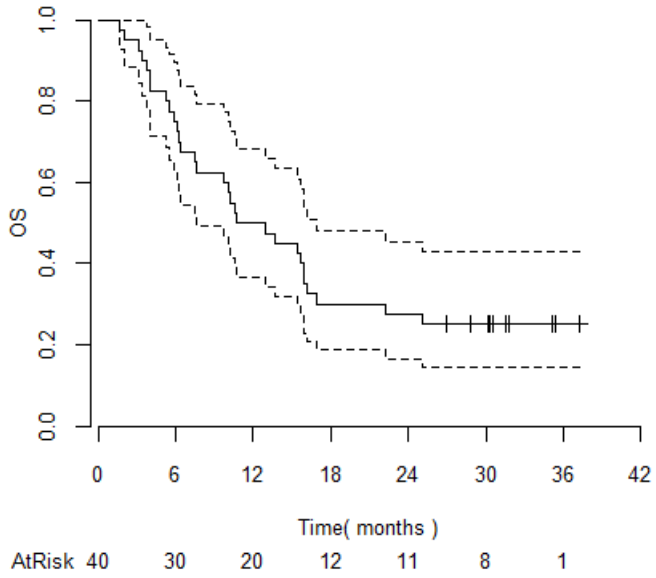
## EFFICACY

### Follow-up time study

| | N | NA | Min | Q1 | Median | Mean | Q3 | Max | Stdev | Var | IQR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tsvglob(c) | 10 | 0 | 27,0 | 30,2 | 31,0 | 31,8 | 34,3 | 37,2 | 3,2 | 10,3 | 4,2 |
| TSvglob | 40 | 0 | 1,6 | 6,1 | 11,8 | 15,3 | 25,6 | 37,2 | 11,1 | 122,6 | 19,5 |

### Overall survival

*Overall survival*




| n | events | median | 0.95LCL | 0.95UCL |
|---|---|---|---|---|
| 40.00 | 30.00 | 11.79 | 7.62 | 16.92 |

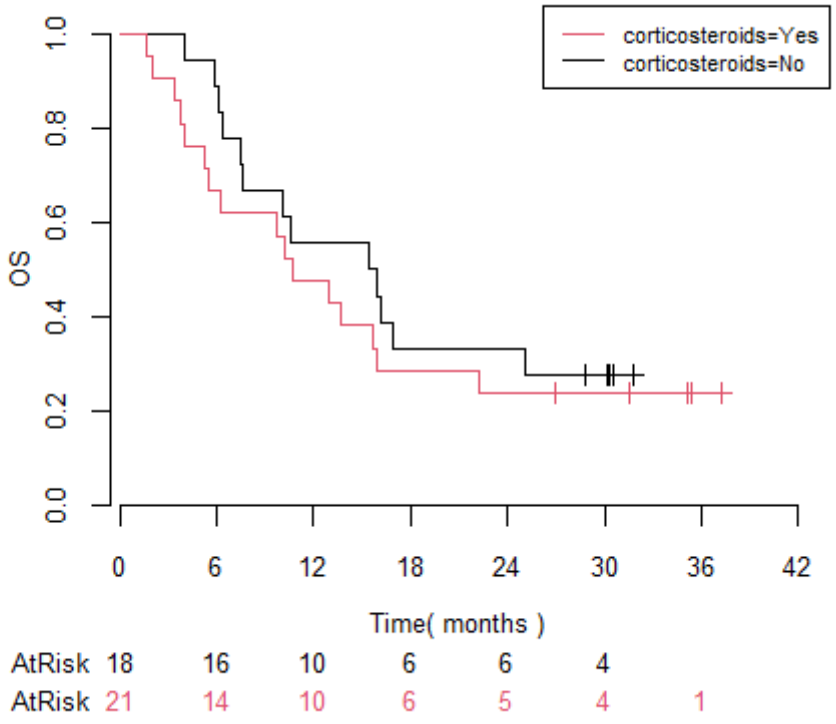
| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 40 | 0 | 1.000 | 0.0000 | 1.000 | 1.000 |
| 3 | 38 | 2 | 0.950 | 0.0345 | 0.885 | 1.000 |
| 6 | 30 | 8 | 0.750 | 0.0685 | 0.627 | 0.897 |
| 9 | 25 | 5 | 0.625 | 0.0765 | 0.492 | 0.795 |
| 12 | 20 | 5 | 0.500 | 0.0791 | 0.367 | 0.682 |
| 15 | 18 | 2 | 0.450 | 0.0787 | 0.319 | 0.634 |
| 18 | 12 | 6 | 0.300 | 0.0725 | 0.187 | 0.482 |
| 21 | 12 | 0 | 0.300 | 0.0725 | 0.187 | 0.482 |
| 24 | 11 | 1 | 0.275 | 0.0706 | 0.166 | 0.455 |
| 27 | 10 | 1 | 0.250 | 0.0685 | 0.146 | 0.428 |
| 30 | 8 | 0 | 0.250 | 0.0685 | 0.146 | 0.428 |
| 33 | 3 | 0 | 0.250 | 0.0685 | 0.146 | 0.428 |
| 36 | 1 | 0 | 0.250 | 0.0685 | 0.146 | 0.428 |

(*) Time in months

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 40 | 0 | 1.000 | 0.0000 | 1.000 | 1.000 |
| 3 | 38 | 2 | 0.950 | 0.0345 | 0.885 | 1.000 |
| 6 | 30 | 8 | 0.750 | 0.0685 | 0.627 | 0.897 |
| 9 | 25 | 5 | 0.625 | 0.0765 | 0.492 | 0.795 |
| 12 | 20 | 5 | 0.500 | 0.0791 | 0.367 | 0.682 |
| 15 | 18 | 2 | 0.450 | 0.0787 | 0.319 | 0.634 |
| 18 | 12 | 6 | 0.300 | 0.0725 | 0.187 | 0.482 |
| 21 | 12 | 0 | 0.300 | 0.0725 | 0.187 | 0.482 |
| 24 | 11 | 1 | 0.275 | 0.0706 | 0.166 | 0.455 |
| 27 | 10 | 1 | 0.250 | 0.0685 | 0.146 | 0.428 |
| 30 | 8 | 0 | 0.250 | 0.0685 | 0.146 | 0.428 |
| 33 | 3 | 0 | 0.250 | 0.0685 | 0.146 | 0.428 |
| 36 | 1 | 0 | 0.250 | 0.0685 | 0.146 | 0.428 |

(*) Time in months

*Overall survival by Steroids (yes vs no)*



1 observation deleted due to missingness

| | n | events | median | 0.95LCL | 0.95UCL |
|---|---|---|---|---|---|
| datdfs$CortisBasal[cond.paval]=0 | 18 | 13 | 15.7 | 7.62 | NA |
| datdfs$CortisBasal[cond.paval]=1 | 21 | 16 | 10.7 | 5.55 | NA |

LOG RANK TEST

n=39, 1 observation deleted due to missingness.

| | N | Observed | Expected | (O-E)^2/E | (O-E)^2/V |
|---|---|---|---|---|---|
| datdfs$CortisBasal[cond.paval]=0 | 18 | 13 | 15 | 0.261 | 0.545 |
| datdfs$CortisBasal[cond.paval]=1 | 21 | 16 | 14 | 0.278 | 0.545 |

Chisq= 0.5 on 1 degrees of freedom, p= 0.5

1 observation deleted due to missingness

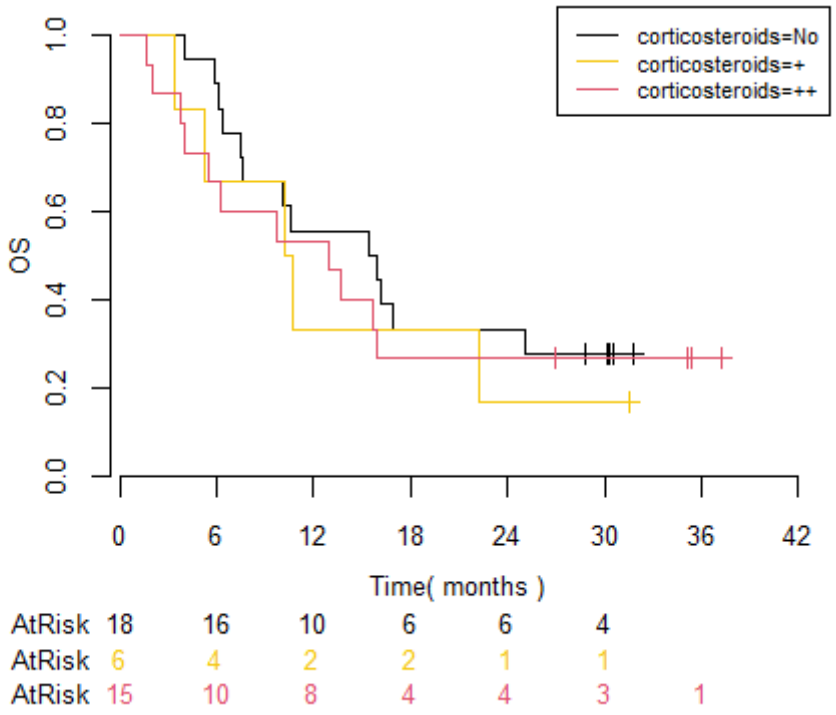
BASELINE STEROIDS = NO

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 18 | 0 | 1.000 | 0.0000 | 1.000 | 1.000 |
| 3 | 18 | 0 | 1.000 | 0.0000 | 1.000 | 1.000 |
| 6 | 16 | 2 | 0.889 | 0.0741 | 0.755 | 1.000 |
| 9 | 12 | 4 | 0.667 | 0.1111 | 0.481 | 0.924 |
| 12 | 10 | 2 | 0.556 | 0.1171 | 0.368 | 0.840 |
| 15 | 10 | 0 | 0.556 | 0.1171 | 0.368 | 0.840 |
| 18 | 6 | 4 | 0.333 | 0.1111 | 0.173 | 0.641 |
| 21 | 6 | 0 | 0.333 | 0.1111 | 0.173 | 0.641 |
| 24 | 6 | 0 | 0.333 | 0.1111 | 0.173 | 0.641 |
| 27 | 5 | 1 | 0.278 | 0.1056 | 0.132 | 0.585 |
| 30 | 4 | 0 | 0.278 | 0.1056 | 0.132 | 0.585 |

BASELINE STEROIDS = YES

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 21 | 0 | 1.000 | 0.0000 | 1.000 | 1.000 |
| 3 | 19 | 2 | 0.905 | 0.0641 | 0.788 | 1.000 |
| 6 | 14 | 5 | 0.667 | 0.1029 | 0.493 | 0.902 |
| 9 | 13 | 1 | 0.619 | 0.1060 | 0.443 | 0.866 |
| 12 | 10 | 3 | 0.476 | 0.1090 | 0.304 | 0.746 |
| 15 | 8 | 2 | 0.381 | 0.1060 | 0.221 | 0.657 |
| 18 | 6 | 2 | 0.286 | 0.0986 | 0.145 | 0.562 |
| 21 | 6 | 0 | 0.286 | 0.0986 | 0.145 | 0.562 |
| 24 | 5 | 1 | 0.238 | 0.0929 | 0.111 | 0.512 |
| 27 | 5 | 0 | 0.238 | 0.0929 | 0.111 | 0.512 |
| 30 | 4 | 0 | 0.238 | 0.0929 | 0.111 | 0.512 |
| 33 | 3 | 0 | 0.238 | 0.0929 | 0.111 | 0.512 |
| 36 | 1 | 0 | 0.238 | 0.0929 | 0.111 | 0.512 |

*Overall survival by Steroids (three categories 0, (0-4), [4])*




1 observation deleted due to missingness

| | n | events | median | 0.95LCL | 0.95UCL |
|---|---|---|---|---|---|
| STEROIDS = - | 18 | 13 | 15.7 | 7.62 | NA |
| STEROIDS = + | 6 | 5 | 10.5 | 5.29 | NA |
| STEROIDS = ++ | 15 | 11 | 12.9 | 5.55 | NA |

LOG RANK TEST

n=39, 1 observation deleted due to missingness.

| | N | Observed | Expected | (O-E)^2/E | (O-E)^2/V |
|---|---|---|---|---|---|
| STEROIDS = - | 18 | 13 | 14.98 | 0.261 | 0.545 |
| STEROIDS = + | 6 | 5 | 4.04 | 0.229 | 0.269 |
| STEROIDS = ++ | 15 | 11 | 9.99 | 0.103 | 0.159 |

Chisq= 0.6 on 2 degrees of freedom, p= 0.7

1 observation deleted due to missingness

STEROIDS = -

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 18 | 0 | 1.000 | 0.0000 | 1.000 | 1.000 |
| 3 | 18 | 0 | 1.000 | 0.0000 | 1.000 | 1.000 |
| 6 | 16 | 2 | 0.889 | 0.0741 | 0.755 | 1.000 |
| 9 | 12 | 4 | 0.667 | 0.1111 | 0.481 | 0.924 |
| 12 | 10 | 2 | 0.556 | 0.1171 | 0.368 | 0.840 |
| 15 | 10 | 0 | 0.556 | 0.1171 | 0.368 | 0.840 |
| 18 | 6 | 4 | 0.333 | 0.1111 | 0.173 | 0.641 |
| 21 | 6 | 0 | 0.333 | 0.1111 | 0.173 | 0.641 |
| 24 | 6 | 0 | 0.333 | 0.1111 | 0.173 | 0.641 |
| 27 | 5 | 1 | 0.278 | 0.1056 | 0.132 | 0.585 |
| 30 | 4 | 0 | 0.278 | 0.1056 | 0.132 | 0.585 |

