STATISTICAL ANALYSIS PLAN (SAP)

MVP-S (DPX-Survivac) and Checkpoint Inhibitor in DLBCL

(SPiReL)

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SPiReL STATISTICAL ANALYSIS PLAN

SAP Signatures

By signing below I approve the attached SAP entitled SPiReL dated 07 MAR 2022

Trial Statistician

Name: George Tomlinson

Signature: _____

Date: _____

Principal Investigator

Name: Dr. Neil Berinstein

Signature: _____

Date: _____

Statistician

Name: Yidi Jiang

Signature: _____

Date: _____

Contributions

The statistical analysis plan (SAP) was developed based on the outlined analyses set out in the trial protocol. The SAP was developed by the statistical analysis team which includes Neil Berinstein, Irina Amitai, Iran Rashedi, George Tomlinson, Yidi Jiang, Kim Roos, Gail Klein, and Kathryn Mangoff. George Tomlinson is the trial statistician and helped answer questions related to trial data and management relevant to the development of the SAP. The SAP will be reviewed by the steering committee. IMV Inc. has participated in the review process. George Tomlinson (trial statistician), Neil Berinstein (principal investigator), and Yidi Jiang (statistician) approved the SAP.

SPiReL STATISTICAL ANALYSIS PLAN

The full statistical analysis plan for SPiReL comprises this document and associated shell tables.

STUDY OVERVIEW

This is a Phase 2 non-randomized, open label, uncontrolled, efficacy and safety study. Study participants will receive two priming doses of 0.5 mL of MVP-S 21 days apart and up to six 0.1 mL maintenance injections every eight weeks with intermittent low-dose oral cyclophosphamide (50 mg BID) for one year or until disease progression, whichever occurs first.

Pembrolizumab 200 mg will be administered every 3 weeks for up to one year or until disease progression, whichever occurs first.

STUDY HYPOTHESES

Combining MVP-S and metronomic cyclophosphamide with pembrolizumab in patients with measurable relapse/refractory DLBCL will:

- result in a clinically significant objective response level that will be at least 24% (CR+PR).
- enhance the activation of the polyfunctional T cells in the peripheral blood activated by DPX-Survivac
- increase the infiltration of tumour sites with lymphocytes compared to pre-treatment biopsies

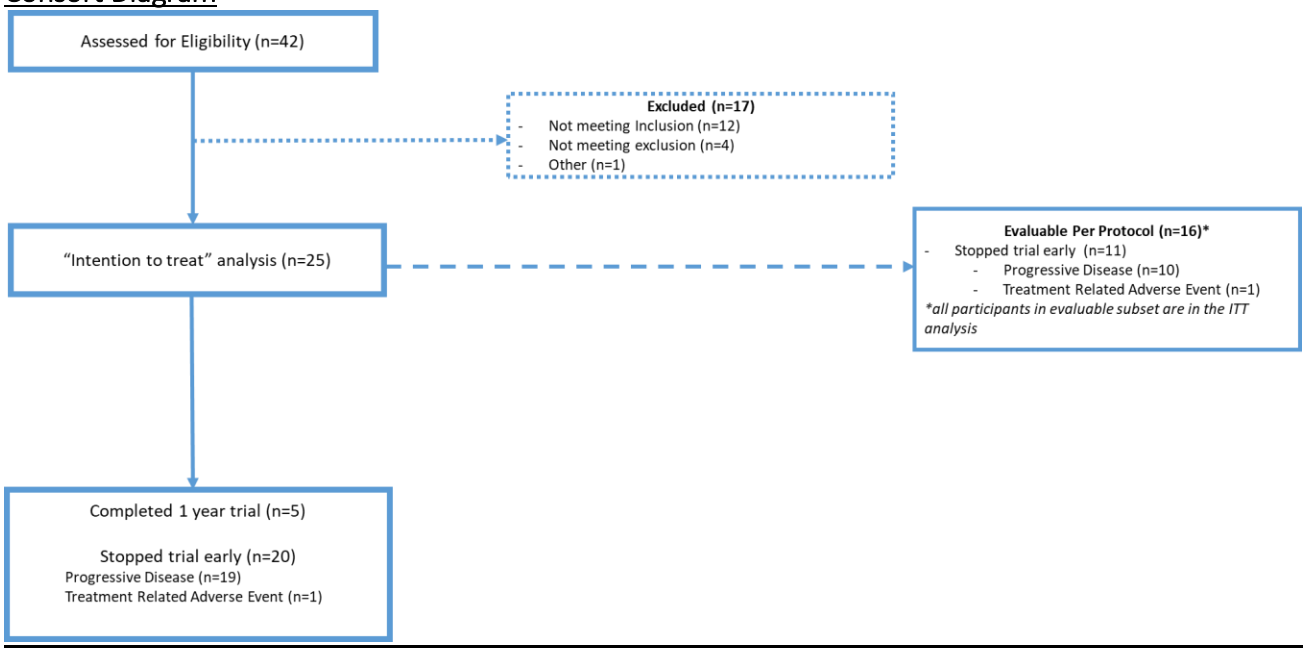
This will be evidence that both mechanisms of anti-tumour activity are elicited by this combination immunotherapy.

