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DURVAST STUDY

"A phase II exploratory study of durvalumab (MEDI4736) in HIV-1 patients with advanced solid tumors" (GECP 16/04- ESR 15-10869)

CLINICAL STUDY REPORT: FINAL REPORT

Sponsor: Fundación GECP

Trial Coordinator in Spain (SLCG): Dr. Gónzalez Cao

1. TITLE PAGE

TITLE: "A phase II exploratory study of durvalumab (MEDI4736) in HIV-1 patients with advanced solid tumors"

2. SYNOPSIS

PD-1/ PD-L1 coinhibitory pathway plays a significant role in the regulation of the immune response in both chronic infectious diseases and cancer.

Preclinical and animal data support the safety and promising activity of anti-PD-1 antibody in HIV-1 infection.

Demonstrated anticancer activity and safety profile of durvalumab (MEDI4736) in cancer clinical trials.

Unlikely drug interactions of durvalumab (MEDI4736) and antiretroviral treatments.

We propose a phase II clinical study designed to assess the feasibility of durvalumab (MEDI4736) in HIV-1-infected individuals with solid tumors. Additionally, we hope to obtain data that let us understand the possible benefit of this treatment in cancer patients and HIV infection, exploring if activity of durvalumab (MEDI4736) could be higher in cancer that has been produced at least in part due to the chronic immunosuppression. Simultaneously, it will allow us to investigate the effect of disrupting this immunoregulatory pathway might have in reversing cancer pathways and HIV-specific T-cell function during persistent chronic HIV infection in humans.

In this regard, our hypothesis is:

HIV patients with cancer have a similar outcome in terms of tolerability when treated with durvalumab (MEDI4736) monotherapy at the recommended dose than non-HIV infected patients

This is a multicenter, national, nonrandomized, open label trial, phase II trial in subjects with advanced solid tumors and HIV-1 infection. Twenty patients will receive durvalumab.

Patients have to be diagnosed of advanced (metastatic or locally advanced disease without cure options with surgery or radiotherapy) cancer of any of these types: lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastro-esophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, Cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity.

Adverse events (AEs) will be assessed throughout and evaluated using National Cancer Institute (NCI) Common Technology Criteria version of Adverse Events version 4.03 (CTCAE v 4.03).

Tumor measurements by PET-CT, CT scan or MRI will be performed every 8 weeks to determine response to treatment. Response will be evaluated using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and immune related response criteria (irRECIST).

Treatment will continue until disease progression, significant clinical deterioration, unacceptable toxicity, any criterion for withdrawal from the trial or trial drug is fulfilled. Treatment may continue past the initial determination of disease progression per RECIST1.1 if the subject`s performance status has remained stable, and if the opinion of the Investigator, the subject will benefit from continued treatment and if other criteria are fulfilled as outline in the protocol.

2.1. 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.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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This study is managed from the Sponsor headquarters, Fundación GECP (Av. Meridiana 358, 6th Floor, 08027, Barcelona)

4. INTRODUCTION

DISEASE BACKGROUND

After more than three decades fighting the Human Immunodeficiency Virus type 1 (HIV-1) – the etiologic agent of the acquired immunodeficiency syndrome (AIDS) – this lentivirus has spread worldwide, causing a pandemic that seriously challenges public health. In 2012, 35 million people were living with HIV-1, 1.6 million people had died from AIDS and 2.3 million people got newly infected (AIDS epidemic update 2013; http://www.unaids.org). Major advances in Antiretroviral Therapy (ART) have resulted in a dramatic decline in HIV-related deaths. However, no current treatment regimen leads to viral eradication or restoration of HIV-specific immune responses capable of durable viral control after cessation of ART. Thus, there is a need for novel interventions that could complement ART in order to eliminate virus or reach a state of "functional cure"(1, 2). It has been shown in murine models and humans that the negative co-signaling molecule programmed-death 1 (PD-1) plays an active and reversible role in mediating T-cell exhaustion in chronic infections (3). Therefore, there is a potential of immunotherapeutic interventions targeting PD-1 in order to augment immune responses or facilitate viral eradication.

Malignancies account for more than a third of all deaths in human immunodeficiency virus (HIV)-positive patients. Although acquired immunodeficiency syndrome-related mortality is decreasing with the introduction of effective antiretroviral therapy, it has been reported a significant increase in the proportion of non-acquired immunodeficiency syndrome defining malignancies (NADC) from 20% in the pre-HAART era to 71% of all tumors now. People infected with HIV are at least 25 times more likely to be diagnosed with anal cancer than uninfected people, 5 times as likely to be diagnosed with liver cancer and 3 times as likely to be diagnosed with lung cancer(4). Often these patients present with advanced disease and at a younger age than general population(5). As HAART has reduced the number of deaths from AIDS, the HIV-infected population has grown in size and become older. The fastest growing proportion of HIV-infected individuals is the over-40 age group. These individuals are now developing cancers common in older age. In 2003, the proportion of these other cancers exceeded the number of AIDS-defining malignancies(6). Lung cancer has now become the leading cause of mortality among the non-acquired immunodeficiency syndrome defining malignancies. Development of lung cancer in patients with HIV has been linked to various factors including not only smoking habit, but also CD4 count, viral load and the intensity and duration of immune deficiency(4).

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death ligand 1 (PD-L1) is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some tumor types. In a number of these cancers, including lung(7), renal(8), pancreatic(9), ovarian cancer(10) and hematologic malignancies(11, 12)tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis.

Programmed cell death ligand 1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell(13, 14). This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination (15).

Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors. PD-L1 is a member of the B7 family of ligands that inhibit T-cell activity through binding to the PD-1 receptor and to CD80 (PD-L1 expression is an adaptive response that helps tumors evade detection and elimination by the immune system. Expression of PD-L1 protein is induced by inflammatory signals that are typically associated with an adaptive immune response (e.g., IFNγ) and can be found on both tumor cells (TC) and tumor-infiltrating IC. The binding of PD-L1 to PD-1 on activated T cells delivers an inhibitory signal to the T cells, preventing them from killing target TC and protecting the tumor from immune elimination (). PD-L1 may also inhibit T cells through binding to CD80, although the exact mechanism is still not elucidated).

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti–PD-L1 agent to the PD-L1 receptor

inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1–mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell–dependent mechanism PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti–PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti–PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (with responses that tend to be more pronounced in patients with tumors that express PD-L1 (. In addition, high mutational burden (e.g., in bladder carcinoma [) may contribute to the responses seen with immune therapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells. Blockade of CTLA-4 binding to CD80/86 by anti–CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti–CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data have now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies, whilst nivolumab and pembrolizumab, two anti–PD-1 agents, and atezolizumab, an anti–PD-L1, agent have been granted approvals by agencies such as the US FDA and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and urothelial carcinoma. In addition, there are data from agents in the anti–PD-1/PD-L1class showing clinical activity in a wide range of tumor types.

DURVALUMAB BACKGROUND

Investigators should be familiar with the current durvalumab Investigator Brochure

Durvalumab is being developed as a potential anticancer therapy for patients with advanced solid tumors. Durvalumab is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

Summary of non-clinical experience

The non-clinical experience is fully described in the current version of the durvalumab Investigator's Brochure.

Durvalumab binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN-γ). Additionally, durvalumab demonstrated a lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in cell-based functional assays. In vivo studies show that durvalumab inhibits tumor growth in a xenograft model via a T lymphocyte (T-cell) dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy. Combination therapy (dual targeting of PD-L1 and cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) resulted in tumor regression in a mouse model of colorectal cancer.

Cynomolgus monkeys were selected as the only relevant species for evaluation of the pharmacokinetics (PK)/pharmacodynamics and potential toxicity of durvalumab. Following intravenous (IV) administration, the PK of durvalumab in cynomolgus monkeys was nonlinear. Systemic clearance (CL) decreased and concentration half-life (t1/2) increased with increasing doses, suggesting saturable target binding-mediated clearance of durvalumab. No apparent gender differences in PK profiles were observed for durvalumab.

In general, treatment of cynomolgus monkeys with durvalumab was not associated with any durvalumab-related adverse effects that were considered to be of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) PK/pharmacodynamics and dose range-finding study, and a GLP 4-week repeat-dose toxicity study were consistent with antidrug antibody (ADA)-associated morbidity and mortality in individual animals. The death of a single animal in the non-GLP, PK/pharmacodynamics, and dose range-finding study was consistent with an ADA-associated acute anaphylactic reaction. The spectrum of findings, especially the clinical signs and microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA immune complex deposition, and ADA:durvalumab immune complexes were identified in a subsequent non-GLP, investigative immunohistochemistry study. Similar observations were reported in cynomolgus monkeys administered human mAbs unrelated to durvalumab. Given that immunogenicity of human mAbs in nonclinical species is generally not predictive of responses in humans, the ADA-associated morbidity and mortality were not considered for the determination of the no-observed-adverse-effect level (NOAEL) of durvalumab.

Data from the pivotal 3-month GLP toxicity study with durvalumab in cynomolgus monkeys showed that subchronic dosing of durvalumab was not associated with any adverse effects. Therefore, the NOAEL of durvalumab in all the general toxicity studies was considered to be 100 mg/kg, the highest dose tested in these studies. In addition to the in vivo toxicology data, no unexpected membrane binding of durvalumab to human or cynomolgus monkey tissues was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues.

Preclinical data suggests that blocking PD-L1 may improve also immune function in HIV patients (16). Different studies have shown that during chronic HIV-1 infection PD-1 expression on HIV-1–specific T cells correlates with viral load and that blocking PD-1 engagement restores T cell effector functions in vitro. Additionally, in vivo PD-1 blockade in chronic SIV infection restored CD8+ T cell function, reduced viral load levels, and increased survival of SIV-infected macaques (17). However, the consequence of in vivo PD-1 blockade to restored CD8+ T cell function, and ultimately reduce viral persistence and reservoirs in HIV-1-infected patients with effective ART, remains to be determined.

Summary of clinical experience

Clinical experience with durvalumab is fully described in the current version of the durvalumab Investigator's Brochure (Version 12.0).

As of the DCO date (12 July 2016), a total of 2878 patients have been exposed to 1or more doses of durvalumab in ongoing open-label AstraZeneca-or MedImmune-sponsored Phase I-III monotherapy and combination therapy studies across all indications.. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

Durvalumab (MEDI4736) is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). As durvalumab is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for durvalumab is interference of the interaction of PD-L1 with PD-1 and CD80.. It is engineered with a triple mutation in the Fc domain to avoid Fc-mediated ADCC. Preliminary results from the phase I study of patients with solid tumors reported clinical activity and durable disease stabilization in different tumor types, with no dose limiting toxicities or grade 3–4 treatment-related adverse events(18). In the phase II trial the drug was tested on 85 pretreated NSCLC patients. From 53 evaluable patients, 12 had an objective response by RECIST criteria (23%). At 2014 ASCO meeting, results from a phase I multi-arm expansion study of the anti PD-L1 MEDI4736 were presented. It was reported that the dose-escalation phase has been completed for doses of 0.1 to 10 mg/kg every 2 weeks with extension to 15 mg/kg every 3 weeks. MEDI4736 was well tolerated at all doses tested, with no treatment-related serious adverse events such as colitis, hyperglycemia, or pneumonitis at any grade(19). Neil Segal and colleagues presented preliminary data on the ongoing study of MEDI4736 at a dosage of 10 mg/kg every 2 weeks for 1 year for 346 patients with solid tumors, including 143 with NSCLC. The median duration of treatment was 8 weeks. As of May 18, 2014, there were very few (6%) grade 3/4 drug-related serious adverse events. Clinical activity was observed as early as 6 weeks, with maintenance for over 67 weeks and off active therapy; overall response rate (ORR) rate in NSCLC was 13%(20). Development is most advanced in non-small cell lung cancer, with a program currently comprising two phase III trials (NCT02352948, NCT02125461)and several phase I combination studies (NCT02000947, NCT02179671, NCT02143466). A pivotal program for MEDI4736 in head and neck cancer began in late 2014.

PD-1 interacts with the ligands PD-L1 (B7-H1) and PD-L2 (B7-DC), which result in diminished T-cell proliferation, altered cytokine production and initiation of T-cell exhaustion and/or apoptosis leading to tumor initiation and progression(21).

PHARMACOKINETICS AND PRODUCT METABOLISM

Study CD-ON-durvalumab-1108: As of 09Feb 2015, PK data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-durvalumab-1108following treatment with durvalumab 0.1 to 10 mg/kg every 2 weeks (Q2W) or 15 mg/kg every 3 weeks (Q3W). The maximum observed concentration (Cmax) increased in an approximately dose-proportional manner over the dose range of 0.1 to 15 mg/kg. The area under the concentration-time curve from 0 to 14 days (AUC0-14) increased in a greater than dose-proportional manner over the dose range of 0.1 to 3 mg/kg and increased dose-proportionally at ≥ 3 mg/kg. These results suggest durvalumab exhibits nonlinear PK likely due to saturable target-mediated CL at doses < 3 mg/kg and approaches linearity at doses ≥ 3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab ≥ 3 mg/kg Q2W. Exposures after multiple doses

showed accumulation consistent with PK parameters estimated from the first dose. In addition, PK simulations indicate that following durvalumab 10 mg/kg Q2W dosing, > 90% of subjects are expected to maintain PK exposure ≥ 40 µg/mL throughout the dosing interval.

As of 09Feb2015, a total of 388subjects provided samples for ADA analysis. Only 8 of 388 subjects (1 subject each in 0.1, 1, 3, and 15 mg/kg cohorts, and 4 subjects in 10 mg/kg cohort) were ADA positive with an impact on PK/pharmacodynamics in 1 subject in the 3 mg/kg cohort.

SAFETY

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy. These events are manageable by available/established treatment guidelines as described in the study protocols.

AEs reported with durvalumab monotherapy in key clinical studies are described below.

ADVERSE EVENT PROFILE OF DURVALUMAB MONOTHERAPY

Study CD-ON-durvalumab-1108: The safety profile of durvalumab monotherapy in the 694 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-durvalumab-1108 has been broadly consistent with that of the overall 1,279 subjects who have received durvalumab monotherapy (not including subjects treated with blinded investigational product) across the clinical development program. The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. As of 07May2015, among the694 subjects treated with durvalumab 10 mg/kg Q2W in Study CD-ON-durvalumab-1108, a total of 378 subjects (54.5%) experienced a treatment-related AE, with the most frequent (occurring in ≥5% of subjects) being fatigue (17.7%), nausea (8.6%), diarrhea (7.3%), decreased appetite (6.8%),pruritus (6.3%), rash (6.1%),and vomiting (5.0%). A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with ≥ Grade 3 events occurring in 65 subjects (9.4%). Treatment-related ≥ Grade 3 events reported in 3 or more subjects (≥ 0.4%) were fatigue (12 subjects, 1.7%); increased aspartate aminotransferase (AST; 7 subjects, 1.0%); increased gamma-glutamyltransferase (GGT; 6 subjects, 0.9%);increased alanine aminotransferase (ALT; 5 subjects, 0.7%); and colitis, vomiting, decreased appetite, and hyponatremia (3 subjects, 0.4% each). Six subjects had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST, dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 subject had a treatment-related Grade 5 event (pneumonia). Treatment-related serious adverse events (SAEs) that occurred in ≥ 2 subjects were colitis and pneumonitis (3 subjects each). A majority of the treatment-related SAEs were ≥ Grade 3 in severity and resolved with or without sequelae. AEs that resulted in permanent discontinuation of durvalumab were considered as treatment related in 18 subjects (2.6%), with colitis being the most frequent treatment-related AE resulting in discontinuation (3 subjects). A majority of the treatment-related AEs resulting in discontinuation of durvalumab were ≥ Grade 3 in severity and resolved with or without sequelae.

Study D4191C00003/ATLANTIC: The safety profile of durvalumab monotherapy in Study CD-ON-durvalumab-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small-cell lung cancer (NSCLC) treated with durvalumab 10 mg/kg Q2W. As of 05May2015, 264 of 303 subjects (87.1%) reported any AE in Study

D4191C00003/ATLANTIC. Overall, events reported in ≥ 10% of subjects were dyspnea (18.8%), fatigue (17.8%), decreased appetite (17.5%), cough (14.2%), pyrexia (12.2%), asthenia (11.9%), and nausea (11.2%). Nearly two-thirds of the subjects experienced AEs that were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current durvalumab study protocols. Grade 3 or higher AEs were reported in 107 of 303 subjects (35.3%). A total of 128 subjects (42.2%) reported AEs that were considered by the investigator as related to investigational product. Treatment-related AEs (all grades) reported in ≥ 2% of subjects were decreased appetite (6.6%); fatigue (5.9%); asthenia (5.0%); nausea (4.6%); pruritus (4.3%); diarrhea, hyperthyroidism, hypothyroidism, and pyrexia (3.3% each); rash (2.6%); weight decreased (2.3%); and vomiting (2.0%). Treatment-related Grade 3 AEs reported in ≥ 2 subjects were pneumonitis (3 subjects) and increased GGT (2 subjects). There was no treatment-related Grade 4 or 5 AEs. Ninety-four of 303 subjects (31.0%) reported any SAE. SAEs that occurred in ≥ 1.0% of subjects were dyspnea (6.6%); pleural effusion, general physical health deterioration (2.3% each); pneumonia (2.0%); hemoptysis, pulmonary embolism (1.3% each); and pneumonitis, respiratory failure, disease progression (1.0% each). Nine subjects had an SAE considered by the investigator as related to durvalumab. Each treatment-related SAE occurred in 1 subject each with the exception of pneumonitis, which occurred in 3 subjects. Fifteen of 303 subjects (5.0%) have died due to an AE (pneumonia [3 subjects]; general physical health deterioration, disease progression, hemoptysis, dyspnea [2 subjects each]; pulmonary sepsis, respiratory distress, cardiopulmonary arrest [verbatim term (VT)], hepatic failure, and sepsis [1 subject each]). None of these events was considered related to durvalumab. Twenty-three of 303 subjects (7.6%) permanently discontinued durvalumab treatment due to AEs. Events that led to discontinuation of durvalumab in ≥ 2 subjects were dyspnea, general physical health deterioration, and pneumonia. Treatment-related AEs that led to discontinuation were increased ALT and increased hepatic enzyme, which occurred in 1 subject each.

EFFICACY

Study CD-ON-durvalumab-1108: Overall, 456 of 694 subjects treated with durvalumab10 mg/kg Q2W were evaluable for response (defined as having ≥ 24 weeks follow-up, measurable disease at baseline, and ≥ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST)v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in triple-negative breast cancer (TNBC; n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; n = 3 each, 33.3% each), NSCLC (n = 86, 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; n = 22, 18.2%). In the PD-L1-positive subset, DCR-24w was highest in advanced cutaneous melanoma (n = 3, 66.7%), NSCLC (n = 86, 36.0%), HCC and bladder cancer (n = 3 each, 33.3% each), and SCCHN (n = 22, 18.2%).

Study D4190C00007: Of the 32 subjects with myelodysplastic syndrome (MDS) treated in Study D4190C00007, 21 subjects had at least 1 post-baseline disease assessment. Among these subjects, the best overall responses were marrow complete remission (mCR) in 4 subjects (19.0%); stable disease (SD) in 4 subjects (19.0%); and progressive disease (PD) in 5 subjects (23.8%). The remaining 8 subjects (38.1%) did not meet the criteria for complete remission (CR), mCR, partial remission (PR), SD, or PD at the date of assessment.

Study CD-ON-durvalumab-1161: Of the 65 subjects with metastatic or unresectable melanoma treated with the combination of durvalumab and BRAF inhibitor (BRAFi; dabrafenib)/MEK inhibitor (MEKi; trametinib), 63 subjects were evaluable for response. A total of 35 subjects (55.6%) had a best overall response of confirmed or unconfirmed PR. The disease control rate (DCR; CR + PR [regardless of confirmation] + SD ≥ 12 weeks) was 79.4%.

5. STUDY OBJECTIVES

Primary objective

To explore the feasibility of durvalumab (MEDI4736) monotherapy at the recommended dose of 1500 mg every 4 weeks in solid tumors in HIV-1-infected patients.

HIV-1-infected patients with cancer have been systematically excluded from clinical trials of anti cancer drugs because of concerns related to drug interactions and the unknown effect of the underlying HIV infection on the safety and activity of the investigational drugs. Anti PD-L1 antibody durvalumab (MEDI4736) could be an active treatment both for cancer and for HIV infection, with non-expected drugs interactions. The aim of this study is to explore the feasibility of durvalumab (MEDI4736) in HIV-1-infected patients who are diagnosed with a solid tumor (lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastroesophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, Cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity) for which no additional oncologic standard treatment is available, or for which the subject declines standard treatment.