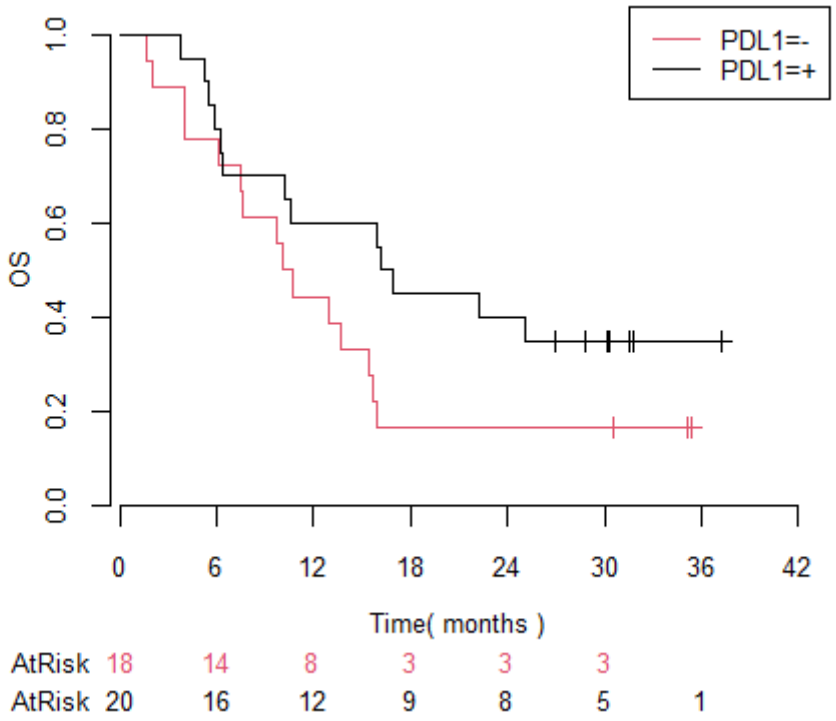
STEROIDS = +

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 6 | 0 | 1.000 | 0.000 | 1.0000 | 1.000 |
| 3 | 6 | 0 | 1.000 | 0.000 | 1.0000 | 1.000 |
| 6 | 4 | 2 | 0.667 | 0.192 | 0.3786 | 1.000 |
| 9 | 4 | 0 | 0.667 | 0.192 | 0.3786 | 1.000 |
| 12 | 2 | 2 | 0.333 | 0.192 | 0.1075 | 1.000 |
| 15 | 2 | 0 | 0.333 | 0.192 | 0.1075 | 1.000 |
| 18 | 2 | 0 | 0.333 | 0.192 | 0.1075 | 1.000 |
| 21 | 2 | 0 | 0.333 | 0.192 | 0.1075 | 1.000 |
| 24 | 1 | 1 | 0.167 | 0.152 | 0.0278 | 0.997 |
| 27 | 1 | 0 | 0.167 | 0.152 | 0.0278 | 0.997 |
| 30 | 1 | 0 | 0.167 | 0.152 | 0.0278 | 0.997 |

STEROIDS == ++

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 15 | 0 | 1.000 | 0.0000 | 1.000 | 1.000 |
| 3 | 13 | 2 | 0.867 | 0.0878 | 0.711 | 1.000 |
| 6 | 10 | 3 | 0.667 | 0.1217 | 0.466 | 0.953 |
| 9 | 9 | 1 | 0.600 | 0.1265 | 0.397 | 0.907 |
| 12 | 8 | 1 | 0.533 | 0.1288 | 0.332 | 0.856 |
| 15 | 6 | 2 | 0.400 | 0.1265 | 0.215 | 0.743 |
| 18 | 4 | 2 | 0.267 | 0.1142 | 0.115 | 0.617 |
| 21 | 4 | 0 | 0.267 | 0.1142 | 0.115 | 0.617 |
| 24 | 4 | 0 | 0.267 | 0.1142 | 0.115 | 0.617 |
| 27 | 4 | 0 | 0.267 | 0.1142 | 0.115 | 0.617 |
| 30 | 3 | 0 | 0.267 | 0.1142 | 0.115 | 0.617 |
| 33 | 3 | 0 | 0.267 | 0.1142 | 0.115 | 0.617 |
| 36 | 1 | 0 | 0.267 | 0.1142 | 0.115 | 0.617 |

*Overall survival by PD-L1*




```
   2 observations deleted due to missingness

         n events median 0.95LCL 0.95UCL
PDL1 =- 18     15   10.4    7.56      16
PDL1 =+ 20     13   16.6   10.28      NA
```

log rank test

n=38, 2 observations deleted due to missingness.

```
        N Observed Expected (O-E)^2/E (O-E)^2/V
PDL1=- 18       15     10.9     1.563      2.65
PDL1=+ 20       13     17.1     0.993      2.65

 Chisq= 2.7  on 1 degrees of freedom, p= 0.1
```

2 observations deleted due to missingness

PDL1 =-

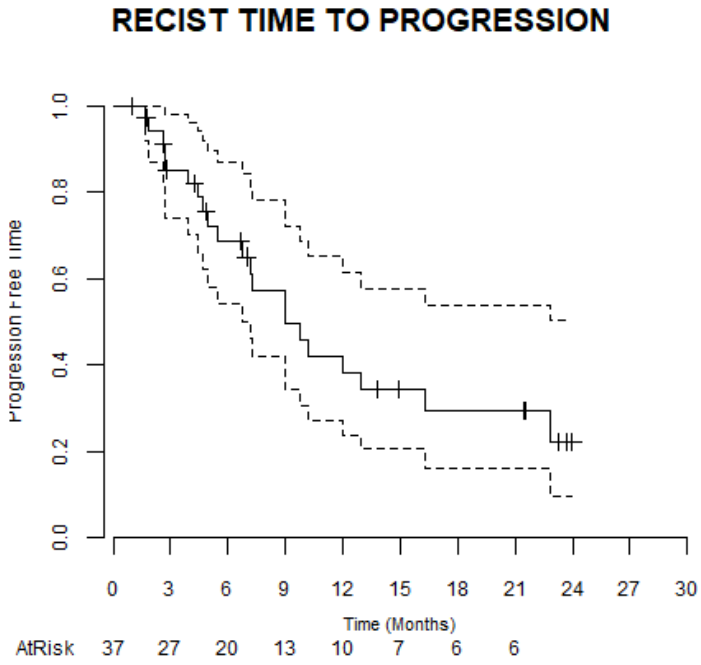
| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 18 | 0 | 1.000 | 0.0000 | 1.0000 | 1.000 |
| 3 | 16 | 2 | 0.889 | 0.0741 | 0.7549 | 1.000 |
| 6 | 14 | 2 | 0.778 | 0.0980 | 0.6076 | 0.996 |
| 9 | 11 | 3 | 0.611 | 0.1149 | 0.4227 | 0.883 |
| 12 | 8 | 3 | 0.444 | 0.1171 | 0.2652 | 0.745 |
| 15 | 6 | 2 | 0.333 | 0.1111 | 0.1734 | 0.641 |
| 18 | 3 | 3 | 0.167 | 0.0878 | 0.0593 | 0.468 |
| 21 | 3 | 0 | 0.167 | 0.0878 | 0.0593 | 0.468 |
| 24 | 3 | 0 | 0.167 | 0.0878 | 0.0593 | 0.468 |
| 27 | 3 | 0 | 0.167 | 0.0878 | 0.0593 | 0.468 |
| 30 | 3 | 0 | 0.167 | 0.0878 | 0.0593 | 0.468 |
| 33 | 2 | 0 | 0.167 | 0.0878 | 0.0593 | 0.468 |

PDL1P=+

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 20 | 0 | 1.00 | 0.0000 | 1.000 | 1.000 |
| 3 | 20 | 0 | 1.00 | 0.0000 | 1.000 | 1.000 |
| 6 | 16 | 4 | 0.80 | 0.0894 | 0.643 | 0.996 |
| 9 | 14 | 2 | 0.70 | 0.1025 | 0.525 | 0.933 |
| 12 | 12 | 2 | 0.60 | 0.1095 | 0.420 | 0.858 |
| 15 | 12 | 0 | 0.60 | 0.1095 | 0.420 | 0.858 |
| 18 | 9 | 3 | 0.45 | 0.1112 | 0.277 | 0.731 |
| 21 | 9 | 0 | 0.45 | 0.1112 | 0.277 | 0.731 |
| 24 | 8 | 1 | 0.40 | 0.1095 | 0.234 | 0.684 |
| 27 | 7 | 1 | 0.35 | 0.1067 | 0.193 | 0.636 |
| 30 | 5 | 0 | 0.35 | 0.1067 | 0.193 | 0.636 |
| 33 | 1 | 0 | 0.35 | 0.1067 | 0.193 | 0.636 |
| 36 | 1 | 0 | 0.35 | 0.1067 | 0.193 | 0.636 |

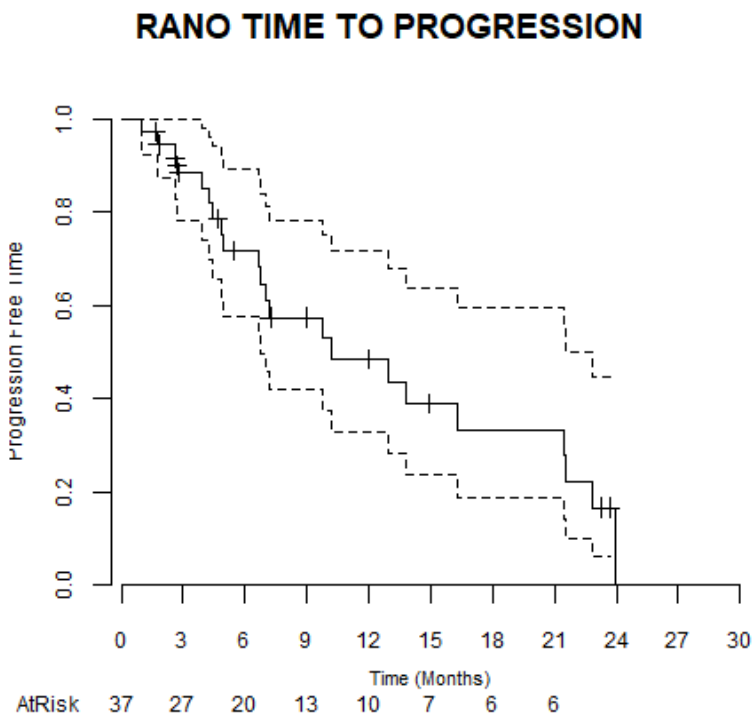
**Time to progression**

*Time to progression by RECIST*



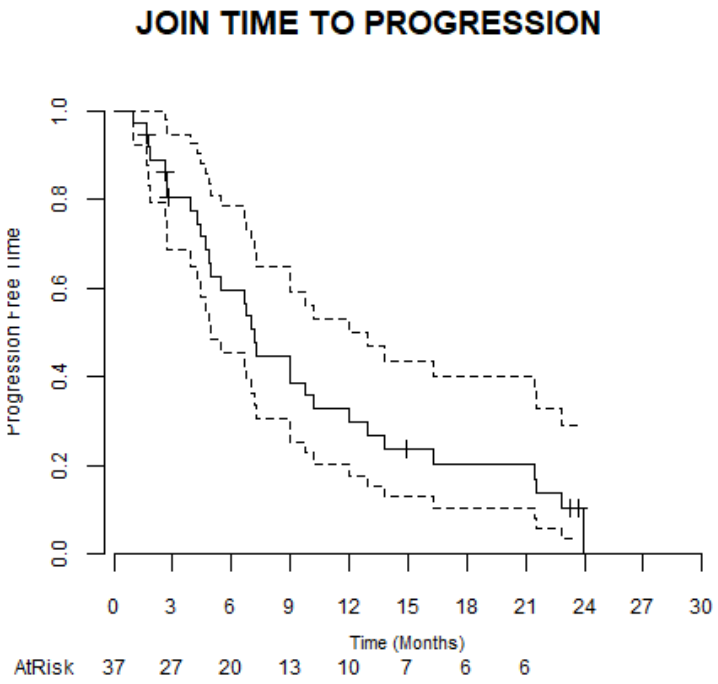

```
3 observations deleted due to missingness

   n  events  median 0.95LCL 0.95UCL
  37      21    8.97    7.20      NA

3 observations deleted due to missingness

 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    0     37       0    1.000  0.0000        1.000        1.000
    3     27       5    0.852  0.0611        0.741        0.981
    6     20       5    0.687  0.0829        0.542        0.870
    9     13       5    0.497  0.0938        0.344        0.720
   12     10       3    0.383  0.0927        0.238        0.615
   15      7       1    0.344  0.0910        0.205        0.578
   18      6       1    0.295  0.0903        0.162        0.538
   21      6       0    0.295  0.0903        0.162        0.538
```

*Time to progression (RANO)*




```
3 observations deleted due to missingness

   n  events  median 0.95LCL 0.95UCL
  37   22      10.18    6.77   21.52


3 observations deleted due to missingness

 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    0     37       0    1.000  0.0000        1.000        1.000
    3     27       4    0.884  0.0545        0.784        0.998
    6     20       5    0.718  0.0805        0.576        0.894
    9     13       4    0.574  0.0909        0.421        0.783
   12     10       2    0.486  0.0960        0.330        0.716
   15      7       2    0.389  0.0984        0.237        0.638
   18      6       1    0.333  0.0988        0.186        0.596
   21      6       0    0.333  0.0988        0.186        0.596
```

*Time to progression (JOIN)*

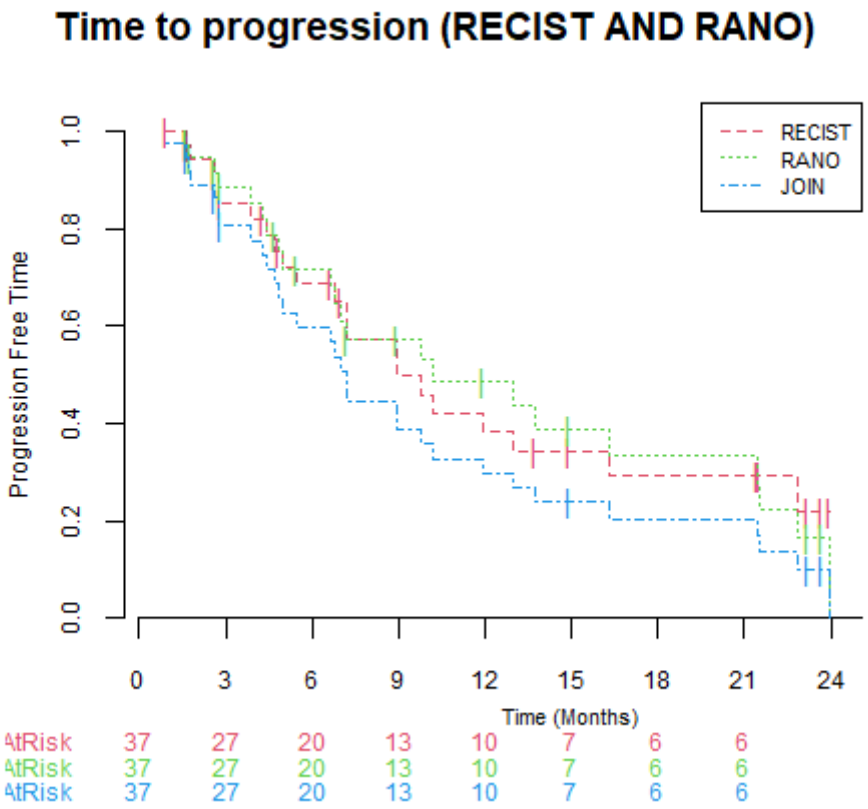



3 observations deleted due to missingness

| n | events | median | 0.95LCL | 0.95UCL |
|---|---|---|---|---|
| 37 | 31 | 7.20 | 4.96 | 12.98 |