STUDY POPULATION

All enrolled participants (N=25) were required to meet all eligibility criteria.

Analysis will be done on two populations; the Intent-to-Treat (ITT) which will be comprised of all 25 enrolled, all of whom received at least one treatment of MVP-S (0.5mL); and the Per Protocol (PP) population, which consists of those participants who are evaluable (n=16) as defined by participants who received 3 MVP-S injections (per protocol of 2 priming injections at 0.5mL each and 1 maintenance at 0.1mL or 3 priming injections as per protocol), 4 pembrolizumab infusions and 1 on treatment CT scan between SD70 and SD104. Baseline characteristics will be presented for the ITT, as well as treatment related Adverse Events (TRAEs) captured from SD0 through till the end of the participants treatment safety period.

Consort Diagram



DESCRIPTIVE STATISTICS

SPiReL Baseline characteristics

A summary of the baseline characteristics of the participants will be generated and tabulated. They will be presented in tables, with no statistical analysis performed.

The following are the Baseline clinical variables:

- age,
- performance status (ECOG),
- relapsed (> 3months from end of last treatment to SD0) vs. refractory (< 3 months from the end of last treatment date to SD0)
- transformed (by pathology and clinical treatment history),
- number of previous treatments (Total Systemic treatments for DLBCL only),
- previous ASCT,
- time from last treatment end (end date of last DLBCL systemic chemotherapy) to Study Day 0
- IPI at screening,
- stage 3 or 4,
- LDH,
- tumour volume at screening
- bulky disease modifier (defined by > 7.5cm lesion at screening)
- positive bone marrow involvement

The following are Baseline Pathology variables. These are identified as ***explicitly*** stated in the individual participant pathology reports (including FISH where available). If a result is not stated, it will be identified as UNKNOWN. When basic pathology may be questioned due to incompleteness found in the pathology reports, the Principal investigator will be consulted for resolution. Additional details of definitions can be found in the Data Management Plan (DMP) and/or the appendix:

- GCB (Y/N)
- Non-GCB (Y/N)
- Leg-type (Y/N)
- Double hit (Y/N)
- Double expressor (Y/N)
- Triple expressor (Y/N)
- MYC expression (positive/negative and % if available)
- BCL2 expression (positive/negative and % if available)
- BCL6 expression (positive/negative and % if available)
- CD5+ (present Y/N and % if available)
- CD10+ (present Y/N and % if available)
- CD20+ (present Y/N and % if available)
- Cyclin D+ (present Y/N and % if available)
- MUM 1+ (present Y/N and % if available)
- Transformed (Y/N as explicitly stated in the pathology report or based on clinical history as reviewed by the Principal Investigator)
- Ki67 (positive/negative and % if available)

Appropriate summary statistics (means, medians, percentages and measures of dispersion such as the standard deviation and interquartile range) will be generated according to the baseline covariates detailed in the "Analysis table". No significance testing will be done on these baseline characteristics and will be represented for all 25 enrolled participants. Analysis will be performed using the number of participants that express each variable Study visits

At all study visits, completeness of follow-up and summary statistics for the values collected at that time will be computed and tabulated as outlined in the "Analysis tables". These results are only descriptive but some of these variables are primary and secondary outcomes and will be compared in the more detailed plan in this document.