Secondary objectives

Graph 1. To assess ORR (RECIST 1.1) and duration of response
Graph 2. To evaluate the PFS rate at 6 months
Graph 3. To evaluate the OS rate at 12 months

Durvalumab (MEDI4736) has demonstrated activity in several cancer types in the general population. In this study, as secondary objective, we will analyze activity of the drug as activity in terms of Response rate according to RECIST1.1 criteria, and according to OS rate at 12 months and PFS at 6 months.
Several data indicate that anti PD-1/PD-L1 treatments in oncology could have activity in terms of OS with long responders, that it is not always correlated to classical endpoint of response rate or median survival.
In this trial given that patients will be included with different solid tumors, and different lines of treatment, activity of the drug is a secondary objective, in order to determine if activity looks similar to activity reported in solid tumors without HIV- infection.

Exploratory objectives

Anti PD-1/PD-L1 antibodies could have a therapeutic effect on HIV infection. We will measure activity of durvalumab (MEDI4736) in terms of antiviral activity, measuring the changes in the viral reservoir, measuring the changes in residual viral replication and exploring changes in the composition and function of circulating T lymphocytes.

For this analysis we will use blood samples (pretreatment and shortly after treatment initiation (2, 4, 12, 24 weeks), and then in the longer time frame every 12 weeks) (+/-3 days). This will include the following:

Graph 4. Analysis by digital droplet PCR (ddPCR) of HIV-1 DNA associated to CD4+ T cells obtained from peripheral blood.

Graph 5. Analysis of residual plasma viremia using an ultrasensitive single copy assay (these patients would be on antiretroviral treatment, so standard techniques for determine viral load with not be useful).

Graph 6. Analysis by ddPCR of HIV-1 RNA expression on CD4+ T cells obtained from peripheral blood.

Graph 7. Change in 2LTR mean levels in CD4+ T cells.

Graph 8. Analysis by multicolor flow cytometry of the percentage of naïve, memory and activated CD4+ and CD8+ T-cell subsets in peripheral blood, including analysis of PD-1 expression.

Graph 9. Analysis by multicolor flow cytometry of the functional effector responses of T cells elicited by different viral and non viral antigens.

Graph 10. Determination of the ex vivo effect of durvalumab on baseline peripheral blood mononuclear cells (PBMCs):

a. To evaluate whether the *ex vivo* gain of lymphocyte effector function after durvalumab signaling blockade predicts anti-HIV function after *in vivo* therapy
b. To evaluate whether the effect of durvalumab signaling blockade on regulatory T cells restrains the enhancement in the lymphocyte effector function

In addition, the study will explore predictive factors of antitumoral activity in pretreatment tumor samples.

Tumor samples obtained by excisional or incisional biopsy (also EBUS samples in case of lung tumors) must be obtained. If it is not possible to obtain a new biopsy, the patients can be included if they have some archival tissue available (there must be analysed taking account if these samples have been performed more than 6 months before of starting durvalumab treatment)

To explore antitumoral effects according to immunohistochemical and molecular predictive markers, perform correlative studies with the objective of analyzing the expression of other biomarkers such as:

Graph 1. mRNA expression (RT-PCR) of Interferon gamma, HLA-DR and PD-L1.
Graph 2. Immunohistochemistry: PDL-1 and HLA-DR.

A set of immune response genes/proteins will be tested (both RT-PCR and immunohistochemistry).

Also, ctDNA analysis will be performed in the planned blood extractions

6. INVESTIGATIONAL PLAN

6.1. OVERALL STUDY DESIGN AND PLAN – DESCRIPTION

This is a multicenter, national, non-randomized, phase II study in HIV-1 infected patients with advanced solid tumors.

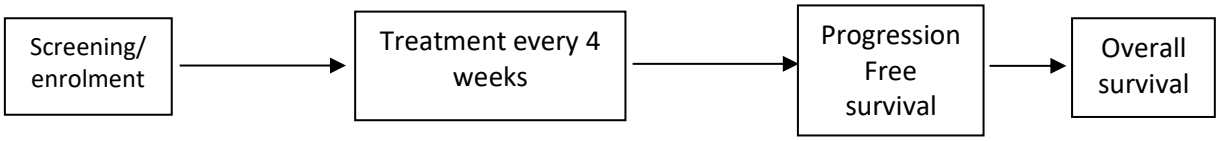
Twenty evaluable patients will be included in the trial. Patients will be included irrespective of number the previous line of treatments.

The clinical trial will be performed in 8 hospitals from the Spanish Lung Cancer Group in Spain with a competitive enrollment.

It is a single arm study. All patients included will received the treatment with durvalumab (MEDI4736). There is not placebo treated patients.

Patients must have stopped the previous treatments for cancer at least 30 days before starting study medication.

Study schema



Study oversight for safety evaluation

The whole trial may be discontinued prematurely in the event of any of the following situations:

Graph 1. New information leading to unfavourable risk-benefit judgement of the trial drug, as inefficacy of the drug for this population, significant previously unknown adverse reactions or unfavourable safety findings.

Graph 2. Sponsor's decision that continuation of the study is unjustifiable for medical or ethical reasons.

6.2. DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

RESEARCH HYPOSTHESIS

Taking into account:

Graph 1. PD-1/ PD-L1 coinhibitory pathway plays a significant role in the regulation of the immune response in both chronic infectious diseases and cancer.

Graph 2. Preclinical and animal data support the safety and promising activity of anti-PD-1 antibody in HIV-1 infection

Graph 3. Demonstrated anticancer activity and safety profile of durvalumab (MEDI4736) in cancer clinical trials.

Graph 4. Unlikely drug interactions of durvalumab (MEDI4736) and antiretroviral treatments.

We propose a phase II clinical study designed to assess the feasibility of durvalumab (MEDI4736) in HIV-1-infected individuals with solid tumors. Additionally we hope to obtain data that let us understand the possible benefit of this treatment in cancer patients and HIV, exploring if activity of

durvalumab (MEDI4736) could be higher in cancer that has been produce at least in part due to the chronic immunosupression. Simultaneously, it will allow us to investigate the effect of disrupting this immunoregulatory pathway might have in reversing cancer pathways and HIV-specific T-cell function during persistent chronic HIV infection in humans.

In this regard, our hypothesis is:

HIV infected patients with cancer have a similar outcome in terms of tolerability when treated with MEDI4736 monotherapy at the recommended dose than non-HIV infected patients.

RATIONALE FOR CONDUCTING THIS STUDY

HIV-1-infected patients with cancer have been systematically excluded from clinical trials of anti cancer drugs because of concerns related to drug interactions and the unknown effect of the underlying HIV infection on the safety and activity of the investigational drugs. Anti PD-L1 antibody durvalumab (MEDI4736) could be an active treatment both for cancer and for HIV infection, with non-expected drugs interactions.

BENEFIT/RISK AND ETHICAL ASSESSMENT

The benefit-risk relationship has been carefully considered in the planning of the trial. Based on the nonclinical and clinical studies available to date, the conduct of the trial is considered justificable using the dose and dose regimen of the durvalumab as specified in this clinical trial protocol.

The trial shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship that would render continuation of the trial unjustificable.

The primary known risks of exposure to durvalumab include:

Graph 1. Infusion-related reactions and
Graph 2. irAEs

In addition, since durvalumab could induce antibody-dependent cell-mediated cytotoxicity (ADCC), there is a potential risk of tumor lysis syndrome.

Clinical trials with antibodies that block PD-1/PD-L1 interaction have been reported to produce objective response rates of 7% to 38% in patients with advanced or metastatic solid tumors, with response duration of 1 year or more for the majority of patients(22-30).

Given the suboptimal treatment options for patients with recurrent locally advanced or metastatic solid tumors in HIV-1 infected patients, and the safety profile of durvalumab, the risk-benefit ratio of treatment with durvalumab in the targeted trial population is considered positive.

This clinical trial protocol will be conducted in compliance with the clinical trial protocol, ICH GCP and the applicable national regulatory requirements.

DETERMINATION OF SAMPLE SIZE

Feasibility will be defined based on the rate of patients that will complete at least 4 treatment cycles. One cycle is four weeks with infusions every four weeks. It is assumed that at least 50% of patients must be complete four cycles for considering feasible the treatment with durvalumab (MEDI4736).

Sample size calculation for an estimated proportion of 50% with a level of confidence of 95% and an accuracy of 22%: 20 patients must be included in this study.

6.3. SELECTION OF STUDY POPULATION

6.3.1. Inclusion Criteria

Graph 1. Written informed consent obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.

Graph 2. Age ≥ 18 years at time of study entry.

Graph 3. Eastern Cooperative Oncology Group (ECOG) 0-2.

Graph 4. Life expectancy of ≥16 weeks.

Graph 5. Adequate normal organ and marrow function as defined below:

Haemoglobin ≥ 9.0 g/dL

Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500 per mm^3)

Platelet count ≥ 100 x 10^9/L (≥100,000 per mm^3)

Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.

AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN

Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

Graph 6. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.

Graph 7. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

Graph 8. Subjects with histologically or cytologically-documented advanced/metastasic lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastroesophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, Cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity, refractory to standard treatment, intolerant of standard treatment, or for which no standard therapy exists or who refuse the standard treatment.

Graph 9. Subjects may be included irrespectively of number of previous lines of treatment for advanced disease.

Graph 10. Prior palliative radiotherapy must have been completed at least 2 weeks prior to start the study treatment (subjects may receive localized palliative radiotherapy while receiving study drug).

Graph 11. Documented HIV-1 infection

Graph 12. Undetectable viral load in the last analysis.

Graph 13. Subjects with brain metastases are eligible if they are asymptomatic, are treated or are neurological stable for at least 2 weeks without the use of steroids or on stable or decreasing dose of < 10 mg daily prednisone or equivalent.

Graph 14. Subjects must be following an antiretroviral therapy at the moment of the inclusion.

6.3.2. Exclusion Criteria

Graph 1. Involvement in the planning and/or conduct of the study. Previous enrollment in the present study.

Graph 2. Participation in another clinical study with an investigational product during the last 4 weeks.

Graph 3. Other untreated coexisting HIV related malignancies.

Graph 4. Any previous treatment with a PD1, PD-L1 or PD-L2 inhibitor, including durvalumab.

Graph 5. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) 28 days prior to the first dose of study drug.

Graph 6. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.

Graph 7. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

Graph 8. Any unresolved toxicity (CTCAE grade 2) from previous anti-cancer therapy. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy).

Graph 9. Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1.

Graph 10. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

Graph 11. Any syndrome that requires systemic corticosteroid/immunosuppressive medications EXCEPT for syndromes which would not be expected to recur in the absence

of an external trigger (vitiligo, autoimmune thyroiditis, or type 1 diabetes mellitus are permitted to enroll).

Graph 12. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).

Graph 13. History of primary immunodeficiency.

Graph 14. History of allogeneic organ transplant.

Graph 15. History of hypersensitivity to durvalumabor any excipient.

Graph 16. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B or C, or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.

Graph 17. Known history of active tuberculosis.

Graph 18. Any serious or uncontrolled medical disorder or active infection non HIV, that would impair the ability of the subject to receive the treatment of protocol therapy under treating physician criteria.

Graph 19. Subjects with previous malignances (except non melanoma skin cancer, and cancer in situ of: bladder, gastric, colon, cervical/dysplasia, melanoma, breast) are excluded unless a complete remission was achieved at least 5 years prior to study entry and no additional therapy is required or anticipated to be required during the study period.

Graph 20. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab.

Graph 21. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control.

Graph 22. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

Graph 23. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.

Graph 24. Subjects with uncontrolled seizures.

Graph 25. Patients with tumoral disease in the head and neck region, such as peritracheal or periesophageal lymph node involvement, with infiltration of structures of the digestive, aerea or vascular pathways that represent a risk of increased bleeding.

Graph 26. Patients with neuroendocrine tumors of pulmonary origin or pulmonary metastases with evidence of active bleeding.

Graph 27. Patients with digestive bleeding.

6.3.3. Removal of Patients from Therapy or Assessment

Permanent discontinuation of investigational product

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

Graph 1. Withdrawal of consent or lost to follow-up.
Graph 2. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing.
Graph 3. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute asafety risk.
Graph 4. Pregnancy or intent to become pregnant.
Graph 5. Any AE that meets criteria for discontinuation as defined in Appendix 1, Section 10.1.3
Graph 6. Adverse event related to durvalumab of any Grade>3 ADRs or repetitive Grade 3 ADRs with the exception of toxicities that do not meet the criteria for discontinuation as defined in Section 10.1.3, Appendix 1
Graph 7. Grade ≥ 3 infusion reaction.
Graph 8. Subject non-compliance that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits.
Graph 9. Initiation of alternative anticancer therapy including another investigational agent.
Graph 10. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab.

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified ashaving permanently discontinued treatment.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section10.3.1 and Appendix 3 or 4, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

Withdrawal of consent

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

Replacement of subjects

Subjects withdrawn from the study will not be replaced.

6.4. TREATMENTS

6.4.1. Treatments Administered

The sponsor will supply durvalumab to the site's pharmacies as a 500-mg vial solution for infusion after dilution.

Durvalumab 1500 mg IV commences on Day 1 following confirmation of eligibility into the study and continues on a Q4W schedule until confirmed PD (unless the investigator considers the subject to continue to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or if other reasons to discontinue study treatment occur.

FLOW CHART

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**Screening**	**Baseline**	**Every 4 weeks**	**Every 8 Weeks**	**Every 12 Weeks**	**First Follow up**	**Follow up month 2 and 3 since last dose**	**Follow up months 4, 6, 8 and 10 since last dose**	**Follow up month 12 since last dose, then every 6 month**
Day	**-28 to -1**	**1**				**30 days since last dose**			
Week	**-4 to -1**	**0**	**4, 8, 12, 16, 20, etc**	**8, 16, 24, 32, 40 and 48**	**12, 24, 36, 48**				
			(-3/+1 days)			**(±3 days)**	**(±7 days)**	**(±7 days)**	**(±14 days)**
Written informed consent/assignment of subject identification number	X								
Preliminary eligibility fulfillment (investigator's opinion)	X								
Demography and history of tobacco	X								
Previous treatments for solid tumors	X								
Archival FFPE tumor tissue sample	X								
Archived or new biopsy, (Section 8.3 further detail)	X								

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	Screening	Baseline	Every 4 weeks	Every 8 Weeks	Every 12 Weeks	First Follow up	Follow up month 2 and 3 since last dose	Follow up months 4, 6, 8 and 10 since last dose	Follow up month 12 since last dose, then every 6 month
Day	**-28 to -1**	**1**				**30 days since last dose**			
Week	**-4 to -1**	**0**	**4, 8, 12, 16, 20, etc**	**8, 16, 24, 32, 40 and 48**	**12, 24, 36, 48**				
			(-3/+1 days)			**(±3 days)**	**(±7 days)**	**(±7 days)**	**(±14 days)**
Formal verification of eligibility criteria	X								
Medical and surgical history	X								
HIV infection history	X								
Hepatitis B and C; HIV serology	X								
Urine hCG or serum βhCG[b]	X			X		X		X (only in month 4 and if the patient ends treatment for a different reason than progression disease)	
Durvalumab administration (monotherapy)		X	X						
Physical examination[c]	X	X	X			X			

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**Screening**	**Baseline**	**Every 4 weeks**	**Every 8 Weeks**	**Every 12 Weeks**	**First Follow up**	**Follow up month 2 and 3 since last dose**	**Follow up months 4, 6, 8 and 10 since last dose**	**Follow up month 12 since last dose, then every 6 month**
Day	**-28 to -1**	**1**				**30 days since last dose**			
Week	**-4 to -1**	**0**	**4, 8, 12, 16, 20, etc**	**8, 16, 24, 32, 40 and 48**	**12, 24, 36, 48**				
			(-3/+1 days)			**(±3 days)**	**(±7 days)**	**(±7 days)**	**(±14 days)**
Vital signs (pre- during and post-infusion vital signs assessments)	X	X [d]	X [d]			X			
Weight	X	X	X			X			
Electrocardiogram[e]	X	X (as clinically indicated)		X (week 16 only)					
Adverse event/serious adverse event assessment[k]	X	X	X	X	X	X	X		
Concomitant medications[k]	X	X	X	X	X	X	X		
ECOG performance status	X	X	X	X	X	X	X	X (only in months 6 and 9 since last dose and if the patient	X (only if the patient completed the treatment

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**Screening**	**Baseline**	**Every 4 weeks**	**Every 8 Weeks**	**Every 12 Weeks**	**First Follow up**	**Follow up month 2 and 3 since last dose**	**Follow up months 4, 6, 8 and 10 since last dose**	**Follow up month 12 since last dose, then every 6 month**
Day	**-28 to -1**	**1**				**30 days since last dose**			
Week	**-4 to -1**	**0**	**4, 8, 12, 16, 20, etc**	**8, 16, 24, 32, 40 and 48**	**12, 24, 36, 48**				
			(-3/+1 days)			**(±3 days)**	**(±7 days)**	**(±7 days)**	**(±14 days)**
								completed the treatment without progression)	without progression)
Serum Chemistry (complete clin chem. panel including Liver enzymes)	X	X[f]	X			X	X		
Thyroid function tests (TSH and fT3 and fT4)[g]	X	X	X			X			
Hematology, CD4+ T cell counts, CD8+ T cell counts and Plasma viral load	X	X[f]	X			X	X		X
Urinalysis[h]	X	X	X						
Coagulation parameters[i]	X								
Blood samples translational study and plasma viral load[l]	X		X (only week 2 and 4)		X				

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	Screening	Baseline	Every 4 weeks	Every 8 Weeks	Every 12 Weeks	First Follow up	Follow up month 2 and 3 since last dose	Follow up months 4, 6, 8 and 10 since last dose	Follow up month 12 since last dose, then every 6 month
Day	**-28 to -1**	**1**				**30 days since last dose**			
Week	**-4 to -1**	**0**	**4, 8, 12, 16, 20, etc**	**8, 16, 24, 32, 40 and 48**	**12, 24, 36, 48**				
			(-3/+1 days)			**(±3 days)**	**(±7 days)**	**(±7 days)**	**(±14 days)**
Flow cytometry collection of whole blood CD4, CD8 subsets[l]	X		X (only week 2 and 4)		X				
Tumor assessment (PET-CT, CT or MRI)[j]	X			X (-5 days)	X (±7 days) (after 48 weeks)				
Palliative radiotherapy						As clinically indicated			
Subsequent anti-cancer therapy						X	X	X	X
Survival status[m]							X	X	X (every 2 month)

b Pre-menopausal female subjects of childbearing potential only. This test has to be done every 2 cycles and in the first follow up.

c Full physical examination at baseline; targeted physical examination at other timepoints.

d Subjects will have their blood pressure and pulse measured before, during and after the infusion at the following times (based on a 60-minute infusion):
- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- At the end of the infusion (at 60 minutes ±5 minutes)

• In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated. If the infusion takes longer than 60 minutes then blood pressure and pulse measurements should be collected every 30 minutes (±5 minutes) and as described above or more frequently if clinically indicated.

e ECG during screening, at Day1 and week 16. Thereafter as clinically indicated. Screening and abnormal ECG at any time in triplicate others single. On Day 1 and week 16, ECGs should be taken within an hour prior to the start of the infusion and at least one time point 0 to 3 hours after the infusion.

f If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. Gamma glutamyltransferase tested at Screening, Day 1 and as clinically indicated.

g Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

h Urinalysis performed at Screening, Day 1, every 4 weeks and as clinically indicated.

i Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated.

j CT (preferred) or MRI scans, preferably with IV contrast, are collected during screening (for baseline) and as close to and prior to initiation of study treatment. Timing of on-treatment (follow-up) CT/MRI scans is every 8 weeks (-5 days) for the first 48 weeks and then every 12 weeks (± 1 week) until PD or off-study. Response according to RECIST 1.1 criteria (CR, PR) requires a confirmatory scan preferably at the next regularly scheduled imaging visit and no earlier than 4 weeks after the prior assessment of CR, PR, or SD. If MRI is used, CT of chest is mandatory). A brain MRI scan is required only following the investigator criteria. For subjects who achieve disease control following 12 months of treatment, tumour assessments should be performed every 12 weeks (± 1 week) relative to the date of first infusion thereafter until confirmed PD by RECIST 1.1 by investigational site review. For subjects who discontinue durvalumab due to toxicity (or symptomatic deterioration), tumour assessments should be performed relative to the date of first infusion as follows: every 8 weeks (± 1 week) for the first 48 weeks , then every 12 weeks(± 1 week) until confirmed PD by RECIST 1.1 by investigational site review. Upon confirmed PD, scans should be conducted according to local standard clinical practice and submitted for central review until a new treatment is started (these scans are optional).

k AEs and concomitant medications will be documented at each trial visit and between visits by weekly telephone contact.

l Blood samples for determination of soluble factors will be collected from all subjects prior to infusion on Day 1 (baseline samples for soluble factors may also be collected at Screening, instead of on Day 1 prior to dosing) and **within 2 hours** before infusion**.**

m Phone contact with subjects who refuse to return for evaluations and agree to be contacted

6.5. DATA QUALITY ASSURANCE

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

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

6.6.1. Statistical and Analytical Plans

In general descriptive summaries will be presented for the efficacy and safety variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages.
Unless otherwise specified, the calculation of proportions will be based on the sample size of the population of interest. Count missing observations will be included in the denominator and presented in a separate category.