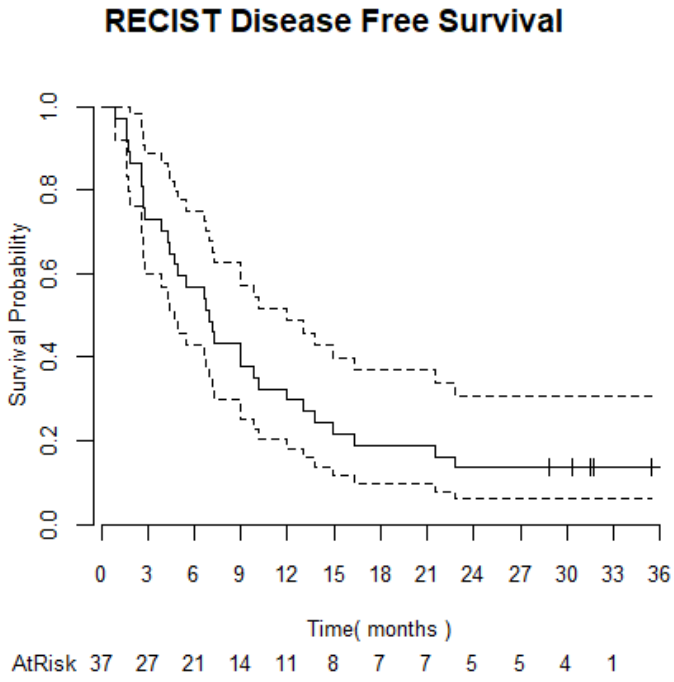
3 observations deleted due to missingness

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 37 | 0 | 1.000 | 0.0000 | 1.000 | 1.000 |
| 3 | 27 | 7 | 0.805 | 0.0662 | 0.685 | 0.946 |
| 6 | 20 | 7 | 0.596 | 0.0838 | 0.453 | 0.785 |
| 9 | 13 | 7 | 0.388 | 0.0837 | 0.254 | 0.592 |
| 12 | 10 | 3 | 0.298 | 0.0787 | 0.178 | 0.500 |
| 15 | 7 | 2 | 0.239 | 0.0734 | 0.130 | 0.436 |
| 18 | 6 | 1 | 0.204 | 0.0704 | 0.104 | 0.401 |
| 21 | 6 | 0 | 0.204 | 0.0704 | 0.104 | 0.401 |


Time to progression (RECIST AND RANO)
RECIST
RANO
JOIN
Progression Free Time
0.0
0.2
0.4
0.6
0.8
1.0
0
3
6
9
12
15
18
21
24
Time (Months)
AtRisk 37 27 20 13 10 7 6 6
AtRisk 37 27 20 13 10 7 6 6
AtRisk 37 27 20 13 10 7 6 6

**Disease free survival**

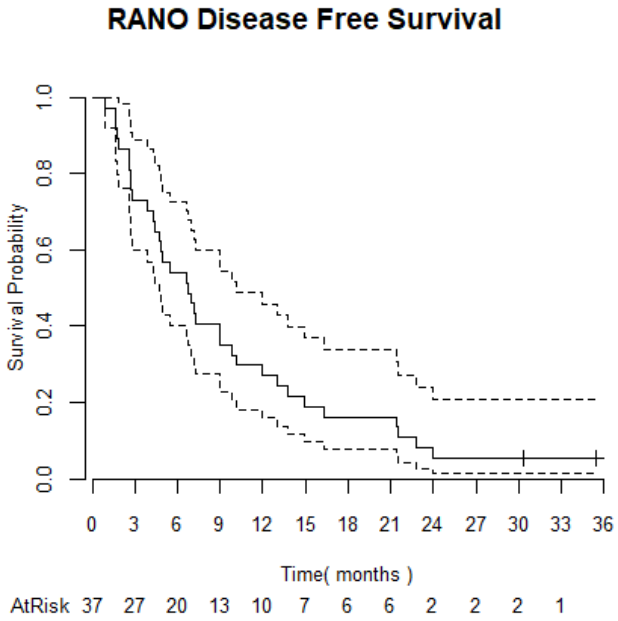
*RECIST Disease free survival*




```
 3 observations deleted due to missingness

 n  events  median 0.95LCL 0.95UCL
37      32    6.97    4.70   11.96
```

```
3 observations deleted due to missingness

 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    0     37       0    1.000  0.0000        1.0000        1.000
    3     27      10    0.730  0.0730        0.5998        0.888
    6     21       6    0.568  0.0814        0.4284        0.752
    9     14       7    0.378  0.0797        0.2504        0.572
   12     11       3    0.297  0.0751        0.1812        0.488
   15      8       3    0.216  0.0677        0.1171        0.399
   18      7       1    0.189  0.0644        0.0971        0.369
   21      7       0    0.189  0.0644        0.0971        0.369
   24      5       2    0.135  0.0562        0.0598        0.305
   27      5       0    0.135  0.0562        0.0598        0.305
   30      4       0    0.135  0.0562        0.0598        0.305
   33      1       0    0.135  0.0562        0.0598        0.305
```

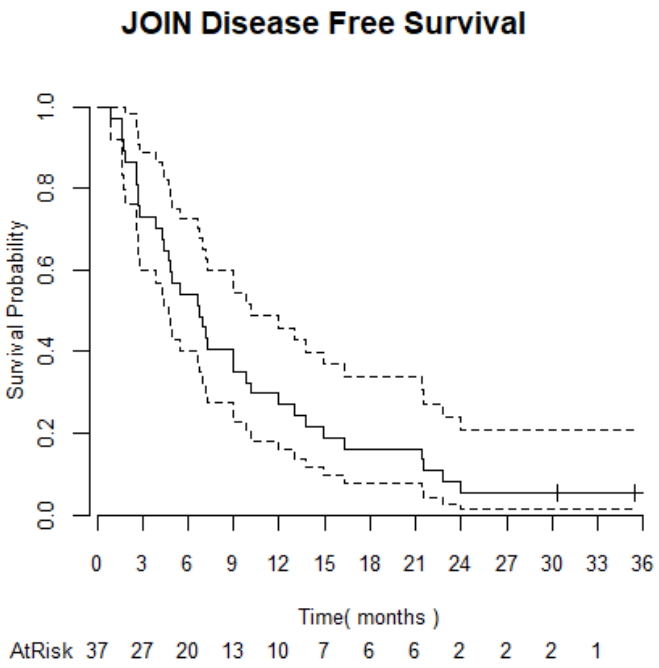
*RANO Disease free survival*



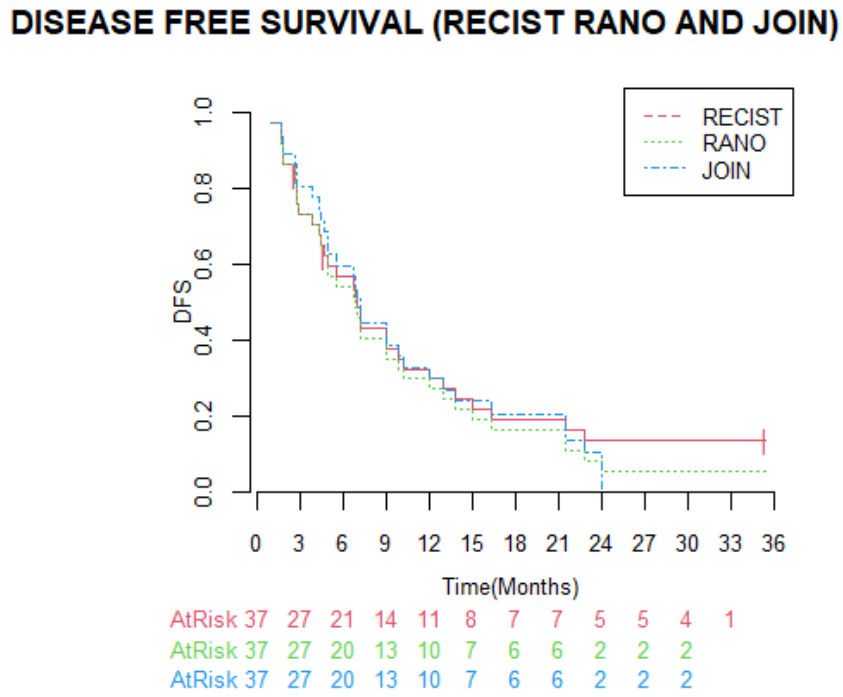

```
3 observations deleted due to missingness

      n  events  median 0.95LCL 0.95UCL
  37.00   35.00    6.77    4.70   10.18
```

```
3 observations deleted due to missingness

 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    0     37       0   1.0000  0.0000       1.0000        1.000
    3     27      10   0.7297  0.0730       0.5998        0.888
    6     20       7   0.5405  0.0819       0.4016        0.728
    9     13       7   0.3514  0.0785       0.2268        0.544
   12     10       3   0.2703  0.0730       0.1592        0.459
   15      7       3   0.1892  0.0644       0.0971        0.369
   18      6       1   0.1622  0.0606       0.0780        0.337
   21      6       0   0.1622  0.0606       0.0780        0.337
   24      2       4   0.0541  0.0372       0.0140        0.208
   27      2       0   0.0541  0.0372       0.0140        0.208
   30      2       0   0.0541  0.0372       0.0140        0.208
```

*JOIN Disease free survival*

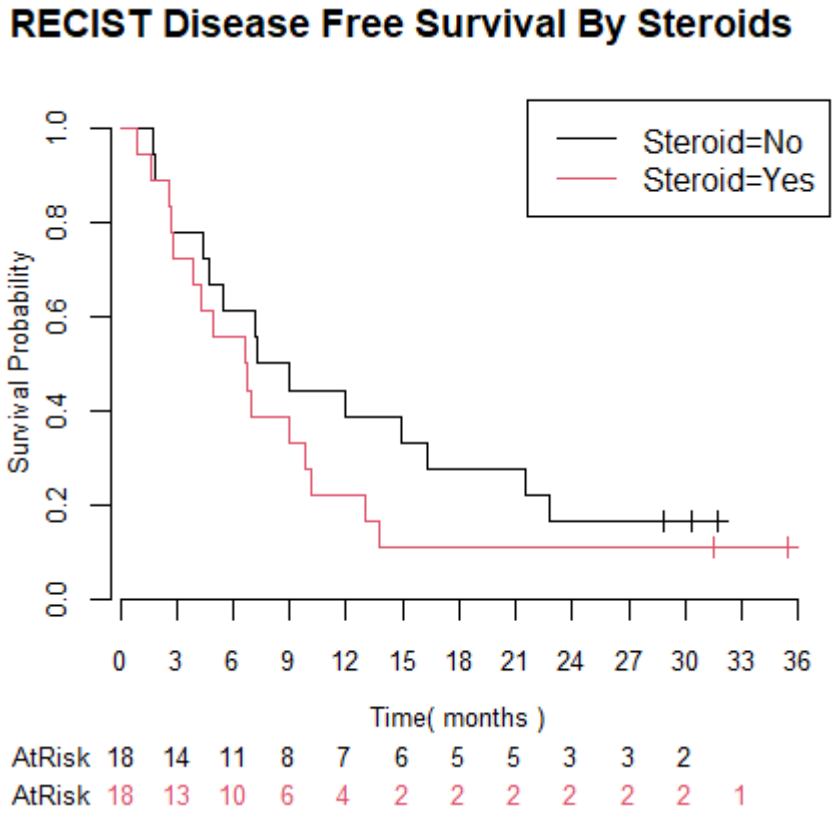



```
   3 observations deleted due to missingness

      n  events  median 0.95LCL 0.95UCL

  37.00   35.00    6.77    4.70   10.18

3 observations deleted due to missingness

 time n.risk n.event survival std.err lower 95% CI upper 95% CI

    0     37       0   1.0000  0.0000       1.0000        1.000

    3     27      10   0.7297  0.0730       0.5998        0.888

    6     20       7   0.5405  0.0819       0.4016        0.728

    9     13       7   0.3514  0.0785       0.2268        0.544

   12     10       3   0.2703  0.0730       0.1592        0.459

   15      7       3   0.1892  0.0644       0.0971        0.369

   18      6       1   0.1622  0.0606       0.0780        0.337

   21      6       0   0.1622  0.0606       0.0780        0.337

   24      2       4   0.0541  0.0372       0.0140        0.208

   27      2       0   0.0541  0.0372       0.0140        0.208

   30      2       0   0.0541  0.0372       0.0140        0.208
```




*Disease free survival by Steroids*

*RECIST Disease free survival by Steroids*



4 observations deleted due to missingness

| | N | events | median | 0.95LCL | 0.95UCL |
|---|---|---|---|---|---|
| Steroids = No | 18 | 15 | 8.10 | 4.70 | 22.8 |
| Steroids = Yes | 18 | 16 | 6.72 | 3.88 | 13.0 |

| | N | Observed | Expected | (O-E)^2/E | (O-E)^2/V |
|---|---|---|---|---|---|
| Steroids = No | 18 | 15 | 17.9 | 0.463 | 1.13 |
| Steroids = Yes | 18 | 16 | 13.1 | 0.630 | 1.13 |