Treatment Exposure & Compliance

Three investigational products are administered to subjects: MVP-S, cyclophosphamide, and pembrolizumab

The following aspects of MVP-S exposure will be summarized:

- Total number of all injections received
- Total number of each type of injection (0.5 mL, 0.1 mL, additional 0.5 mL) received
- Total number of injections delayed and omitted while subject was on study
    - Whether delay or omitted injections were per protocol or other

The following aspects of cyclophosphamide exposure will be summarized as best as possible from the information in the participant diaries:

- Number of 14-day cycles completed per subject
    - Number of BID cycles completed
    - Number of QD cycles completed
- Number of subjects with dose interruptions
- Number of subjects with at least one dose decrease during the study

The following aspects of pembrolizumab exposure will be summarized:

- Total number of all infusions received
- Total number of infusions interrupted while subject was on study
- Whether infusions interrupted were per protocol or other

Missed doses of MVP-S and pembrolizumab due to adverse events followed the guidance as set out in the protocol. There are no expectations to use this information the statistical analyses but will be presented as part of the Adverse Event analysis.

ANALYSIS OF OUTCOMES

The Primary Outcome is to document a minimal objective response rate of 24% (CR+PR) to treatment with MVP-S and intermittent low-dose cyclophosphamide administered together with anti-PD-1 (pembrolizumab) in patients with recurrent, survivin-expressing B cell lymphomas using modified Cheson criteria. This analysis will be performed on both the ITT and PP study populations.

From the Protocol

A. Primary outcomes/endpoint(s)

Objective clinical and radiologic response rate will be determined using Modified Cheson Criteria.

B. Efficacy review

The primary outcome is the objective response rate to treatment with MVP-S and intermittent low-dose cyclophosphamide and pembrolizumab, in patients with recurrent survivin-expressing B cell lymphomas, using Modified Cheson criteria.

C. Primary outcome analysis

A one-stage design requires treating and evaluating 25 subjects for response in the ITT. The intended sample size is 25 evaluable subjects, however, there were 16 evaluable subjects for a Per Protocol (PP) analytical set. This analysis will include quantitation of Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD). It will indicate one response per participant, which will be the best response achieved over the course of their participation. We would like calculations of the CR rate, CR + PR rates (overall objective response), and CR, PR + SD (disease control rate). We would like the analysis of the ITT and PP populations.

If the overall objective responses (CR and PR) are observed in at least 6 of 25 subjects, the treatment will be considered worthy of further testing. The design has more than 90% power to conclude that the treatment is effective if it's true response rate were equal to 35% or more. The design also has less than 5% probability to conclude that the treatment is effective if its true response rate were equal to 10% or less. (If the power is 0.5 then the trial has a less than 5% chance to conclude that the trial is ineffective if it's true response rate is greater than 10%).

In addition, this study would be considered positive if overall objective responses (CR + PR) were seen in 5 of the 16 participants in the PP study population. If the overall objective responses (CR + PR) are observed in at least 5 of 16 subjects, the treatment will be considered worthy of further testing. The design has more than 90% power to conclude that the treatment is effective if its true response rate were equal to 44% or more. The design also has less than 1.7% probability to conclude that the treatment is effective if its true response rate were equal to 10% or less.

Standard descriptive statistical methods will be used to summarize the data. The response rate will be estimated along with its exact 95% confidence interval.

Missing data on primary outcome

Only observed values will be used in the analyses but the extent of missing data will be clearly reported.

Secondary Outcomes

1. Changes in tumour volume and individual profiles of tumour volume versus time. Tumour volume recorded at screening will be compared quantitatively to treatment and end of study (EOS) imaging. Data such as the degree of change or total tumour volume, from screening/baseline through end-of-study, will be plotted on a waterfall plot to demonstrate quantitative best individual responses using modified Cheson Criteria and irRC.