SAFETY ANALYSES

Analysis of safety endpoint(s)
The extent of exposure to trial drug will be characterized by duration (weeks), number of administrations, cumulative dose (mg/kg), dose intensity (mg/kg/week), relative dose intensity (actual dose given/planned dose) and number of dose delays.
Safety analysis will be performed on the Safety analysis set. The safety endpoints will be tabulated using descriptive statistics.
Safety assessments will be based on review of incidence of AEs including AESIs, ADRs, and changes in vital signs, ECGs, body weight, and laboratory values (hematology, serum chemistry).
The on-treatment period is defined as the time from the first trial drug administration to the last drug administration date +29 days or the earliest date of subsequent anticancer drug therapy minus 1 day, whichever occurs first, unless otherwise stated.

EFFICACY ANALYSES

Analysis of efficacy endpoint(s)
Kaplan Meier method will be used to estimate the survival function. Secondary measurements will be PFS rate at 6 months and OS rate at 12 months.

EXPLORATORY ANALYSES

Analysis of immunohistochemistry
Immunohistochemistry results (defined as positive or negative) in the pretreatment sample with their relation to response and survival.

Analysis of gene expression
Analysis of gene expression in relation to response and survival.

Analysis of anti HIV activity in blood
Analysis by digital droplet PCR (ddPCR) of HIV-1 DNA associated to CD4+ T cells obtained from peripheral blood.

Analysis of residual plasma viremia
Using an ultrasensitive single copy assay (these patients would be on antiretroviral treatment, so standard techniques for determine viral load with not be useful).

Analysis of HIV-1 RNA expression
Analysis by ddPCR of HIV-1 RNA expression on CD4+ T cells obtained from peripheral blood.

Analysis of 2LTR
Change in 2LTR mean levels in CD4+ T cells.

Analysis of CD4+ and CD8+ T-cell subsets in peripheral blood
Analysis by multicolor flow cytometry of the percentage of naïve, memory and activated CD4+ and CD8+ T-cell subsets in peripheral blood, including analysis of PD-1 expression.

Analysis of functional effector responses of T cells
Analysis by multicolor flow cytometry of the functional effector responses of T cells elicited by different viral and non viral antigens.

Analysis of predictive factors of antitumoral activity in pretreatment tumor samples
mRNA expression (RT-PCR) of Interferon gamma, HLA-DR and PD-L1.

Immunohistochemestry: PDL-1 and HLA-DR.

A set of immune response genes/proteins will be tested (both RT-PCR and inmunohistochemistry).

7. EFFICACY EVALUATION

7.1. DATA SETS ANALYSED

21 patients were enrolled in the study although patient 00200014 was finally considered as an inclusion error so it did not enter in the analysis. 20 patients from 7 different sites were considered for the analysis.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Baseline clinical characteristics

		Total (N=20)
Gender		
Female	n (%)	4 (20.00)
Male	n (%)	16 (80.00)
Age		
	n	20
	Mean (SD)	53.50 (10.50)
	Median [Q1,Q3]	54.00 [48.00, 60.00]
	Min, Max	30.00, 73.00
Race		

		Total (N=20)
Caucasian	n (%)	19 (95.00)
Other	n (%)	1 (5.00)
ECOG (PS)		
0-1	n (%)	19 (95.00)
2	n (%)	1 (5.00)
Smoking status		
Former smoker	n (%)	9 (45.00)
Never smoker	n (%)	2 (10.00)
Smoker	n (%)	9 (45.00)
No of prior systemic therapies		
0	n (%)	8 (40.00)
1	n (%)	4 (20.00)
>=2	n (%)	8 (40.00)
Basal CD4-count cells/mm3		
<200	n (%)	1 (5.00)
200-350	n (%)	8 (40.00)
>350	n (%)	11 (55.00)
Type of Cancer		
Anal	n (%)	2 (10.00)
Bladder	n (%)	1 (5.00)
Melanoma	n (%)	2 (10.00)
NSCLC	n (%)	14 (70.00)
SCLC	n (%)	1 (5.00)
Years since cancer diagnosis		
	n	20
	Mean (SD)	1.80 (2.80)
	Median [Q1,Q3]	1.00 [0.00, 2.50]
	Min, Max	0.00, 10.00
LungCancer(Y/N)		
Yes	n (%)	15 (75.00)
No	n (%)	5 (25.00)

Lung cancer type

		Total (N=15)
Lung cancer type		
NSCLC	n (%)	14 (93.33)
SCLC	n (%)	1 (6.67)
Lung cancer type(detail)		

		Total (N=15)
NSCLC EGFR-, ALK-	n (%)	14 (93.33)
SCLC	n (%)	1 (6.67)

% are computed over the number of patients with Lung cancer (n=15)

NSCLC histology

		Total (N=14)
NSCLC Histology		
Adenocarcinoma	n (%)	8 (57.14)
Squamous	n (%)	3 (21.43)
NOS/Undifferenciated	n (%)	3 (21.43)

% are computed over the population with NSLC lung cancer (n=14)

HIV diagnosis and Dolutegravir

		Dolutegravir (N=10)	No Dolutegravir (N=10)	Total (N=20)
Years since HIV diagnosis				
	n	10	10	19
	Missing	1	0	1
	Mean (SD)	14.56 (12.13)	20.50 (7.60)	17.68 (10.18)
	Median [Q1,Q3]	16.00 [2.00, 26.00]	18.50 [16.00, 25.00]	18.00 [11.00, 26.00]
	Min, Max	1.00, 29.00	11.00, 33.00	1.00, 33.00
HIV-1 group transmission				
Missing	n	0	0	0
Valid	n	10	10	20
Heterosexual individuals	n (%)	3 (30.00)	3 (30.00)	6 (30.00)
MSM	n (%)	3 (30.00)	3 (30.00)	6 (30.00)
IDUs	n (%)	3 (30.00)	3 (30.00)	6 (30.00)

		Dolutegravir (N=10)	No Dolutegravir (N=10)	Total (N=20)
Unknown	n (%)	1 (10.00)	1 (10.00)	2 (10.00)
CD4 at baseline				
	n	10	10	20
	Mean (SD)	361.40 (115.72)	472.50 (221.64)	416.95 (181.27)
	Median [Q1,Q3]	370.50 [288.00, 430.00]	397.00 [309.00, 596.00]	397.00 [294.00, 513.00]
	Min, Max	164.00, 543.00	244.00, 945.00	164.00, 945.00
Plasma Viral load at baseline				
	n	9	9	18
	Missing	1	1	2
	Mean (SD)	24.67 (17.43)	26.11 (14.53)	25.39 (15.58)
	Median [Q1,Q3]	22.00 [19.00, 40.00]	20.00 [20.00, 40.00]	21.00 [19.00, 40.00]
	Min, Max	0.00, 50.00	0.00, 40.00	0.00, 50.00

Baseline characteristics and Integrase Inhibitors

In the next table the patients are grouped based on whether the antiretroviral treatment includes Integrase Inhibitors or not.

Baseline characterisgics and Integrase Inhibitors					
		NRTIs + INSTIs (N=14)	NRTIs + non-INSTIs (N=6)	Total (N=20)	P Value Test
Gender					
Female	n (%)	2 (14.29)	2 (33.33)	4 (20.00)	Fisher: 0.5492
Male	n (%)	12 (85.71)	4 (66.67)	16 (80.00)	
Age					
	n	14	6	20	
	Mean (SD)	53.71 (12.29)	53.00 (5.06)	53.50 (10.50)	T-Test: 0.8935
	Median [Q1,Q3]	54.00 [48.00, 63.00]	54.00 [48.00, 58.00]	54.00 [48.00, 60.00]	
	Min, Max	30.00, 73.00	46.00, 58.00	30.00, 73.00	
Race					
Caucasian	n (%)	14 (100.00)	5 (83.33)	19 (95.00)	Fisher: 0.3000

Baseline characterisgics and Integrase Inhibitors					
		NRTIs + INSTIs (N=14)	NRTIs + non-INSTIs (N=6)	Total (N=20)	P Value Test
Other	n (%)	0 (0.00)	1 (16.67)	1 (5.00)	
ECOG(PS)					
0-1	n (%)	13 (92.86)	6 (100.00)	19 (95.00)	Fisher: 1.0000
2	n (%)	1 (7.14)	0 (0.00)	1 (5.00)	
Smoking status					
Former smoker	n (%)	7 (50.00)	2 (33.33)	9 (45.00)	Fisher: 0.5059
Never smoker	n (%)	2 (14.29)	0 (0.00)	2 (10.00)	
Smoker	n (%)	5 (35.71)	4 (66.67)	9 (45.00)	
No of prior systemic therapies					
0	n (%)	4 (28.57)	4 (66.67)	8 (40.00)	Fisher: 0.3354
1	n (%)	3 (21.43)	1 (16.67)	4 (20.00)	
>=2	n (%)	7 (50.00)	1 (16.67)	8 (40.00)	
Basal CD4-count cells/mm3					
<200	n (%)	1 (7.14)	0 (0.00)	1 (5.00)	Fisher: 0.4040
200-350	n (%)	4 (28.57)	4 (66.67)	8 (40.00)	
>350	n (%)	9 (64.29)	2 (33.33)	11 (55.00)	
Type of Cancer					
Anal	n (%)	1 (7.14)	1 (16.67)	2 (10.00)	Fisher: 1.0000
Bladder	n (%)	1 (7.14)	0 (0.00)	1 (5.00)	
NSCLC	n (%)	9 (64.29)	5 (83.33)	14 (70.00)	
Melanoma	n (%)	2 (14.29)	0 (0.00)	2 (10.00)	
SCLC	n (%)	1 (7.14)	0 (0.00)	1 (5.00)	
Years since cancer diagnosis					
	n	14	6	20	
	Mean (SD)	2.43 (3.13)	0.33 (0.82)	1.80 (2.80)	Wilcoxon: 0.0645
	Median [Q1,Q3]	1.00 [0.00, 4.00]	0.00 [0.00, 0.00]	1.00 [0.00, 2.50]	
	Min, Max	0.00, 10.00	0.00, 2.00	0.00, 10.00	

Cancer diagnosis and Integrase Inhibitors

Lung cancer incidence and characteristics, classifying the patients based on whether the antiretroviral treatment includes Integrase Inhibitors or not.

Cancer diagnosis and Integrase Inhibitors					
		NRTIs + INSTIs (N=10)	**NRTIs + non-INSTIs (N=5)**	**Total (N=15)**	**P Value Test**
Lung cancer(y/n)					
Yes	n (%)	10 (100.00)	5 (100.00)	15 (100.00)	NA
Lung cancer type					
NSCLC	n (%)	9 (90.00)	5 (100.00)	14 (93.33)	Fisher: 1.0000
SCLC	n (%)	1 (10.00)	0 (0.00)	1 (6.67)	
Lung cancer type(detail)					
NSCLC EGFR-, ALK-	n (%)	9 (90.00)	5 (100.00)	14 (93.33)	Fisher: 1.0000
SCLC	n (%)	1 (10.00)	0 (0.00)	1 (6.67)	

% are computed over the population with lung cancer (n=15)

NSCLC histology and Integrase Inhibitors

NSCLC and Integrase Inhibitors					
		NRTIs + INSTIs (N=9)	**NRTIs + non-INSTIs (N=5)**	**Total (N=14)**	**P Value Test**
NSCLC Histology					
Adenocarcinoma	n (%)	6 (66.67)	2 (40.00)	8 (57.14)	Fisher: 0.7483
Sqamous	n (%)	1 (11.11)	2 (40.00)	3 (21.43)	
NOS/Undifferenciated	n (%)	2 (22.22)	1 (20.00)	3 (21.43)	

% are computed over the population with NSLC lung cancer (n=14)

HIV diagnosis and Integrase Inhibitors

HIV diagnosis and Integrase Inhibitors					
		NRTIs + INSTIs (N=14)	**NRTIs + non-INSTIs (N=6)**	**Total (N=20)**	**P Value Test**
Years since HIV diagnosis					
	n	13	6	19	
	Missing	1	0	1	
	Mean (SD)	16.38 (11.21)	20.50 (7.58)	17.68 (10.18)	T-Test: 0.4283
	Median [Q1,Q3]	16.00 [6.00, 26.00]	18.50 [17.00, 25.00]	18.00 [11.00, 26.00]	
	Min, Max	1.00, 31.00	11.00, 33.00	1.00, 33.00	
HIV-1 group transmission					
Heterosexual individuals	n (%)	4 (28.57)	2 (33.33)	6 (30.00)	Fisher: 0.3139
IDUs	n (%)	3 (21.43)	3 (50.00)	6 (30.00)	
MSM	n (%)	6 (42.86)	0 (0.00)	6 (30.00)	
Unknown	n (%)	1 (7.14)	1 (16.67)	2 (10.00)	
Basal CD4+T cell count (cells/mm3)					
	n	14	6	20	
	Mean (SD)	419.21 (144.56)	411.67 (265.49)	416.95 (181.27)	Wilcoxon: 0.3546
	Median [Q1,Q3]	414.50 [300.00, 543.00]	312.00 [273.00, 384.00]	397.00 [294.00, 513.00]	
	Min, Max	164.00, 657.00	244.00, 945.00	164.00, 945.00	
Basal Plasma Viral load (copies/mL)					
	n	12	6	18	
	Missing	2	0	2	
	Mean (SD)	25.17 (15.68)	25.83 (16.86)	25.39 (15.58)	Wilcoxon: 1.0000
	Median [Q1,Q3]	21.00 [19.50, 40.00]	30.00 [15.00, 40.00]	21.00 [19.00, 40.00]	
	Min, Max	0.00, 50.00	0.00, 40.00	0.00, 50.00	

Type of cancer

Metastasis		
		Total (N=20)
Type of cancer		
Anal	n (%)	2 (10.00)
Bladder	n (%)	1 (5.00)
Melanoma	n (%)	2 (10.00)
NSCLC	n (%)	14 (70.00)
SCLC	n (%)	1 (5.00)

Summary of metastatic sites

Site of Metastasis		
		Total (N=20)
Lung		
	n (%)	15 (75.00)
Liver		
	n (%)	3 (15.00)
CNS		
	n (%)	3 (15.00)
Node		
	n (%)	14 (70.00)
Adenal		
	n (%)	4 (20.00)
Other		
	n (%)	4 (20.00)
Number of metastatic sites		
1	n (%)	5 (25.00)
2	n (%)	9 (45.00)
3	n (%)	4 (20.00)
5	n (%)	2 (10.00)

Site of Metastasis		
		Total (N=20)
Total metastasis sites by patient		
	n	20
	Median [Q1,Q3]	2 [1, 3]
	Min, Max	1, 5

Summary of metastatic sittes by type of cancer

Type of cancer							
Metastasis		**Anal (N=2)**	**Bladder (N=1)**	**Melanoma (N=2)**	**NSCLC (N=14)**	**SCLC (N=1)**	**Total (N=20)**
Lung							
No	n (%)	0 (0.00)	1 (100.00)	0 (0.00)	4 (28.57)	0 (0.00)	5 (25.00)
Yes	n (%)	2 (100.00)	0 (0.00)	2 (100.00)	10 (71.43)	1 (100.00)	15 (75.00)
Liver							
No	n (%)	1 (50.00)	1 (100.00)	2 (100.00)	13 (92.86)	0 (0.00)	17 (85.00)
Yes	n (%)	1 (50.00)	0 (0.00)	0 (0.00)	1 (7.14)	1 (100.00)	3 (15.00)
CNS							
No	n (%)	1 (50.00)	1 (100.00)	1 (50.00)	13 (92.86)	1 (100.00)	17 (85.00)
Yes	n (%)	1 (50.00)	0 (0.00)	1 (50.00)	1 (7.14)	0 (0.00)	3 (15.00)
Nodes							
No	n (%)	1 (50.00)	0 (0.00)	1 (50.00)	4 (28.57)	0 (0.00)	6 (30.00)
Yes	n (%)	1 (50.00)	1 (100.00)	1 (50.00)	10 (71.43)	1 (100.00)	14 (70.00)
Adenal							
No	n (%)	2 (100.00)	1 (100.00)	2 (100.00)	10 (71.43)	1 (100.00)	16 (80.00)
Yes	n (%)	0 (0.00)	0 (0.00)	0 (0.00)	4 (28.57)	0 (0.00)	4 (20.00)
Others							
No	n (%)	1 (50.00)	0 (0.00)	1 (50.00)	14 (100.00)	0 (0.00)	16 (80.00)
Yes	n (%)	1 (50.00)	1 (100.00)	1 (50.00)	0 (0.00)	1 (100.00)	4 (20.00)

7.3. MEASUREMENTS OF TREATMENT COMPLIANCE

Distribution of time on treatment (months)

Time on treatment (months)		
		Total (N=20)
Treatment duration(months)		
	n	20
	Mean (SD)	8.73 (11.57)
	Median [Q1,Q3]	3.35 [1.64, 12.47]
	Min, Max	0.20, 45.70

Distribution of time on treatment (months) by PD-L1

A total of 15 patients has PD-L1 evaluated

The median two sample test support the alternative hypothesis that the effect of PD_L1 positive on treatment duration is greater than that of PD-L1 Negative

Time on treatment and PD-L1					
		Negative (N=11)	Positive (N=4)	Total (N=15)	P Value Test
Treatment duration(months)					
	n	11	4	15	
	Mean (SD)	5.97 (8.57)	13.18 (6.14)	7.90 (8.45)	Wilcoxon: 0.0623
	Median [Q1,Q3]	2.27 [1.45, 9.46]	15.06 [9.03, 17.33]	3.91 [1.84, 13.67]	Median two sample test: 0.0159
	Min, Max	0.20, 29.53	4.40, 18.20	0.20, 29.53	

Distribution of time on treatment(months) for patients with/without Integrase Inhibitors

The use on Integrase Inhibitors does not have a significant effect on the time on treatment.

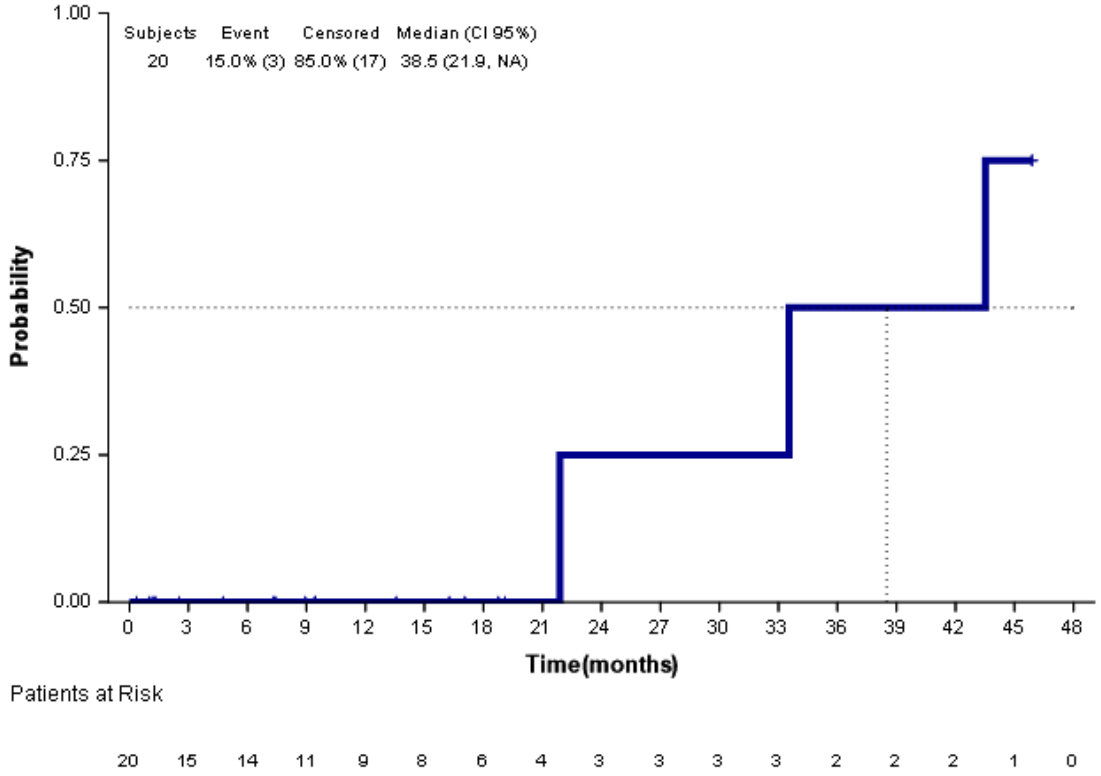
Time on treatment and Integrase Inhibitors					
		INSTI (N=14)	No INSTI (N=6)	Total (N=20)	P Value Test
Time on treatment(months)					
	n	14	6	20	
	Mean (SD)	10.90 (13.13)	3.67 (3.99)	8.73 (11.57)	Wilcoxon: 0.2792
	Median [Q1,Q3]	4.85 [1.84, 16.46]	2.53 [1.08, 4.40]	3.35 [1.64, 12.47]	
	Min, Max	0.82, 45.70	0.20, 11.27	0.20, 45.70	

TIME IN THE STUDY

Using a Kaplan Meier model, the median of follow up time (time in the study), can be estimated.

