STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE: **Avelumab in patients with newly diagnosed Glioblastoma Multiforme**

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Version 5

STUDY SPONSOR: Clinique Neuro-Outaouais

STUDY DRUG and INDICATION: Avelumab, glioblastoma multiforme

TYPE OF STUDY: Phase 2, single center, open ended, open label addition of avelumab to standard therapy

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1. STATISTICAL STATEMENT AND ANALYTICAL PLAN

1.1. Sample Size Considerations

A convenience sample of thirty (30) patients is based on recruitment feasibility. This sample size will permit estimation of dichotomous outcome rates with margins of error of less than 18% (based on a significance level of 0.05) and estimation of continuous parameter means to within 0.36 standard deviations. This is an early stage study, so analysis will focus on descriptive statistics. Continuous parameters will be summarized by means and 95% confidence intervals or by medians and interquartile ranges, as appropriate. Dichotomous outcomes will be summarized with point estimates of the rate, as well as 95% confidence intervals. Time-to-event data will be summarized using Kaplan-Meier curves.

1.2. Analyses

Complete analysis will be done when all patients have completed week 52 or end of study visit and repeated every 52 weeks thereafter. Interim descriptive analyses will be done when the first 10 patients have completed week 52 or the end of study visit and repeated when the first 20 patients have done so as well.

1.3. Efficacy data

1.3.1. Primary Endpoints

Safety and tolerability based on avelumab related adverse events leading to permanent or transient discontinuation of avelumab
Treatment related adverse events of special interest will include those of autoimmune origin (irAE).
The adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0

1.3.2. Secondary Endpoints

Based on the results of Stupp *et al* (2005) (3), if avelumab had no effect then we would expect to see one-year overall survival and progression-free survival rates of 60% and 27%, respectively. We will conclude that we have preliminary evidence of benefit if either of our observed rates is significantly better based on a one-sided t-test at the 0.2 level of significance. With our projected sample of 30, this corresponds to concluding benefit if at least 21 patients survive to one-year or if at least 11 have survived without progression of disease.

Radiological tumor response will be graded according to the immunotherapy Response Assessment for Neuro-Oncology (iRANO)

Progression of Disease (PD) will be defined as a ≥25% increase on the 12 month MRI or CT scan in the sum of the product of the biperpendicular diameters of enhancing disease; or new lesions; or substantial worsened T2/FLAIR; or significant clinical neurological decline unexplained by a change in medication or concurrent comorbities. The SPD is the sum of the products of biperpendicular diameters of the measurable enhancing lesions (max 5 lesions).

Complete Response (CR) will be defined as the disappearance on the month 12 MRI or CT scan of all enhancing disease, no new lesions, with stable or improved T2/FLAIR; no more than physiological steroids; clinically stable or improved

Partial Response (PR) will be defined as a ≥50% decrease on the month 12 MRI or CT scan in the sum of the product of the biperpendicular diameters of enhancing disease, no new lesions, stable or improved T2/FLAIR, stable (>2 months) or decreased steroid dose, clinically stable or improved

Stable Disease (SD) will be defined at 12 months when a patient do not qualify for complete response, partial response, or progressive disease, stable or improved T2/FLAIR; stable (>2 months) or decreased steroid dose, clinically stable or improved

Overall survival (OS) will be defined as the time from baseline to the date of death from any cause.

Objective Response Rate (ORR) will be defined the number of patients with either CR or PR divided by the total number of patients.

Progression Free Survival (PFS) will be defined as the time from baseline to documented PD or death from any cause.
Results will be stratified according to MGMT status, baseline age (>50yrs), baseline Karnofsky performance score (score of 100), radical tumor resection vs biopsy, primary versus secondary GBM,

1.3.3. Exploratory

The incidence of PD-L1 expression on tumor cells and microglia/macrophages within the tumor will be determined and correlated to OS and PFS and other iRANO endpoints

The histological immunoscore will be determined and tested for association with OS, PFS, and other iRANO endpoints using logistic regression.

The association between 12 months OS and PFS with baseline neurocognitive function as measured by the evoked potential P300 (normal), the baseline corticosteroid dose, the average daily corticosteroid dose over the whole study duration, the extent to which patients complete the full 6 cycles of temozolomide based on temozolomide toxicity and the incidence and severity of treatment related irAE's will be tested using logistic regression.

The change if any in histological markers on tissue obtained from repeat resection

The estimation of the time period in which radiological progression was seen in clinically stable patients whose imaging was subsequently followed by radiological stabilization or regression
The estimation of the time period in clinically stable patients before radiological evidence of tumor regression occurred

The change in P300 will be determined and correlated with clinical outcomes as per iRAN