2. Document the toxicity profile. Evidence of toxicity will be assessed at each visit and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE v 4.03). For each specific adverse event occurring in any participant, related to the treatment, we will tabulate each by grade and severity:

a. Number of participants who have this adverse event.
b. Number of adverse events in total.
c. Treatment related adverse events occurring in > 10% of participants (n=3)
d. Injection Site Reactions (ISRs) and events of special interest (immune-related). ISRs will be analyzed by comparing; Grade 3 and 4 ISRs observed (Yes/No); Grade 1 and 2 observed ISR (Yes/No); and total ISRs observed.
e. Lab values that were abnormal were listed as AEs

For reporting, treatment related Adverse Events will be counted once in each participant and at their highest grade, unless; multiple events occur but are related to different study drugs; the Principal investigator feels there was sufficient time between when the AE resolved and restarted to be counted as two separate instances.

3. To document duration of response using modified Cheson criteria and immune-related response criteria (irRc). Duration of response is defined as the time from the best response observed in the participant until the time the participant is observed to experience progressive disease (PD). In some cases, the participant may not show or have available evidence of radiologic progression, in which case other diagnostic tests may be used to determine progression (as identified by an Investigator where such progression is identified on the participant's Response Assessment Form). If a date of progression is not clear, the start date of a new treatment will be used as the date of progression. If the participant does not have an observed progression after completion of the trial, and including at follow-up visits, the start date of a new treatment will be used as the date of progression. Participants who did not have an end date to their duration of response at the end of the trial, will be censored, and will be left as ongoing and identified as such. If there is no date of progression or start date of a new treatment, but there is a date of death, date of death will be used.

4. To document time to next treatment (TTNT) (or death) and survival, Progression Free Survival (PFS) and Overall Survival (OS); Progression Free Survival (calculated as the date of enrollment (SD0) to the date of observed progressive disease as defined by Modified

Cheson Criteria or date of death) and Overall Survival (calculated as the date of enrollment (SD0) to the date of death or the last known date alive if available for participants for which there is no date of death) will be documented using Kaplan-Meier curves. Time to next treatment is calculated as the time the participant begins the study (SD0) to the start date of a new treatment, chemotherapy or radiation. Participants who do not have a new treatment start date will be left blank and indicated as ongoing, unless date of death is available.

From the Protocol

A. Secondary outcomes/endpoint(s)

The irRC criteria will also be utilized to evaluate the duration of response. Evidence of toxicity will be assessed at each visit and recorded as rate of adverse events per CTCAE v 4.03. When subjects have completed their participation in the study, by either remaining on trial to SD394 (SD364 + 30 days safety), or discontinuing study participation early, they will be followed up to the documented time to next treatment and obtain survival times.

B. Secondary outcome efficacy review

Secondary objectives are to document evidence of tumour regression using clinical and radiologic criteria for waterfall analysis. The duration of response will be determined using routine clinical and radiologic criteria (Modified Cheson criteria) as well as using irRC.

C. Secondary outcome analysis

Secondary outcomes are to document: evidence of tumour regression using clinical and radiologic criteria for waterfall analysis. Tumour volume recorded at screening/baseline imaging will be compared to treatment and end of study imaging. The degree of change/volume of response will be plotted on a waterfall plot to demonstrate the degree of individual responses. The duration of response will be determined using routine clinical and radiologic criteria (modified Cheson criteria) as well as using irRC.

When subjects have completed their participation in the study, they will be followed up to document time to next treatment and obtain survival times will be plotted using Kaplan Meier Curves.

Missing data on secondary outcomes

Only observed values will be used in the analyses but the extent of missing data will be clearly reported.

Exploratory Outcomes

1. To document the changes in circulating T cell immune responses to survivin and relationship to peripheral tumour volume. Generation of survivin-specific ELISpot responses is a biologic parameter that may potentially predict for clinical response to DPX-Survivac-based treatment regimen. We will seek to determine whether generation of ELISpot responses correlates with primary or secondary endpoints. In addition we will seek to determine if any biomarkers are associated with generation of ELISpot responses.

Only subjects with evaluable baseline (SD0 or SD7) and at least 2 on-treatment samples will be considered eligible for this analysis. For each subject/ time point, the ELISpot response values for all the HLA-matched individual peptides (both wild-type and modified as in MVP-S), their respective pools, and the corresponding positive and negative controls will be reported. Sample acceptance criteria status (pass or fail) will also be reported for each sample. Analyses for samples which pass the acceptance criteria will be performed using the response values from the peptide pool group only; all other values will be listed only.
ELISpot responses are quantified in duplicates at each time point and reported as spot forming units (SFU) per million cells. Results reported as the mean SFU per million will be used for all descriptive statistics and data representation purpose Positive ELISpot responder is defined as subjects with ≥1 on-treatment response (background subtracted SFU per million value) greater than the cut-off whereby, the cut-off is calculated as the mean of peptide pool response at baseline + 2 Standard Deviations.

