Full title: A Phase II, Open Label, Randomised Study of Ipilimumab with Temozolomide versus Temozolomide alone after surgery and chemoradiotherapy in patients with recently diagnosed Glioblastoma (IPI-GLIO)

Statistics Report

Version 1.0 – 09Nov2023
Trial Registration: ISRCTN84434175

Based on Protocol Version 4.0 – 21Apr2021

Based on Statistical Analysis Plan (SAP) version 1.0 – 23Sep2021
Based on SAP Data Definitions and Tables version 1.0 – 23Sep2021

Oxford Clinical Trials Research Unit (OCTRU)
Centre for Statistics in Medicine (CSM)

Ensure that the Statistics Report is finalised and approved in a timely manner following completion of the final analysis using the sign-off form OF-006 as per OCTRU SOP GEN-055.

Contents

1. INTRODUCTION

This document details the analysis for the main paper(s) reporting results from the *Phase II, Open Label, Randomised Study of Ipilimumab with Temozolomide versus Temozolomide alone after surgery and chemoradiotherapy in patients with recently diagnosed glioblastoma* (IPI-GLIO*)*. The results reported in these papers follow the strategy set out in the Statistical Analysis Plan (SAP, version 1.0 – 23Sep2021) see Appendix 1. Exploratory analyses not pre-specified in the protocol and/or SAP will be expected to follow the broad principles laid down in the SAP and will be reported as post-hoc analyses in this report. The two randomised groups are referred to as the intervention (Ipilimumab+Temozolomide) and control (Temozolomide) groups.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of the analysis strategy; If reported, the analyses will be marked as post-hoc; the source of the suggestion will be acknowledged, and the reader will be advised to rely on the pre-specified analysis for the interpretation of the results.

Any deviations from the SAP are described and justified in this report.

1.1 Key Personnel

Key people involved in the drafting, reviewing and approving this statistical report, together with their role in the trial and their contact details.

Author (Acting Trial Statistician) Jonathan Cook

Reviewers (Chief Investigator, Trial Manager, Lead Statistician)

Chief Investigator: Dr Paul Mulholland

Trial Manager: Timothy Coutts

Lead Statistician: Assoc Prof Susan Dutton, Prof Jonathan Cook

Approvers (Prof Jonathan Cook, Dr Paul Mulholland)

Note: Samia Hussain was previously involved as the Trial Statistician and along with Assoc Prof Susan Dutton prepared the original draft and commented on draft versions of this report.

2. CHANGES FROM PREVIOUS VERSIONS OF THE STATISTICAL REPORT

A summary of key changes from earlier versions of the Statistical Report, usually these occur as additional analyses requested by the Chief Investigator or journal editors but may include long-term follow-up or sub-studies that are analysed after the initial version of the report is completed. No have occurred to date.

Version number Issue date	Author of this issue	Protocol Version & Issue date	Significant changes from previous version together with reasons
V1.0_DDMMMYYYY	Samia Hussain	Protocol_4.0 – 21Apr2021	Not applicable as this is the 1st issue

3. STUDY METHODS

3.1 Software employed

An updated version of STATA 17.0 (Stata Corp LP, www.stata.com), was used for data cleaning and analysis.

3.2 Data quality

The data was received via secure transfer, and it was cleaned using STATA 17. The data received for each data lock was checked and if there were any discrepancies, they were reported to the trial team and were resolved. All the data required for the analysis according to SAP was available i.e., all the key variables required to analyse the primary and secondary outcomes were available. However, any missing data for the baseline was queried and any missing study participation dates for survival analysis were replaced with the date last known alive. Potential inconsistencies in the treatment cycle data was queried.

Overall survival (OS) was based on the date of death and where the date of death was missing, it was replaced with the last known alive date or the last date of participation or the consent withdrawal date (if the patient had withdrawn consent). Progression Free Survival (PFS) was generated based on progression date, MRI date and the reason for stopping Temozolomide.

3.3 Interim Analysis of trial progress and recruitment

The data was monitored by Radiotherapy & Imaging Oversight Committee throughout the trial. The final number of participants randomised was 119/120. IPI-GLIO had to hold its recruitment from 16Mar2020 to 27July2020 (when 77 participants were randomised), and from 07Sep2020 to 8Oct2020 (when 81 participants were randomised) due to COVID-19. Recruitment was correspondingly extended for 8 months. Since at least 77 participants have a longer follow-up time (at least 18+8=26 months), 119 participants would still give the same power (80%) of the study.

3.4 Changes to original randomisation

Overall, the recruitment and randomisation took place according to the randomisation plan and there were no changes.

3.5 Deviations from the original planned randomisation or statistical analysis plan

In the original approved protocol (V1.0- 17Aug2018), it refers to using 80% confidence interval along with one-sided p-value for OS. This was latter modified (V4.0 – 21Apr2021) to refer to 60% confidence interval which

is the corresponding (2-sided) significance level which matches with a one-sided 20% significance level. There were no deviations from the randomisation or the original SAP that impacted the analysis. Table formats vary from those originally envisioned in the SAP data definitions and tables document.

3.6 Suggested Statistical Methods Section for Publication

The treatment groups were compared for OS using Cox proportional hazards regression both unadjusted and adjusted for the stratification factors (Methylation Status and Cancer resection status). For the treatment comparison Cox regression modelling was carried out to report the hazard ratio (HR) at 60% confidence interval and the associated one-sided (with reference to favouring the Ipilimumab with Temozolomide group) p-value. Survival rates were calculated at 18 months and 36 months with 60% confidence intervals for the two treatment groups. Unadjusted log rank test between treatment groups of the time to survival was used. Survival was presented graphically using Kaplan Meier plots.

The secondary objective of assessing the progression free survival is defined as time from randomisation until progression or death, where progression is as determined in standard care (either Response Assessment in Neuro Oncology RANO or MDT-determined). Time to progression was analysed using the same methods as for the primary analysis of overall survival. The hazard ratio with 60% confidence interval comparing treatment groups was calculated, along with the proportion of patients who are progression free at 18 months.

The secondary objectives included the safety and tolerability of ipilimumab and temozolomide compared with temozolomide alone. Toxicity was analysed using the adverse and serious adverse events. Treatment related toxicity was tabulated by type and Common Terminology Criteria for Adverse Events (CTCAE) grade of toxicity, with a chi square test used for any between treatment comparisons.

All analyses were performed on an intention-to-treat basis: defined as all patients who were randomised. All randomised patients were analysed as being in the group they were randomised to, regardless of whether they received the allocated treatment. A planned sensitivity analysis of the primary outcome to address the impact of COVID-19 pandemic was not carried out given the small number of participants who had completed follow-up prior to the pandemic starting.

4. STUDY METHODS

The primary objective was to evaluate whether ipilimumab in addition to the current standard of care following surgery and radiotherapy will improve survival in patients with newly diagnosed glioblastoma.

4.1 Primary outcome

OS, where length of survival is defined in whole days, as the time from randomisation until death from any cause. For those patients who were not observed to die during the trial, the length of survival was censored at the last known alive date. This means that all participants contributed to the results of the trial regardless of how long they were in the trial.

4.2 Secondary outcomes

The planned secondary outcomes were:

- PFS at 18 months: defined as time from randomisation until progression or death, where progression is as determined in standard care (either Response Assessment in Neuro Oncology RANO or MDT-determined).
- Safety and tolerability of the trial interventions: Any toxicity grade ≥3 graded according to CTCAE v4.03 and length of time for toxicity to resolve.
- To evaluate whether the addition of ipilimumab to the current standard of care following surgery and radiotherapy will improve survival in patients with newly diagnosed glioblastoma in the long-term.

4.3 Analytical methods

The treatment groups were compared for overall survival using Cox proportional hazards regression both unadjusted and adjusted for the stratification factors. To compare treatments Cox regression models were used to report the HR at 60% confidence interval and the associated one-sided p-value. Survival rates were calculated at 18 months and 36 months with 60% confidence intervals for the two treatment groups. Unadjusted log rank test between treatment groups of the time to survival was used. Survival was presented graphically using Kaplan Meier plots.

Reporting of the results is based on the CONSORT statement.

5. RESULTS

5.1 Study participants

Overall, 119 participants were recruited in the trial and randomised, 40 in the control group and 79 in the intervention group. The data in this report are classified according to treatment allocation irrespective of any non-compliance with treatment allocation (i.e. the “intention to treat (ITT) population”).

The following table (table 1) gives an overview of the potential patient non-inclusions from the study. Figure 1 is the CONSORT flow diagram showing patient flow from assessment for eligibility through consent, randomisation, follow-up and statistical analysis.