Time in the study is computed as the time, in months, from the inclusion date to the last contact date. A patient who dies will be censored at the death date.

Kaplan Meier model graph of follow up-time



The probability of a follow up time less than 21 months is very low.

Kaplan Meier model summary results

Subjects	Event	% Events	Censored	% Censored	Median	CI 95%
20	3	15.0	17	85.0	38.5	(21.9, NA)

Kaplan Meier estimated Median follow up time is 38.5 months 95%CI (21.9, NA)

Descriptive analysis of time in the study

		Total (N=20)
Time in the study (months)		
	n	20
	Mean (SD)	14.17 (13.47)
	Median [Q1,Q3]	9.44 [3.65, 18.92]
	Min, Max	0.36, 45.89

7.4. EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

11.4.1 Analysis of Efficacy

TARGET LESSIONS MEASURES CHANGE AND BEST RESPONSE

The waterfall plot is representing for each patient the response to the treatment based on the tumor burden.

The horizontal (x) axis corresponds to the different patients. A reference line is drawn representing a baseline measure (0%) change.

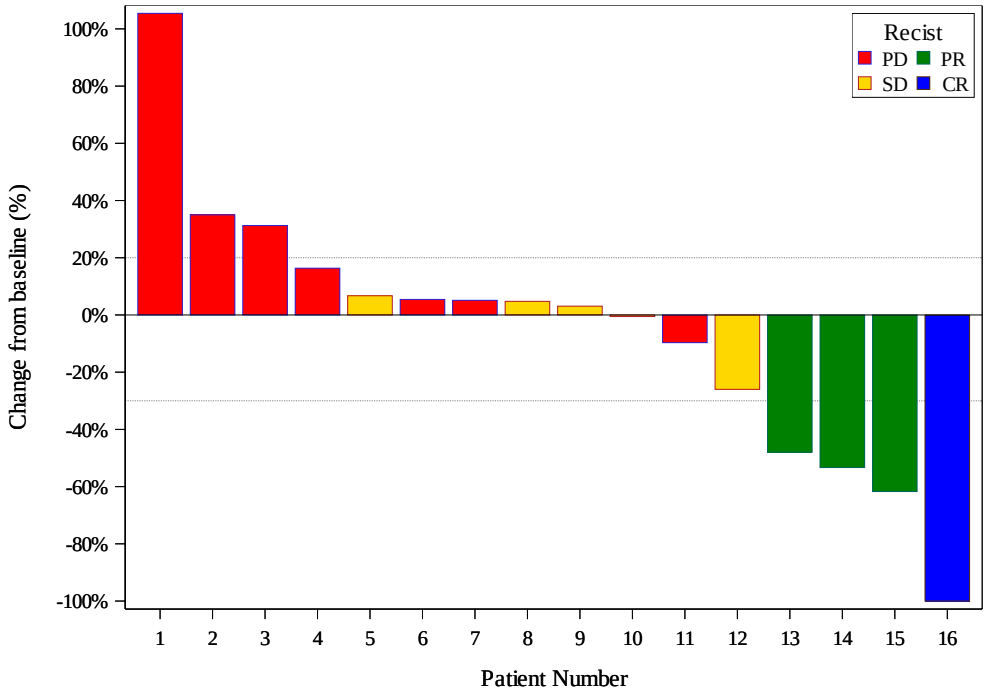
The vertical (y) axis measures the maximum percent change from baseline (e.g percent growth or reduction of the tumor by radiologic measurement. Those vertical bars that are above the reference line represent growth in tumor size, non-responders or progressive disease. Vertical bars below the reference line are drawn for each patient that has achieved some degree of tumor reduction.

In the waterfall plot data is represent ordered from the worst value, such as greatest progression of disease, on the left side of the plot, to the best value, i.e., most reduction of the tumor, on the right side of the plot.

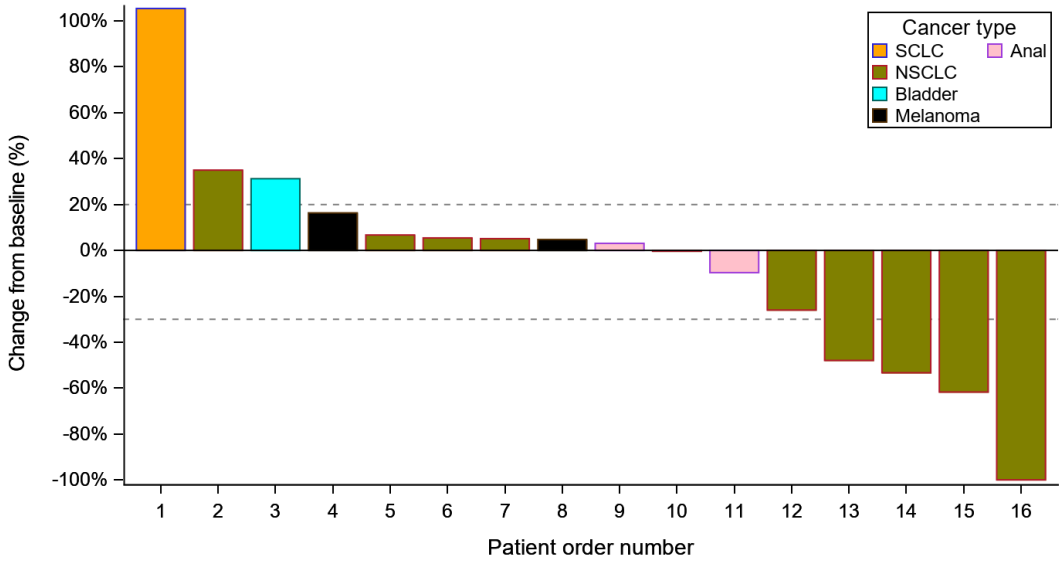
There is one patient with 0% as maximum change from baseline. Vertical bar does not appear since the height is cero. The best response for this patient is SD (Stable disease)

Waterfall plot of target lesions measure change and best response

Waterfall plot of target lessions measure change and best response by patient



Waterfall plot of target lessions measure change and best response by patient-color type of cancer



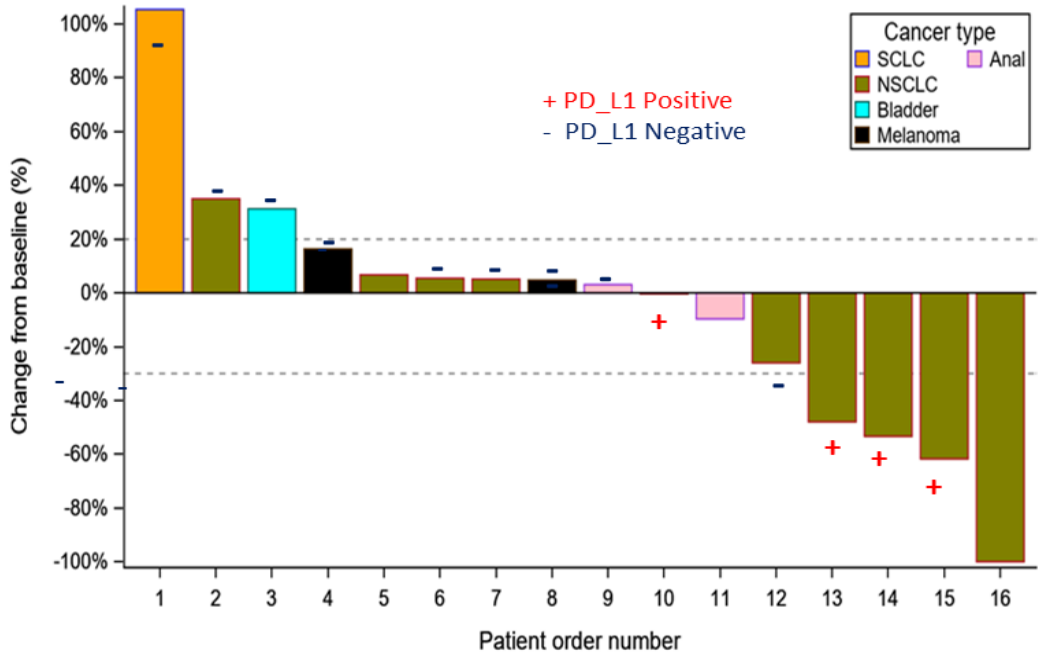
Distribution of patients with tumor assessment by cancer type

		Total (N=16)
Cancer type		
Anal	n (%)	2 (12.50)
Bladder	n (%)	1 (6.25)
Melanoma	n (%)	2 (12.50)
NSCLC	n (%)	10 (62.50)
SCLC	n (%)	1 (6.25)

Distribution of patients by cancer type- global

		Total (N=20)
Cancer type		
Anal	n (%)	2 (10.00)
Bladder	n (%)	1 (5.00)
Melanoma	n (%)	2 (10.00)
NSCLC	n (%)	14 (70.00)
SCLC	n (%)	1 (5.00)

Waterfall plot of target lessions measure change and best response by patient-color type of cancer and PD-L1

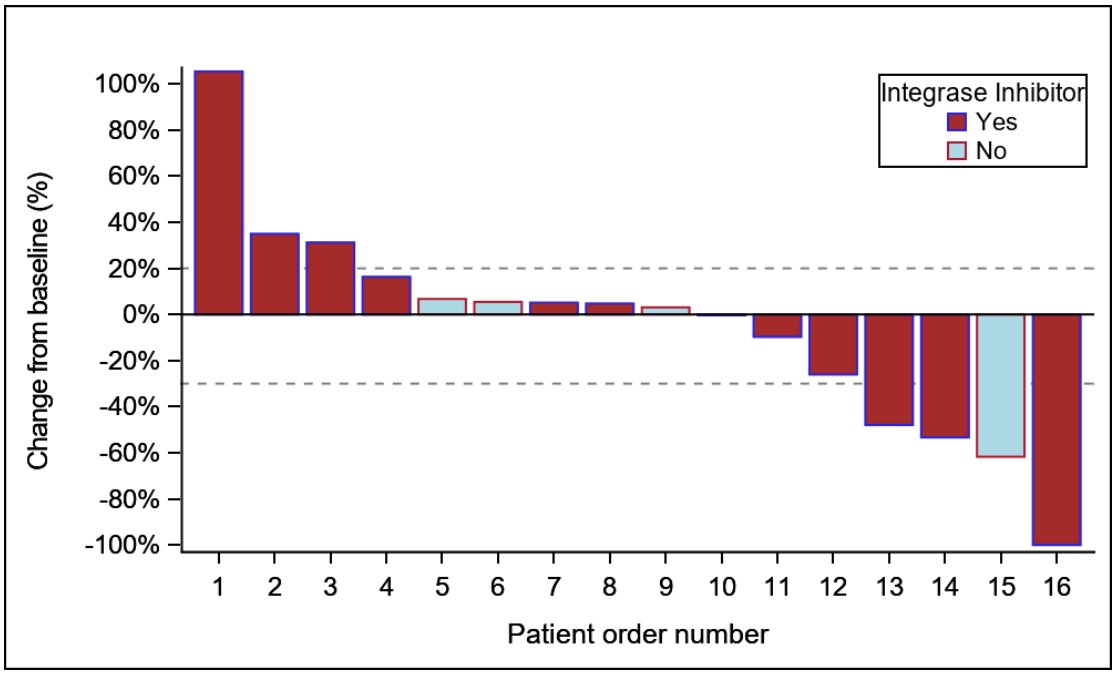


Distribution of responders patients by Type of tumor-and PD-L1l

Type of tumor and PD-L1					
		NA (N=3)	Negative (N=9)	Positive (N=4)	Total (N=16)
Type of cancer					
Anal	n (%)	1 (33.33)	1 (11.11)	0 (0.00)	2 (12.50)
NSCLC	n (%)	2 (66.67)	4 (44.44)	4 (100.00)	10 (62.50)
Bladder	n (%)	0 (0.00)	1 (11.11)	0 (0.00)	1 (6.25)
Melanoma	n (%)	0 (0.00)	2 (22.22)	0 (0.00)	2 (12.50)
SCLC	n (%)	0 (0.00)	1 (11.11)	0 (0.00)	1 (6.25)

Only responders are included in the above table

Waterfall plot of target lessions measure change and best response by patient-(color INTSI)



Distribution of patients with tumor assessment by integrase inhibitors yes/no (N=16)

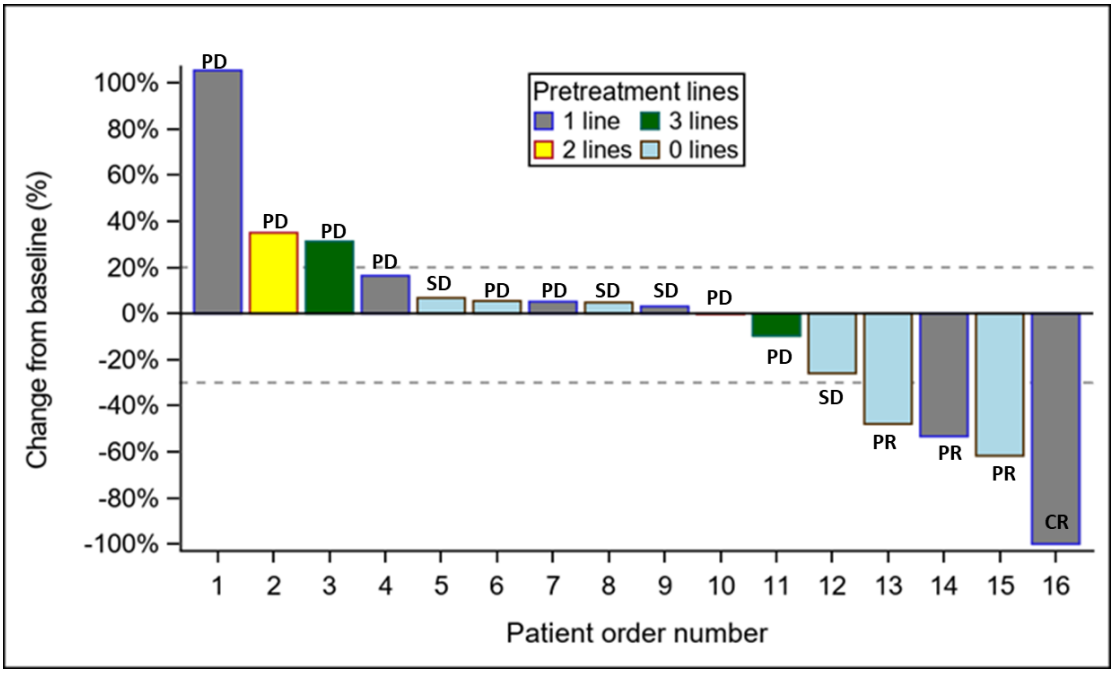
		Total (N=16)
Integrase inhibitor		
No	n (%)	4 (25.00)
Yes	n (%)	12 (75.00)

Distribution of patients by integrase inhibitors yes/no - Global (N=20)

		Total (N=20)
Integrase Inhibitor		
Yes	n (%)	14 (70.00)
No	n (%)	6 (30.00)

Waterfall plot of target lesions measure change, best response and pretreatment lines by patient

In the following graph the color is associated with the number of pretreatment lines for each patient. Also the best response is indicated with the text on the vertical bar. The hight if the bar corresponds to the best % change from baseline of the tumor measures.



Distribution of patients with tumor assessment by number of pretreatment lines (N=16)

		Total (N=16)
Pre-treatment lines		
0 lines	n (%)	6 (37.50)
1 line	n (%)	6 (37.50)
2 lines	n (%)	2 (12.50)
3 lines	n (%)	2 (12.50)

Distribution of patients by number of pretreatment lines - Global (N=20)

		Total (N=20)
Pre-treatment lines		
0 lines	n (%)	8 (40.00)
1 line	n (%)	7 (35.00)
2 lines	n (%)	2 (10.00)
3 lines	n (%)	3 (15.00)

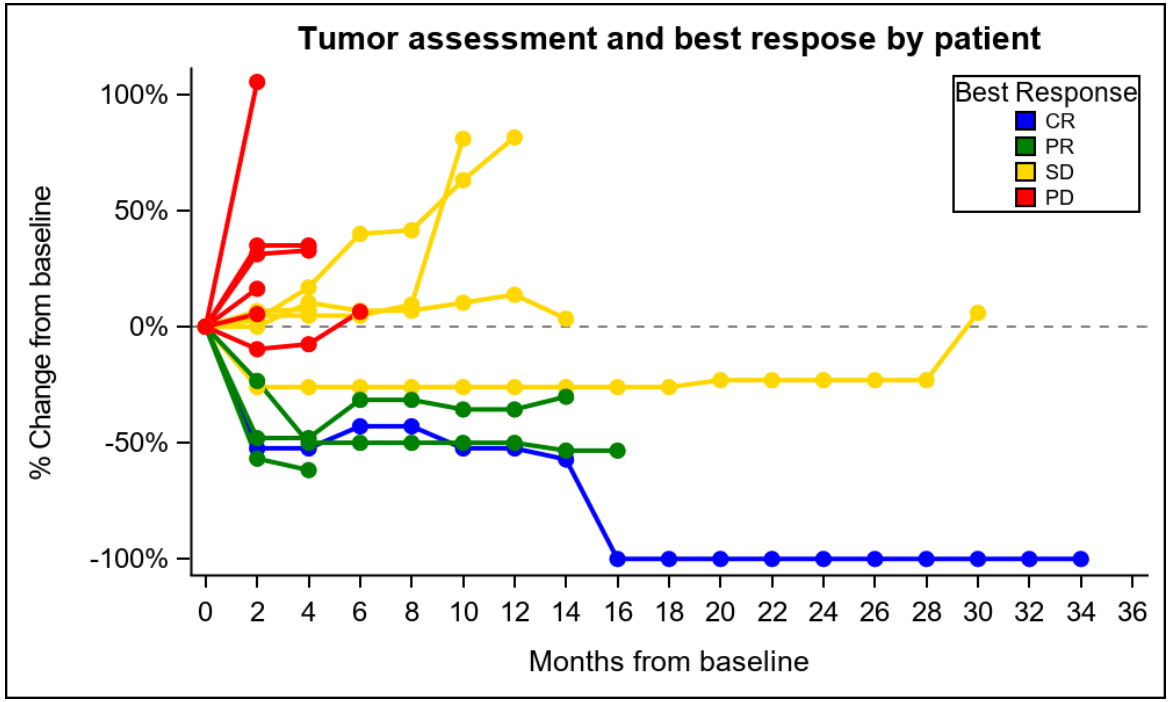
SPIDER PLOT OF TUMOR RESPONSE

The spider plot request is representing the tumor response by week. The tumor response is measure as percent change of measurements with respect to the baseline.

Each line corresponds to each patient, The color of the line is based on the best response (RECIST).

Five patients are excluded from this graph due to the fact that tumor measure is taken only once (at baseline).