PBMC samples for the purpose of ELISpot analysis, will be collected as per protocol. Delays in blood draws due to adverse events, if within a week of the designated time point, were collected and analyzed. In some situations, samples were missed due to greater delays and were omitted completely. The PBMC samples delayed by 1 week will be identified as unscheduled but will be analyzed. In cases where ELISpot testing "failed", samples were retested, if there were sufficient samples available. In cases where no samples were available for retesting, the value at that time point will be left blank and noted in a footnote. If this value would be crucial in determining ELISpot evaluability or response and is unavailable, the participant will not be considered ELISpot evaluable.

2. To document changes in T cell and T cell subset infiltration and gene expression pathways in treatment compared to pre-treatment tumour biopsies.

Owing to the limited quantity of the tumour tissues and a limited number of paired tissue samples (baseline and on-treatment), this analysis will not be formally performed. Samples will be retained for potential future analysis if new technologies become available. However, baseline levels of T cells subsets as potential biomarkers of treatment response will be assessed as a part of multiplex immunohistochemistry (IHC) (see #3 below). This will

also include future reviews of the efficacy of the novel assays used in determining outcomes,

3. To assess potential biomarkers of immune and clinical response from subject clinical, biological and immunologic data from pre-treatment and on-treatment tumour biopsies.

Multiple potential biomarker candidates will be assessed using different assays on baseline/ screening tumour samples, which are available for all 25 enrolled participants and will be assessed as variable that may influence primary and secondary outcomes. The statisticians will decide how to show the stats (quartiles etc.) some variables are reported as Y/N and some have values. These may come from:

(1) pathology reports (variables described in baseline and univariate analysis sections),
(2) multiplex IHC results from Akoya (variables described in univariate analysis section),
(3) Survivin Results, from analyses by Neogenomics (variables described in univariate analysis section).

We intend to perform exploratory analyses to look at pre-treatment tumour biopsies as well as changes in tumour biopsies with treatment. Tumour biopsy samples have been obtained pre-treatment and on-treatment to assess for changes in lymphocyte infiltrates, lymphocyte subsets, and gene expression profiles with treatment. However, insufficient numbers of interpretable on treatment tumour biopsies have been obtained for these analyses. And thus changes in infiltrates or gene expression exploratory analyses will not be performed. Additional novel biomarkers may be evaluated as they become available. If an injection site biopsy is required for clinical management during the course of this trial, portions of this biopsy may be studied for evidence of antigen specific T cell infiltrates, other biomarkers or immune activity.

4. To evaluate other relevant biologic assays that may be identified during the conduct of the trial that may have immune or clinical relevance on samples already collected.

We are performing additional analyses which are expected to be reported on at a later date and to be included an Addendum to this SAP. Eventually they will be considered as additional biomarkers and include:

- Clinically validated PDL1 assay
- Presence of 9P24.1 genomic amplification (Yes/No)
- Intracellular cytokine flow cytometry analysis (exact read-out here have not yet been defined)
- Other immunogenomics analyses from DNA and RNA sequencing (full details not available at this time)
- Expanded biologic analyses with additional combination variables

From the Protocol

A. Exploratory outcome analysis

Exploratory endpoints will be evaluated and will be important in determining whether the treatment is promising and worthy of further clinical evaluation assuming activity (i.e. minimal response rate of 24%, or 6 responses among 25 patients). We expect that both previously documented mechanisms of immune activity should be elicited by this immunotherapy combination. That is we would expect to see evidence of increases in circulating survivin specific T cells in the majority of patients. We would also expect to see increases in lymphocyte infiltration and gene expression in at least 24% of patients (i.e. 6 of 25 patients). Quantitative assessments of both of these parameters have been obtained and standard paired t-tests will be used to compare pre- and post-treatment assessments.

Missing data on outcomes

Only observed values will be used in the analyses but the extent of missing data will be clearly reported.