Table 1: Reasons for exclusion and non-participation

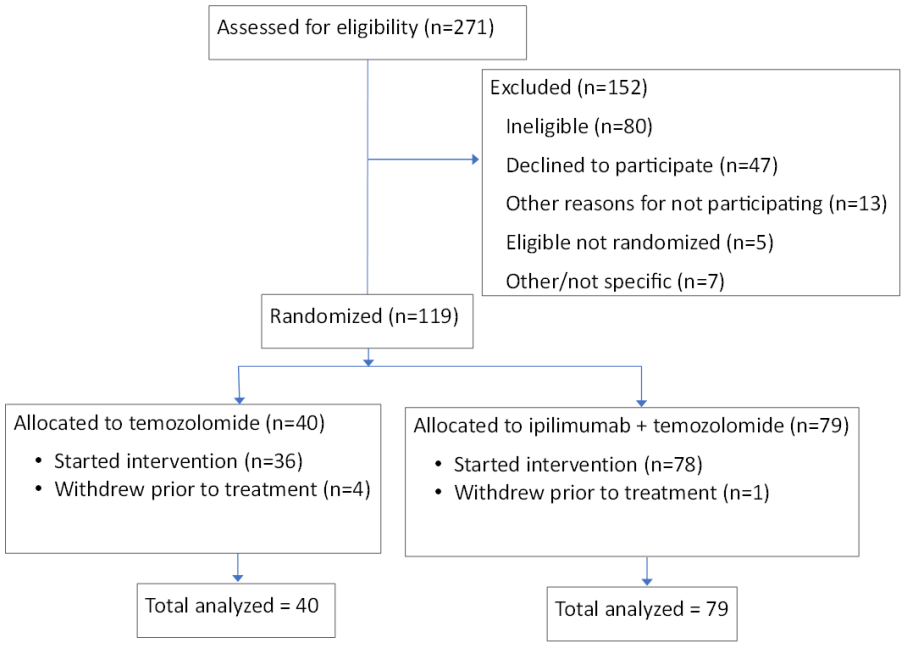
REASON FOR EXCLUSION	*Number of patients*
Not meeting inclusion criteria	
Not between age 18-70 years	0
Not newly diagnosed histologically-confirmed de-novo supratentorial glioblastoma (including gliosarcoma), by WHO guidelines with >20% surgical debulking (surgeon defined)	13
Radiotherapy to have begun more than 49 days of surgery	3
Did not complete standard radiotherapy and concurrent temozolomide	12
Clinically inappropriate for adjuvant temozolomide and not capable of completing adjuvant temozolomide without dose reduction, based on investigator judgement	5
Life expectancy of less than 12 weeks	0
ECOG performance status 2 and above	1
The patient is not willing and not able to comply with the protocol scheduled follow-up visits and examinations for the duration of the study	0
Did not give written (signed and dated) informed consent	
Haematological and biochemical indices not within the ranges.	15
Meeting exclusion criteria	
Pregnant or breast-feeding women or women of childbearing potential unless effective methods of contraception are used	0
Males not willing to agree with contraception advice	0
Multifocal glioblastoma	7
Secondary glioblastoma (i.e., previous histological or radiological diagnosis of lower grade glioma)	1
Known extracranial metastatic or leptomeningeal diseases	0
Any treatment for glioblastoma other than surgery and temozolomide chemoradiotherapy	1
Dexamethasone dose >3mg daily (or equivalent) at time of randomisation	0
Intratumoural or peritumoural haemorrhage deemed significant by the treating physician	0
Clinically relevant, active, known or suspected autoimmune disease	1
History of significant gastrointestinal impairment, as judged by the investigator	0
Any evidence of severe or uncontrolled diseases (e.g. unstable or uncompensated respiratory, cardiac, hepatic or renal disease)	0
Serious and opportunistic infection within 4 weeks of screening	0
Known hypersensitivity to trial medications or any of their excipients e.g. hypersensitivity to dacarbazine (DTIC), patients with rare hereditary problems	0

of galactose intolerance, the Lapp lactase deficiency or glycose-galactose malabsorption	
Past medical history of interstitial lung disease, idiopathic pulmonary fibrosis, drug-induced interstitial disease which required steroid treatment or any evidence of clinically active interstitial lung disease	0
Any condition requiring systemic treatment with corticosteroids (>10mg prednisolone daily or equivalent) or other immunosuppressive medications within 14 days or randomisation. Inhaled or topical steroids, and adrenal replacement steroid doses > 10mg daily prednisolone or equivalent are permitted in the absence of active autoimmune disease	2
Treatment with any other investigational agent, or participation in another interventional clinical trial within 28 days prior to enrolment. Participation in other interventional trials after IPI-GLIO is permitted	0
Any other active malignancy, with the exception of adequately treated cone-biopsied in situ carcinoma of the cervix uteri and non-melanoma skin lesions	1
Patients with a known history or who are known to be serologically positive for Hepatitis B, Hepatitis C or HIV	1
Other psychological, social or medical condition, physical examination finding or a laboratory abnormality that the Investigator considers would make the patient a poor trial candidate or could interfere with protocol compliance or the interpretation of trial results	5
Ineligible - unspecified reason	8
Outside of study window	3
Patient deceased during screening period	1
Total ineligible	**80**
Total eligible not randomised	**5**
Reason for Declining	Number
Concerned about potential side effects	5
Patient unable to travel to hospital for additional visits	1
patient chose another trial	2
Does not want immunotherapy	3
patient chose to have treatment locally	2
overwhelmed by diagnosis	1
Patient overwhelmed by PIS	1
Patient declined appointment	1
unable to tolerate TMZ	1
concerns quality of life might be compromised	3
patient declined due to impact of study	1
negatives outweigh the positives, want to consider other treatment options	1
impact of side effects on quality of life	1
geographical reasons	1

concern on the effect of treatment on coeliac disease	1
fearful of the prospect of treatment	1
not keen, anxious, concerned regarding asthma	1
patient declined due to impact on family & symptoms	1
Patient has decided on the current standard of care	1
No reason given	7
Patient decision	2
Decided against being randomised due to COVID-19	1
patient declined to take part, PIS not sent	1
Declined chemo	1
Decided to have treatment at another centre	1
QOL deteriorating	1
Did not want to take part	3
Total Declined	**47***
Other Reasons for not participating	**13+**
No capacity to start tx within timepoints	-
Clinician decision for no chemotherapy due to COVID-19	-
To be seen at hospital, no response	-
information sent, no reply received	-
recruitment on hold due to COVID-19	-
Other/not specific	**7**

Note: *Includes 1 patient who was randomised in error, this patient was excluded from the trial. **+** breakdown not available.