Spider plot of tumor response and patient best response



Tumor assessment during the study by patient

Tumor assessment Overall Response and Best response																				
Patient and treatment		Overall responses and diameter																		Best response
Patient Id	Treatment	Baseline diameter	Resp (diam) 1	Resp (diam) 2	Resp (diam) 3	Resp (diam) 4	Resp (diam) 5	Resp (diam) 6	Resp (diam) 7	Resp (diam) 8	Resp (diam) 9	Resp (diam) 10	Resp (diam) 11	Resp (diam) 12	Resp (diam) 13	Resp (diam) 14	Resp (diam) 15	Resp (diam) 16	Resp (diam) 17	
00200002	Dolutegravir	78																		NE
00200003	Dolutegravir	21	PR(10)	PR(10)	PR(12)	PR(12)	PR(10)	PR(10)	PR(9)	CR(0)	CR(0)	CR(0)	CR(0)	CR(0)	CR(0)	CR(0)	CR(0)	CR(0)	CR(0)	CR
00200004	No Dolutegravir	45																		NE
00200009	No Dolutegravir	73	PR(38)	PR(38)	PD(50)	PD(50)	PD(47)	PD(47)	PD(51)											PR
00200011	Dolutegravir	58	SD(58)	SD(64)	SD(62)	SD(62)	SD(64)	SD(66)	SD(60)											SD
00200017	No Dolutegravir	81	PR(35)	PD(31)																PR
00200018	Dolutegravir	30	SD(23)	PR(15)	PD(15)	PD(15)	PD(15)	PD(15)	PD(14)	PD(14)										PR
01100001	No Dolutegravir	64	PD(84)	PD(85)																PD
01100005	No Dolutegravir	78	PD(82)																	PD
01100010	No Dolutegravir	159	PD(185)																	PD
01100021	Dolutegravir	93	PD(84)	PD(86)	PD(99)															PD
03500008	No Dolutegravir	118																		NE
03500012	Dolutegravir	65																		NE
03500020	No Dolutegravir	92	PD(97)																	PD
03600013	Dolutegravir	120	PD(162)	PD(162)																PD
04600015	No Dolutegravir	65	SD(67)	SD(76)	PD(91)	PD(92)	PD(106)	PD(118)												SD
05300007	Dolutegravir	100	SD(74)	SD(74)	SD(74)	SD(74)	SD(74)	SD(74)	SD(74)	SD(74)	SD(74)	SD(77)	SD(77)	SD(77)	SD(77)	SD(77)	PD(106)			SD
05300016	Dolutegravir	92	PD(189)																	PD
05300019	Dolutegravir	21	SD(22)	SD(22)	SD(22)	SD(23)	PD(38)													SD
10100006	No Dolutegravir	134	SD(143)	PD(144)																SD

Tumor assessment during the study by patient months from baseline to the assessment date

		Overall response and months from baseline assessmentt																	
Patient number and ATR		Baseline date	First (month)	Second (month)	Third (month)	Fourth (month)	Fith (month)	Sixth (month)	Seventh (month)	Eigth (month)	Nineth (month)	10th (month)	11th (month)	12th (month)	13th (month)	14th (month)	15th (month)	16th (month)	17th (month)	Best (month)
Patient ID	Medication ATR																			
00200002	Dolutegravir	16/05/2017	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
00200003	Dolutegravir	17/05/2017	PR(4)	PR(6)	PR(8)	PR(11)	PR(14)	PR(17)	PR(20)	CR(22)	CR(25)	CR(28)	CR(31)	NE(35)	CR(36)	CR(39)	CR(42)	CR(45)	CR	CR
00200004	No Dolutegravir	19/05/2017	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
00200009	No Dolutegravir	30/08/2017	PR(4)	PR(6)	PD(9)	PD(11)	PD(14)	PD(17)	PD(18)	PD	NE	NE	NE	NE	NE	NE	NE	NE	NE	PR
00200011	Dolutegravir	20/10/2017	SD(3)	SD(6)	SD(7)	SD(9)	SD(11)	SD(15)	SD	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	SD
00200017	No Dolutegravir	10/05/2018	PR(4)	PD	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	PR
00200018	Dolutegravir	22/05/2018	SD(4)	PR(5)	PD(7)	PD(9)	PD(10)	PD(12)	PD(14)	PD	NE	NE	NE	NE	NE	NE	NE	NE	NE	PR
01100001	No Dolutegravir	28/04/2017	PD(3)	PD	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	PD
01100005	No Dolutegravir	02/06/2017	PD	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	PD
01100010	No Dolutegravir	20/09/2017	PD	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	PD
01100021	Dolutegravir	13/06/2018	PD(4)	PD(6)	PD	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	PD
03500008	No Dolutegravir	25/08/2017	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Patient number and ATR		Overall response and months from baseline assessmentt																		
		Baseline date	First (month)	Second (month)	Third (month)	Fourth (month)	Fith (month)	Sixth (month)	Seventh (month)	Eigth (month)	Nineth (month)	10th (month)	11th (month)	12th (month)	13th (month)	14th (month)	15th (month)	16th (month)	17th (month)	Best (month)
Patient ID	Medication ATR																			
03500012	Dolutegravir	08/11/2017	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
03500020	No Dolutegravir	26/06/2018	PD	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	PD
03600013	Dolutegravir	08/11/2017	PD(4)	PD(4)	PD	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	PD
04600015	No Dolutegravir	23/03/2018	SD(5)	SD(7)	PD(8)	PD(10)	PD(12)	PD	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	SD
05300007	Dolutegravir	10/07/2017	SD(4)	SD(6)	SD(8)	SD(9)	SD(12)	SD(13)	SD(15)	SD(17)	SD(20)	SD(20)	SD(22)	NE(25)	SD(28)	SD(29)	PD	NE	NE	SD
05300016	Dolutegravir	28/03/2018	PD	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	PD
05300019	Dolutegravir	28/05/2018	SD(4)	SD(6)	SD(8)	SD(9)	PD	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	SD
10100006	No Dolutegravir	05/07/2017	SD(3)	PD	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	SD

Best response during the treatment period

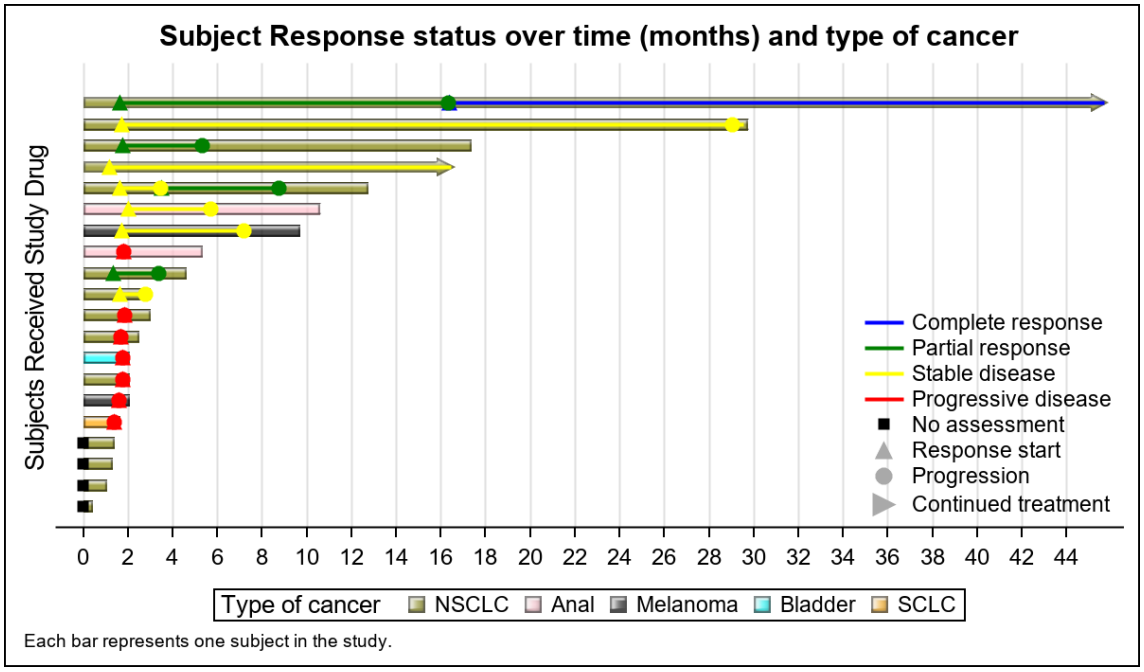
Best response

		Total (N=20)
Best response		
CR	n (%)	1 (5.00)
PR	n (%)	3 (15.00)
SD	n (%)	5 (25.00)
PD	n (%)	7 (35.00)
NE	n (%)	4 (20.00)

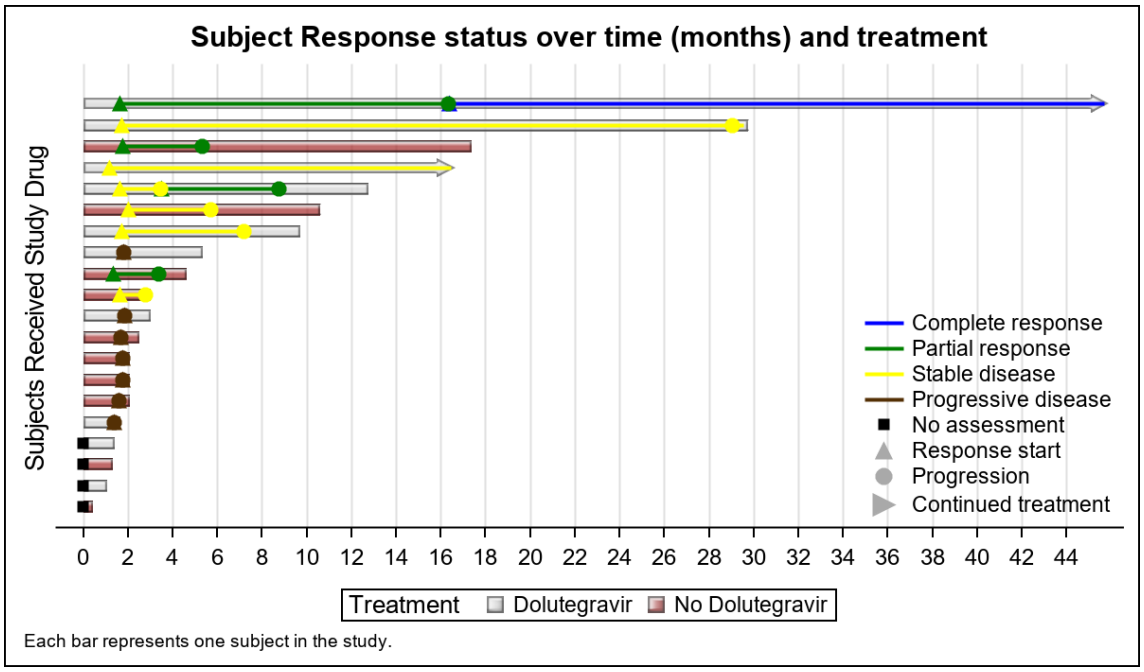
Tumor response status during the treatment

In this section all treated patients are included.

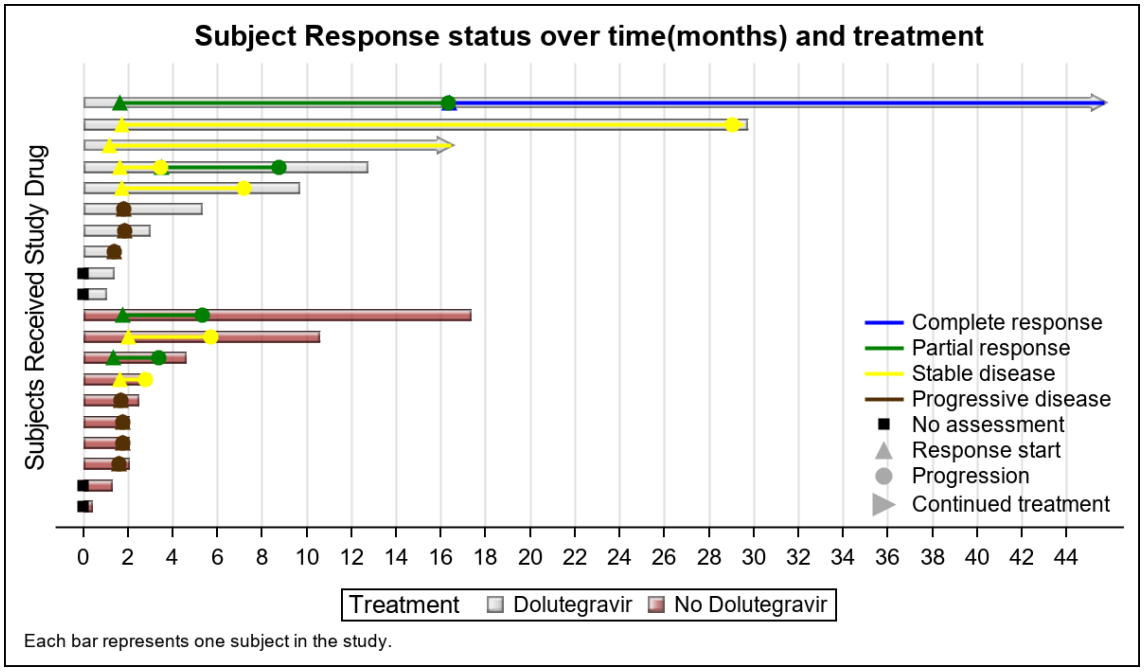
Tumor response status over time colored by type of cancer



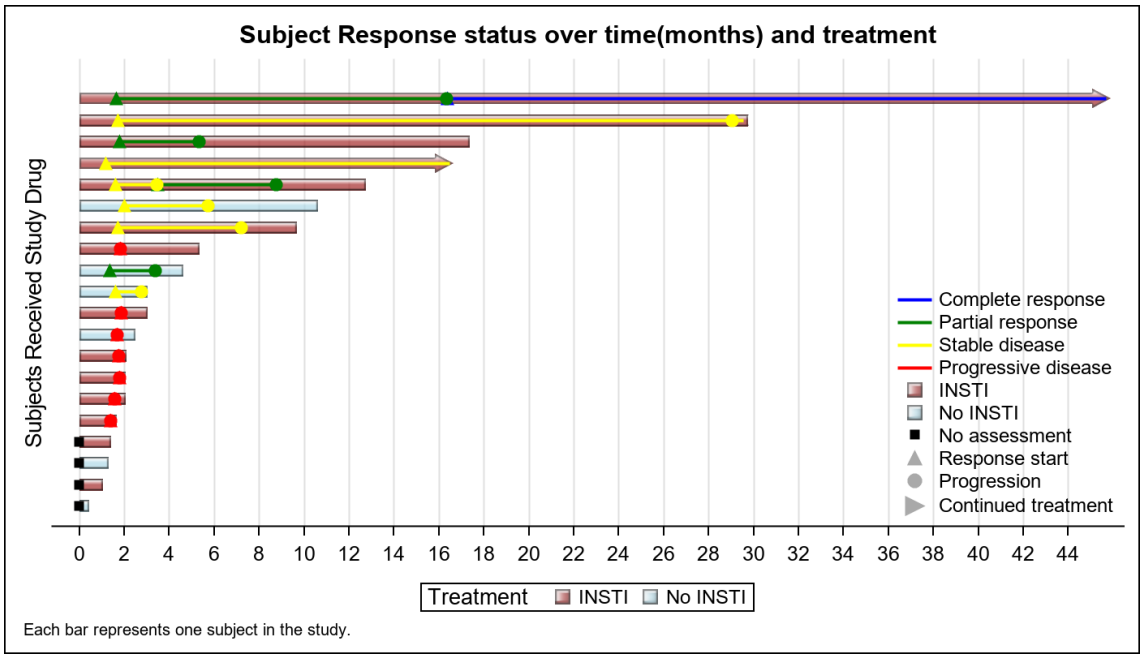
Tumor response status colored by treatment with Dolutegravir



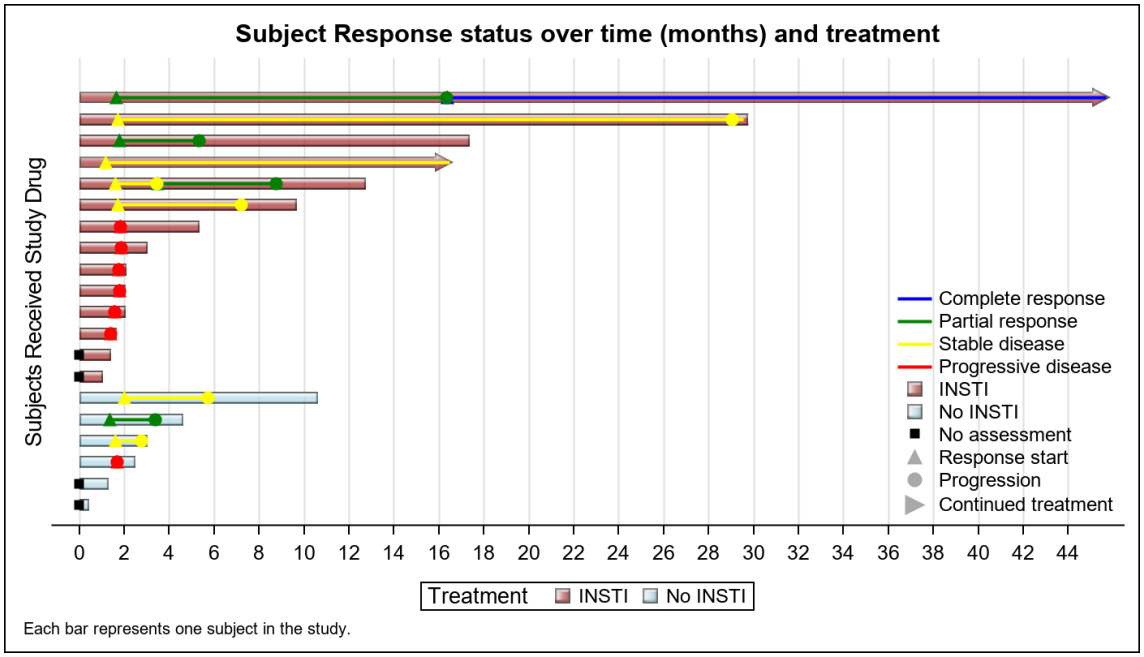
Tumor response status colored by treatment with Dolutegravir (grouped)



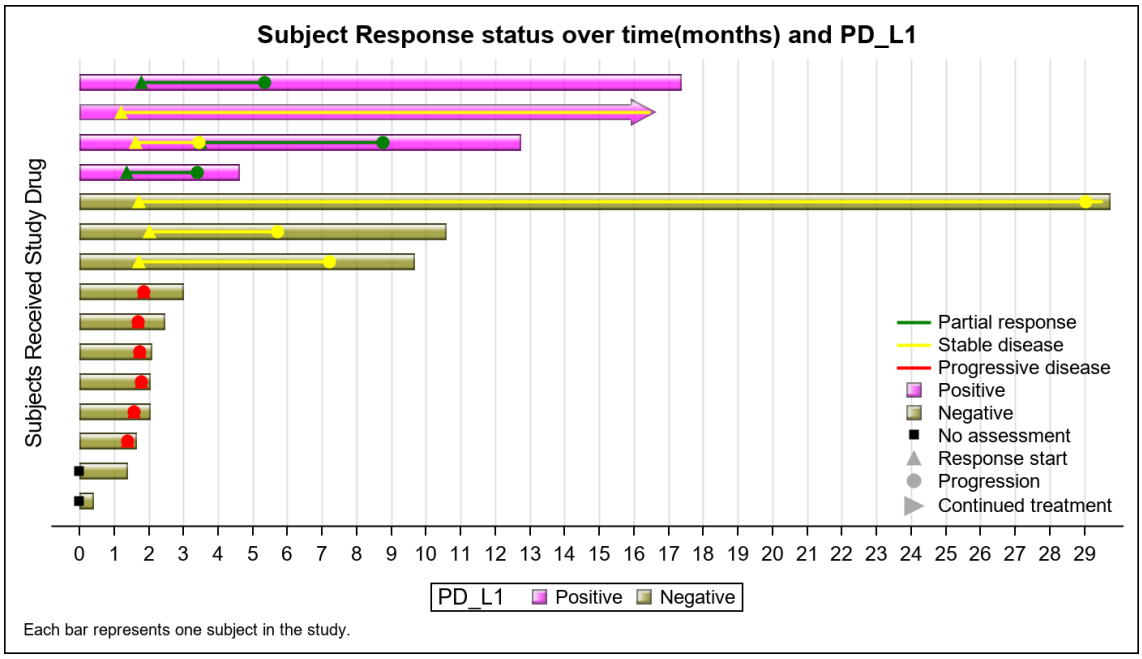
Tumor response status colored by treatment with INSTI/NNRTI



Tumor response status colored by treatment with INSTI/NNRTI (grouped)



Tumor response status colored by baseline PD-L1



5 cases are excluded due to the fact that PD_L1 value is not available

DURATION OF RESPONSE

Only patients with best response Stable disease, Partial Response or Complete response during the treatment period are included in the response analysis.