Chisq= 1.1 on 1 degrees of freedom, p= 0.3

4 observations deleted due to missingness

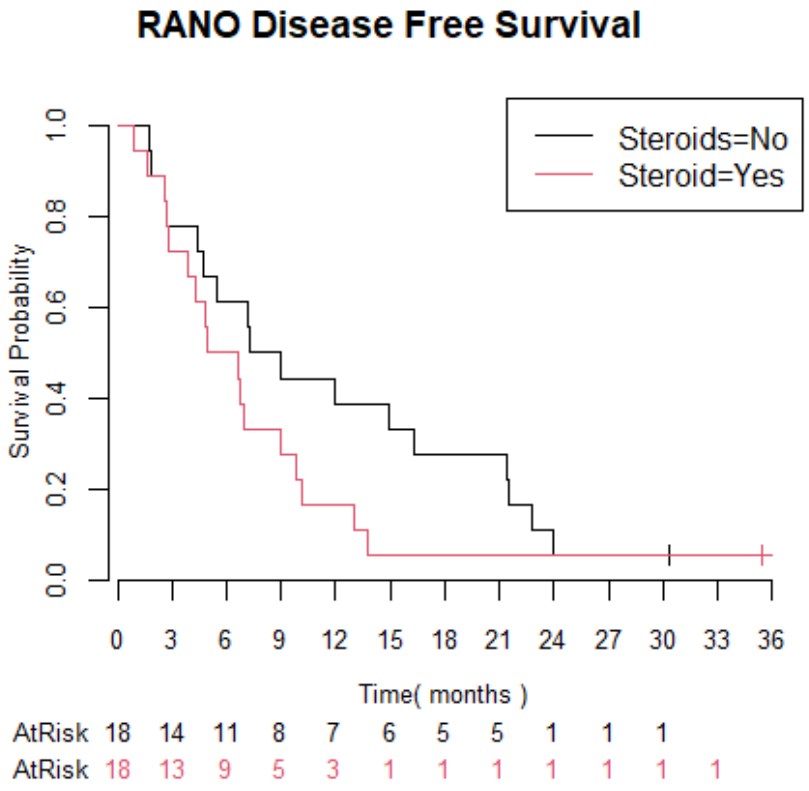
Steroids = No

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 18 | 0 | 1.000 | 0.0000 | 1.0000 | 1.000 |
| 3 | 14 | 4 | 0.778 | 0.0980 | 0.6076 | 0.996 |
| 6 | 11 | 3 | 0.611 | 0.1149 | 0.4227 | 0.883 |
| 9 | 8 | 3 | 0.444 | 0.1171 | 0.2652 | 0.745 |
| 12 | 7 | 1 | 0.389 | 0.1149 | 0.2179 | 0.694 |
| 15 | 6 | 1 | 0.333 | 0.1111 | 0.1734 | 0.641 |
| 18 | 5 | 1 | 0.278 | 0.1056 | 0.1319 | 0.585 |
| 21 | 5 | 0 | 0.278 | 0.1056 | 0.1319 | 0.585 |
| 24 | 3 | 2 | 0.167 | 0.0878 | 0.0593 | 0.468 |

Steroids = Yes

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 18 | 0 | 1.000 | 0.0000 | 1.0000 | 1.000 |
| 3 | 13 | 5 | 0.722 | 0.1056 | 0.5423 | 0.962 |
| 6 | 10 | 3 | 0.556 | 0.1171 | 0.3675 | 0.840 |
| 9 | 6 | 4 | 0.333 | 0.1111 | 0.1734 | 0.641 |
| 12 | 4 | 2 | 0.222 | 0.0980 | 0.0936 | 0.527 |
| 15 | 2 | 2 | 0.111 | 0.0741 | 0.0301 | 0.410 |
| 18 | 2 | 0 | 0.111 | 0.0741 | 0.0301 | 0.410 |
| 21 | 2 | 0 | 0.111 | 0.0741 | 0.0301 | 0.410 |
| 24 | 2 | 0 | 0.111 | 0.0741 | 0.0301 | 0.410 |

*RANO Disease free survival by Steroids*



4 observations deleted due to missingness

| | n | events | median | 0.95LCL | 0.95UCL |
|---|---|---|---|---|---|
| Steroids = No | 18 | 17 | 8.10 | 4.70 | 21.5 |
| Steroids = Yes | 18 | 17 | 5.82 | 3.88 | 10.2 |

n=36, 4 observations deleted due to missingness.

| | N | Observed | Expected | (O-E)^2/E | (O-E)^2/V |
|---|---|---|---|---|---|
| Steroids = No | 18 | 17 | 20.9 | 0.712 | 1.96 |
| Steroids = Yes | 18 | 17 | 13.1 | 1.130 | 1.96 |

Chisq= 2 on 1 degrees of freedom, p= 0.2

4 observations deleted due to missingness

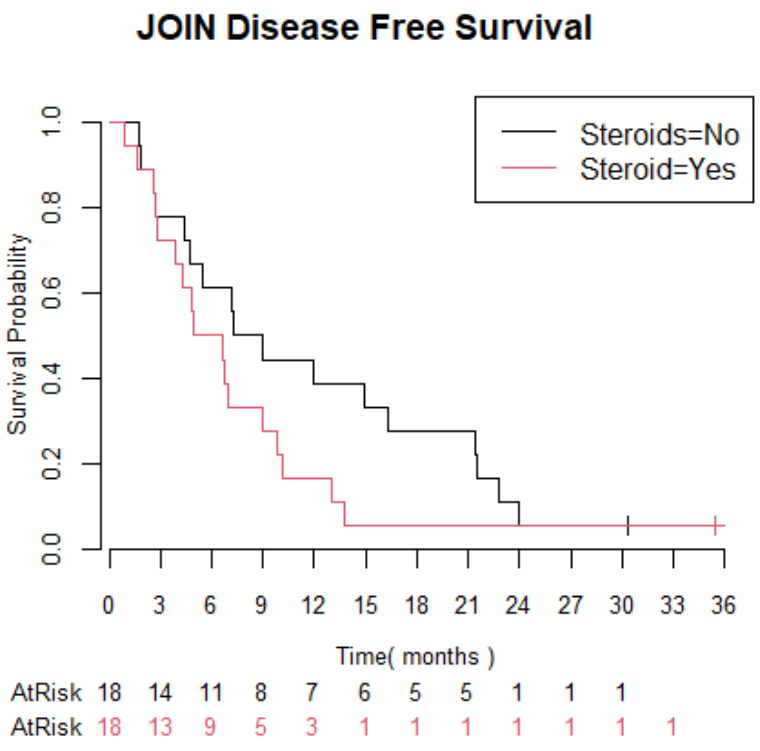
Steroids = No

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 18 | 0 | 1.0000 | 0.000 | 1.00000 | 1.000 |
| 3 | 14 | 4 | 0.7778 | 0.098 | 0.60760 | 0.996 |
| 6 | 11 | 3 | 0.6111 | 0.115 | 0.42274 | 0.883 |
| 9 | 8 | 3 | 0.4444 | 0.117 | 0.26516 | 0.745 |
| 12 | 7 | 1 | 0.3889 | 0.115 | 0.21793 | 0.694 |
| 15 | 6 | 1 | 0.3333 | 0.111 | 0.17344 | 0.641 |
| 18 | 5 | 1 | 0.2778 | 0.106 | 0.13188 | 0.585 |
| 21 | 5 | 0 | 0.2778 | 0.106 | 0.13188 | 0.585 |
| 24 | 1 | 4 | 0.0556 | 0.054 | 0.00827 | 0.373 |
| 27 | 1 | 0 | 0.0556 | 0.054 | 0.00827 | 0.373 |
| 30 | 1 | 0 | 0.0556 | 0.054 | 0.00827 | 0.373 |

Steroids = Yes

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 18 | 0 | 1.0000 | 0.0000 | 1.00000 | 1.000 |
| 3 | 13 | 5 | 0.7222 | 0.1056 | 0.54231 | 0.962 |
| 6 | 9 | 4 | 0.5000 | 0.1179 | 0.31502 | 0.794 |
| 9 | 5 | 4 | 0.2778 | 0.1056 | 0.13188 | 0.585 |
| 12 | 3 | 2 | 0.1667 | 0.0878 | 0.05932 | 0.468 |
| 15 | 1 | 2 | 0.0556 | 0.0540 | 0.00827 | 0.373 |
| 18 | 1 | 0 | 0.0556 | 0.0540 | 0.00827 | 0.373 |
| 21 | 1 | 0 | 0.0556 | 0.0540 | 0.00827 | 0.373 |
| 24 | 1 | 0 | 0.0556 | 0.0540 | 0.00827 | 0.373 |
| 27 | 1 | 0 | 0.0556 | 0.0540 | 0.00827 | 0.373 |
| 30 | 1 | 0 | 0.0556 | 0.0540 | 0.00827 | 0.373 |

*JOIN Disease free survival by Steroids*



4 observations deleted due to missingness

| | n | events | median | 0.95LCL | 0.95UCL |
|---|---|---|---|---|---|
| Steroids = No | 18 | 17 | 8.10 | 4.70 | 21.5 |
| Steroids = Yes | 18 | 17 | 5.82 | 3.88 | 10.2 |

n=36, 4 observations deleted due to missingness.

| | N | Observed | Expected | (O-E)^2/E | (O-E)^2/V |
|---|---|---|---|---|---|
| Steroids = No | 18 | 17 | 20.9 | 0.712 | 1.96 |
| Steroids = Yes | 18 | 17 | 13.1 | 1.130 | 1.96 |

Chisq= 2 on 1 degrees of freedom, p= 0.2

4 observations deleted due to missingness

Steroids = No

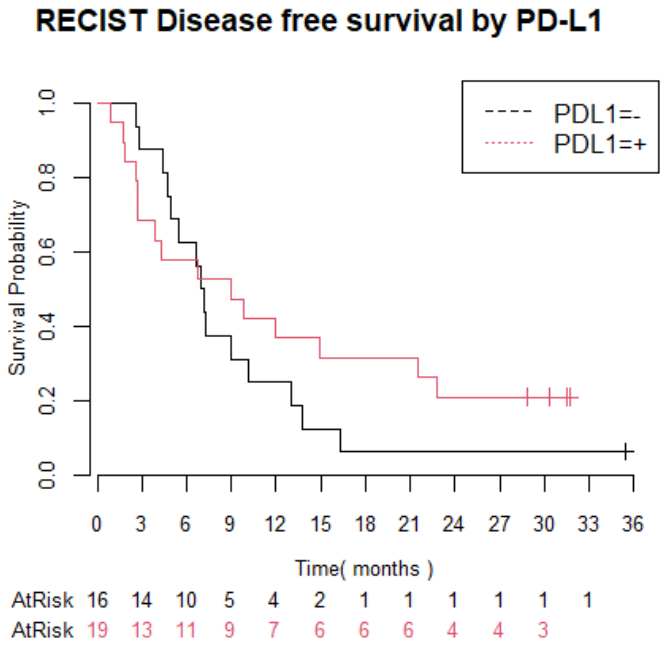
| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 18 | 0 | 1.0000 | 0.000 | 1.00000 | 1.000 |
| 3 | 14 | 4 | 0.7778 | 0.098 | 0.60760 | 0.996 |
| 6 | 11 | 3 | 0.6111 | 0.115 | 0.42274 | 0.883 |
| 9 | 8 | 3 | 0.4444 | 0.117 | 0.26516 | 0.745 |
| 12 | 7 | 1 | 0.3889 | 0.115 | 0.21793 | 0.694 |
| 15 | 6 | 1 | 0.3333 | 0.111 | 0.17344 | 0.641 |
| 18 | 5 | 1 | 0.2778 | 0.106 | 0.13188 | 0.585 |
| 21 | 5 | 0 | 0.2778 | 0.106 | 0.13188 | 0.585 |
| 24 | 1 | 4 | 0.0556 | 0.054 | 0.00827 | 0.373 |
| 27 | 1 | 0 | 0.0556 | 0.054 | 0.00827 | 0.373 |
| 30 | 1 | 0 | 0.0556 | 0.054 | 0.00827 | 0.373 |

Steroids = Yes

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 18 | 0 | 1.0000 | 0.0000 | 1.00000 | 1.000 |
| 3 | 13 | 5 | 0.7222 | 0.1056 | 0.54231 | 0.962 |
| 6 | 9 | 4 | 0.5000 | 0.1179 | 0.31502 | 0.794 |
| 9 | 5 | 4 | 0.2778 | 0.1056 | 0.13188 | 0.585 |
| 12 | 3 | 2 | 0.1667 | 0.0878 | 0.05932 | 0.468 |
| 15 | 1 | 2 | 0.0556 | 0.0540 | 0.00827 | 0.373 |
| 18 | 1 | 0 | 0.0556 | 0.0540 | 0.00827 | 0.373 |
| 21 | 1 | 0 | 0.0556 | 0.0540 | 0.00827 | 0.373 |
| 24 | 1 | 0 | 0.0556 | 0.0540 | 0.00827 | 0.373 |
| 27 | 1 | 0 | 0.0556 | 0.0540 | 0.00827 | 0.373 |
| 30 | 1 | 0 | 0.0556 | 0.0540 | 0.00827 | 0.373 |

*Disease free survival by PD-L1*

RECIST Disease free survival by PD-L1



5 observations deleted due to missingness

| | n | events | median | 0.95LCL | 0.95UCL |
|---|---|---|---|---|---|
| PDL1P = - | 16 | 15 | 7.08 | 4.96 | 13.8 |
| PDL1P = + | 19 | 15 | 8.97 | 3.88 | NA |

n=35, 5 observations deleted due to missingness.

| | N | Observed | Expected | (O-E)^2/E | (O-E)^2/V |
|---|---|---|---|---|---|
| PDL1P = - | 16 | 15 | 12.7 | 0.428 | 0.786 |
| PDL1P = + | 19 | 15 | 17.3 | 0.313 | 0.786 |