Figure 1: Consort Diagram

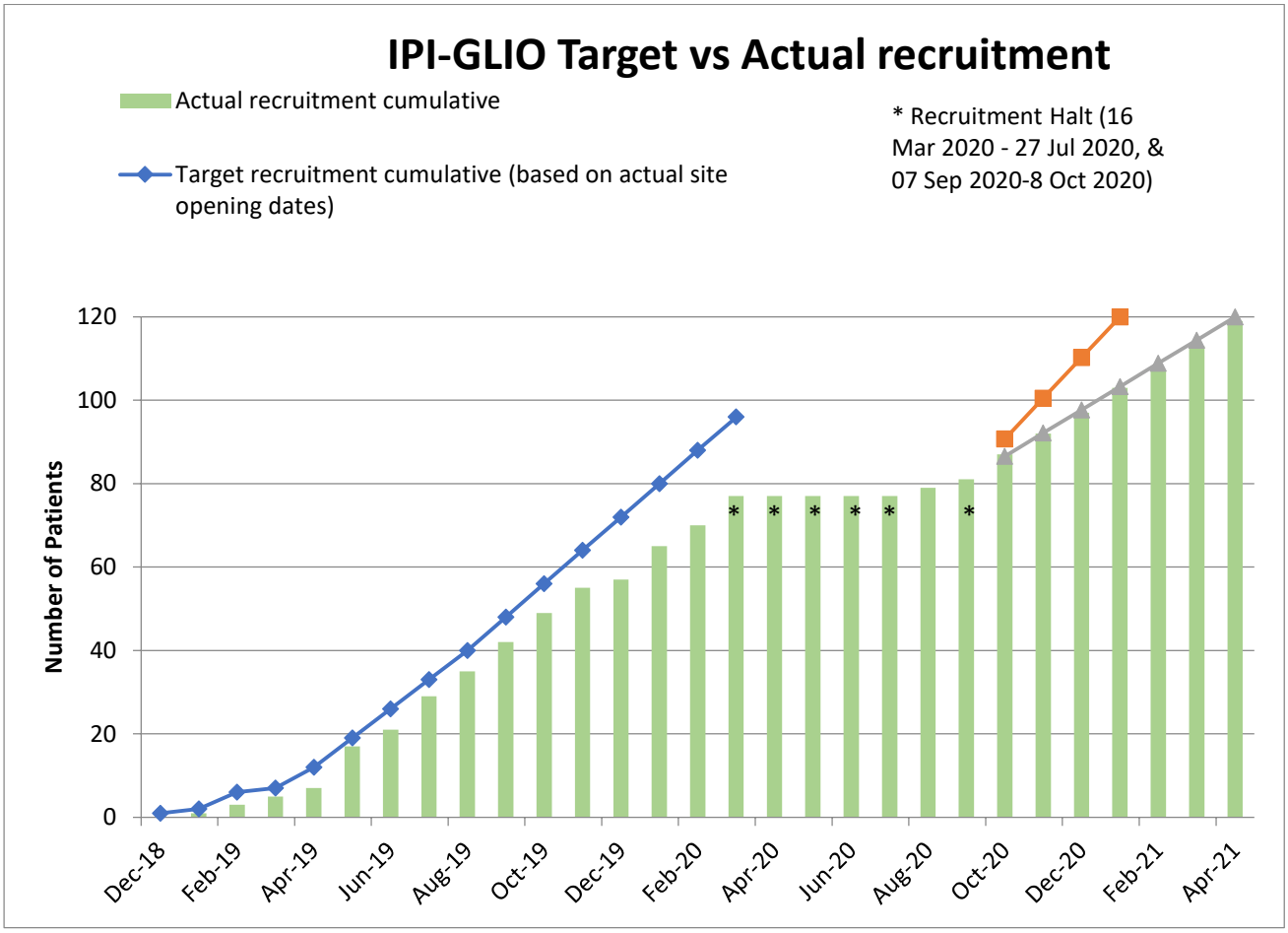


5.2 Recruitment

The sample size calculation was based on a median survival difference between the two treatment groups and 72 events at the end of follow-up (at least 18 months). IPI-GLIO recruitment began on 21st December 2018 and ended on 12th May 2021. There were two pauses in recruitment from 16Mar2020 to 28July2020 and from 07Sep2020 to 09Oct2020. The first was due to COVID-19 and was due to indirect safety concerns i.e., a risk benefit decision considering the rapidly developing COVID-19 pandemic and expected impact on NHS services. The second was due to a delay while confirmation was received from the funder about continuation of the study. The sample size was checked at this time and the sufficiency of recruitment and follow-up to achieve the required number of events (given the assumptions in the original sample size calculation) was confirmed. This Figure 2 gives actual recruitment against predicted.

In total 119 participants were randomised. They were followed up for a minimum of 18 months. Survival data follow-up was completed on 31st October 2022.

Figure 2: IPI-GLIO Predicted v actual recruitment



5.3 Baseline Characteristics

The following data represents the characteristics of the 119 patients who were randomised. The following tables (Tables 2-4) show the base line characteristics of the participants.

Table 2: Stratification factors according to the treatment group and overall

Stratification factor	***Control (n=40)***		***Intervention (n=79)***		***Total (n=119)***	
	n	**%**	**n**	**%**	**n**	**%**
Surgical resection status						
Gross total resection	24	60.00	48	60.76	72	60.50
Subtotal resection	16	40.00	31	39.24	47	39.50
MGMT						
Methylated	16	40.00	31	39.24	47	39.50
Unmethylated	21	52.50	40	50.63	61	51.26
Unknown MGMT status	3	7.50	8	10.13	11	9.24

Table 3: Baseline characteristics of participants according to the treatment group and overall (continuous variables)

	Control (n=40)			***Intervention (n=79)***			***Total (n=119)***		
	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
Age (yrs)	47.6	49.0	12.3	52.9	57.0	11.6	51.1	54.0	12.0
Height (cm)	173.5	173.0	8.9	174.2	176.1	9.8	173.9	175.0	9.5
Weight (kg)	81.4	81.5	13.6	85.3	82.1	19.8	84.0	82.1	18.0
BSA (m^2)	1.96	1.97	0.19	1.99	1.98	0.25	1.98	1.98	0.23
Gap between prior radiotherapy and surgery (days)	76.0	76.5	6.3	9	76.0	8.3	76.0	76.0	7.7
Gap between prior chemotherapy and surgery (days)	77.4	75.0	12.6	76.3	75.0	7.7	76.7	75.0	9.6
BP Systolic (mm Hg)	126.0	124.0	15.4	129.4	129.5	13.4	128.2	127.0	14.1
BP Diastolic (mm Hg)	78.4	77.5	9.9	78.6	79.0	10.2	78.5	78.0	10.1
Pulse (beats/min)	77.4	77.0	11.6	76.4	74.5	14.3	76.8	76.0	13.3
Heart rate (beats/min)	77.6	78.0	11.2	72.6	70.0	10.9	74.2	73.0	11.2

Table 4: Baseline characteristics of participants according to the treatment group and overall (binary & categorical variables)

	Control (n=40)		*Intervention (n=79)*		*Total (n=119)*	
	n	%	n	%	n	%
Gender						
Female	14	35.00	24	30.38	38	31.93
Male	26	65.00	55	69.62	81	68.07
Side of brain						
Right	19	47.50	39	49.37	58	48.74
Left	21	52.50	40	50.63	61	51.26
Tumour location						
Frontal	13	32.50	22	27.85	35	29.41
Occipital	1	2.50	7	8.86	8	6.72
Parietal	10	25.00	12	15.19	22	18.49
Temporal	12	30.00	31	39.24	43	36.13
Other	4	10.00	7	8.86	11	9.24
IDH mutation status						
IDH 1 mutation	3	7.50	9	11.39	12	10.08
IDH 2 mutation	1	2.50	0	0.00	1	0.84
Wild-Type IDH	36	90.00	70	88.61	106	89.08
ECOG performance status						
0	28	70.00	55	69.62	83	69.75
1	12	30.00	24	30.38	36	30.25

There were 14 women (35%) in the Temozolomide group vs 24 (30%) in the Ipilimumab+Temozolomide group. 28 (70%) participants had ECOG performance status=0 in the Temozolomide group vs 55 (70%) in the Ipilimumab+Temozolomide group.

5.3.1 Numbers Analysed

The analytical strategy was to analyse intention-to-treat population, i.e., all patients were analysed as randomised and included in the survival outcomes. No imputation of data was undertaken.

5.4 Compliance

5.4.1 Treatment compliance

There were 119 randomised participants in the study and out of those 6 withdrew, 4 from the control group and two from the intervention group. Of those allocated to temozolomide, 4 (12.50%) did not receive temozolomide as they withdrew before receiving treatment. Cycle data was missing for one participant in the temozolomide group known to have received some temozolomide treatment. In total temozolomide cycle data was available for 560 cycles (372 and 188 cycles in the temozolomide and the Ipilimumab groups respectively).

The following table (Table 5) presents the number of treatment cycles completed by treatment group and overall.

Table 5: Details of Temozolomide & Ipilimumab cycles completed split by randomised treatment group

Treatment Cycle data (participant level)	*Control (n=39*)*		*Intervention (n=79)*		*Total (n=119)*	
	n	**%**	**n**	**%**	**n**	**%**
Temozolomide cycles						
No treatment cycles	4	10.26	3	3.80	7	5.93
One treatment cycle	1	2.56	6	7.59	7	5.93
Two treatment cycles	2	5.13	5	6.33	7	5.93
Three treatment cycles	1	2.56	6	7.59	7	5.93
Four treatment cycles	1	2.56	5	6.33	6	5.08
Five treatment cycle	4	10.26	6	7.59	10	8.47
Six treatment cycles	26	66.67	48	60.76	74	62.71
Received a reduced dose of treatment for one or more cycles	4	11.43	10	13.16	14	12.61
Ipilimumab cycles						
No treatment cycles			1	1.27		
One treatment cycle			4	5.06		
Two treatment cycles			7	8.86		
Three treatment cycles			6	7.59		
Four treatment cycles			61	77.22		
Total treatment cycles			79	100.00		

Note: * data was missing for one participant in the temozolomide data group known to have received some temozolomide treatment. The patient did not wish to continue to provide study data, but was willing to be monitored for survivorship.

Further details of treatment compliance are presented in the following table (Table 6 protocol deviations) about deviations and the CONSORT diagram.

Table 6: protocol deviations

Deviation Subcategory	Total
Category 01.01: IMP Supply/ storage/ retrieval/ destruction	2
Category 01.02: IMP Prescription/ administration/ compliance	2
Category 02.02: IC process	4
Category 04.03: Safeguard of the safety and well-being of subject	238
Category 06.03: Monitoring	1
Category 06.05: Document control	2
Category 08.01: Protocol compliance (selection criteria)	4
Category 08.02: Protocol compliance (assessment of efficacy)	122
Category 08.03: Protocol compliance (safety reporting)	19
Category 08.04: Protocol compliance (others)	166
Category 09.06: Analysis/reporting (laboratory)	2
Total	562*

Note *Of which 203 were due to COVID-19, including where assessments were not done due to telephone. Telephone consultations also replaced some temozolomide treatment visits - treatment was dispensed according to local policy (e.g. posted out to the patient).

5.4.2 Withdrawals & Protocol Violations

In total 4 participants withdrew in the control (temozolomide) group and 2 patients in intervention (the Ipilimumab+temozolomide) group. All patients were included in the time to event analyses as per treatment allocation, but these participants were censored at their withdrawal date.

5.4.3 Blinding

IPI-GLIO was an unblinded, open labelled stratified randomised Phase II multicentre clinical trial (CTIMP). Patients with newly diagnosed de-novo glioblastoma following surgery and radical radiotherapy with temozolomide with/without the addition of ipilimumab were recruited from 7 sites in the UK.

5.5 Results

The primary outcome is overall survival, where death is an event and those who have not died have been censored at their last known alive date. OS has been analysed on the intention-to-treat population using Kaplan Meier plots, log-rank test, and Cox proportional hazards regression models, both unadjusted and adjusting for the stratification factors (methylation status & cancer resection status). Estimated median survival and the proportion surviving at 18 and 36 months are reported in Table 7 along with 60% confidence intervals (CIs). The results of the unadjusted and the adjusted analysis of OS are given in Table 8. Figure 3 shows the Kaplan-Meier curve for OS and the corresponding numbers at risk by treatment group.