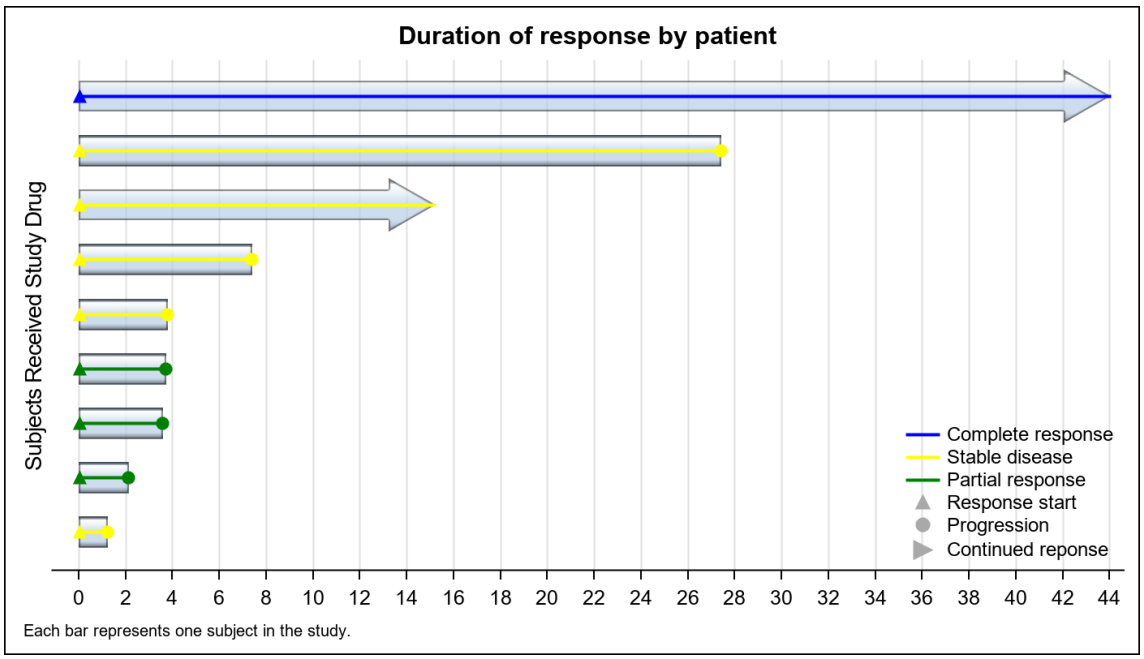
Duration of response is the time from response (R) to progression/death (P/D).

The duration of response is shown and analyzed for three different criteria to group de patients, based on three baseline characteristics.

1.- Type of cancer
2.- Antiretroviral treatment – With or without Dolutegravir
3- Antiretroviral treatment- With INTSIs or without INSTI

Duration of response global

Duration of response global



Applying a Kaplan -Meyer model the median duration of response is estimated

Kaplan Meier Estimated median duration of response – global

Subjects	Event	% Events	Censored	% Censored	Media n	CI 95% LL	CI 95% UL
9	6	66.7	3	33.3	6.2	3.1	NA

The median estimated is 6.2 months CI95% (3.1-NA)

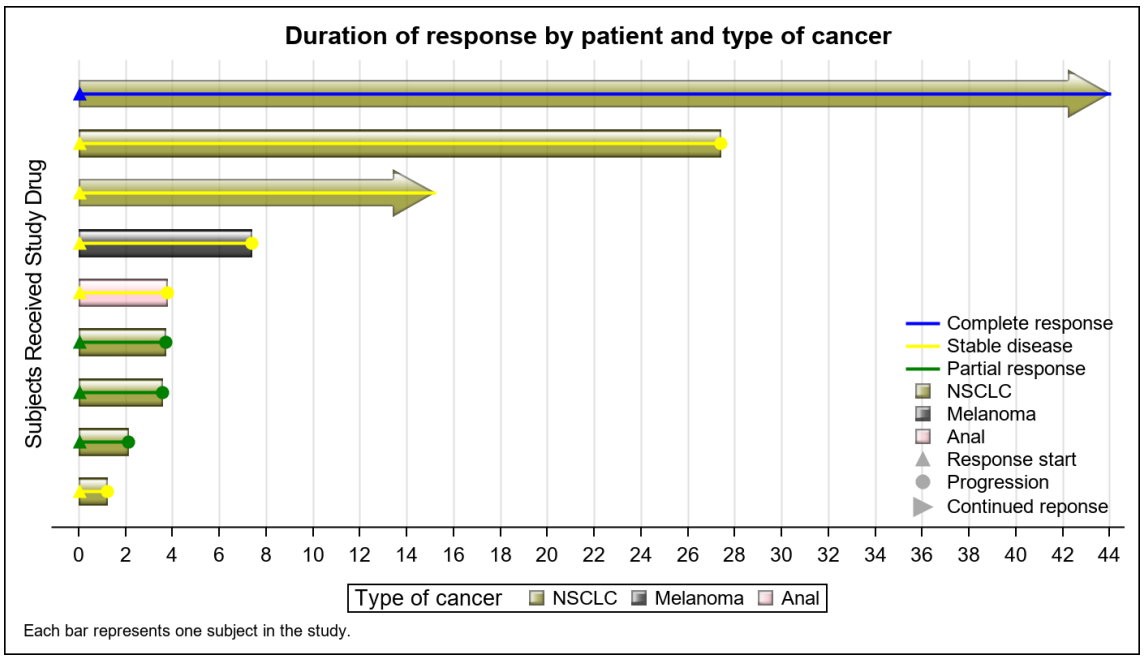
The descriptive analysis of the response duration gives the following results

Summary table of response duration- global

		Total (N=9)
Duration of response(months)		
	n	9
	Mean (SD)	12.05 (14.65)
	Median [Q1,Q3]	3.78 [3.58, 15.24]
	Min, Max	1.22, 44.05

Duration of response by type of cancer

Duration of response by type of cancer



Applying a Kaplan -Meyer model the median duration of response is estimated for each type of cancer

Kaplan Meier Estimated median duration of response- type of cancer

Strata	Subjects	Event	% Events	Censored	% Censored	Median	CI 95%
Anal	1	1	100.0	0	0.0	3.8	(NA,NA)
Melanoma	1	1	100.0	0	0.0	7.4	(NA,NA)
NSCLC	7	5	71.4	2	28.6	3.7	1.2

The median duration of response cannot be estimated with the Kaplan -Meier model in the melanoma group

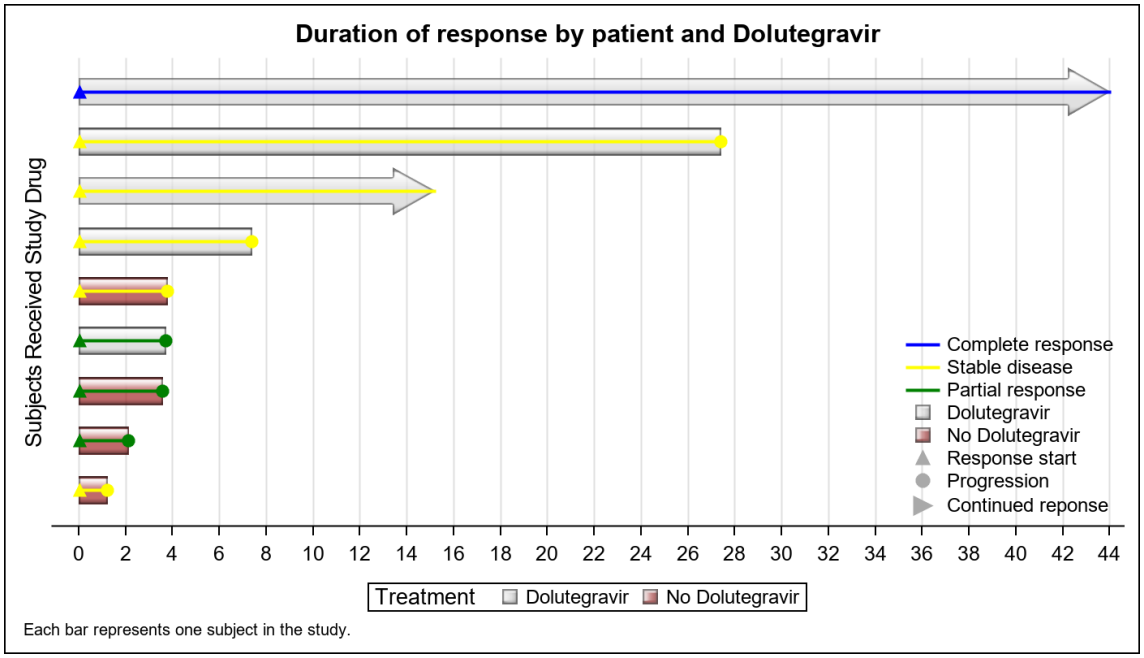
The descriptive analysis of the response duration gives the following results

Descriptive analysis of response duration by type of cancer

		Type of cancer			
		Anal (N=1)	Melanoma (N=1)	NSCLC (N=7)	Total (N=9)
Duration of response(months)					
	n	1	1	7	9
	Mean (SD)	3.78 (.)	7.39 (.)	13.90 (16.35)	12.05 (14.65)
	Median [Q1,Q3]	3.78 [3.78, 3.78]	7.39 [7.39, 7.39]	3.71 [2.10, 27.40]	3.78 [3.58, 15.24]
	Min, Max	3.78, 3.78	7.39, 7.39	1.22, 44.05	1.22, 44.05

Duration of response by ATR with or without Dolutegravir

Duration of response by ATR with or without Dolutegravir



Applying a Kaplan -Meyer model the median duration of response is estimated for patients stratified by treatment with or without Dolutegravir

Kaplan Meier Estimated median duration of response- Dolutegravir/ no Dolutegravir

Strata	Subjects	Event	% Events	Censored	% Censored	Median	CI 95%
Dolutegravir	5	3	60.0	2	40.0	27.4	(3.7, NA)
No Dolutegravir	4	4	100.0	0	0.0	2.8	(1.2, 3.8)

Log-Rank test p-value=0.0108

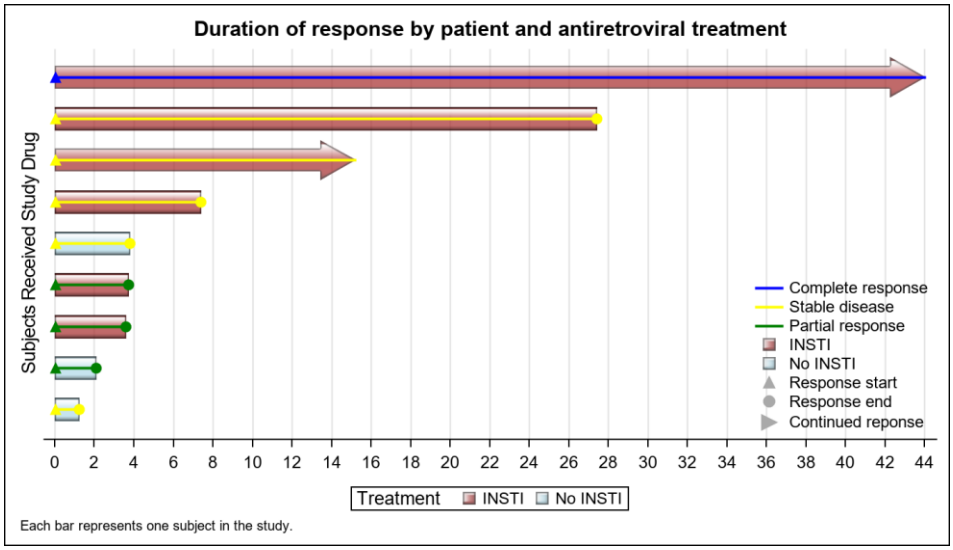
The descriptive analysis of the response duration gives the following result

Descriptive analysis of response duration - Dolutegravir/ no Dolutegravir

Antiretroviral treatment					
		Dolutegravir (N=5)	No Dolutegravir (N=4)	Total (N=9)	P Value Test
Duration of response(months)					
	n	5	4	9	
	Mean (SD)	19.56 (16.43)	2.67 (1.22)	12.05 (14.65)	Wilcoxon: 0.0709
	Median [Q1,Q3]	15.24 [7.39, 27.40]	2.84 [1.66, 3.68]	3.78 [3.58, 15.24]	
	Min, Max	3.71, 44.05	1.22, 3.78	1.22, 44.05	

Duration of response by treatment with INSTIs or no INSTIs

Duration of response by treatment with INSTIs or no INSTIs



Applying a Kaplan -Meyer model the median duration of response is estimated for patients with INSTI or No INSTI

Kaplan Meier Estimated median duration of response- INSTIs or no INSTIs

Strata	Subjects	Event	% Events	Censored	% Censored	Median	CI 95%
INSTI	6	4	66.7	2	33.3	17.4	(3.6, NA)
No INSTI	3	3	100.0	0	0.0	2.1	(1.2, 3.8)

Log-Rank test p-value=0.0364

The descriptive analysis of the response duration gives the following results

Descriptive analysis of response duration - INSTIs or no INSTIs

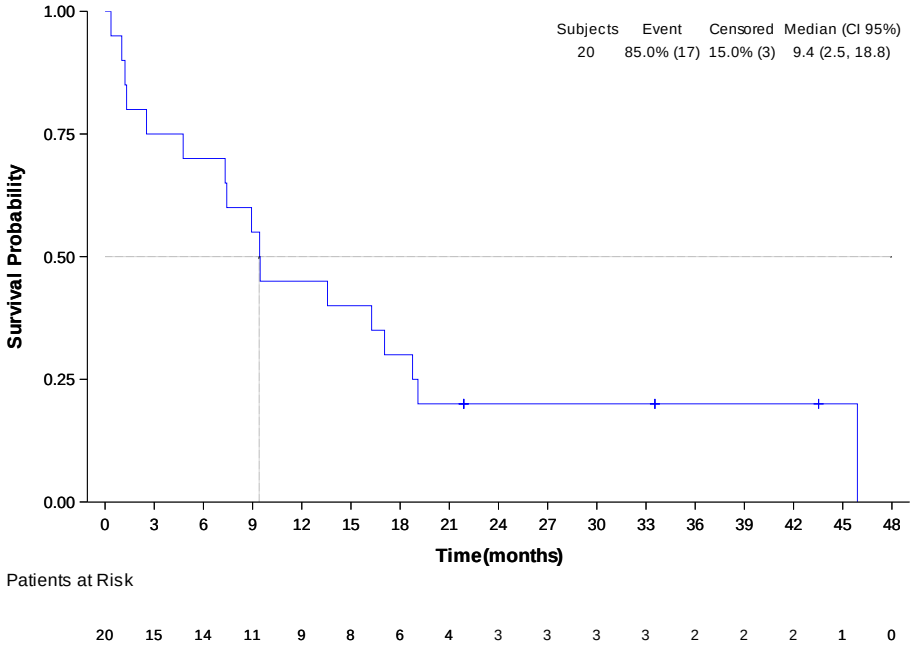
Antiretroviral treatment					
		INSTI (N=6)	No INSTI (N=3)	Total (N=9)	P Value Test
Duration of response(months)					
	n	6	3	9	
	Mean (SD)	16.90 (16.07)	2.37 (1.30)	12.05 (14.65)	Wilcoxon: 0.1318
	Median [Q1,Q3]	11.32 [3.71, 27.40]	2.10 [1.22, 3.78]	3.78 [3.58, 15.24]	
	Min, Max	3.58, 44.05	1.22, 3.78	1.22, 44.05	

OS ANALYSIS

OS is defined as the time from the inclusion date to the death, due to any cause. A patient who does not dies, is censored at the last contact date.

OS analysis

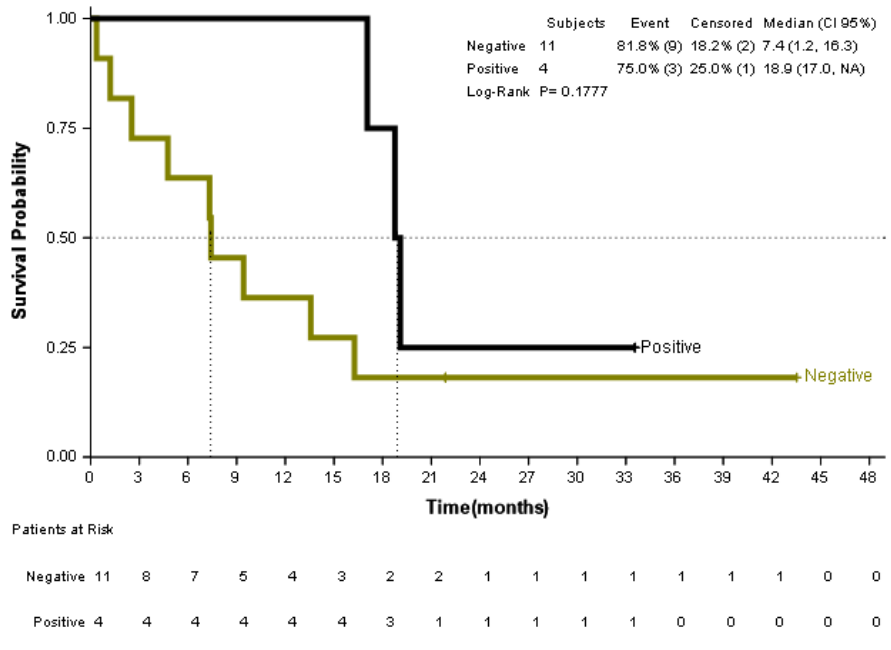
Kaplan Meier model result of the OS analysis



The median overall survival estimated is 9.4 months (CI95% 2.5 -18.8)

OS analysis by PD-L1

Kaplan Meier curve of OS - Strata PD-L1



Kaplan-Meier model- Summary results

Strata	Subjects	Event	% Events	Censored	% Censored	Median	CI 95%
Negative	11	9	81.8	2	18.2	7.4	(1.2, 16.3)
Positive	4	3	75.0	1	25.0	18.9	(17.0, NA)

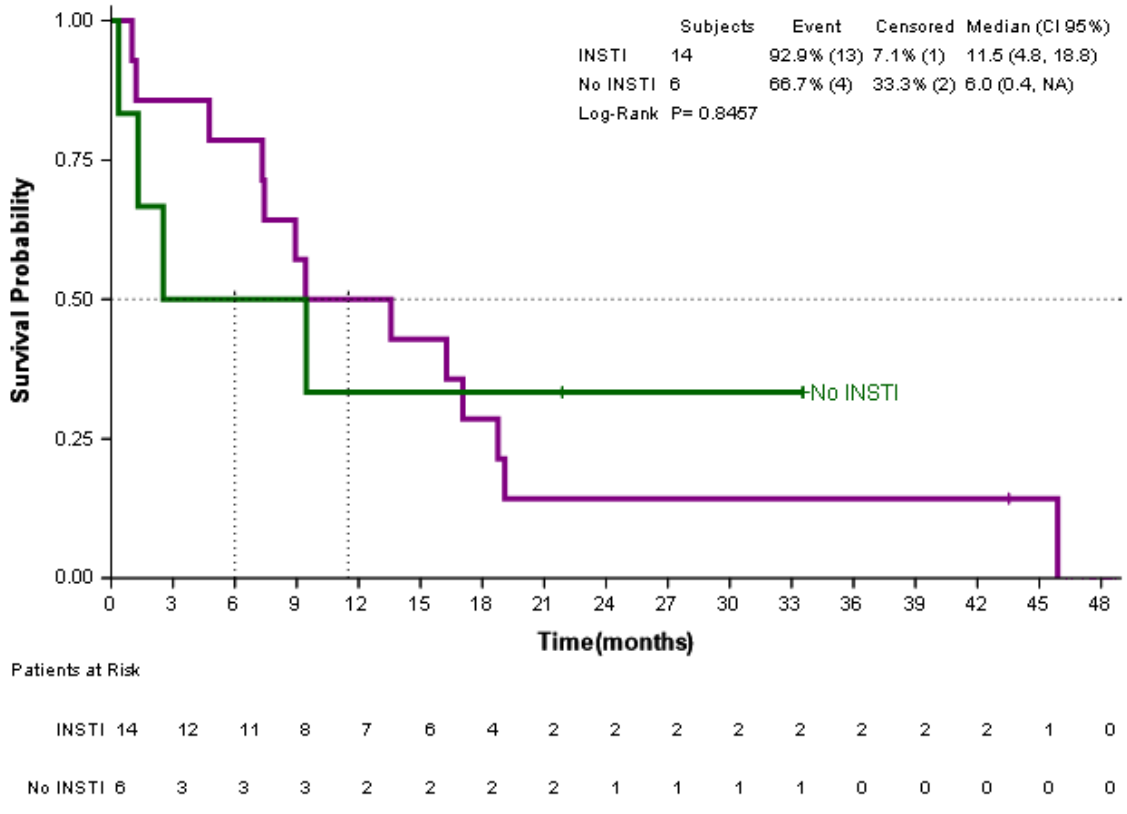
Log-rank test

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	1.8171	1	0.1777

No statistically significant effect of PD_L1 in the OS probability distribution function is found

OS analysis by Integrase Inhibitors

Kaplan Meier curve of OS- Strata Integrase Inhibitors



Kaplan-Meier model- Summary results

Strata	Subjects	Event	% Events	Censored	% Censored	Median	CI 95% LL	CI 95% UL
INSTI	14	13	92.9	1	7.1	11.5	4.8	18.8
No INSTI	6	4	66.7	2	33.3	6.0	0.4	NA