Chisq= 0.8 on 1 degrees of freedom, p= 0.4

5 observations deleted due to missingness

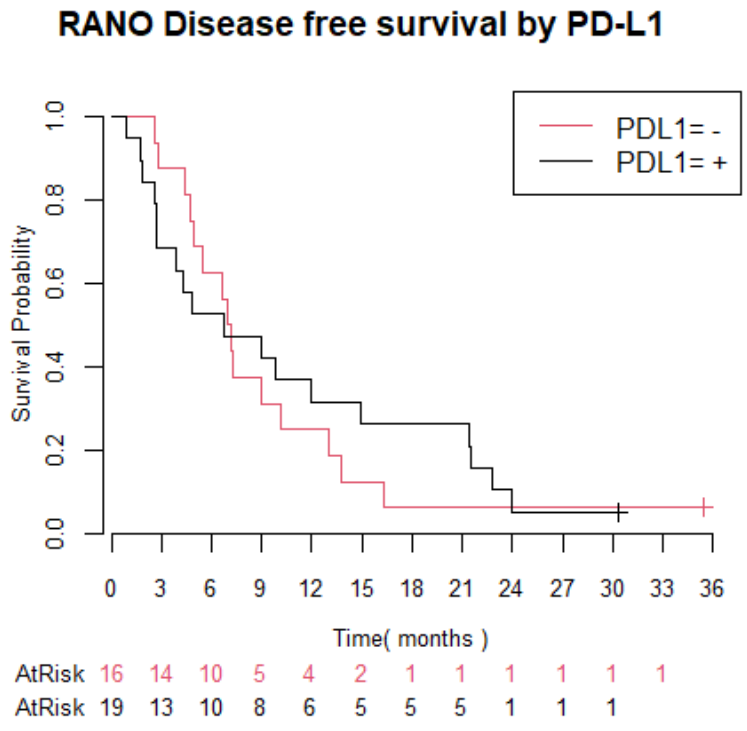
PDL1P=-

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 16 | 0 | 1.0000 | 0.0000 | 1.00000 | 1.000 |
| 3 | 14 | 2 | 0.8750 | 0.0827 | 0.72707 | 1.000 |
| 6 | 10 | 4 | 0.6250 | 0.1210 | 0.42761 | 0.914 |
| 9 | 5 | 5 | 0.3125 | 0.1159 | 0.15108 | 0.646 |
| 12 | 4 | 1 | 0.2500 | 0.1083 | 0.10699 | 0.584 |
| 15 | 2 | 2 | 0.1250 | 0.0827 | 0.03419 | 0.457 |
| 18 | 1 | 1 | 0.0625 | 0.0605 | 0.00937 | 0.417 |
| 21 | 1 | 0 | 0.0625 | 0.0605 | 0.00937 | 0.417 |
| 24 | 1 | 0 | 0.0625 | 0.0605 | 0.00937 | 0.417 |
| 27 | 1 | 0 | 0.0625 | 0.0605 | 0.00937 | 0.417 |
| 30 | 1 | 0 | 0.0625 | 0.0605 | 0.00937 | 0.417 |

PDL1P = +

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 19 | 0 | 1.000 | 0.0000 | 1.0000 | 1.000 |
| 3 | 13 | 6 | 0.684 | 0.1066 | 0.5041 | 0.929 |
| 6 | 11 | 2 | 0.579 | 0.1133 | 0.3946 | 0.850 |
| 9 | 9 | 2 | 0.474 | 0.1145 | 0.2949 | 0.761 |
| 12 | 7 | 2 | 0.368 | 0.1107 | 0.2045 | 0.664 |
| 15 | 6 | 1 | 0.316 | 0.1066 | 0.1629 | 0.612 |
| 18 | 6 | 0 | 0.316 | 0.1066 | 0.1629 | 0.612 |
| 21 | 6 | 0 | 0.316 | 0.1066 | 0.1629 | 0.612 |
| 24 | 4 | 2 | 0.211 | 0.0935 | 0.0881 | 0.503 |
| 27 | 4 | 0 | 0.211 | 0.0935 | 0.0881 | 0.503 |
| 30 | 3 | 0 | 0.211 | 0.0935 | 0.0881 | 0.503 |

RANO Disease free survival by PD-L1



5 observations deleted due to missingness

| | n | events | median | 0.95LCL | 0.95UCL |
|---|---|---|---|---|---|
| PDL1P = - | 16 | 15 | 7.08 | 4.96 | 13.8 |
| PDL1P = + | 19 | 18 | 6.77 | 3.88 | 21.5 |

n=35, 5 observations deleted due to missingness.

LOG RANK TEST

| | N | Observed | Expected | (O-E)^2/E | (O-E)^2/V |
|---|---|---|---|---|---|
| PDL1P = - | 16 | 15 | 14.3 | 0.0363 | 0.0675 |
| PDL1P = + | 19 | 18 | 18.7 | 0.0277 | 0.0675 |

Chisq= 0.1 on 1 degrees of freedom, p= 0.8

5 observations deleted due to missingness

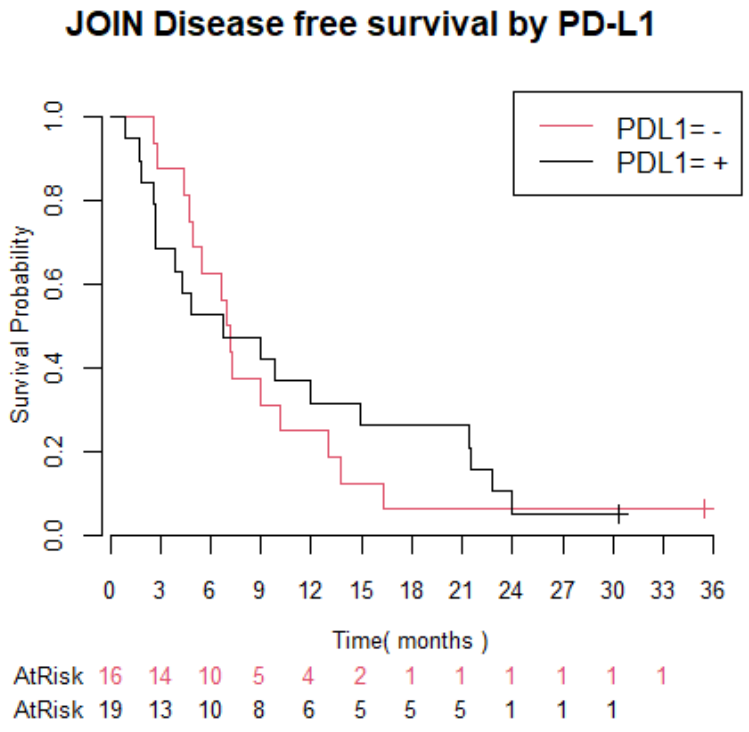
PDL1P = -

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 16 | 0 | 1.0000 | 0.0000 | 1.00000 | 1.000 |
| 3 | 14 | 2 | 0.8750 | 0.0827 | 0.72707 | 1.000 |
| 6 | 10 | 4 | 0.6250 | 0.1210 | 0.42761 | 0.914 |
| 9 | 5 | 5 | 0.3125 | 0.1159 | 0.15108 | 0.646 |
| 12 | 4 | 1 | 0.2500 | 0.1083 | 0.10699 | 0.584 |
| 15 | 2 | 2 | 0.1250 | 0.0827 | 0.03419 | 0.457 |
| 18 | 1 | 1 | 0.0625 | 0.0605 | 0.00937 | 0.417 |
| 21 | 1 | 0 | 0.0625 | 0.0605 | 0.00937 | 0.417 |
| 24 | 1 | 0 | 0.0625 | 0.0605 | 0.00937 | 0.417 |

PDL1P = +

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 19 | 0 | 1.0000 | 0.0000 | 1.00000 | 1.000 |
| 3 | 13 | 6 | 0.6842 | 0.1066 | 0.50411 | 0.929 |
| 6 | 10 | 3 | 0.5263 | 0.1145 | 0.34355 | 0.806 |
| 9 | 8 | 2 | 0.4211 | 0.1133 | 0.24851 | 0.713 |
| 12 | 6 | 2 | 0.3158 | 0.1066 | 0.16291 | 0.612 |
| 15 | 5 | 1 | 0.2632 | 0.1010 | 0.12401 | 0.558 |
| 18 | 5 | 0 | 0.2632 | 0.1010 | 0.12401 | 0.558 |
| 21 | 5 | 0 | 0.2632 | 0.1010 | 0.12401 | 0.558 |
| 24 | 1 | 4 | 0.0526 | 0.0512 | 0.00781 | 0.355 |

JOIN Disease free survival by PD-L1



| | n | events | median | 0.95LCL | 0.95UCL |
|---|---|---|---|---|---|
| PDL1P = - | 16 | 15 | 7.08 | 4.96 | 13.8 |
| PDL1P = + | 19 | 18 | 6.77 | 3.88 | 21.5 |

LOG RANK TEST

n=35, 5 observations deleted due to missingness.

| | N | Observed | Expected | (O-E)^2/E | (O-E)^2/V |
|---|---|---|---|---|---|
| PDL1P = - | 16 | 15 | 14.3 | 0.0363 | 0.0675 |
| PDL1P = + | 19 | 18 | 18.7 | 0.0277 | 0.0675 |

Chisq= 0.1 on 1 degrees of freedom, p= 0.8

5 observations deleted due to missingness

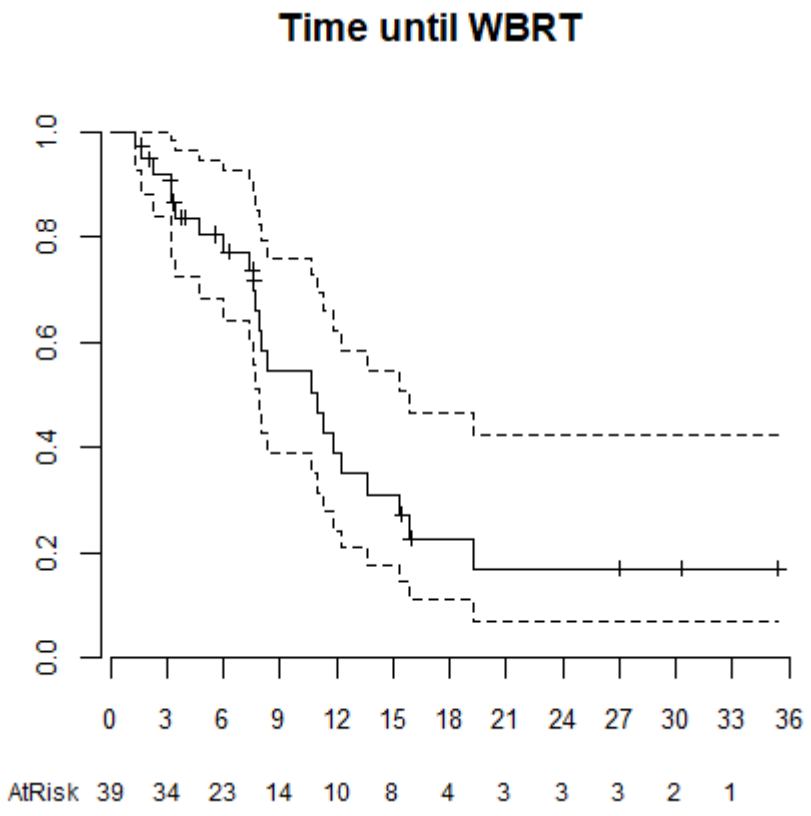
PDL1P = -

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 16 | 0 | 1.0000 | 0.0000 | 1.00000 | 1.000 |
| 3 | 14 | 2 | 0.8750 | 0.0827 | 0.72707 | 1.000 |
| 6 | 10 | 4 | 0.6250 | 0.1210 | 0.42761 | 0.914 |
| 9 | 5 | 5 | 0.3125 | 0.1159 | 0.15108 | 0.646 |
| 12 | 4 | 1 | 0.2500 | 0.1083 | 0.10699 | 0.584 |
| 15 | 2 | 2 | 0.1250 | 0.0827 | 0.03419 | 0.457 |
| 18 | 1 | 1 | 0.0625 | 0.0605 | 0.00937 | 0.417 |
| 21 | 1 | 0 | 0.0625 | 0.0605 | 0.00937 | 0.417 |
| 24 | 1 | 0 | 0.0625 | 0.0605 | 0.00937 | 0.417 |
| 27 | 1 | 0 | 0.0625 | 0.0605 | 0.00937 | 0.417 |
| 30 | 1 | 0 | 0.0625 | 0.0605 | 0.00937 | 0.417 |
| 33 | 1 | 0 | 0.0625 | 0.0605 | 0.00937 | 0.417 |

PDL1P = +

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 19 | 0 | 1.0000 | 0.0000 | 1.00000 | 1.000 |
| 3 | 13 | 6 | 0.6842 | 0.1066 | 0.50411 | 0.929 |
| 6 | 10 | 3 | 0.5263 | 0.1145 | 0.34355 | 0.806 |
| 9 | 8 | 2 | 0.4211 | 0.1133 | 0.24851 | 0.713 |
| 12 | 6 | 2 | 0.3158 | 0.1066 | 0.16291 | 0.612 |
| 15 | 5 | 1 | 0.2632 | 0.1010 | 0.12401 | 0.558 |
| 18 | 5 | 0 | 0.2632 | 0.1010 | 0.12401 | 0.558 |
| 21 | 5 | 0 | 0.2632 | 0.1010 | 0.12401 | 0.558 |
| 24 | 1 | 4 | 0.0526 | 0.0512 | 0.00781 | 0.355 |
| 27 | 1 | 0 | 0.0526 | 0.0512 | 0.00781 | 0.355 |
| 30 | 1 | 0 | 0.0526 | 0.0512 | 0.00781 | 0.355 |

**Time until radiotherapy**



1 observation deleted due to missingness

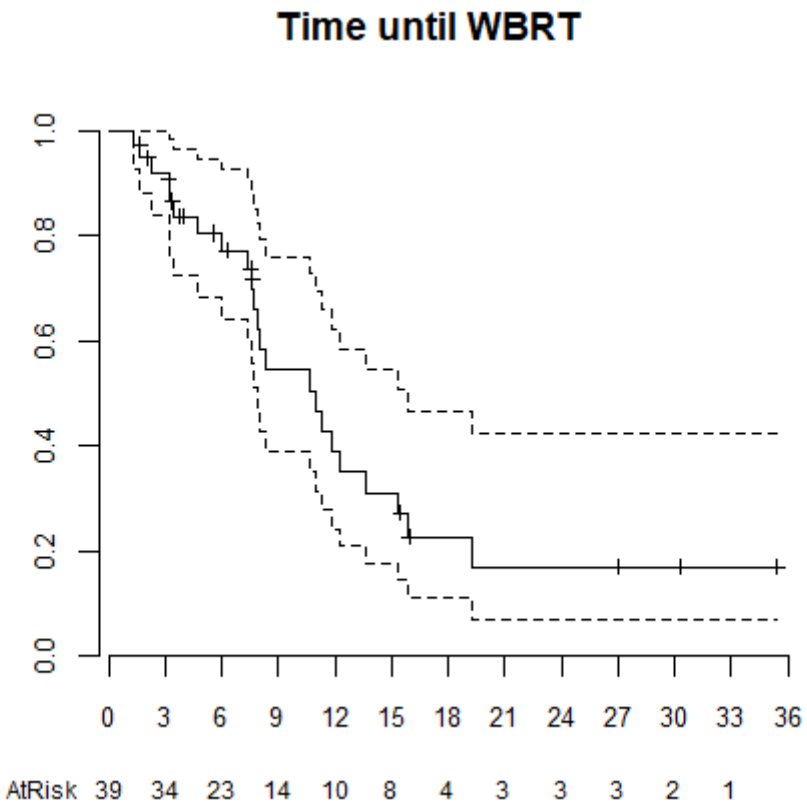
| n | events | median | 0.95LCL | 0.95UCL |
|---|---|---|---|---|
| 39.00 | 23.00 | 10.97 | 7.85 | 15.87 |