Data will be presented as observed and entered into the EDC. No imputation will be performed for missing data except for the following date imputations.

For partial or missing Adverse Event dates, a conservative rule will be used for determining whether an event was treatment emergent; if the missing data do not make it possible to determine whether the event was treatment emergent, it will be marked as treatment emergent.

Similarly, for concomitant medications with partial/missing dates, ambiguity regarding whether the medication was taken concomitant with study treatment, it will be marked as concomitant.

No coding will be performed for Concomitant Medications. Coding for Adverse Events will be completed using general categories as found in the CTCAE 4.03.

The “date of resolution” or “outcome” of Adverse Events may be unknown for the following reasons: participant death, participant lost to follow-up, participant starting a new treatment/course of therapy. In the circumstance of a Treatment Related Adverse Event (TRAE) without a “date of resolution” and no way to obtain this data point, it will be left as “ongoing” in REDCap but it will be censored and given a “date of resolution” for the purpose of statistical analysis according to the following rules: the date participant death (if known), or the start of a new treatment date (if known), whichever comes first. If neither of these are known, the End of Study (EOS) date will be used. The “outcome” data point

will identified as Unknown. Adverse Events that are not treatment related will be resolved in the same manner as TRAEs, however, will not be held to the strict rules of "date of resolution" should one not be available or obtainable and will instead be censored as 30 days after onset.

As per protocol, all SAE's will be followed for 90 days maximum. If still ongoing after 90 days, the SAE will be censored and given a "date of resolution" of 90 days after onset, and an "outcome" as unknown.

UNIVARIATE AND MULTIVARIATE ANALYSES

As per protocol, a univariate analysis will be done to demonstrate the impact of all the variables on the clinical response and ELISpot endpoints. Because of the small sample size, a multivariate analysis will be limited by the number of variables that can be included in the analysis. A multivariate analysis will not be part of the formal statistical analysis plan.

Subgroup analyses of primary, secondary and ELISpot endpoints

T Cell activation therapy induced generation or enhancement of pre-existing immunity to survivin is considered a prerequisite for the anti-tumour effect of MVP-S. Therapy with MVP-S is expected to increase the frequency and activity of survivin-specific anti-tumour T cells. Survivin-peptide specific T cell immune response will be measured by methods such as ELISpot assay to enumerate T cells that produce molecules associated with anti-tumour immune responses such as IFN-γ and/or Granzyme-B. Other exploratory immunologic assessments may be performed on frozen PBMC samples and subject plasma if a novel method becomes available during the course of the study. Tumour-specific T cells must migrate to the tumour site to mediate anti-tumour activity. Both MVP-S and pembrolizumab should facilitate the migration of antigen-specific T cells into tumour sites. We will quantitate changes in T cell infiltration and the expression profile of T cells in tumour sites using pre- and on-treatment biopsies. The pre-existing immune profile within the pre-treatment tumour biopsy may influence or predict clinical response or the peripheral immune response. If the subject ends trial participation due to progression and soon after undergoes a post-study tumour biopsy just prior to starting another therapy, we will aim to obtain a sample for comparison of immune and pathologic data to the pre- and on- treatment samples.

Analysis will be performed on the collected clinical, biologic and immunologic variables obtained from subjects to look for variables that distinguish subjects with objective clinical or immunological outcomes from the entire treated population.

Outcomes

Clinical (and immunologic) response will be defined using the following primary, secondary outcomes and ELISpot.

1. Complete Response (see appendix for definition)
2. Partial Response (see appendix for definition)
3. Best overall objective response; CR + PR
4. Disease Control Rate; CR, PR, + Stable Disease (SD)
5. Progression Free Survival (date of progression as per the Response Assessment Form (RAF) or death – SD0. If there is no date or progression or date of death, start date of new treatment can be used. For participants without progression, they will be left as blank and noted as ongoing).
6. Overall Survival (date of death or last known date alive – SD0)
7. Duration of Response [SD0 – Date of progression (PD) on RAF. If date of progression is unknown, then start date of new treatment or death will be used].
8. Time to next treatment (Start date of next treatment (chemotherapy or radiation) – SD0)
9. ELISpot (positive vs negative)

Clinical Response (CR, PR, SD and PD) are defined as per the Modified Cheson Criteria (see appendix) and was evaluated based on the comparison from CT scan results at Screening, where a minimum of 1 target lesion (to a maximum of 6) were followed and assessed again at SD70 or SD91, then again at SD175 and EOS/SD365 and any other confirmatory or disease re-staging CT scan results. In cases where more than 6 were observed, they were identified but not counted towards the SPD. In cases where PD was later determined to be pseudo-progression, the next available CT scan results and determination of best response will be used.