The secondary outcome of progression free survival defines progression or death (whichever is first) as the event and patients who have not progressed or died are censored at their last known progression free date. Estimated median progression free survival and the proportion being progression free at 18 and 36 months are reported in Table 7 This latter has been calculated based on their most recent MRI scan date. The results of the unadjusted and the adjusted analysis of OS are given in Table 9. Figure 4 shows the Kaplan-Meier curve for progression free survival and the corresponding numbers at risk by treatment group.

Table 7: Median overall survival and progression free survival – ITT population

	Control (n=40)		*Intervention (n=79)*	
	Median Survival	**60% CI**	**Median Survival**	**60% CI**
OS (months)	23.0	17.3, 26.4	18.2	16.0, 23.9
18m OS (proportion)	0.58	0.50, 0.65	0.51	0.46, 0.56
36m OS (proportion)	0.17	0.11, 0.25	0.15	0.10, 0.21
PFS (months)	12.5	11.2, 22.4	10.8	10.1, 11.3
18m PFS (proportion)	0.42	0.33, 0.51	0.24	0.19, 0.29
36m PFS (proportion)	0.06	0.02, 0.12	0.03	0.01, 0.06

Table 8: Overall Survival by treatment group - ITT population

Variable	*Hazard Ratio*	*Std. error*	*P (1-sided)*	*P (2-sided)*	*60% CI*
Unadjusted analysis					
Treatment (unadjusted)	1.08	0.28	0.62†	0.75	0.87, 1.35
Adjusted analysis*					
Treatment (adjusted)	1.09	0.30	0.62†	0.77	0.86, 1.38
Methylation status	0.26	0.08		<0.001	0.20, 0.33
Cancer resection Status	0.40	0.11		0.001	0.32, 0.51

*Notes: * Adjusted for minimisation factors (surgical resection status and methylation status).*
† One-sided p-value, 0.20 (20% significance level) favouring the intervention would be considered significant).

Table 9: Hazard ratio for PFS by treatment - ITT population

Variable	*Hazard Ratio*	*Std. error*	*P (1-sided)*	*P (2-sided)*	*60% CI*
Unadjusted analysis					
Treatment (unadjusted)	1.22	0.30	0.79†	0.42	0.99, 1.50
Adjusted analysis*			0.86†		
Treatment (adjusted)	1.34	0.36		0.29	1.06, 1.68
Methylation status	0.44	0.12		0.002	0.35, 0.55
Cancer resection Status	0.56	0.15		0.03	0.44, 0.70

*Notes: * Adjusted for minimisation factors (surgical resection status and methylation status).*
† One-sided p-value, 0.20 (20% significance level) favouring the intervention would be considered significant).

There was no evidence of a difference between the treatment groups in overall survival in favour of the intervention group in either the adjusted or the unadjusted analysis (Table 8). There was no evidence of a difference in favour of intervention group in for PFS. Based upon a 2-sided comparison there was evidence of a difference in favour of the control group in the adjusted analysis of PFS (but narrowly not the unadjusted analysis – table 9).

A planned sensitivity analysis for assessing the impact of COVID-19 was not carried out give the relatively small number of individuals (n=32) who had completed follow-up before the pandemic started (nominally defined as 20Mar2023), and very few deaths (n=5) took place in the pre-pandemic period.

Figure 3: Overall survival - Kaplan Meier curve

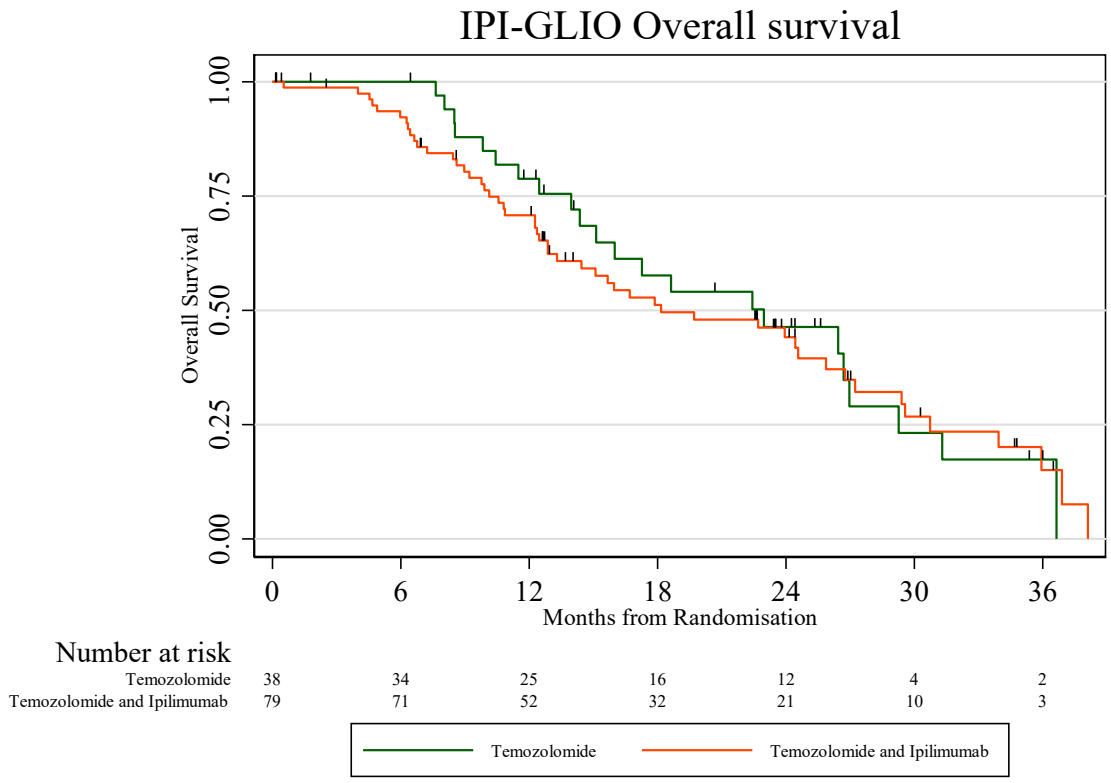
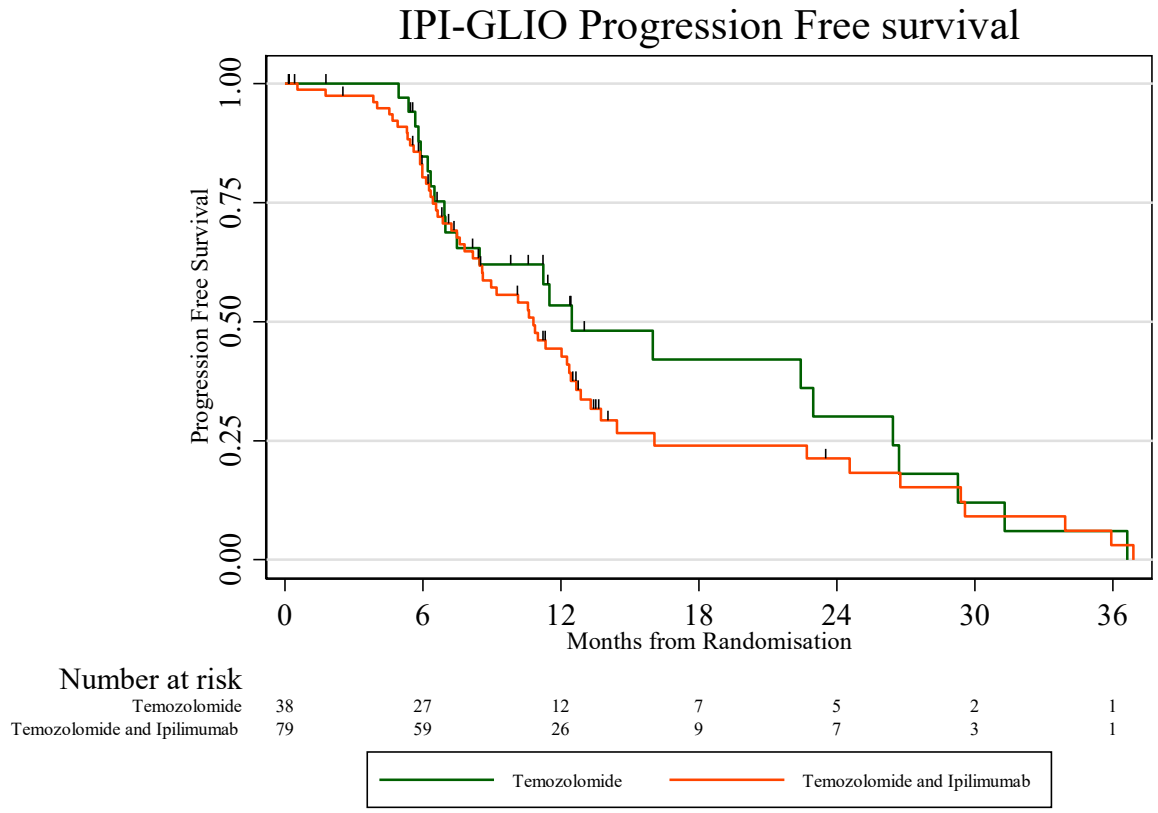


Figure 4: Progression Free Survival -Kaplan Meier Plot



5.6 Safety (Harms)

The safety of the treatment was monitored throughout the study and all the adverse events (AEs) were reported to RIOC to ensure safety of the participants. Total no of AEs reported were 1403, 332 vs 1071 in the Temolozomide vs Temozolomide & Ipilimumab group. 7 participants did not have any AEs recorded for them. Table 10 lists all the AEs by treatment group according to the MedDRA (preferred) term with Table 11 listing only the 125 AEs which were CTACE grade 3 and above). Average number of AEs per participant were reported as follows:

- Temolozomide – Mean 8.3, SD 7.4, minimum=0, maximum=33, median=6.5, n=40;
- Temozolomide & Ipilimumab – Mean 13.6, SD 10.2, minimum=0, maximum=47, median 10.0 n=79;
- Overall – Mean 11.8, SD 9.7, minimum=0, maximum=47, median=9.0, n=119.