1 observation deleted due to missingness

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 39 | 0 | 1.000 | 0.0000 | 1.0000 | 1.000 |
| 3 | 34 | 3 | 0.921 | 0.0438 | 0.8389 | 1.000 |
| 6 | 23 | 5 | 0.771 | 0.0718 | 0.6427 | 0.926 |
| 9 | 14 | 6 | 0.544 | 0.0932 | 0.3889 | 0.761 |
| 12 | 10 | 4 | 0.389 | 0.0935 | 0.2425 | 0.623 |
| 15 | 8 | 2 | 0.311 | 0.0895 | 0.1768 | 0.547 |
| 18 | 4 | 2 | 0.227 | 0.0830 | 0.1106 | 0.465 |
| 21 | 3 | 1 | 0.170 | 0.0793 | 0.0682 | 0.424 |
| 24 | 3 | 0 | 0.170 | 0.0793 | 0.0682 | 0.424 |
| 27 | 3 | 0 | 0.170 | 0.0793 | 0.0682 | 0.424 |
| 30 | 2 | 0 | 0.170 | 0.0793 | 0.0682 | 0.424 |
| 33 | 1 | 0 | 0.170 | 0.0793 | 0.0682 | 0.424 |

OTHER EFFICACY ENDPOINTS

**Time to radiotherapy**




```
  1 observation deleted due to missingness

  n  events  median 0.95LCL 0.95UCL
 39      23   10.97    7.85   15.87
```

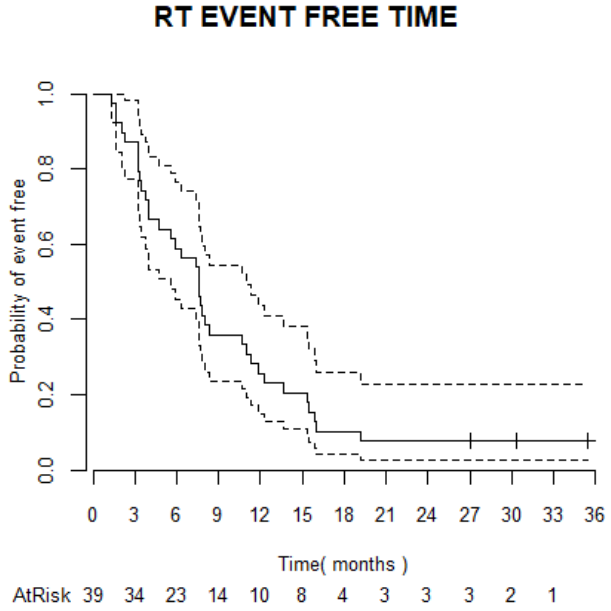
This variable is affected by a competing risk: an exitus due to disease under study is represented as a censored item. A censored time could be also due to good patient's status that still didn't required WBRT at last follow-up time. Therefore this endpoint should be interpreted carefully.

1 observation deleted due to missingness

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 39 | 0 | 1.000 | 0.0000 | 1.0000 | 1.000 |
| 3 | 34 | 3 | 0.921 | 0.0438 | 0.8389 | 1.000 |
| 6 | 23 | 5 | 0.771 | 0.0718 | 0.6427 | 0.926 |
| 9 | 14 | 6 | 0.544 | 0.0932 | 0.3889 | 0.761 |
| 12 | 10 | 4 | 0.389 | 0.0935 | 0.2425 | 0.623 |
| 15 | 8 | 2 | 0.311 | 0.0895 | 0.1768 | 0.547 |
| 18 | 4 | 2 | 0.227 | 0.0830 | 0.1106 | 0.465 |
| 21 | 3 | 1 | 0.170 | 0.0793 | 0.0682 | 0.424 |
| 24 | 3 | 0 | 0.170 | 0.0793 | 0.0682 | 0.424 |
| 27 | 3 | 0 | 0.170 | 0.0793 | 0.0682 | 0.424 |
| 30 | 2 | 0 | 0.170 | 0.0793 | 0.0682 | 0.424 |
| 33 | 1 | 0 | 0.170 | 0.0793 | 0.0682 | 0.424 |

**RT event free time**

This is a post-hoc variable where the event is or to have received posterior rt or exitus (whichever occurs first). Event free is the opposite (not to have received RT and to be alive).



1 observation deleted due to missingness

| n | events | median | 0.95LCL | 0.95UCL |
|---|---|---|---|---|
| 39 | 36 | 7.62 | 5.55 | 10.97 |

1 observation deleted due to missingness

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 39 | 0 | 1.0000 | 0.0000 | 1.0000 | 1.000 |
| 3 | 34 | 5 | 0.8718 | 0.0535 | 0.7729 | 0.983 |
| 6 | 23 | 11 | 0.5897 | 0.0788 | 0.4539 | 0.766 |
| 9 | 14 | 9 | 0.3590 | 0.0768 | 0.2360 | 0.546 |
| 12 | 10 | 4 | 0.2564 | 0.0699 | 0.1503 | 0.438 |
| 15 | 8 | 2 | 0.2051 | 0.0647 | 0.1106 | 0.380 |
| 18 | 4 | 4 | 0.1026 | 0.0486 | 0.0405 | 0.260 |
| 21 | 3 | 1 | 0.0769 | 0.0427 | 0.0259 | 0.228 |
| 24 | 3 | 0 | 0.0769 | 0.0427 | 0.0259 | 0.228 |
| 27 | 3 | 0 | 0.0769 | 0.0427 | 0.0259 | 0.228 |
| 30 | 2 | 0 | 0.0769 | 0.0427 | 0.0259 | 0.228 |
| 33 | 1 | 0 | 0.0769 | 0.0427 | 0.0259 | 0.228 |

**Time until response**

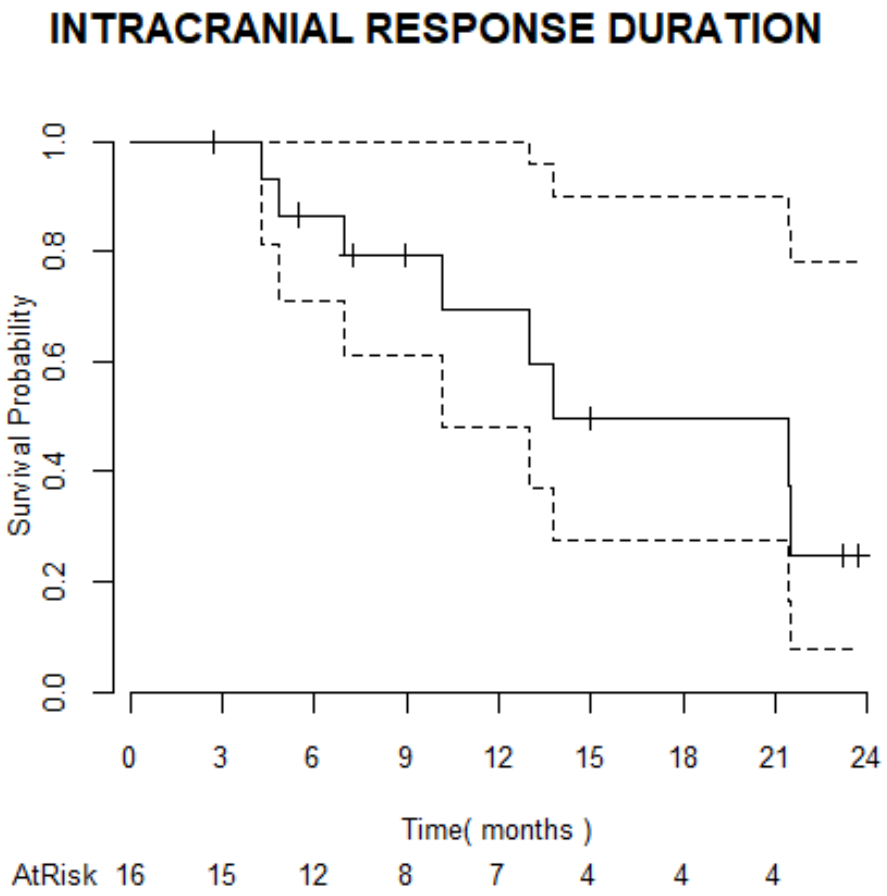
*Time until response by RECIST (by days)*

| n | Min. | 1st Qu. | Median | Mean | 3rd Qu. | Max. |
|---|---|---|---|---|---|---|
| 18 | 29 | 43 | 76 | 89 | 132 | 197 |

*Time until response by RANO (by days)*

| n | Min. | 1st Qu. | Median | Mean | 3rd Qu. | Max. |
|---|---|---|---|---|---|---|
| 17 | 40 | 64 | 82 | 82 | 91 | 162 |

**Intracranial response duration**



1 observation deleted due to missingness

| n | events | median | 0.95LCL | 0.95UCL |
|---|---|---|---|---|
| 16 | 8 | 14 | 10 | NA |

1 observation deleted due to missingness

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 16 | 0 | 1.000 | 0.0000 | 1.000 | 1.000 |
| 3 | 15 | 0 | 1.000 | 0.0000 | 1.000 | 1.000 |
| 6 | 12 | 2 | 0.867 | 0.0878 | 0.711 | 1.000 |
| 9 | 8 | 1 | 0.794 | 0.1061 | 0.612 | 1.000 |
| 12 | 7 | 1 | 0.695 | 0.1313 | 0.480 | 1.000 |
| 15 | 4 | 2 | 0.497 | 0.1513 | 0.273 | 0.902 |
| 18 | 4 | 0 | 0.497 | 0.1513 | 0.273 | 0.902 |
| 21 | 4 | 0 | 0.497 | 0.1513 | 0.273 | 0.902 |

11.4.2 Efficacy Conclusions

Please refer to point 13 of this report.

2. SAFETY EVALUATION

2.1. ADVERSE EVENTS (AES)

12.2.2 Display of Adverse Events

**AE table ordered by frequency (>=10%)**

| | | G1 | | G2 | | G3 | | G4 | | G5 | | Any Grade | | >=G3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| aename | medra | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Fatigue | 10016256 | 12 | 30% | 15 | 38% | 0 | 0% | 0 | 0% | 0 | 0% | 27 | 68% | 0 | 0% |
| Anemia | 10002272 | 5 | 13% | 6 | 15% | 8 | 20% | 0 | 0% | 0 | 0% | 19 | 48% | 8 | 20% |
| Cough | 10011224 | 9 | 23% | 2 | 5% | 0 | 0% | 0 | 0% | 0 | 0% | 11 | 28% | 0 | 0% |
| Dyspnea | 10013963 | 9 | 23% | 1 | 3% | 1 | 3% | 0 | 0% | 0 | 0% | 11 | 28% | 1 | 3% |
| Nausea | 10028813 | 10 | 25% | 1 | 3% | 0 | 0% | 0 | 0% | 0 | 0% | 11 | 28% | 0 | 0% |
| Respiratory, thoracic and mediastinal disorders - Other, specify | 10038738 | 3 | 8% | 2 | 5% | 4 | 10% | 1 | 3% | 0 | 0% | 10 | 25% | 5 | 13% |
| Back pain | 10003988 | 4 | 10% | 1 | 3% | 4 | 10% | 0 | 0% | 0 | 0% | 9 | 23% | 4 | 10% |
| Headache | 10019211 | 8 | 20% | 1 | 3% | 0 | 0% | 0 | 0% | 0 | 0% | 9 | 23% | 0 | 0% |
| Vomiting | 10047700 | 8 | 20% | 1 | 3% | 0 | 0% | 0 | 0% | 0 | 0% | 9 | 23% | 0 | 0% |
| Constipation | 10010774 | 6 | 15% | 2 | 5% | 0 | 0% | 0 | 0% | 0 | 0% | 8 | 20% | 0 | 0% |
| Diarrhea | 10012727 | 4 | 10% | 4 | 10% | 0 | 0% | 0 | 0% | 0 | 0% | 8 | 20% | 0 | 0% |
| Mucositis oral | 10028130 | 6 | 15% | 2 | 5% | 0 | 0% | 0 | 0% | 0 | 0% | 8 | 20% | 0 | 0% |
| Platelet count decreased | 10035528 | 3 | 8% | 1 | 3% | 3 | 8% | 1 | 3% | 0 | 0% | 8 | 20% | 4 | 10% |
| Anorexia | 10002646 | 4 | 10% | 3 | 8% | 0 | 0% | 0 | 0% | 0 | 0% | 7 | 18% | 0 | 0% |
| Skin and subcutaneous tissue disorders - Other, specify | 10040785 | 4 | 10% | 3 | 8% | 0 | 0% | 0 | 0% | 0 | 0% | 7 | 18% | 0 | 0% |
| Alanine aminotransferase increased | 10001551 | 2 | 5% | 3 | 8% | 1 | 3% | 0 | 0% | 0 | 0% | 6 | 15% | 1 | 3% |
| Upper respiratory infection | 10046300 | 1 | 3% | 4 | 10% | 1 | 3% | 0 | 0% | 0 | 0% | 6 | 15% | 1 | 3% |
| Alopecia | 10001760 | 2 | 5% | 3 | 8% | 0 | 0% | 0 | 0% | 0 | 0% | 5 | 13% | 0 | 0% |
| Aspartate aminotransferase increased | 10003481 | 2 | 5% | 3 | 8% | 0 | 0% | 0 | 0% | 0 | 0% | 5 | 13% | 0 | 0% |
| Conjunctivitis | 10010741 | 3 | 8% | 2 | 5% | 0 | 0% | 0 | 0% | 0 | 0% | 5 | 13% | 0 | 0% |
| Dysgeusia | 10013911 | 4 | 10% | 1 | 3% | 0 | 0% | 0 | 0% | 0 | 0% | 5 | 13% | 0 | 0% |
| Gastrointestinal disorders - Other, specify | 10017947 | 5 | 13% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 5 | 13% | 0 | 0% |
| Musculoskeletal and connective tissue disorder - Other, specify | 10028395 | 4 | 10% | 1 | 3% | 0 | 0% | 0 | 0% | 0 | 0% | 5 | 13% | 0 | 0% |
| Nervous system disorders - Other, specify | 10029205 | 3 | 8% | 0 | 0% | 2 | 5% | 0 | 0% | 0 | 0% | 5 | 13% | 2 | 5% |
| Serum amylase increased | 10040139 | 1 | 3% | 3 | 8% | 1 | 3% | 0 | 0% | 0 | 0% | 5 | 13% | 1 | 3% |
| Watering eyes | 10047848 | 5 | 13% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 5 | 13% | 0 | 0% |
| Dizziness | 10013573 | 4 | 10% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 4 | 10% | 0 | 0% |
| Eye disorders - Other, specify | 10015919 | 4 | 10% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 4 | 10% | 0 | 0% |
| General disorders and administration site conditions - Other, specify | 10018065 | 3 | 8% | 1 | 3% | 0 | 0% | 0 | 0% | 0 | 0% | 4 | 10% | 0 | 0% |
| Hyperglycemia | 10020639 | 0 | 0% | 3 | 8% | 1 | 3% | 0 | 0% | 0 | 0% | 4 | 10% | 1 | 3% |
| Investigations - Other, specify | 10022891 | 2 | 5% | 2 | 5% | 0 | 0% | 0 | 0% | 0 | 0% | 4 | 10% | 0 | 0% |
| Metabolism and nutrition disorders - Other, specify | 10027433 | 3 | 8% | 1 | 3% | 0 | 0% | 0 | 0% | 0 | 0% | 4 | 10% | 0 | 0% |
| Neutrophil count decreased | 10029366 | 0 | 0% | 1 | 3% | 2 | 5% | 1 | 3% | 0 | 0% | 4 | 10% | 3 | 8% |
| Urinary tract infection | 10046571 | 0 | 0% | 2 | 5% | 2 | 5% | 0 | 0% | 0 | 0% | 4 | 10% | 2 | 5% |
| Weight loss | 10047900 | 3 | 8% | 1 | 3% | 0 | 0% | 0 | 0% | 0 | 0% | 4 | 10% | 0 | 0% |
| Edema limbs | 10050068 | 4 | 10% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 4 | 10% | 0 | 0% |