Variables

Clinical variables

We will conduct univariate analysis by exploring the outcomes listed above, with the following clinical variables:

- Age (range),
- performance status (ECOG; 0-1),
- relapsed (> 3months from end of last treatment to SD0) vs. refractory (< 3 months from the end of last treatment date to SD0)
- transformed (by pathology and clinical treatment history),
- number of previous treatments (Total for Systemic treatment for DLBCL only; 1-3),
- previous ASCT,
- time from last treatment end (end date of last DLBCL systemic chemotherapy) to Study Day 0

- IPI at screening (I-IV),
- stage 3 or 4,
- LDH (range),
- tumour volume at screening
- bulky disease modifier (defined by > 7.5cm lesion at screening)
- positive bone marrow involvement (Y/N)
- evaluate using ITT and PP populations

Exploratory variables

Exploratory variable include those results obtained from tumour samples taken at screening, which we have for all 25 enrolled participants. These may come from:

1. Pathology
    - GCB (Y/N)
    - Non-GCB (Y/N)
    - Leg-type (Y/N)
    - Double hit (Y/N)
    - Double expressor* (Y/N)
    - Triple expressor* (Y/N)
    - MYC expression (positive/negative and % if available)
    - BCL2 expression (positive/negative and % if available)
    - BCL6 expression (positive/negative and % if available)
    - CD5+ (present Y/N and % if available)
    - CD10+ (present Y/N and % if available)
    - CD20+ (present Y/N and % if available)
    - Cyclin D+ (present Y/N and % if available)
    - MUM 1+ (present Y/N and % if available)
    - Transformed (Y/N as explicitly stated in the pathology report or based on clinical history as reviewed by the Principal Investigator)
    - Ki67 (positive/negative and % if available – when only upper and lower limits provide, the mean will be used)

* either explicitly reported in the pathology report or interpreted based on the results of MYC, BCL2, BCL6 positivity as stated in the path report or using the % positivity as identified by the WHO: MYC+ (>/=40%) BCL2+ (>/=50%) BCL6+ (>/=30%) as explained in the DMP

2. Multiplex IHC (Akoya BioSciences, Opal Panel, and using CST #E1L3N antibody) where all the data is quantitative and we can make it qualitative (positive/negative) based on thresholds found in the literature, or based on results obtained from the review of the continuous variable. The data distribution for these variables are likely to be skewed, log-transformation will be applied before the analysis.

- Baseline CD4*
- Baseline CD4FOxP3*
- Baseline CD8*
- Baseline FoxP3*
- CD20 PDL1 (continuous and Y/N)
    a. ≥5% or <5% cell percent's (tumour)
    b. ≥10% or <10% cell percent's (tumour)
    c. H-score ≥10 or <10 + > in bins 2+ and 3+ (tumour)
    d. H-score ≥30 or <30 + > in bins 2+ and 3+ (tumour)

- PD1 expression (continuous and Y/N)

*These data include quantitate data for:

a. Total cell counts
b. Cell per cents (IMV >5%)
c. Cell densities (>200)[1,2] for, CD4 and CD8
d. In addition these data are obtained from;
    i. Tumour
    ii. Non-tumour
    iii. Total sample

Our initial approach has been to focus on the CELL DENSITIES (c) or CELL PER CENTS (b) from the TUMOUR area thinking that this makes the most biologic sense.

We will perform all analyses on data for cell subsets WITHIN THE TUMOURS. We will perform analyses on both cell density data and cell percentages data. Univariate analyses using quantitative CD20+/PDL1 Data and positive versus negative expression as defined above. For all other markers we will use both percent and cell densities. We will apply statistical approaches to identify natural positive versus negative cut-offs for these markers.