Table 10: AE (MedDRA preferred term) by treatment group

AE MedDRA term	*Control*	*Intervention*	*Total*
Abdominal mass	0	1	1
Abdominal pain	1	9	10
Abdominal pain lower	0	1	1
Abdominal pain upper	0	3	3
Acne	0	2	2
Adrenal insufficiency	0	1	1
Alanine aminotransferase increased	4	7	11
Alanine aminotransferase increased	1	1	2
Alopecia	9	24	33
Altered state of consciousness	0	1	1
Amnesia	2	0	2
Anaemia	1	6	7
Anxiety	2	5	7
Aphasia	5	16	21
Arthralgia	4	9	13
Aspartate aminotransferase increased	1	5	6
Aspartate aminotransferase increased	0	1	1
Asthenia	1	2	3
Asthma	0	1	1
Ataxia	2	0	2
Atrial fibrillation	0	1	1
Aura	2	0	2
Autoimmune colitis	0	5	5
Back pain	2	7	9
Balance disorder	4	4	8
Balanoposthitis	0	1	1
Blepharospasm	0	1	1
Blood alkaline phosphatase increased	0	2	2
Blood bilirubin increased	0	3	3
Blood calcium increased	0	1	1
Blood cholesterol increased	0	2	2
Blood cortisol	0	1	1
Blood creatinine increased	0	1	1
Blood phosphorus decreased	0	2	2
Blood potassium decreased	0	1	1
Bradyphrenia	0	1	1
Brain oedema	2	2	4
Breast mass	0	1	1
C-reactive protein increased	0	1	1
COVID-19	0	2	2

COVID-19 pneumonia	1	0	1
Catheter site bruise	0	1	1
Cellulitis	0	1	1
Cerebrospinal fluid leakage	1	0	1
Cerumen impaction	1	0	1
Chalazion	0	1	1
Chest discomfort	1	0	1
Chest pain	1	1	2
Cognitive disorder	0	2	2
Cold-stimulus headache	0	1	1
Colitis	0	8	8
Communication disorder	0	1	1
Confusional state	2	4	6
Constipation	11	33	44
Contusion	0	2	2
Coordination abnormal	1	1	2
Cough	2	13	15
Cushingoid	5	1	6
Deafness unilateral	0	1	1
Decreased appetite	5	21	26
Decreased appetite	0	4	4
Deep vein thrombosis	0	1	1
Dehydration	1	2	3
Depressed mood	1	3	4
Depression	0	2	2
Dermatitis	0	1	1
Diarrhoea	5	53	58
Diarrhoea	0	1	1
Diarrhoea haemorrhagic	0	1	1
Diplopia	1	1	2
Disorientation	0	1	1
Dizziness	3	12	15
Dizziness postural	1	7	8
Dry eye	1	2	3
Dry mouth	0	1	1
Dry skin	4	11	15
Dysaesthesia	1	0	1
Dysgeusia	0	1	1
Dyspepsia	2	2	4
Dysphagia	1	4	5
Dyspnoea	2	4	6
Dyspnoea	2	0	2
Ear pain	1	0	1
Epistaxis	0	2	2
Erectile dysfunction	0	1	1
Erythema	0	1	1

Eye infection	2	4	6
Eye inflammation	1	0	1
Eye pain	1	3	4
Eye pruritus	0	2	2
Face oedema	3	2	5
Facial paralysis	1	0	1
Facial paresis	0	1	1
Fall	1	1	2
Fatigue	19	98	117
Fatigue	0	1	1
Feeling abnormal	0	2	2
Feeling cold	1	0	1
Fever	2	5	7
Flank pain	0	2	2
Flatulence	0	1	1
Fungal infection	0	1	1
Fungal skin infection	0	2	2
Gait disturbance	0	1	1
Gastritis	0	3	3
Gastrooesophageal reflux disease	0	4	4
Generalised tonic-clonic seizure	1	0	1
Genital ulceration	0	1	1
Gingival bleeding	0	1	1
Gout	0	2	2
Haematochezia	0	1	1
Haematoma	2	0	2
Hallucination, olfactory	0	4	4
Hallucination, visual	1	0	1
Head discomfort	0	6	6
Headache	18	59	77
Heart rate irregular	0	1	1
Hemianopia	1	0	1
Hemianopia homonymous	1	0	1
Hemiparesis	3	4	7
Herpes zoster	0	3	3
Human chorionic gonadotropin increased	0	1	1
Hyperbilirubinaemia	0	2	2
Hyperglycaemia	3	2	5
Hypertension	11	20	31
Hyperthyroidism	0	1	1
Hypoacusis	1	0	1
Hypoaesthesia	6	4	10
Hypoalbuminaemia	0	1	1
Hypocalcaemia	0	1	1

Hypokalaemia	1	0	1
Hypokalaemia	0	1	1
Hypophysitis	0	1	1
Hypotension	0	1	1
Hypothyroidism	1	2	3
Immune-mediated hepatitis	0	1	1
Immunisation reaction	0	2	2
Incontinence	0	1	1
Infection	0	1	1
Influenza	0	1	1
Infusion related reaction	0	1	1
Ingrown hair	0	1	1
Insomnia	2	2	4
Itching scar	0	1	1
Joint swelling	2	2	4
Lacrimation increased	1	0	1
Large intestine perforation	0	1	1
Lethargy	1	1	2
Lipase increased	0	7	7
Lower respiratory tract infection	2	3	5
Lung infection	0	1	1
Lymphadenopathy	0	1	1
Lymphocyte count decreased	0	6	6
Lymphopenia	4	15	19
Memory impairment	1	5	6
Mobility decreased	0	3	3
Mouth ulceration	0	2	2
Mucosal inflammation	0	1	1
Muscle spasms	1	6	7
Muscle strain	0	1	1
Muscle twitching	0	1	1
Muscular weakness	11	8	19
Muscular weakness	3	4	7
Musculoskeletal chest pain	0	3	3
Musculoskeletal pain	1	0	1
Musculoskeletal stiffness	0	2	2
Myalgia	0	2	2
Myopathy	1	2	3
Nasopharyngitis	3	6	9
Nausea	16	49	65
Nephrolithiasis	0	1	1
Neuralgia	1	1	2
Neuropathy peripheral	1	0	1
Neurotoxicity	4	3	7
Neutropenia	2	7	9

Neutrophil count decreased	0	1	1
Neutrophil count decreased	0	3	3
Oedema peripheral	0	2	2
Onychomadesis	0	1	1
Oral candidiasis	2	7	9
Oral herpes	0	1	1
Oropharyngeal pain	2	1	3
Pain	0	2	2
Pain in extremity	2	3	5
Pain in extremity	1	1	2
Pain in jaw	0	1	1
Pallor	0	1	1
Palpitations	0	1	1
Paraesthesia	2	2	4
Partial seizures	2	1	3
Periarthritis	1	0	1
Periorbital cellulitis	0	1	1
Peripheral swelling	1	1	2
Platelet count decreased	1	13	14
Pleural effusion	0	1	1
Pollakiuria	0	4	4
Poor quality sleep	0	1	1
Presyncope	0	2	2
Proctitis	0	1	1
Productive cough	0	4	4
Pruritus	4	46	50
Pruritus	0	1	1
Pruritus generalised	0	1	1
Pulmonary embolism	3	3	6
Pyrexia	0	3	3
Pyrexia	1	1	2
Quadrantanopia	0	1	1
Radiation skin injury	2	0	2
Rash	3	54	57
Rash generalised	1	2	3
Rash macular	0	1	1
Rash maculo-papular	0	11	11
Rash papular	0	1	1
Rash pruritic	0	3	3
Raynaud's phenomenon	0	1	1
Rectal haemorrhage	0	1	1
Regurgitation	0	1	1
Renal pain	1	1	2
Respiratory tract infection	0	1	1
Retinal disorder	0	1	1
Rhinitis	0	1	1