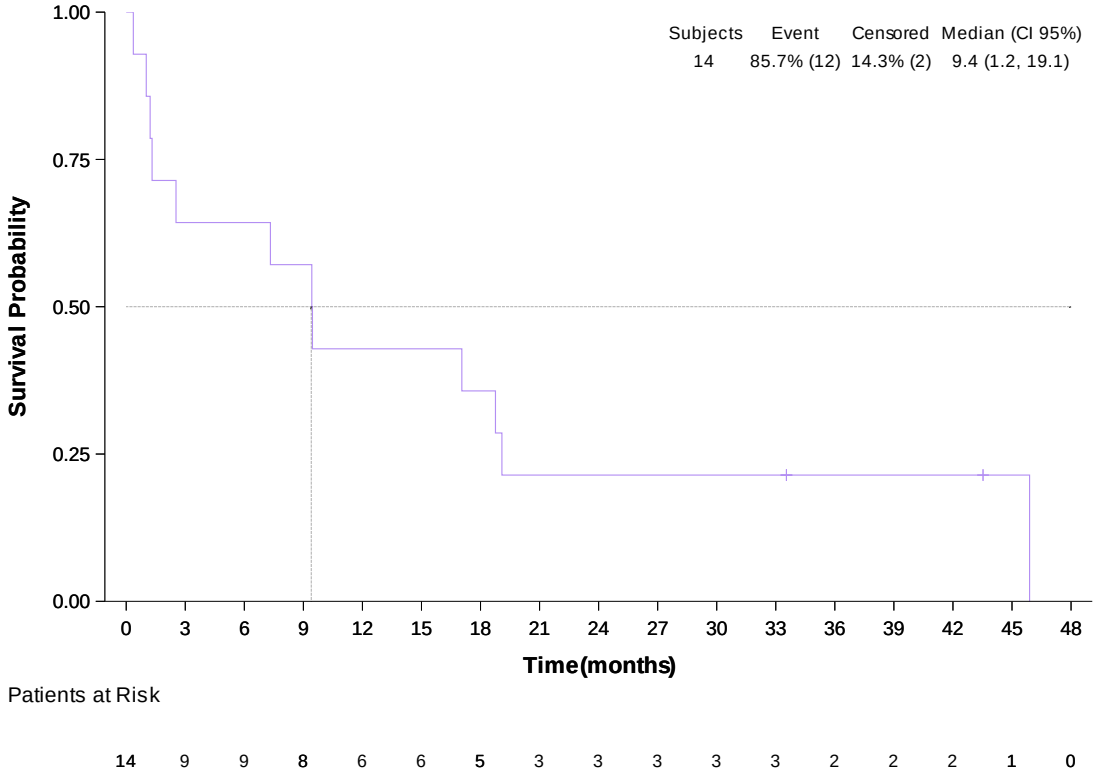
Log-rank test

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	0.0379	1	0.8457

No statistically significant effect of the presence of Integrase Inhibitors in the OS probability distribution function is found

OS analysis – patients with NSCLC

Kaplan Meier curve of OS- NSCLC patients

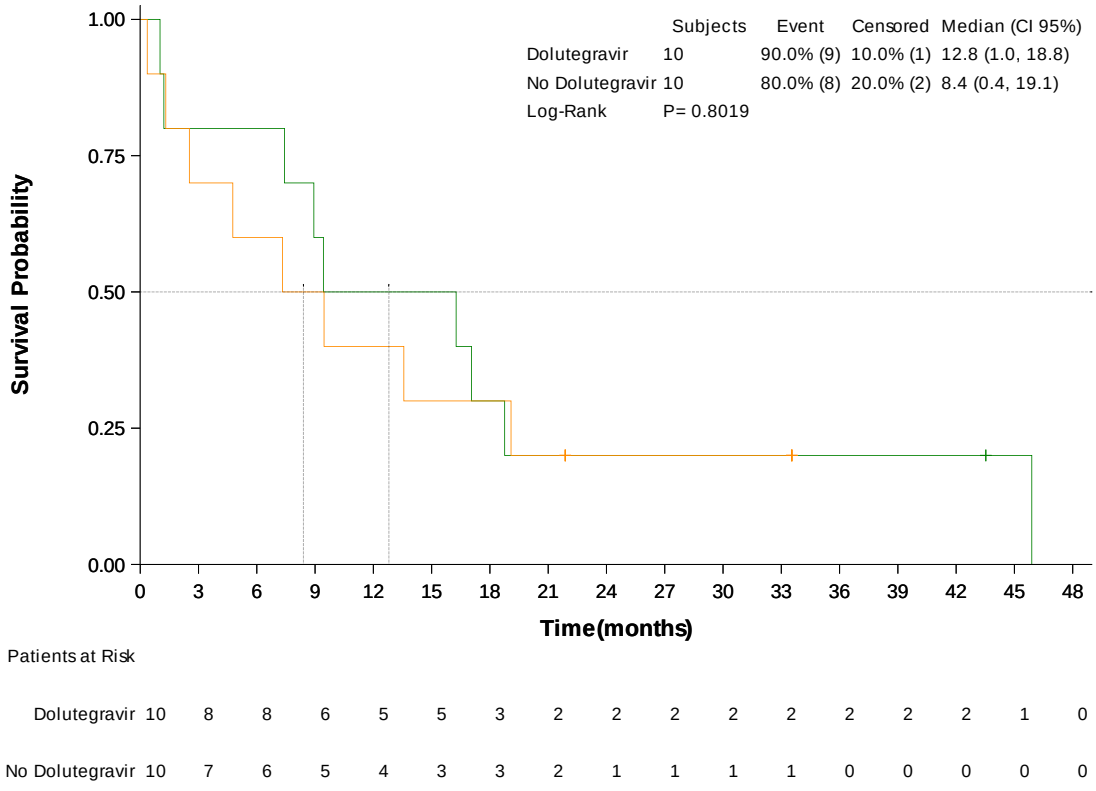


Kaplan-Meier model- Summary results

Subjects	Event	% Events	Censored	% Censored	Median	CI 95% LL	CI 95% UL
14	12	85.7	2	14.3	9.4	1.2	19.1

OS analysis by Dolutegravir

Kaplan Meier curve of OS- Strata Dolutegravir



Kaplan-Meier model- Summary results

Strata	Subjects	Event	% Events	Censored	% Censored	Median	CI 95%
Dolutegravir	10	9	90.0	1	10.0	12.8	(1.0, 18.8)
No Dolutegravir	10	8	80.0	2	20.0	8.4	(0.4, 19.1)

Log-rank test

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	0.0630	1	0.8019

No statistically significant effect of the presence of Dolutegravir in the OS probability distribution function is found

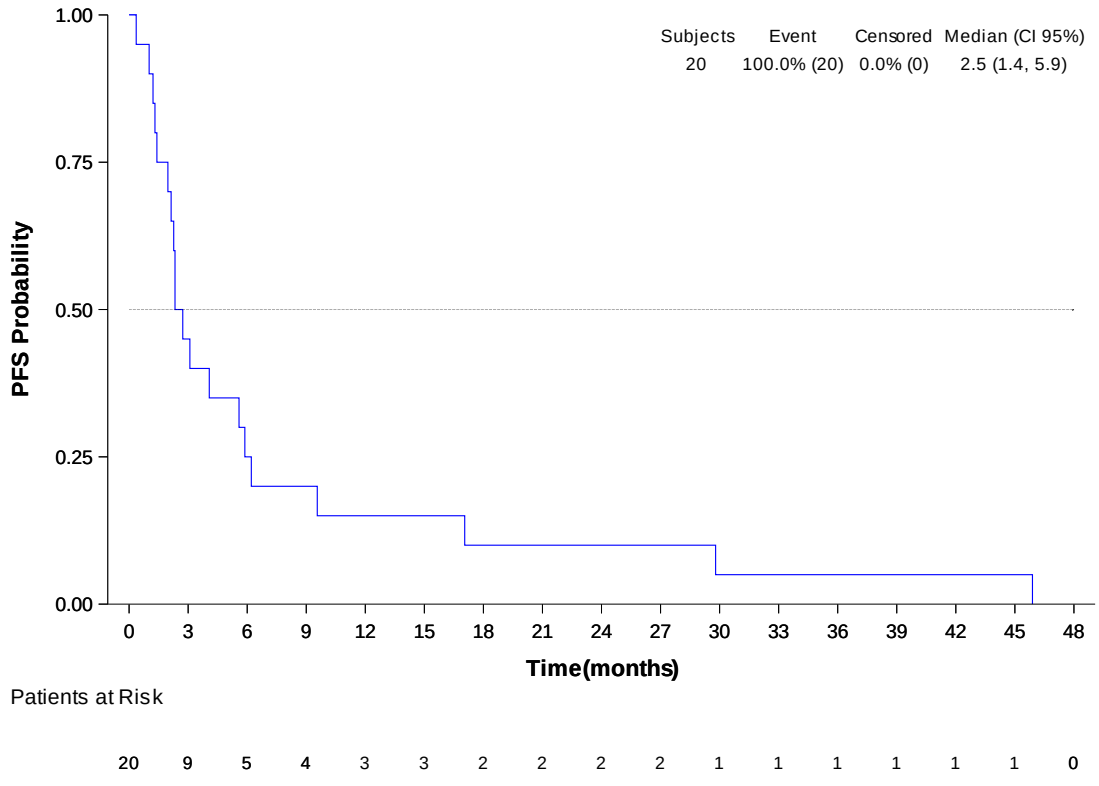
PFS ANALYSIS

PFS is defined as the time from the inclusion date to the progression or death, due to any cause, date. A patient who does not progresses neither dies, is censored at the last tumor evaluation where no progression is detected.

A patient with tumor evaluation, only at baseline, will be censored at the day 1 after the inclusion date.

PFS analysis global

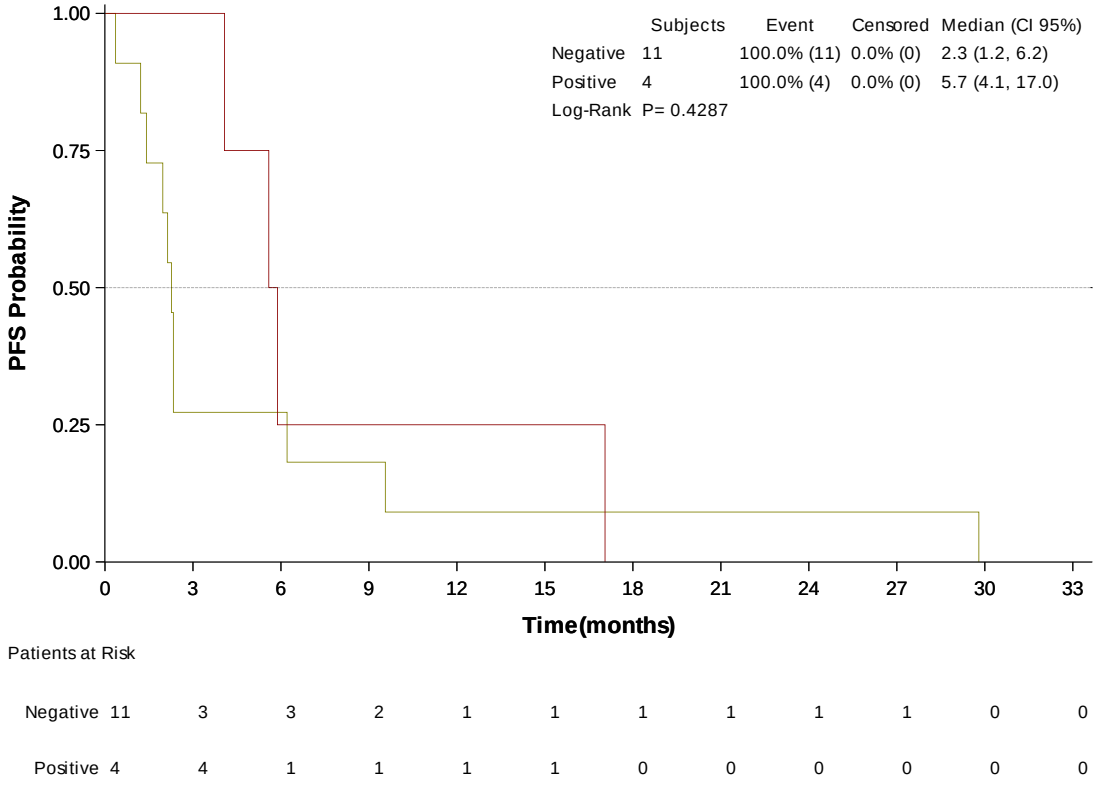
Kaplan Meier model result of the PFS analysis



The median PFS estimated is 2.5 months (CI95% 1.4-5.9)

PFS analysis by PD-L1

Kaplan Meier curve of PFS – Strata PD-L1



Kaplan-Meier model- Summary results

Strata	Subjects	Event	% Events	Censored	% Censored	Media n	CI 95% LL	CI 95% UL
Negative	11	11	100.0	0	0.0	2.3	1.2	6.2
Positive	4	4	100.0	0	0.0	5.7	4.1	17.0

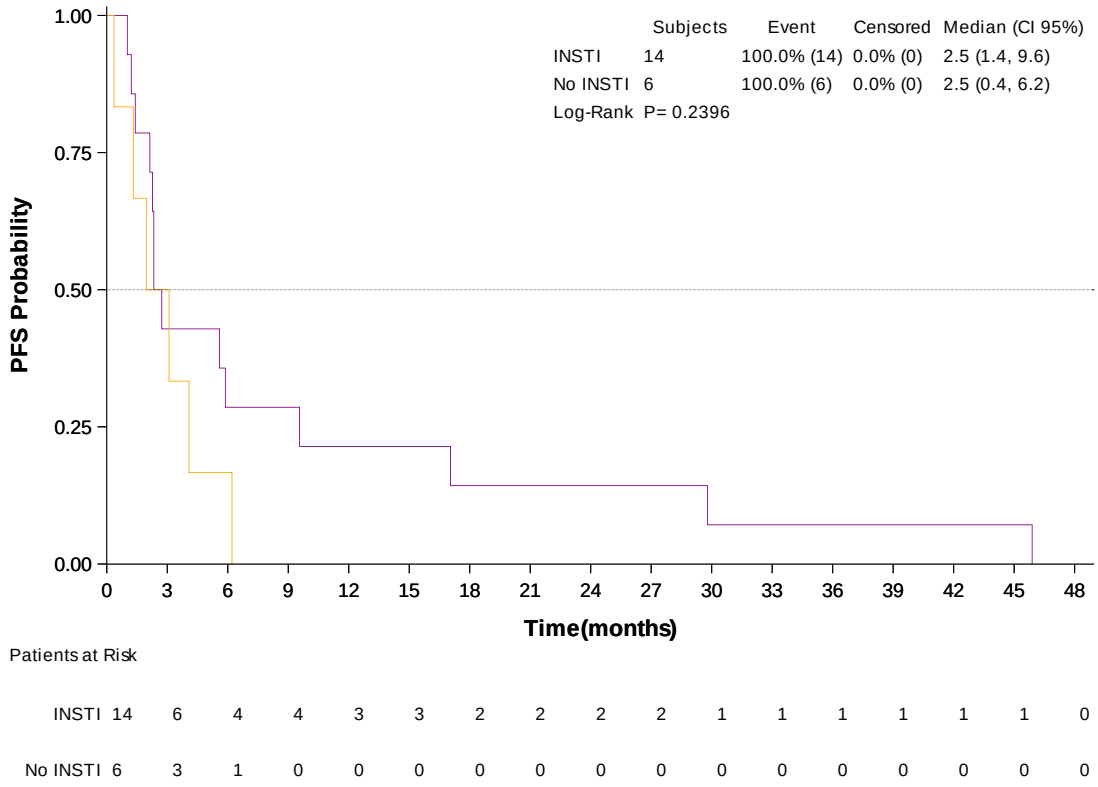
Log-rank test

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	0.6262	1	0.4287

No statistically significant effect of PD_L1 in the PFS probability distribution function is found

PFS analysis by Integrase Inhibitors

Kaplan Meier curve of PFS – Strata Integrase Inhibitors



Kaplan-Meier model- Summary results

Strata	Subjects	Event	% Events	Censored	% Censored	Median	CI 95%
INSTI	14	14	100.0	0	0.0	2.5	(1.4, 9.6)
No INSTI	6	6	100.0	0	0.0	2.5	(0.4, 6.2)

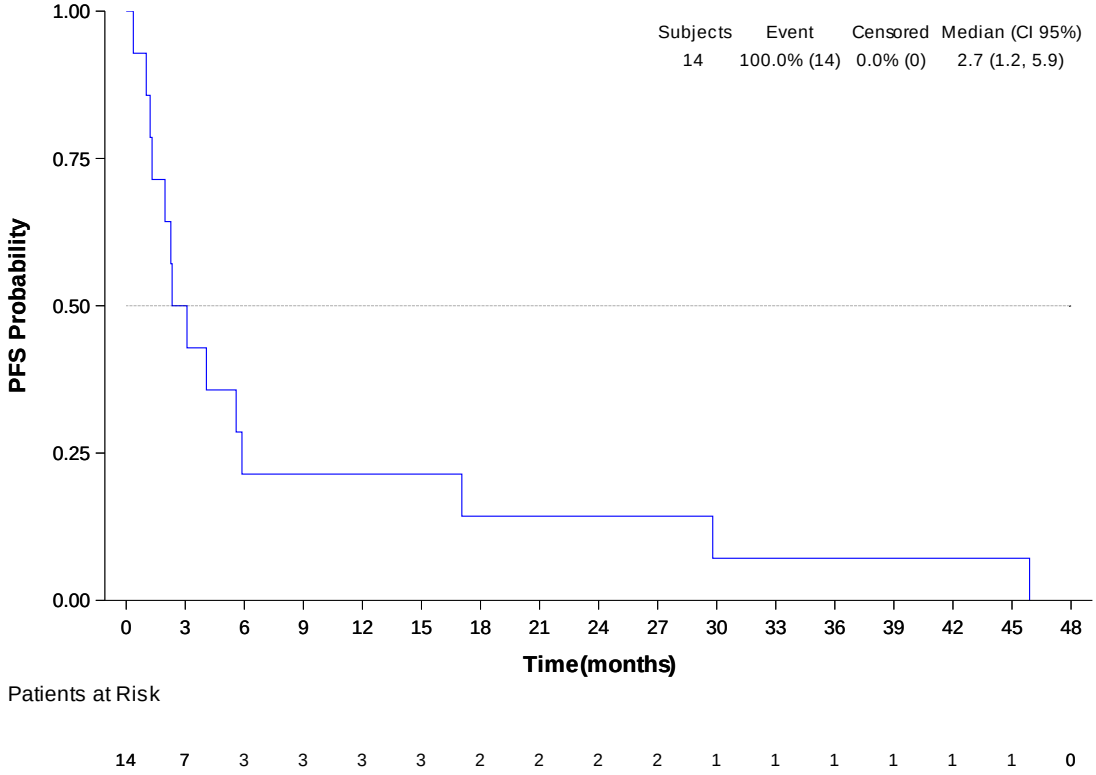
Log-rank test

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	1.3827	1	0.2396

No statistically significant effect of the presence of Integrase Inhibitors, in the PFS probability distribution function is found

PFS analysis in patients with NSCLC

Kaplan Meier curve of PFS – NSCLC patients

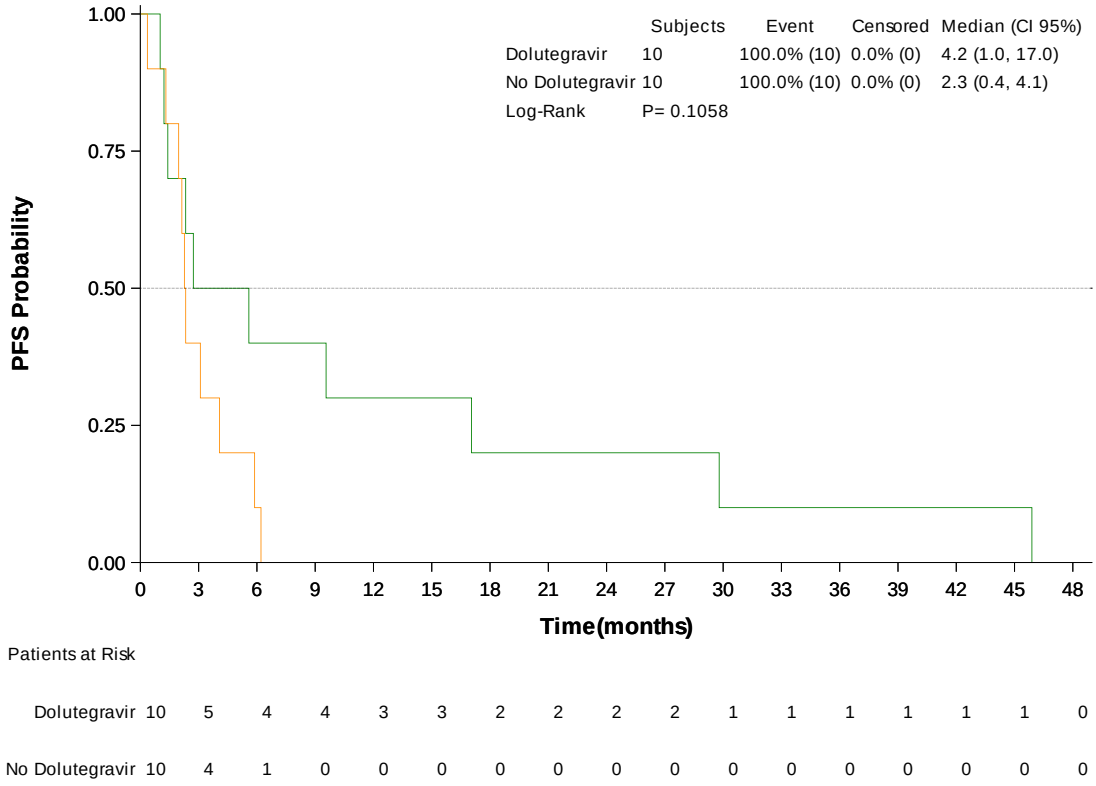


Kaplan-Meier model- Summary results

Subjects	Event	% Events	Censored	% Censored	Median	CI 95%
14	14	100.0	0	0.0	2.7	(1.2, 5.9)

PFS analysis by Dolutegravir

Kaplan Meier curve of PFS – Strata Dolutegravir



Kaplan-Meier model- Summary results

Strata	Subjects	Event	% Events	Censored	% Censored	Median	CI 95%
Dolutegravir	10	10	100.0	0	0.0	4.2	(1.0, 17.0)
No Dolutegravir	10	10	100.0	0	0.0	2.3	(0.4, 4.1)

Log-rank test

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	2.6161	1	0.1058

No statistically significant effect of the presence of Dolutegravir, in the PFS probability distribution function is found

11.4.2 Efficacy Conclusions

Durvalumab treatment is confirmed after a long follow-up as a feasible and active treatment in HIV-1-infected cancer patients under cART. HIV-1-infected subjects on suppressive antiretroviral therapy and advanced cancer had clinical benefit in 45% of cases, including patients with long lasting responses.