3. From Neogenomics (Rabbit Polyclonal Antibody, Novus, NB500 201)
    - Survivin H score
    - Survivin per cent cells positive
    - Survivin Scores per bin (1+, 2+, 3+)

The plan is to investigate the predictive values of these biomarkers obtained from the screening tumour samples using both ITT (n=25) as well as the evaluable PP group (n=16).

CHANGES TO ANALYSIS

As Outlined in the Protocol:

We have defined the variables for analysis more precisely. We have expanded the protocol to include analysis on ITT and PP. Inclusion criteria was updated in protocol v8 (22APR2020) to include participants who had <10% survivin expression and those participants would have been analyzed separately, however, there were no participants enrolled that did not meet the >10% survivin expression, so there was no impact on statistical analysis.

PROTOCOL DEVIATIONS

As per protocol, any protocol deviations which are deemed to be significant and could likely impact the results, will be assessed on a case-by-case basis.

Three CAPA's are listed below:

1. ELISpot analysis as performed by CAPRION BioSciences was resolved such that IMV performed analysis on the same samples, the results of which have been used in the analysis. Due to multiple analyses on the same samples, some samples were depleted such that further analysis could not be performed and as such will not be reported on. These are part of the Missing Data Outcomes Section.

2. Multiple MVP-S injections being done on the same leg of a single participant, which may confound the results of the ISRs for that participant, such that they may be recorded as more extreme than would be observed had the protocol been followed correctly such that alternating thighs and quadrants be used for MVP-S injections (except when the ISR is too severe to do so). This is for participant 45-1.

3. A patient was provided a participant # before having consented to participate in the trial, and ultimately chose not to participate, thereby resulting in an extra participant # being assigned (46-5) but no data collected.

For Ontario sites, protocol deviations that occurred due to COVID-19 restrictions did not have to be reported unless to reduce immediate harm to a participant. The sponsor endorsed this with other sites specifically for "out of Window" study visits or those that were performed by telephone instead of in-person study visits.

Protocol Deviations Affecting:

1. Participant Safety
    a. None at this time

2. Data Integrity
    a. PBMC samples not drawn in response to limitations of attending on-site visits due to COVID-19 were documented for participants at QE II.
    b. PBMC samples not obtained due to participant suffering from Adverse Events
    c. PBMC samples for which ELISpot analysis could not be completed or duplicated (all of which have been described above and documented) and will be identified as a footnote
3. Study Efficacy
    a. Most common is that of not taking Injection Site Reaction photos, or measuring them in such a manner that could be confirmed by the sponsor. However, this was corrected in a protocol amendment that photos only need to be taken when there is evidence of an ISR, and that a ruler should be included for measurement when possible. This would not be included in Data Integrity as part of the study is not to confirm the size of an ISR, or to alter the Investigators judgment on the grade, severity of an ISR. Sizes of injection site reactions are not being used for any analysis.
    b. Tumour biopsy slides not being obtained while the participant is on study. This was not always possible for the following circumstances: participant had no tumour or tumour was too small to biopsy; it would have been invasive for the participant based on tumor location; participant was progressing and did not consent; or in the judgement of the investigator it was in the best interest of the participant to not obtain the sample.
    c. The number of slides or tubes collected for tumour or PBMC samples respectively. Often due to the physical condition of the participant, either biological or due to adverse events. In some cases, the participant had a high red blood cell count making it difficult to separate for the process of PBMCs. The sample quality was lower, but still produced viable results. Re-training of the staff was performed to aid in troubleshooting this process for future instances and the Lab Manual was updated to provide guidance.
    d. COVID-19 measures for study visits were adjusted to telephone visits when possible to reduce risk of exposure to this study population, but also in response to hospital and institutional restrictions.
    e. Eligibility bloodwork to be confirmed and completed within 48 hours prior to SD0 was often completed on SD0 and reviewed instead. Protocol was amended to ensure that bloodwork obtained and reviewed at SD0 could be used for eligibility provided the Investigator reviewed before enrollment and cyclophosphamide dispensed. SD0 bloodwork could be used for both eligibility and SD0 visits. No participants were enrolled with bloodwork results that did not meet eligibility requirements.
    f. One instance where a Bone Marrow result was not obtained as part of the Screening Procedures but was obtained at a later date. The result is not required for eligibility.

REFERENCES

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