Rhinitis allergic	0	1	1
Rhinorrhoea	1	0	1
SARS-CoV-2 test positive	1	0	1
Scar pain	1	0	1
Seizure	12	33	45
Sensory loss	1	0	1
Septic rash	0	1	1
Sinus tachycardia	1	0	1
Sinusitis	1	1	2
Skin injury	0	1	1
Slow speech	0	1	1
Somnolence	1	0	1
Speech disorder	0	1	1
Steroid diabetes	1	0	1
Stomatitis	1	4	5
Subcutaneous abscess	1	0	1
Subdural haematoma	0	1	1
Swelling face	3	1	4
Swelling of eyelid	0	1	1
Syncope	1	1	2
Tension headache	0	1	1
Terminal dribbling	1	0	1
Thrombocytopenia	7	24	31
Thyroid function test abnormal	0	1	1
Tinnitus	3	3	6
Tremor	1	0	1
Unresponsive to stimuli	1	0	1
Upper respiratory tract infection	1	4	5
Upper-airway cough syndrome	1	0	1
Urinary incontinence	0	3	3
Urinary retention	0	1	1
Urinary tract infection	1	3	4
Urticaria	0	3	3
Vestibular disorder	0	1	1
Viral infection	0	1	1
Vision blurred	1	3	4
Visual impairment	0	1	1
Vitamin D decreased	0	1	1
Vitreous floaters	0	1	1
Vomiting	18	23	41
Weight decreased	0	4	4
Weight increased	4	0	4
White blood cell count decreased	0	4	4
Total	**332**	**1,071**	**1,403**

Table 11: AE (MedDRA preferred term) by treatment group CTCAE grade 3 and over by treatment group

AE MedDRA term	Control	Intervention	Total
Abdominal pain	0	1	1
Alopecia	1	0	1
Anaemia	0	1	1
Aphasia	0	1	1
Ataxia	1	0	1
Autoimmune colitis	0	4	4
Brain oedema	0	1	1
COVID-19	0	1	1
COVID-19 pneumonia	1	0	1
Cerebrospinal fluid leakage	1	0	1
Colitis	0	5	5
Confusional state	2	1	3
Decreased appetite	0	2	2
Dehydration	1	1	2
Diarrhoea	0	8	8
Diarrhoea haemorrhagic	0	1	1
Fatigue	0	2	2
Hemianopia	1	0	1
Hemiparesis	1	0	1
Hyperglycaemia	2	0	2
Hypertension	2	2	4
Immune-mediated hepatitis	0	1	1
Incontinence	0	1	1
Large intestine perforation	0	1	1
Lipase increased	0	1	1
Lower respiratory tract infection	0	1	1
Lung infection	0	1	1
Lymphocyte count decreased	0	1	1
Lymphopenia	4	5	9
Mobility decreased	0	1	1
Muscular weakness	2	2	4
Muscular weakness	1	1	2
Neutropenia	0	2	2
Neutrophil count decreased	0	1	1
Neutrophil count decreased	0	2	2
Periorbital cellulitis	0	1	1
Platelet count decreased	0	2	2
Presyncope	0	1	1

Proctitis	0	1	1
Pruritus	1	1	2
Pulmonary embolism	2	3	5
Pyrexia	0	1	1
Pyrexia	0	1	1
Rash	0	4	4
Rash maculo-papular	0	2	2
Seizure	1	9	10
Slow speech	0	1	1
Thrombocytopenia	2	9	11
Unresponsive to stimuli	1	0	1
Upper respiratory tract infection	0	1	1
Urinary tract infection	0	1	1
Vomiting	3	3	6
Weight increased	1	0	1
White blood cell count decreased	0	1	1
Total	**31**	**94**	**125**

The following tables (see tables 12-16), describe the adverse events among the study participants according to CTCAE grades based on MEDRA coding and system organ class. CTCAE grade was available for 1400 of the 1403 AEs. AE outcome was available for 1384 of the AE. Figures 5 and 6 gives CTCAE graded adverse events and adverse event status by treatment group.

Figure 5: CTCAE graded adverse events by treatment group

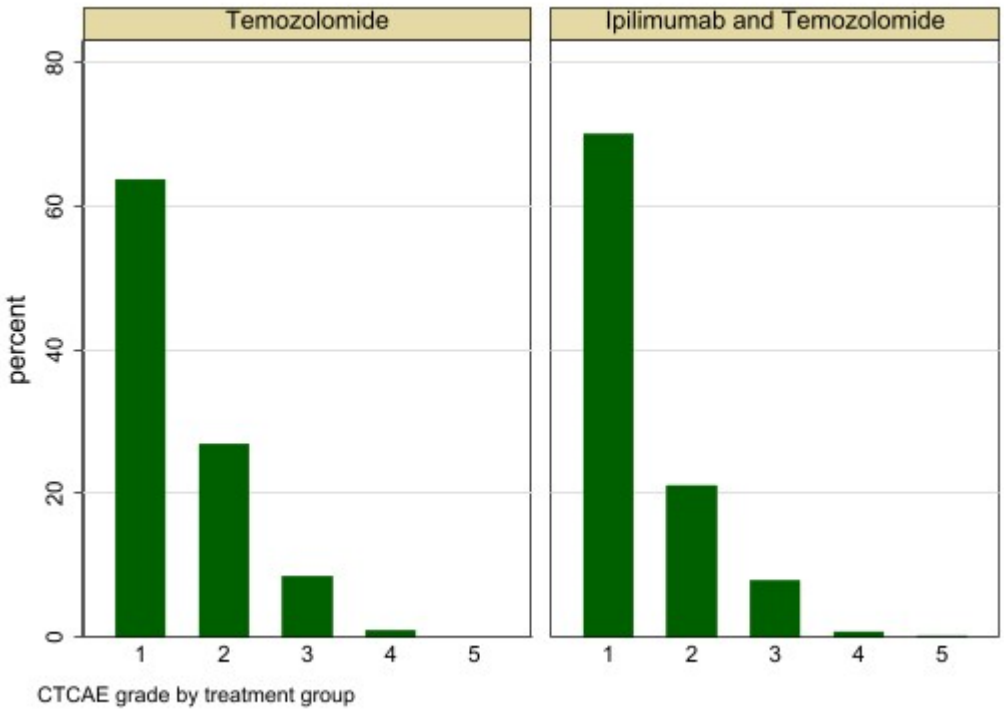


Table 10~~12~~: Summary of the adverse events (CTCAE graded) using MedDRA coding by intervention groups – ITT population

CTCAE grade	***Control***		***Intervention***		***Total***	
	n	*%*	*n*	*%*	*n*	*%*
1	211	63.75	749	70.07	960	68.57
2	89	26.89	226	21.14	315	22.50
3	28	8.46	84	7.86	112	8.00
4	3	0.91	8	0.75	11	0.79
5	0	0.00	2	0.19	2	0.14
Total	**331**	**100.00**	**1,069**	**100.00**	**1400**	**100.00**

Figure 6: Adverse event status by treatment group

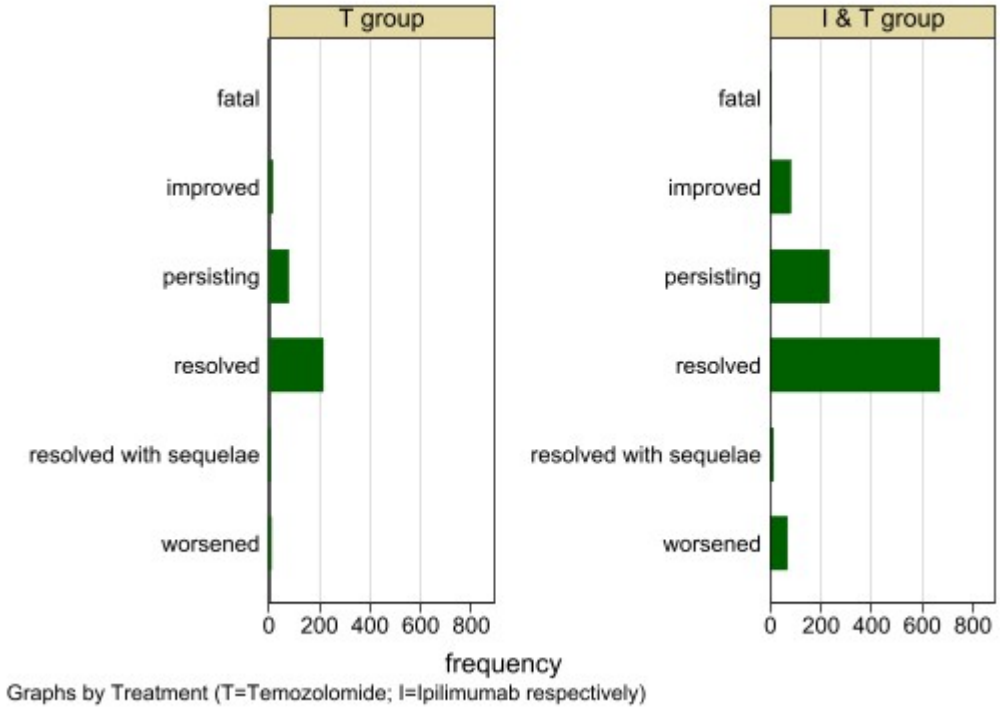


Table 11~~13~~: Adverse events grade 3 and above by treatment group and overall

AEs above grade 3	*Control*	*Intervention*	*Total*
	n (%)	n (%)	n (%)
0	300 (90.63%)	975 (91.21%)	1275 (91.07%)
1	31 (9.37%)	94 (8.79%)	125 (8.93%)
Total	**331 (100%)**	**1069 (100%)**	**1400 (100%)**

Table 1214: Adverse events according to the system organ classification in the treatment groups