## AE table with >=G3 events

| | | G1 | | G2 | | G3 | | G4 | | G5 | | Any Grade | | >=G3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| aename | medra | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Anemia | 10002272 | 5 | 13% | 6 | 15% | 8 | 20% | 0 | 0% | 0 | 0% | 19 | 48% | 8 | 20% |
| Respiratory, thoracic and mediastinal disorders - Other, specify | 10038738 | 3 | 8% | 2 | 5% | 4 | 10% | 1 | 3% | 0 | 0% | 10 | 25% | 5 | 13% |
| Back pain | 10003988 | 4 | 10% | 1 | 3% | 4 | 10% | 0 | 0% | 0 | 0% | 9 | 23% | 4 | 10% |
| Platelet count decreased | 10035528 | 3 | 8% | 1 | 3% | 3 | 8% | 1 | 3% | 0 | 0% | 8 | 20% | 4 | 10% |
| Neutrophil count decreased | 10029366 | 0 | 0% | 1 | 3% | 2 | 5% | 1 | 3% | 0 | 0% | 4 | 10% | 3 | 8% |
| Nervous system disorders - Other, specify | 10029205 | 3 | 8% | 0 | 0% | 2 | 5% | 0 | 0% | 0 | 0% | 5 | 13% | 2 | 5% |
| Urinary tract infection | 10046571 | 0 | 0% | 2 | 5% | 2 | 5% | 0 | 0% | 0 | 0% | 4 | 10% | 2 | 5% |
| Blood and lymphatic system disorders - Other, specify | 10005329 | 1 | 3% | 0 | 0% | 2 | 5% | 0 | 0% | 0 | 0% | 3 | 8% | 2 | 5% |
| Hypomagnesemia | 10021028 | 0 | 0% | 1 | 3% | 2 | 5% | 0 | 0% | 0 | 0% | 3 | 8% | 2 | 5% |
| Seizure | 10039906 | 1 | 3% | 0 | 0% | 2 | 5% | 0 | 0% | 0 | 0% | 3 | 8% | 2 | 5% |
| GGT increased | 10056910 | 1 | 3% | 0 | 0% | 2 | 5% | 0 | 0% | 0 | 0% | 3 | 8% | 2 | 5% |
| Febrile neutropenia | 10016288 | 0 | 0% | 0 | 0% | 1 | 3% | 0 | 0% | 1 | 3% | 2 | 5% | 2 | 5% |
| Dyspnea | 10013963 | 9 | 23% | 1 | 3% | 1 | 3% | 0 | 0% | 0 | 0% | 11 | 28% | 1 | 3% |
| Alanine aminotransferase increased | 10001551 | 2 | 5% | 3 | 8% | 1 | 3% | 0 | 0% | 0 | 0% | 6 | 15% | 1 | 3% |
| Upper respiratory infection | 10046300 | 1 | 3% | 4 | 10% | 1 | 3% | 0 | 0% | 0 | 0% | 6 | 15% | 1 | 3% |
| Serum amylase increased | 10040139 | 1 | 3% | 3 | 8% | 1 | 3% | 0 | 0% | 0 | 0% | 5 | 13% | 1 | 3% |
| Hyperglycemia | 10020639 | 0 | 0% | 3 | 8% | 1 | 3% | 0 | 0% | 0 | 0% | 4 | 10% | 1 | 3% |
| Lipase increased | 10024574 | 0 | 0% | 1 | 3% | 1 | 3% | 0 | 0% | 0 | 0% | 2 | 5% | 1 | 3% |
| Pneumonitis | 10035742 | 1 | 3% | 0 | 0% | 1 | 3% | 0 | 0% | 0 | 0% | 2 | 5% | 1 | 3% |
| Renal and urinary disorders - Other, specify | 10038359 | 0 | 0% | 1 | 3% | 1 | 3% | 0 | 0% | 0 | 0% | 2 | 5% | 1 | 3% |
| Thromboembolic event | 10043565 | 1 | 3% | 0 | 0% | 1 | 3% | 0 | 0% | 0 | 0% | 2 | 5% | 1 | 3% |
| Death NOS | 10011914 | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 1 | 3% | 1 | 3% | 1 | 3% |
| Fracture | 10017076 | 0 | 0% | 0 | 0% | 1 | 3% | 0 | 0% | 0 | 0% | 1 | 3% | 1 | 3% |
| Hallucinations | 10019077 | 0 | 0% | 0 | 0% | 0 | 0% | 1 | 3% | 0 | 0% | 1 | 3% | 1 | 3% |
| Hypertriglyceridemia | 10020870 | 0 | 0% | 0 | 0% | 1 | 3% | 0 | 0% | 0 | 0% | 1 | 3% | 1 | 3% |
| Hyponatremia | 10021038 | 0 | 0% | 0 | 0% | 1 | 3% | 0 | 0% | 0 | 0% | 1 | 3% | 1 | 3% |
| White blood cell decreased | 10049182 | 0 | 0% | 0 | 0% | 1 | 3% | 0 | 0% | 0 | 0% | 1 | 3% | 1 | 3% |
| Acute kidney injury | 10069339 | 0 | 0% | 0 | 0% | 1 | 3% | 0 | 0% | 0 | 0% | 1 | 3% | 1 | 3% |

## Related AE Table with frequency (>= 10 %)

| | | G1 | | G2 | | G3 | | G4 | | G5 | | Any Grade | | >=G3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| aename | medra | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Fatigue | 10016256 | 10 | 25% | 13 | 33% | 0 | 0% | 0 | 0% | 0 | 0% | 23 | 58% | 0 | 0% |
| Anemia | 10002272 | 5 | 13% | 6 | 15% | 8 | 20% | 0 | 0% | 0 | 0% | 19 | 48% | 8 | 20% |
| Nausea | 10028813 | 9 | 23% | 1 | 3% | 0 | 0% | 0 | 0% | 0 | 0% | 10 | 25% | 0 | 0% |
| Mucositis oral | 10028130 | 6 | 15% | 2 | 5% | 0 | 0% | 0 | 0% | 0 | 0% | 8 | 20% | 0 | 0% |
| Platelet count decreased | 10035528 | 3 | 8% | 2 | 5% | 3 | 8% | 0 | 0% | 0 | 0% | 8 | 20% | 3 | 8% |
| Vomiting | 10047700 | 7 | 18% | 1 | 3% | 0 | 0% | 0 | 0% | 0 | 0% | 8 | 20% | 0 | 0% |
| Diarrhea | 10012727 | 3 | 8% | 4 | 10% | 0 | 0% | 0 | 0% | 0 | 0% | 7 | 18% | 0 | 0% |
| Alanine aminotransferase increased | 10001551 | 2 | 5% | 2 | 5% | 1 | 3% | 0 | 0% | 0 | 0% | 5 | 13% | 1 | 3% |
| Anorexia | 10002646 | 5 | 13% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 5 | 13% | 0 | 0% |
| Aspartate aminotransferase increased | 10003481 | 3 | 8% | 2 | 5% | 0 | 0% | 0 | 0% | 0 | 0% | 5 | 13% | 0 | 0% |
| Dysgeusia | 10013911 | 4 | 10% | 1 | 3% | 0 | 0% | 0 | 0% | 0 | 0% | 5 | 13% | 0 | 0% |
| Serum amylase increased | 10040139 | 2 | 5% | 3 | 8% | 0 | 0% | 0 | 0% | 0 | 0% | 5 | 13% | 0 | 0% |
| Skin and subcutaneous tissue disorders - Other, specify | 10040785 | 2 | 5% | 3 | 8% | 0 | 0% | 0 | 0% | 0 | 0% | 5 | 13% | 0 | 0% |
| Lipase increased | 10024574 | 1 | 3% | 2 | 5% | 1 | 3% | 0 | 0% | 0 | 0% | 4 | 10% | 1 | 3% |
| Rash acneiform | 10037847 | 4 | 10% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 4 | 10% | 0 | 0% |

## Related AE Table with >=G3 events

| | | G1 | | G2 | | G3 | | G4 | | G5 | | Any Grade | | >=G3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| aename | medra | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Anemia | 10002272 | 5 | 13% | 6 | 15% | 8 | 20% | 0 | 0% | 0 | 0% | 19 | 48% | 8 | 20% |
| Platelet count decreased | 10035528 | 3 | 8% | 2 | 5% | 3 | 8% | 0 | 0% | 0 | 0% | 8 | 20% | 3 | 8% |
| Blood and lymphatic system disorders - Other, specify | 10005329 | 1 | 3% | 0 | 0% | 2 | 5% | 0 | 0% | 0 | 0% | 3 | 8% | 2 | 5% |
| Hypomagnesemia | 10021028 | 0 | 0% | 1 | 3% | 2 | 5% | 0 | 0% | 0 | 0% | 3 | 8% | 2 | 5% |
| Febrile neutropenia | 10016288 | 0 | 0% | 0 | 0% | 1 | 3% | 0 | 0% | 1 | 3% | 2 | 5% | 2 | 5% |
| Acute kidney injury | 10069339 | 0 | 0% | 0 | 0% | 2 | 5% | 0 | 0% | 0 | 0% | 2 | 5% | 2 | 5% |
| Alanine aminotransferase increased | 10001551 | 2 | 5% | 2 | 5% | 1 | 3% | 0 | 0% | 0 | 0% | 5 | 13% | 1 | 3% |
| Lipase increased | 10024574 | 1 | 3% | 2 | 5% | 1 | 3% | 0 | 0% | 0 | 0% | 4 | 10% | 1 | 3% |
| Neutrophil count decreased | 10029366 | 0 | 0% | 1 | 3% | 1 | 3% | 0 | 0% | 0 | 0% | 2 | 5% | 1 | 3% |
| Pneumonitis | 10035742 | 1 | 3% | 0 | 0% | 1 | 3% | 0 | 0% | 0 | 0% | 2 | 5% | 1 | 3% |
| Respiratory, thoracic and mediastinal disorders - Other, specify | 10038738 | 1 | 3% | 0 | 0% | 1 | 3% | 0 | 0% | 0 | 0% | 2 | 5% | 1 | 3% |
| Renal and urinary disorders - Other, specify | 10038359 | 0 | 0% | 0 | 0% | 1 | 3% | 0 | 0% | 0 | 0% | 1 | 3% | 1 | 3% |
| Thromboembolic event | 10043565 | 0 | 0% | 0 | 0% | 1 | 3% | 0 | 0% | 0 | 0% | 1 | 3% | 1 | 3% |
| Upper respiratory infection | 10046300 | 0 | 0% | 0 | 0% | 1 | 3% | 0 | 0% | 0 | 0% | 1 | 3% | 1 | 3% |
| Vascular disorders - Other, specify | 10047065 | 0 | 0% | 0 | 0% | 1 | 3% | 0 | 0% | 0 | 0% | 1 | 3% | 1 | 3% |
| GGT increased | 10056910 | 0 | 0% | 0 | 0% | 1 | 3% | 0 | 0% | 0 | 0% | 1 | 3% | 1 | 3% |

12.2.3 Analysis of Adverse Events

Please refer to point 12.2.2 of this report.

12.2.4 Listing of Adverse Events by Patient

Please refer to point 12.2.2 of this report.

2.2. DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.3.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events

12.3.1.1 Deaths

Not applicable.

12.3.1.2 Other Serious Adverse Events

Please refer to point 12.2.2 of this report.

2.3. SAFETY CONCLUSIONS

Please refer to point 13 of this report.