8. SAFETY EVALUATION

8.1. EXTENT OF EXPOSURE

In this section adverse events happening during the study are analyzed.

First a summary of the toxicity reported is tabulated.

Also, the maximum toxicity grade reported by adverse event and patient is tabulated, indicating the frequency and percentage of occurrence

The summary tables of maximum reported toxicity grade by patient and preferred term are generated, grouped the corresponding MedDRA Preferred term (PT), sorted by decreasing total incidence of PT.

When calculating the incidence of adverse events, or any sub-classification, there of causality, seriousness, relation to study medication, etc, each Adverse Event is only counted once (corresponding to the maximum toxicity grade by patient and AE) and any repetitions of adverse events will be ignored; the denominator used is the corresponding total population size.

The incidence of serious AE is also tabulated.

8.2. ADVERSE EVENTS (AES)

8.2.1. Brief Summary of Adverse Events

Summary of Treatment Emergent Adverse Events

		Total (N=20)
Summary of TEAE		
Patients with at least one TEAE	n (%)	20 (100.00)
Patients with at least one TEAE grade 3/4	n (%)	11 (55.00)
Patients with at least one TEAE that the investigator considers related with study medication	n (%)	9 (45.00)
Patients with at least one TEAE grade 3/4 that the investigator considers related with study medication	n (%)	1 (5.00)
Patients with at least one serious TEAE	n (%)	14 (70.00)
Patients with at least one serious TEAE with outcome death	n (%)	4 (20.00)
Patients with at least one serious TEAE causing study treatment permanent discontinuation	n (%)	3 (15.00)
Patients with at least one serious TEAE that the investigator considers related with study medication	n (%)	1 (5.00)

12.2.2 Display of Adverse Events

Please refer to point 12.2.4 of this report.

12.2.3 Analysis of Adverse Events

Please refer to point 12.2.4 of this report.

12.2.4 Listing of Adverse Events by Patient

Maximum toxicity of TEAEs by patient

TEAE MedDRA Preferred Term	All grades		Maximum toxicity NCI grade									
			G1		G2		G3		G4		G5	
	n	%	n	%	n	%	n	%	n	%	n	%
Asthenia	14	70%	10	50%	4	20%	-	-	-	-	-	-
Pain	12	60%	6	30%	4	20%	2	10%	-	-	-	-
Arthralgia	10	50%	7	35%	3	15%	-	-	-	-	-	-
Cough	7	35%	4	20%	3	15%	-	-	-	-	-	-
Dyspnea	7	35%	5	25%	2	10%	-	-	-	-	-	-
Anorexia	7	35%	7	35%	-	-	-	-	-	-	-	-
Constipation	7	35%	6	30%	1	5%	-	-	-	-	-	-
Fever	6	30%	4	20%	2	10%	-	-	-	-	-	-
Lung infection	4	20%	-	-	1	5%	3	15%	-	-	-	-
Pruritus	4	20%	4	20%	-	-	-	-	-	-	-	-
Upper respiratory infection	4	20%	1	5%	2	10%	1	5%	-	-	-	-
Vomiting	4	20%	4	20%	-	-	-	-	-	-	-	-
Anxiety	3	15%	2	10%	1	5%	-	-	-	-	-	-
Hypotension	3	15%	1	5%	2	10%	-	-	-	-	-	-
Serum amylase increased	3	15%	-	-	-	-	1	5%	2	10%	-	-
Diarrhea	3	15%	1	5%	2	10%	-	-	-	-	-	-
Dysphagia	3	15%	2	10%	1	5%	-	-	-	-	-	-
Other	3	15%	2	10%	1	5%	-	-	-	-	-	-
Nausea	3	15%	3	15%	-	-	-	-	-	-	-	-
Mucositis oral	3	15%	2	10%	1	5%	-	-	-	-	-	-
Creatinine increased	2	10%	1	5%	1	5%	-	-	-	-	-	-
Death NOS	2	10%	-	-	-	-	-	-	-	-	2	10%
Non respiratory infection	2	10%	2	10%	-	-	-	-	-	-	-	-
Ataxia	2	10%	2	10%	-	-	-	-	-	-	-	-
Hepatic toxicity	2	10%	1	5%	-	-	1	5%	-	-	-	-
Headache	2	10%	2	10%	-	-	-	-	-	-	-	-
Pancreatitis	2	10%	-	-	-	-	2	10%	-	-	-	-
Thromboembolic event	2	10%	-	-	1	5%	-	-	-	-	1	5%

TEAE MedDRA Preferred Term	All grades		Maximum toxicity NCI grade									
			G1		G2		G3		G4		G5	
	n	%	n	%	n	%	n	%	n	%	n	%
Anemia	2	10%	-	-	1	5%	1	5%	-	-	-	-
Neutropenia	2	10%	1	5%	1	5%	-	-	-	-	-	-
Sore throat	2	10%	2	10%	-	-	-	-	-	-	-	-
Arrhythmia	1	5%	1	5%	-	-	-	-	-	-	-	-
Confusion	1	5%	1	5%	-	-	-	-	-	-	-	-
Somnolence	1	5%	1	5%	-	-	-	-	-	-	-	-
Tachypnea	1	5%	1	5%	-	-	-	-	-	-	-	-
Dysuria	1	5%	1	5%	-	-	-	-	-	-	-	-
Prostate syndrom	1	5%	1	5%	-	-	-	-	-	-	-	-
Seborreic dermatitis	1	5%	1	5%	-	-	-	-	-	-	-	-
Tooth sensivity	1	5%	1	5%	-	-	-	-	-	-	-	-
Respiratory insufficiency	1	5%	-	-	-	-	1	5%	-	-	-	-
Hemoptysis	1	5%	-	-	1	5%	-	-	-	-	-	-
Hypertension	1	5%	-	-	-	-	1	5%	-	-	-	-
Hyperkalemia	1	5%	1	5%	-	-	-	-	-	-	-	-
Percardial effusion	1	5%	1	5%	-	-	-	-	-	-	-	-
Wheight loss	1	5%	-	-	1	5%	-	-	-	-	-	-
Paronychia	1	5%	1	5%	-	-	-	-	-	-	-	-
Dyspepsia	1	5%	1	5%	-	-	-	-	-	-	-	-
Dysphasia	1	5%	1	5%	-	-	-	-	-	-	-	-
Gastric hemorrhage	1	5%	-	-	-	-	1	5%	-	-	-	-
Hypercalcemia	1	5%	-	-	1	5%	-	-	-	-	-	-
Iron deficiency	1	5%	-	-	1	5%	-	-	-	-	-	-
Vascular arterial ischemia	1	5%	-	-	-	-	-	-	1	5%	-	-
Myalgia	1	5%	1	5%	-	-	-	-	-	-	-	-
Pharyngitis	1	5%	1	5%	-	-	-	-	-	-	-	-
Dysphonia	1	5%	1	5%	-	-	-	-	-	-	-	-
Lipase increased	1	5%	-	-	-	-	-	-	1	5%	-	-
Rash maculo-papular	1	5%	1	5%	-	-	-	-	-	-	-	-
Syphilis	1	5%	-	-	1	5%	-	-	-	-	-	-
Dizziness	1	5%	1	5%	-	-	-	-	-	-	-	-

Maximum toxicity of TEAEs related to study medication by patient

TEAE MedDRA Preferred Term	All grades		Maximum toxicity NCI grade									
			G1		G2		G3		G4		G5	
	n	%	n	%	n	%	n	%	n	%	n	%
Arthralgia	4	20%	3	15%	1	5%	-	-	-	-	-	-
Asthenia	4	20%	2	10%	2	10%	-	-	-	-	-	-
Pruritus	3	15%	3	15%	-	-	-	-	-	-	-	-
Diarrhea	2	10%	1	5%	1	5%	-	-	-	-	-	-
Nausea	2	10%	2	10%	-	-	-	-	-	-	-	-
Dysuria	1	5%	1	5%	-	-	-	-	-	-	-	-
Seborreic dermatitis	1	5%	1	5%	-	-	-	-	-	-	-	-
Constipation	1	5%	1	5%	-	-	-	-	-	-	-	-
Vomiting	1	5%	1	5%	-	-	-	-	-	-	-	-
Neutropenia	1	5%	-	-	1	5%	-	-	-	-	-	-
Mucositis oral	1	5%	1	5%	-	-	-	-	-	-	-	-
Hepatic toxicity	1	5%	-	-	-	-	1	5%	-	-	-	-
Pain	1	5%	-	-	1	5%	-	-	-	-	-	-
Rash maculo-papular	1	5%	1	5%	-	-	-	-	-	-	-	-

Maximum toxicity of TEAE by patient and relation to study medication

TEAE MedDRA Preferred Term	All grades		Relation to study medication																													
			Not related										Related										UK/Not applicable									
			Maximum toxicity NCI grade										Maximum toxicity NCI grade										Maximum toxicity NCI grade									
			G1		G2		G3		G4		G5		G1		G2		G3		G4		G5		G1		G2		G3		G4		G5	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Asthenia	14	70%	10	50%	2	10%	-	-	-	-	-	-	-	-	2	10%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pain	12	60%	6	30%	3	15%	2	10%	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Arthralgia	10	50%	5	25%	2	10%	-	-	-	-	-	-	2	10%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cough	7	35%	4	20%	3	15%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dyspnea	7	35%	5	25%	2	10%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anorexia	7	35%	7	35%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Constipation	7	35%	5	25%	1	5%	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fever	6	30%	4	20%	2	10%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lung infection	4	20%	-	-	1	5%	3	15%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pruritus	4	20%	1	5%	-	-	-	-	-	-	-	-	3	15%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Upper respiratory infection	4	20%	1	5%	2	10%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vomiting	4	20%	3	15%	-	-	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anxiety	3	15%	2	10%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypotension	3	15%	1	5%	2	10%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum amylase increased	3	15%	-	-	-	-	1	5%	2	10%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diarrhea	3	15%	-	-	1	5%	-	-	-	-	-	-	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dysphagia	3	15%	2	10%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other	3	15%	2	10%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nausea	3	15%	2	10%	-	-	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

TEAE MedDRA Preferred Term	All grades		Relation to study medication																													
			Not related										Related										UK/Not applicable									
			Maximum toxicity NCI grade										Maximum toxicity NCI grade										Maximum toxicity NCI grade									
			G1		G2		G3		G4		G5		G1		G2		G3		G4		G5		G1		G2		G3		G4		G5	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Mucositis oral	3	15%	1	5%	1	5%	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Creatinine increased	2	10%	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Death NOS	2	10%	-	-	-	-	-	-	-	-	2	10%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Non respiratory infection	2	10%	2	10%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ataxia	2	10%	2	10%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hepatic toxicity	2	10%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Headache	2	10%	2	10%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pancreatitis	2	10%	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	5%	-	-	-	-
Thromboembolic event	2	10%	-	-	1	5%	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anemia	2	10%	-	-	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Neutropenia	2	10%	1	5%	-	-	-	-	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sore throat	2	10%	2	10%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Arrhythmia	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Confusion	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Somnolence	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tachypnea	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dysuria	1	5%	-	-	-	-	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prostate syndrom	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Seborreic dermatitis	1	5%	-	-	-	-	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tooth sensivity	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Respiratory insufficiency	1	5%	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hemoptysis	1	5%	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

TEAE MedDRA Preferred Term	All grades		Relation to study medication																													
			Not related										Related										UK/Not applicable									
			Maximum toxicity NCI grade										Maximum toxicity NCI grade										Maximum toxicity NCI grade									
			G1		G2		G3		G4		G5		G1		G2		G3		G4		G5		G1		G2		G3		G4		G5	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Hypertension	1	5%	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hyperkalemia	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Percardial effusion	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Wheight loss	1	5%	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Paronychia	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dyspepsia	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dysphasia	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gastric hemorrhage	1	5%	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypercalcemia	1	5%	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Iron deficiency	1	5%	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vascular arterial ischemia	1	5%	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Myalgia	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pharyngitis	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dysphonia	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lipase increased	1	5%	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rash maculo-papular	1	5%	-	-	-	-	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Syphilis	1	5%	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dizziness	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

8.3. 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

Maximum toxicity of SAE by patient

SAE Meddra Preferred Term	All grades		Maximum toxicity NCI grade									
			G1		G2		G3		G4		G5	
	n	%	n	%	n	%	n	%	n	%	n	%
Lung infection	5	25%	-	-	-	-	5	25%	-	-	-	-
Death NOS	3	15%	-	-	-	-	-	-	-	-	3	15%
Pain	3	15%	1	5%	-	-	1	5%	-	-	1	5%
Pancreatitis	2	10%	-	-	-	-	2	10%	-	-	-	-
Confusion	1	5%	-	-	-	-	1	5%	-	-	-	-
Creatinine increased	1	5%	-	-	1	5%	-	-	-	-	-	-
Coronavirus infection	1	5%	-	-	-	-	1	5%	-	-	-	-
Respiratory insufficiency	1	5%	-	-	-	-	1	5%	-	-	-	-
Hemoptysis	1	5%	-	-	-	-	1	5%	-	-	-	-
Oral hemorrhage	1	5%	-	-	1	5%	-	-	-	-	-	-
Thromboembolic event	1	5%	-	-	-	-	-	-	-	-	1	5%
Gastric hemorrhage	1	5%	-	-	-	-	-	-	-	-	1	5%
Other	1	5%	1	5%	-	-	-	-	-	-	-	-
Upper respiratory infection	1	5%	-	-	-	-	1	5%	-	-	-	-
Hypercalcemia	1	5%	-	-	1	5%	-	-	-	-	-	-
Vascular arterial ischemia	1	5%	-	-	-	-	-	-	1	5%	-	-
Hepatic toxicity	1	5%	-	-	-	-	1	5%	-	-	-	-

Maximum toxicity of SAE by patient and relation to study medication

SAE Meddra Preferred Term	All grades		Relation to study medication																													
			Not related										Related										Not applicable									
			Maximum toxicity NCI grade										Maximum toxicity NCI grade										Maximum toxicity NCI grade									
			G1		G2		G3		G4		G5		G1		G2		G3		G4		G5		G1		G2		G3		G4		G5	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Lung infection	5	25%	-	-	-	-	5	25%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Death NOS	3	15%	-	-	-	-	-	-	-	-	3	15%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pain	3	15%	1	5%	-	-	1	5%	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pancreatitis	2	10%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	1	5%	-	-	-	-
Confusion	1	5%	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Creatinine increased	1	5%	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Coronavirus infection	1	5%	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Respiratory insufficiency	1	5%	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hemoptysis	1	5%	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Oral hemorrhage	1	5%	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thromboembolic event	1	5%	-	-	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gastric hemorrhage	1	5%	-	-	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other	1	5%	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Upper respiratory infection	1	5%	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypercalcemia	1	5%	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vascular arterial ischemia	1	5%	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hepatic toxicity	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	5%	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Only Pancreatitis Grade 3 is Possibly related to study medication.

8.4. SAFETY CONCLUSIONS

Durvalumab treatment is confirmed after a long follow-up as a safe treatment in HIV-1-infected cancer patients under cART. Most of adverse events were grade 1-2, with only two cases of grade 3 toxicity related to therapy (pancreatitis and hepatotoxicity)

9. DISCUSSION AND OVERALL CONCLUSIONS

Patients infected with HIV-1 who are receiving suppressive cART have a near-normal life expectancy, and now cancer, mainly NSCLC, is one of the leading causes of mortality.2 Previous retrospective data supported the safety of treatment with anti–PD-1/PD-L1 antibodies in HIV-1–infected patients.8,9However, until recently, most cancer clinical trials have excluded HIV-1–infected patients.11,12

The DURVAST study demonstrates that immunotherapy with durvalumab in HIV-1–infected people is feasible and safe, with most drug-related AEs grade 1-2. These results complement previous data reported from the phase 1 study conducted by Uldrick et al13 in 30 patients with cancer with HIV-1 infection treated with pembrolizumab. Similar to our results, pembrolizumab was well tolerated without unexpected toxic effects and no signs of viral reactivation. Our results are also consistent with previous studies of durvalumab treatment in pretreated HIV-1–uninfected people with NSCLC, in whom the incidence of grade 3 AEs ranged from 8% to 18% and grade 4 AEs appeared in less than 1%.5

Moreover, the antitumoral activity of durvalumab in our study was higher than anticipated. Among 16 patients evaluable for response, the disease control rate was 50%, including long-lasting responses . Although the number of patients was small, it is not possible to rule out the fact that HIV-1 infection by itself, or the cART treatment, was positively associated with antitumoral activity. Our results suggest a longer duration of clinical benefit in patients treated with integrase strand-transfer inhibitors. We speculate the possibility that integrase strand-transfer inhibitors could be associated with antitumoral immune response of durvalumab. Conversely, the antitumoral activity found with pembrolizumab in the study from Uldrick et al13 was low, with only 1 of 19 patients with non–AIDS-defining cancers having a partial response, probably owing to the inclusion in this study of nonimmunosensitive tumor types, such as cholangiocarcinoma, breast cancer, and pancreatic cancer.

In agreement with the Uldrick et al study,13 our results confirm that treatment with durvalumab is also safe regarding sustained control of HIV-1 infection. All patients continued CART treatment, and plasma viremia remained undetected. In addition, CD4+ and CD8+ T-cell counts were stable throughout durvalumab treatment. Although other studies exclude patients with low basal CD4+ T-cell counts, we found no correlation of clinical benefit with basal CD4+ or CD8+ T-cell counts. Of note, 1 patient with NSCLC with a CD4+ T-cell count of less than 200 cells/mm3 had no side effects and a long-lasting partial response, suggesting that treating patients with low basal CD4+ T-cell counts might be safe. Although an increase in viral transcription could be hypothetically associated with PD-1 blockade in CD4+ T lymphocytes infected by HIV-1, the maintenance of cART precludes the reactivation of the viral reservoir.7,14 Thus, reinvigoration of CD8+ PD-1+ T lymphocytes on induction of viral reactivation could in fact be associated with reduced viral reservoirs.15

Limitations: This study is limited by the small sample size, which does not allow completely ruling out the existence of unexpected complications owing to the use of durvalumab to treat HIV-1– infected individuals with cancer. Nevertheless, data from previous studies and retrospective case series also support the feasibility and safety of treatment with anti–PD-1/PD-L1 antibodies in this context.

In summary, treatment with durvalumab in patients with advanced tumors and HIV-1 infection is feasible and safe. Larger studies are needed to validate the suggested favorable antitumoral activity of durvalumab in HIV-1–infected people. HIV-1–infected patients with advanced cancer should have access to cancer therapies with immune checkpoint inhibitors.

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