System Organ Class	Control	Intervention	Total
Blood & Lymphatic S..	14	53	67
Cardiac Disorders	1	2	3
Ear and labyrinth d..	6	5	11
Endocrine disorders	6	6	12
Eye disorders	6	17	23
Gastrointestinal Disorders	56	214	270
General Disorders	29	123	152
Hepatobiliary	0	3	3
Immune System Disorders	0	2	2
Infections & Infestation	14	46	60
Injury; poisoning a..	3	7	10
Investigations	12	70	82
Metabolism & Nutrition disorders	11	34	45
Musculoskeletal disorders	28	56	84
Neoplasms benign; m..	1	0	1
Nervous System Disorders	83	174	257
Psychiatric disorders	9	24	33
Renal and urinary d..	2	11	13
Reproductive system disorders	0	4	4
Respiratory, thoracic disorders	13	30	43
Skin and subcutaneous disorders	25	165	190
Social circumstances	0	1	1
Vascular disorders	13	24	37
Total	**332**	**1,071**	**1,403**

Table 13~~15~~: Adverse events categorised by CTCAE grade 3 and above or not by participant in the control (Temozolomide) group

	AE_above_g3		
ssid	0	1	Total
IP-AD-1110	19	0	19
IP-GU-1021	6	1	7
IP-GU-1033	9	0	9
IP-GU-1064	6	0	6
IP-GU-1075	4	0	4
IP-GU-1115	26	1	27
IP-MA-1009	10	6	16
IP-MA-1012	6	0	6
IP-MA-1018	6	0	6
IP-MA-1036	7	3	10
IP-MA-1041	4	0	4
IP-MA-1065	6	1	7
IP-MA-1091	8	3	11
IP-MA-1100	2	0	2
IP-MA-1120	8	1	9
IP-MV-1004	6	0	6
IP-MV-1005	21	2	23
IP-MV-1024	31	2	33
IP-MV-1056	13	0	13
IP-MV-1069	16	2	18
IP-MV-1080	3	2	5
IP-MV-1087	7	0	7
IP-MV-1102	10	0	10
IP-MV-1103	12	0	12
IP-MV-1107	10	0	10
IP-OX-1017	7	2	9
IP-OX-1039	5	1	6
IP-OX-1044	5	0	5
IP-OX-1054	8	1	9
IP-OX-1095	2	1	3
IP-UC-1029	2	1	3
IP-UC-1032	5	0	5
IP-UC-1078	3	1	4
IP-WG-1118	7	0	7
Total	300	31	331

Table 14~~16~~: Adverse events categorised by CTCAE grade 3 and above or not by participant in the intervention (Temozolomide + Ipilimumab) group

ssid	AE_above_g3 0	1	Total
IP-AD-1011	0	1	1
IP-AD-1019	17	2	19
IP-AD-1028	14	0	14
IP-AD-1040	9	1	10
IP-AD-1094	7	0	7
IP-GU-1008	31	4	35
IP-GU-1026	23	1	24
IP-GU-1031	19	1	20
IP-GU-1037	21	0	21
IP-GU-1055	11	9	20
IP-GU-1061	12	0	12
IP-GU-1074	9	0	9
IP-GU-1088	3	1	4
IP-GU-1093	26	7	33
IP-GU-1096	6	1	7
IP-GU-1114	47	0	47
IP-GU-1116	33	7	40
IP-MA-1010	12	1	13
IP-MA-1016	7	3	10
IP-MA-1025	27	5	32
IP-MA-1034	12	6	18
IP-MA-1035	6	0	6
IP-MA-1048	6	1	7
IP-MA-1052	24	1	25
IP-MA-1059	8	1	9
IP-MA-1060	6	0	6
IP-MA-1067	4	0	4
IP-MA-1070	7	1	8
IP-MA-1076	8	0	8
IP-MA-1081	6	0	6
IP-MA-1085	14	0	14
IP-MA-1089	8	1	9
IP-MA-1097	8	6	14
IP-MA-1098	3	1	4
IP-MA-1099	12	3	15
IP-MA-1106	1	0	1
IP-MA-1108	17	1	18
IP-MA-1109	4	0	4
IP-MA-1111	4	0	4
IP-MA-1112	4	0	4
IP-MV-1001	11	0	11
IP-MV-1002	19	0	19
IP-MV-1007	36	1	37
IP-MV-1015	26	0	26
IP-MV-1027	12	0	12
IP-MV-1049	38	0	38
IP-MV-1051	27	0	27
IP-MV-1066	19	0	19
IP-MV-1072	12	1	13
IP-MV-1079	12	0	12
IP-MV-1082	5	0	5
IP-MV-1090	7	0	7
IP-MV-1105	21	0	21
IP-OX-1030	6	0	6
IP-OX-1045	2	1	3
IP-OX-1058	6	0	6
IP-OX-1062	14	0	14
IP-OX-1063	3	0	3
IP-OX-1073	7	0	7
IP-OX-1077	1	1	2
IP-UC-1014	7	3	10
IP-UC-1023	18	2	20
IP-UC-1038	3	0	3
IP-UC-1042	10	1	11
IP-UC-1043	8	1	9
IP-UC-1046	10	0	10
IP-UC-1068	6	2	8
IP-UC-1071	1	2	3
IP-UC-1083	9	1	10
IP-UC-1084	2	1	3
IP-UC-1101	11	2	13
IP-UC-1113	17	1	18
IP-WG-1003	20	1	21
IP-WG-1006	7	0	7
IP-WG-1020	4	1	5
IP-WG-1057	20	0	20
IP-WG-1117	19	2	21
IP-WG-1119	23	4	27
Total	975	94	1,069

Table 17 summarises the occurrence of an adverse events of (CTCAE) grade 3 and above by the treatment groups and overall at the participant level.

Table 15~~17~~: Relationship between CTCAE adverse events grade 3 and above and the treatment allocated (participant level)

AE_above_grade3	*Control*	*Intervention*	*Total*
	n (%)	*n (%)*	*n (%)*
0	23 (57.5%)	37 (46.8%)	60 (50.4%)
1	17 (42.5%)	42 (53.2%)	59 (49.6%)
Total	**40 (100%)**	**79 (100%)**	**119 (100%)**

Pearson chi2(1) = 1.21 P = 0.27

There were 17 (42.5%) and 42 (53.2%) participants in the control (Temozolomide) and intervention (the Ipimumab+Temozolomide) groups respectively who had at least one adverse event (CTCAE grade 3 or above). There was no evidence of a difference (p=0.27).

The following table (Table 18) show the details of serious adverse events (SAEs) that occurred per participant. In total there were 95 confirmed SAEs, which were classified as either a SAE (but not a Serious Adverse Response (SAR)), SAR (excluding any Suspected Unexpected Serious Adverse Response (SUSAR)) or a SUSAR. All SAEs were given a MedDRA System Organ Class. Of the 95 SAEs, 70 and 25 related to participants in the intervention and control groups respectively. Of these 42 were classified as a SAR but not a SUSAR with 34 and 8 in the intervention and control groups respectively. In total 16 SUSARs were reported (with 15 and 1 in the intervention and control groups respectively), 3 of the 16 were subsequently downgraded. The SAEs were classified in terms of the reason for the seriousness designation as 2 being “death” (both for participants in the intervention group), 73 as “hospitalisation or prolongation of hospitalisation” (56 of which were in participants in the intervention group), 1 in being “life threatening” (related to a participant in the intervention group), and 19 as a “other important medical events” (11 and 8 in the intervention and the control group participants respectively). The outcome of the 95 SAEs were 2 deaths, 66 being classed as “recovered” (46 and 20 in the intervention and the control group participants respectively), 5 as “recovered with sequalae” (4 and 1) , 21 were “recovering” (81 and 1 in the intervention and the control group participants respectively), and 1 had unknown outcome (relating to a participant in the control group).

Table 16~~18~~: Details of serious adverse events, classified as SAR, SUSAR and system organ class.