3. DISCUSSION AND OVERALL CONCLUSIONS

Lung cancer is the most common solid tumor to metastasize to the central nervous system (CNS) and about one quarter of patients diagnosed with stage IV non-small cell lung cancer (NSCLC) have brain metastases at diagnosis.1 Historically, whole brain radiotherapy (WBRT) had been the cornerstone of treatment for brain metastases in patients with advanced NSCLC, especially when stereotactic radiosurgery (SRS) and surgery were not feasible or indicated. However, the use of WBRT has diminished due to modest survival benefit and its negative impact on cognitive function and quality of life, and due to emerging evidence that SRS may benefit patients with higher disease burden in the brain metastases.2 In addition, the incorporation of highly CNS-penetrant targeted therapies in oncogene-addicted NSCLC modified the clinical management of patients with asymptomatic brain metastases harboring EGFR and ALK positive tumors such that local therapy could be deferred.3

Although most clinical trials excluded or underrepresented patients with NSCLC who have previously untreated brain metastases,4 immunotherapy had showed encouraging intracranial efficacy in patients with oncogene driver-negative PD-L1–positive NSCLC who have untreated brain metastases or progressing after previous radiotherapy.5 Several post-hoc exploratory analyses of phase III clinical trials showed that chemotherapy combined with immunotherapy improved overall survival (OS) compared with chemotherapy alone regardless of the presence of brain metastases.6,7 However, these trials were not specifically designed to evaluate the intracranial efficacy of chemoimmunotherapy and excluded patients receiving corticosteroids.

We designed this phase II clinical trial to evaluate the safety and the efficacy of atezolizumab combined with carboplatin and pemetrexed in patients with advanced non-squamous NSCLC with untreated brain metastases. We present the final analysis in this report.

**Study design and eligibility**

This was an open-label, single-arm, phase II clinical trial conducted at 15 hospitals in Spain. Patients were aged ≥18 years, had Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1, and had stage IV non-squamous NSCLC with untreated brain metastases that did not exhibit neurological symptoms or that were controlled with anticonvulsants or low dose of dexamethasone (≤4mg once daily), with measurable disease in the body by computed tomography (CT) per response evaluation criteria in solid tumors version (RECIST) 1.1 criteria in the body and in the brain by magnetic resonance imaging (MRI) per RANO response assessment criteria for brain metastases (RANO-BM).8 Patients had adequate bone marrow, liver, and renal function.

Exclusion criteria included known EGFR mutations or ALK rearrangements; presence of leptomeningeal carcinomatosis or metastases in the brain stem, medulla or lesions causing obstructive hydrocephalus; oligometastatic disease in the brain amenable for surgical treatment or SRS; contraindication for immunotherapy (history of active autoimmune, infectious disease or interstitial lung disease); previous malignancies within 3 years of study entry; previous treatment with immune checkpoint inhibitors; hepatitis B or C infection or HIV positivity.

The study complied with the Declaration of Helsinki, International Council on Harmonisation Good Clinical Practice, local laws and regulatory requirements. Independent Ethics Committees or Institutional Review Boards approved the protocol. Patients provided written informed consent.

**Study procedures and treatment**

Patients were treated with atezolizumab 1200 mg intravenously every 3 weeks in combination with carboplatin (AUC 5) plus pemetrexed (500 mg per square meter). All the patients received premedication with folic acid, vitamin B12, and dexamethasone according to guidelines for pemetrexed use. After completing 4 to 6 cycles, patients continued with pemetrexed plus atezolizumab maintenance until unacceptable toxicity, disease progression, patient decision, completion of 2 years of therapy or patient withdrawal of consent (Data Supplement).

A body CT scan and a brain MRI were performed at baseline, every 6 weeks until the 12th week and thereafter every 9 weeks until disease progression. Patients with progression exclusively in the brain could receive brain radiotherapy staying within the study if they continued to derive clinical benefit and had ECOG PS ≤ 2. In case of systemic progression without brain progression, a novel line of systemic treatment was considered.

Adverse events and abnormal laboratory findings were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Investigators determined whether adverse events were treatment-related according to the study protocol and standard regulatory requirements. Dose reductions were not permitted for atezolizumab which could be interrupted, delayed, or discontinued depending on tolerability. Reductions were permitted for pemetrexed and carboplatin in accordance with two levels of dosage specified in the trial protocol. PD-L1 tumor proportion score expression was determined at each center following clinical practice.

**Study outcomes**

The two primary endpoints were safety assessed by NCI-CTCAE version 4.0 and progression-free survival (PFS) according to RECIST v1.1 and RANO-BM and criteria. Overall PFS was defined as the time

from diagnosis until death from any cause or objective tumor progression evaluated by the investigators using RANO-BM in the brain and RECIST v1.1 in the body, whichever occurred first.

Secondary endpoints were the intracranial and systemic response rate, the duration of response (time from first documented complete or partial response to disease progression or death) and overall survival (OS). OS was defined as the time from inclusion to death from any cause. Exploratory endpoints were to determine the time to the need for salvage radiation therapy to the brain and to evaluate the correlation between PD-L1 expression in tumor tissue and efficacy endpoints.

**Statistics**

Safety and efficacy were assessed in the intention-to-treat population cohort of 40 patients using the Bayesian Multc Lean design.11,12 Details about prior and posterior distributions are detailed in the protocol. A sample size of 40 patients ensured that, if the trial is not terminated early, a posterior 90% credibility interval (CrI) would have width of 0.257 at most, under the assumption of 50% PFS rate at 12 weeks. Futility and excess of toxicity stopping rules based on posterior probabilities were evaluated sequentially every 5 patients (Data Supplement). Posterior distributions with CrI at 95 % were calculated for response or toxicity rates. Kaplan–Meier method was used to estimate PFS and OS. Data for patients who were alive or lost to follow-up were censored for OS at the time they were last known to be alive. Data for patients who were alive and did not have disease progression or who were lost to follow-up were censored for the analysis of PFS at the time of the last imaging assessment. The stratified log-rank test was used to assess differences in PFS and OS among different subgroups. Hazard ratios and associated 95% confidence intervals (CI) were calculated with the use of a stratified Cox proportional-hazards model.

Data collection and data quality was ensured by the Spanish Lung Cancer Group. All analyses were based on the study database lock on March 31st 2022.

**Results**

*Patients and disease characteristics*

Study enrollment was completed between November 2018 and December 2019. Forty-three patients were registered, but forty patients met eligibility criteria and were enrolled at 13 sites (Fig 1). Baseline patient characteristics are shown in Table 1. The median age was 62.5 years. Twenty-nine (72.5%) patients were male and most had a smoking history (85%). Brain metastases were diagnosed concurrently with lung cancer in most patients (92.5%). PD-L1 expression was positive in 20 patients (50%), negative in 18 patients (45%) and unknown in 2 patients (5%). The median total number of brain metastases per patient was 5, ranging between 1 to 20. Twenty-two (55%) patients received dexamethasone during the week prior to inclusion, regardless of pemetrexed premedication.

*Efficacy*

The study was completed since the boundaries for futility or unacceptable toxicity were not reached at any moment. The overall PFS rate at 12 weeks was 62.2% (95% CrI, 47.1 to 76.2; Data Supplement), above the expected 50%. Seventeen patients (42.7%, 95% CrI, 28.1 to 57.9; Table 2) had a confirmed intracranial response (12 [70.6%] partial responses and 5 [29.4%] complete responses), while additional 17 patients had stable disease in the brain and 5 had progressive disease. The median time to intracranial response was 82 days and the median duration of response in the brain among the 16

evaluable patients with CNS response was 14 months (95% CI, 10 to not reached, Data Supplement). Eighteen patients (45%, 95% CrI, 28.1 to 57.9; Table 2) achieved a systemic response (17 [94%] partial responses and 1 [6%] complete response), while 16 patients achieved stable disease and 4 patients had progressive disease. Most responses were concordant in the brain and in the body, except for 6 (15%) patients (Fig 2). Three patients had systemic progression with stable disease in the brain and 3 patients had intracranial progression with partial response or stable disease in the body. In an exploratory analysis, no significant differences were observed in the intracranial or systemic ORR according to PD-L1 expression (Data Supplement).

With a minimum follow-up of 27 months, the median intracranial PFS was 6.9 months (95% CI, 4.7 to 11.9; Fig 3a) and the median systemic PFS was 8.9 months (95% CI, 6.7 to 13.8; Fig 3b). The median OS was 11.8 months (95% CI, 7.6 to 16.9; Fig 3c). Estimated 1-year and 2-years OS rate were 50% (95% CI, 36.7 to 68.2) and 27.5% (95% CI, 16.6 to 45.5), respectively. No significant differences were observed in OS according to PD-L1 expression and baseline corticosteroids (Data Supplement). Nevertheless, the 2-year OS rate for patients with positive PD-L1 was 40.0% (95% CI, 23.4 to 68.4), while in patients with negative PD-L1 was 16.7% (95% CI, 5.9 to 46.8).

*Treatment at intracranial progression*

During the study, twenty-four patients (60%) received brain radiotherapy due to progressive disease. Sixteen patients received WBRT and 8 patients received SRS. Median time to brain radiotherapy was 10.9 months (95% CI, 7.8 to 15.9; Data Supplement). Thirteen patients died before receiving brain radiotherapy mainly due to systemic progression. Median event-free survival, defined as time from inclusion to brain radiotherapy or death, was 7.6 months (95% CI, 5.5 to 10.9; Data Supplement).

*Toxicity*

The median number of cycles of carboplatin was 4 and of atezolizumab and pemetrexed was 8; 3 patients completed the planned two years of treatment. The rate of Grade 3-4 toxicity during the first 9 weeks was 27.5%, below the predefined boundary of 35%. Most neurological adverse events, regardless of their relationship with treatment, were Grade 1 and 2 (Table 3). Only five patients (12.5%) experienced Grade 3-4 neurological toxicity consisting of Grade 4 hallucinations in 1 patient, Grade 3 seizure in 2 patients and Grade 3 sciatica and spinal cord compression in 1 patient each.

Twenty-eight patients (70%) had Grade 3-4 treatment-related adverse events, but only 7 (17.5%) were deemed serious: acute kidney injury and pneumonitis in 2 patients each, while nephritis, pulmonary embolism and febrile neutropenia was seen in 1 patient each (Data Supplement). One patient experienced Grade 5 toxicity consisting of febrile neutropenia and sepsis, that was considered related with chemotherapy.

**Discussion**

The results of this phase II clinical trial show that patients with advanced NSCLC with untreated brain metastases can benefit from initiating systemic treatment with atezolizumab combined with chemotherapy. Previous exploratory analysis from pivotal phase III clinical trials have demonstrated that patients with brain metastases benefited from the addition of immunotherapy to chemotherapy versus chemotherapy alone. However, these reports were based on subgroup analyses with significant attrition since most studies excluded patients with untreated brain lesions or receiving corticosteroids or were not designed to evaluate the efficacy outcomes in the CNS.

To our knowledge, this is the first study centered on this special population that evaluates the activity and safety of a PD-L1 inhibitor combined with platinum-based chemotherapy in patients with NSCLC with untreated brain metastases who were not amenable for surgery or stereotactic surgery. This phase II trial has a Bayesian sequential design to minimize the risk of harm or futility on this vulnerable population. Forty patients were included, and the study was successfully completed. Some patients had significant disease burden based on the total number of brain metastases and that half of the patients were receiving corticosteroids at baseline. The patients received atezolizumab combined with carboplatin and pemetrexed, which was previously evaluated in the IMpower132 trial in advanced non-squamous NSCLC; however, this study excluded patients with untreated brain metastases and those requiring corticosteroids.13

We assessed efficacy outcomes in the brain using RANO-BM to allow future cross-trial comparisons.8 In our study, chemoimmunotherapy yielded similar ORR in the brain and in the body and responses were highly concordant in both compartments. Chemoimmunotherapy led to a complete intracranial response in 5 patients. Brain pseudoprogression is uncommon but was reported with single immunotherapy in a large NSCLC cohort.14 In our study, we did not observe any case of pseudoprogression. An exploratory analysis did not show significant correlation between intracranial response and PD-L1 expression or corticosteroids treatment at baseline.

In our study, the median intracranial PFS by RANO-BM was 6.9 months, consistent with previous PFS reported in the pooled analysis of Keynote-021G, -189 and -407 trials.6 This exploratory analysis included a subset of patients with untreated brain metastases but did not report the intracranial efficacy and PFS was exclusively measured by RECIST v1.1. In an exploratory analysis of the CheckMate-9LA trial, the combination of two cycles of chemotherapy plus nivolumab and ipilimumab yielded a promising median intracranial PFS of 13.5 months in patients with previously treated and stable brain metastases, without corticosteroids and asymptomatic.7 However, this study population was highly selected and cannot be directly compared with our study, which is enriched with more vulnerable patients. Nevertheless, in our study the 2-year OS was 27.5% in the overall population and 40% in patients with positive expression of PD-L1, similar to that reported in the seminal study of pembrolizumab which focused on patients with PD-L1 positive NSCLC with untreated brain metastases.5 Taking into consideration the limited statistical power of our study, we did not observe significant differences in the OS based on corticosteroids treatment at baseline.

Most patients who progressed in the brain were deemed candidates for salvage brain radiotherapy consisting mostly of WBRT, but also several patients were rescued with SRS. The median time to brain radiotherapy was 10.9 months. In our study, systemic therapy allowed to defer WBRT which may have negative impact on quality of life and cognitive function.15 However, initiating systemic therapy and deferring brain local therapy in patients with lung cancer should be always discussed within a multidisciplinary tumor board with the presence of radiation oncologists and neurosurgeons.3

Most neurological adverse events were mild or moderate, except 4 patients who had Grade 3 and 1 with Grade 4 neurological toxicity that fully recovered. Serious treatment-related adverse events were observed only in 17.5% and there was only 1 patient with Grade 5 toxicity related to chemotherapy. This safety profile is consistent with the previously published data using this treatment combination.13

Our study has several limitations including the reduced sample size which limits the statistical power to conduct subgroup analyses. Another important limitation is the lack of a control arm to evaluate

the most appropriate treatment strategy in patients with NSCLC and brain metastases. Several trials are currently evaluating how to integrate brain radiation with immunotherapy or chemoimmunotherapy.

In summary, atezolizumab combined with carboplatin and pemetrexed has activity in patients with untreated brain metastases from treatment naïve advanced non-squamous NSCLC. Systemic and intracranial efficacy was similar, thus highlighting that atezolizumab plus chemotherapy can extend survival in this highly vulnerable population of patients. Future studies targeting additional immune checkpoints or integrating systemic therapies with stereotactic radiotherapy to improve the control rate and minimize the risk of brain toxicity are warranted.

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