SAE ID	MedDRA System Organ Class	MedDRA Preferred Term	CTCAE	Outcome	Seriousness	Conclusion
IPISAE1023	Blood & Lymphatic System Disorders	Lymphopenia	3	Recovered	Other important medical event(s)	SUSAR
IPISAE1022	Blood & Lymphatic System Disorders	Lymphopenia	3	Recovering	Other important medical event(s)	SUSAR
IPISAE1032	Blood & Lymphatic System Disorders	Lymphopenia	3	Recovering	Other important medical event(s)	SAR
IPISAE1058	Blood & Lymphatic System Disorders	Lymphopenia	3	Recovering	Other important medical event(s)	SAR
IPISAE1054	Blood & Lymphatic System Disorders	Lymphopenia	3	Recovered with sequalae	Other important medical event(s)	SAR
IPISAE1044	Blood & Lymphatic System Disorders	Lymphopenia	3	Recovered	Other important medical event(s)	SAR
IPISAE1007	Blood & Lymphatic System Disorders	Lymphopenia	3	Unknown	Other important medical event(s)	SAR
IPISAE1008	Blood & Lymphatic System Disorders	Lymphopenia	3	Recovered	Other important medical event(s)	SAE
IPISAE1024	Blood & Lymphatic System Disorders	Lymphopenia	3	Recovering	Other important medical event(s)	SAE
IPISAE1015	Blood & Lymphatic System Disorders	Neutropenia	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1014	Blood & Lymphatic System Disorders	Thrombocytopenia	4	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SUSAR (subsequently downgraded)
IPISAE1047	Blood & Lymphatic System Disorders	Thrombocytopenia	4	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SUSAR
IPISAE1050	Blood & Lymphatic System Disorders	Thrombocytopenia	4	Recovered	Other important medical event(s)	SAR
IPISAE1082	Blood & Lymphatic System Disorders	Thrombocytopenia	4	Recovered	Other important medical event(s)	SAR
IPISAE1049	Blood & Lymphatic System Disorders	Thrombocytopenia	3	Recovered	Other important medical event(s)	SAR
IPISAE1064	Blood & Lymphatic System Disorders	Thrombocytopenia	4	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1091	Cardiac Disorders	Atrial fibrillation	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1093	Gastrointestinal Disorders	Autoimmune colitis	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SUSAR
IPISAE1089	Gastrointestinal Disorders	Autoimmune colitis	3	Recovered with sequalae	In-patient hospitalisation or Prolongation of existing hospitalisation	SUSAR
IPISAE1040	Gastrointestinal Disorders	Autoimmune colitis	3	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1010	Gastrointestinal Disorders	Autoimmune colitis	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1060	Gastrointestinal Disorders	Autoimmune colitis	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR

SAE ID	MedDRA System Organ Class	MedDRA Preferred Term	CTCAE	Outcome	Seriousness	Conclusion
IPISAE1027	Gastrointestinal Disorders	Colitis	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1006	Gastrointestinal Disorders	Colitis	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1083	Gastrointestinal Disorders	Colitis	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1077	Gastrointestinal Disorders	Colitis	3	Recovered with sequalae	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1011	Gastrointestinal Disorders	Diarrhoea	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1021	Gastrointestinal Disorders	Diarrhoea	2	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1019	Gastrointestinal Disorders	Diarrhoea	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1003	Gastrointestinal Disorders	Diarrhoea	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1069	Gastrointestinal Disorders	Diarrhoea	3	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1062	Gastrointestinal Disorders	Diarrhoea	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1076	Gastrointestinal Disorders	Diarrhoea haemorrhagic	3	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1046	Gastrointestinal Disorders	Gastritis	2	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SUSAR
IPISAE1086	Gastrointestinal Disorders	Gastrointestinal toxicity	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SUSAR
IPISAE1028	Gastrointestinal Disorders	Large intestine perforation	3	Recovered	Life-threatening	SUSAR
IPISAE1020	Gastrointestinal Disorders	Proctitis	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1052	Gastrointestinal Disorders	Vomiting	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1005	Gastrointestinal Disorders	Vomiting	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1088	Gastrointestinal Disorders	Vomiting	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1055	General Disorders & Administration Site Conditions	Face oedema	2	Recovered	Other important medical event(s)	SAR

SAE ID	MedDRA System Organ Class	MedDRA Preferred Term	CTCAE	Outcome	Seriousness	Conclusion
IPISAE1095	General Disorders & Administration Site Conditions	Fatigue	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SUSAR (subsequently downgraded)
IPISAE1078	General Disorders & Administration Site Conditions	Pyrexia	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SUSAR
IPISAE1057	General Disorders & Administration Site Conditions	Pyrexia	1	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1016	General Disorders & Administration Site Conditions	Pyrexia	1	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1029	General Disorders & Administration Site Conditions	Pyrexia	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1036	General Disorders & Administration Site Conditions	Pyrexia	1	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1038	Hepatobiliary	Immune-mediated hepatitis	3	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1074	Infections & Infestations	COVID-19	4	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SUSAR
IPISAE1072	Infections & Infestations	COVID-19 pneumonia	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1012	Infections & Infestations	Lung infection	3	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SUSAR
IPISAE1080	Infections & Infestations	Periorbital cellulitis	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1018	Infections & Infestations	Upper respiratory tract infection	3	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1068	Investigations	Neutrophil count decreased	3	Recovered	Other important medical event(s)	SAR
IPISAE1079	Investigations	Neutrophil count decreased	3	Recovered	Other important medical event(s)	SAR
IPISAE1041	Investigations	Platelet count decreased	3	Recovered	Other important medical event(s)	SAR
IPISAE1026	Metabolism & Nutrition Disorders	Dehydration	3	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1084	Metabolism & Nutrition Disorders	Hyperglycaemia	4	Recovered	Other important medical event(s)	SAE
IPISAE1059	Musculoskeletal & Connective Tissue Disorders	Muscular weakness	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1061	Musculoskeletal & Connective Tissue Disorders	Muscular weakness	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE

SAE ID	MedDRA System Organ Class	MedDRA Preferred Term	CTCAE	Outcome	Seriousness	Conclusion
IPISAE1002	Nervous System Disorders	Seizure	5	Fatal	Death	SUSAR (subsequently downgraded)
IPISAE1033	Nervous System Disorders	Aphasia	1	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1070	Nervous System Disorders	Brain oedema	4	Recovered with sequalae	In-patient hospitalisation or Prolongation of existing hospitalisation	SUSAR
IPISAE1056	Nervous System Disorders	Brain oedema	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1013	Nervous System Disorders	Brain oedema	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1067	Nervous System Disorders	Cerebrospinal fluid leakage	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1039	Nervous System Disorders	Generalised tonic-clonic seizure	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1085	Nervous System Disorders	Generalised tonic-clonic seizure	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1100	Nervous System Disorders	Headache	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1102	Nervous System Disorders	Headache	3	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1101	Nervous System Disorders	Lethargy	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SUSAR
IPISAE1051	Nervous System Disorders	Presyncope	3	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1045	Nervous System Disorders	Seizure	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1081	Nervous System Disorders	Seizure	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1071	Nervous System Disorders	Seizure	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1065	Nervous System Disorders	Seizure	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1053	Nervous System Disorders	Seizure	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1105	Nervous System Disorders	Seizure	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1042	Nervous System Disorders	Seizure	2	Recovered with sequalae	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE

SAE ID	MedDRA System Organ Class	MedDRA Preferred Term	CTCAE	Outcome	Seriousness	Conclusion
IPISAE1094	Nervous System Disorders	Seizure	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1097	Nervous System Disorders	Seizure	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1043	Nervous System Disorders	Seizure	3	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1096	Nervous System Disorders	Seizure	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1048	Nervous System Disorders	Seizure	4	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1031	Nervous System Disorders	Unresponsive to stimuli	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1037	Psychiatric disorders	Confusional state	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1035	Psychiatric disorders	Confusional state	3	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1103	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	2	Recovered	Other important medical event(s)	SAR
IPISAE1025	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	5	Fatal	Death	SAE
IPISAE1099	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	3	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1017	Skin and subcutaneous tissue disorders	Rash	2	Recovering	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1009	Skin and subcutaneous tissue disorders	Rash	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAR
IPISAE1030	Skin and subcutaneous tissue disorders	Rash maculo-papular	3	Recovered	Other important medical event(s)	SAR
IPISAE1104	Vascular disorders	Haematoma	2	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE
IPISAE1001	Vascular disorders	Hypertension	3	Recovered	In-patient hospitalisation or Prolongation of existing hospitalisation	SAE

6. EXECUTIVE SUMMARY

IPI-GLIO was an unblinded, open labelled stratified randomised Phase II multicentre clinical trial (CTIMP). Patients with newly diagnosed de-novo glioblastoma following surgery and radical radiotherapy with concomitant temozolomide were recruited from 7 sites in the UK. The study aimed to evaluate whether the addition of ipilimumab to the current standard of care, temozolomide, following surgery and radiotherapy would improve survival in patients with newly diagnosed glioblastoma.

Patients who met the eligibility criteria were randomly allocated in a 2:1 ratio to receive either Intervention (ipilimumab + temozolomide) or Control (temozolomide alone). 119 patients were randomised, 40 in the control groups (Temozolomide) and 79 in the intervention groups (Temozolomide + Ipilimumab). 38 (32%) of the participants were women. Participants' ECOG performance status was 0 for 70% of the participants, with the remaining (30%) participants being ECOG performance status 1. The median overall survival was 23.0 months 60% CI (17.3-26.4) for Temozolomide and 18.2 months 60% CI (16.0-23.9) for Temozolomide & Ipilimumab.

Limitations of the study were that the study included a pause of recruitment due to the COVID-19 pandemic and the additional risks that the patients had during this period and during follow-up. However, the trial did complete recruitment and follow-up as planned. This was a phase 2 trial with a larger than usual significance level used and therefore the trial has been reported with 60% confidence intervals throughout as required. There was no evidence of a difference between the treatment groups and more adverse events were observed in the intervention group. This combination treatment is therefore not recommended for use in clinical practice or for a phase 3 trial in this population.

Version number Issue date	Author	Significant changes from previous version
V1.0_XXXX2023	Jonathan Cook	Not applicable as this is the 1st issue

7. APPENDIX

7.1 Protocol

Attached as follows.

7.2 Statistical Analysis Plan

Attached as follows.

7.3 Statistical Analysis Plan – Data Definitions and Tables

Attached as follows.

IPI-GLIO_Protocol_V
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