Combination of DPX-Survivac, Low Dose Cyclophosphamide, and Pembrolizumab in Recurrent/Refractory DLBCL: The SPiReL Study

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Introduction & Background

Recurrent and Refractory Diffuse Large B cell Lymphoma is an unmet medical need. Although about 60% of patients with DLBCL will be cured, the 30% of patients not cured by first line therapy, salvage chemotherapy, or stem cell transplant have poor survival outcomes. Before CAR T cell therapy, survival was estimated to be less than 6 months [1]. CAR T therapies have improved the outcome for some of these patients but have significant toxicities, are expensive and are not broadly available [2,3,4]. Innovative approaches that target novel pathways need to be explored.

The regimen used in the SPiReL clinical trial is designed to activate T cells that recognize the tumour specific antigen, survivin. These T cells are activated using three agents:

- **DPX-Survivac** is a T cell immunotherapy against survivin-expressing tumours [5],
- **Pembrolizumab** is a potent IgG4 inhibitor of the programed cell death receptor (PD-1) [6],
- **Intermittent low dose cyclophosphamide** to reduce T reg function and enhance the T cell response to DPX-Survivac [7].

Objectives

Primary Objective:

- to document the objective response rate to treatment with DPX-Survivac 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 [8].

Secondary Objectives:

- to document evidence of tumour regression using waterfall analyses,
- to document the toxicity profile,
- to document duration of response using Modified Cheson Criteria[8] and immune-related response criteria [9] (irRc).

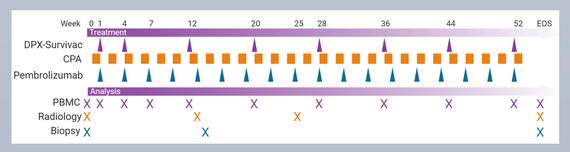
Exploratory Objectives:

- to document the changes in circulating T cell immune responses to survivin and relationship to peripheral B cell numbers,
- to document changes in T cell and T cell subset infiltration and gene expression pathways in treatment compared to pre-treatment tumour biopsies,
- to assess potential biomarkers of immune and clinical response from pre-treatment and on-treatment tumour biopsies.

Trial Design

Participants with recurrent/refractory DLBCL, with ECOG 0-1 and confirmed survivin expression are eligible. Participants must also be ineligible for curative therapy.

- Study treatment includes administering two doses of 0.5 mL of DPX-Survivac, subcutaneously, 3 weeks apart followed by up to six 0.1 mL doses every 8 weeks.
- Intermittent low dose cyclophosphamide is taken orally at 50 mg twice daily for 7 days followed by 7 days off.
- Pembrolizumab 200 mg IV is administered every 3 weeks.
- Study participants continue trial participation for up to one year or until disease progression, whichever occurs first.



ClinicalTrials.gov Registration #: NTC03349450

Results

The SPiReL trial is being conducted at 5 Canadian centres. Recruitment began in March 2018, with a goal of 25 evaluable participants. Results presented include data from March 2018 to December 1, 2019 from 31 screened participants, 17 of whom have been enrolled.

Baseline Demographics of Enrolled Participants	
	N =17
Male	6 (35.3%)
Female	11(64.7%)
Age, median (range)	75 (50-82)
ECOG = 1	8 (47%)
ECOG = 0	9 (53%)
Stage III/IV	13 (76.5%)
LDH, median (range)	286 (154-730)
GCB	11 (64.7%)
non-GCB	6 (35.3%)
Leg type	1 (5.8%)
% Survivin positive DLBCL cells, median (range)	95 (70-100)
Transformed	3 (17.6%)
Relapsed DLBCL	7 (41.1%)
Refractory DLBCL	10 (58.8%)
Previous ASCT	3 (17.6%)
Number of previous treatments, median (range)	2 (1-6)
Time from end of last Treatment to SD0 (days), median (range)	191 (21-3423)

Figure 1: Baseline demographic information for enrolled participants (N = 17).

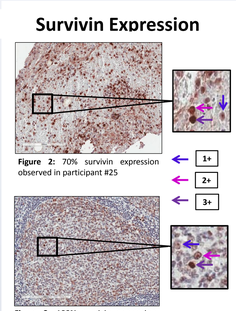
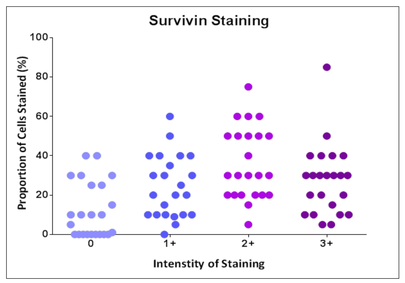


Figure 2: 70% survivin expression observed in participant #25

Figure 3: 100% survivin expression observed in participant #12

Figure 4 (below): The levels of survivin expression found in tumour samples at screening for N = 23 participants are shown below. 100% of samples analyzed for survivin came back positive. The total number of tumour samples sent for analysis was 27. The results of 4 tumour samples are not included due to inadequate biopsies for which results could not be obtained; 2 necrotic tissue, 2 follicular lymphoma.



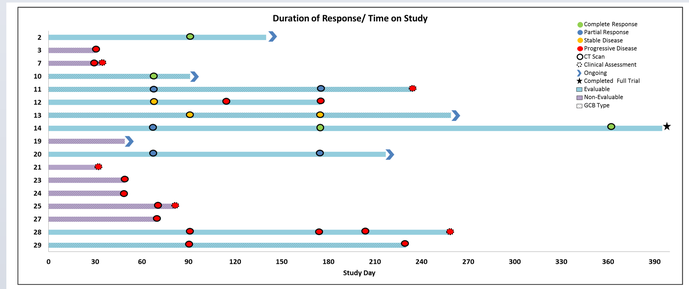


Figure 5: Duration of Response by Radiological Assessment is shown for all enrolled participants (N = 17). Response is assessed at SD70 or SD91, SD175, SD364 and End-of-Study. Imaging can occur outside of these timepoints if clinical progression is suspected. Discontinuation of trial participation has been related to disease progression (N = 11). Leg Type was observed in participant 28, recurrence observed in the leg of participant 29, both of whom were treated through PD due to clinical benefit. Three participants have transformed histology (3, 19 and 23).

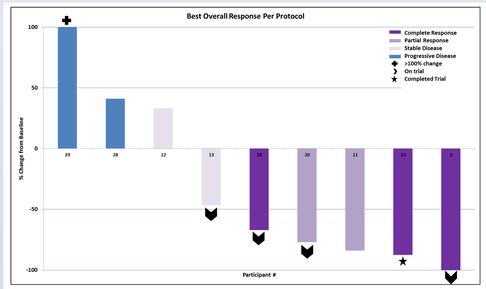


Figure 6: Best Overall Response, using the Modified Cheson Criteria[8], for evaluable participants. Per protocol, participants are evaluable if they receive three doses of DPX-Survivac and four pembrolizumab infusions. Participant 14 completed the 1-year trial with CR by criteria (80% regression in tumour size, and all lymph nodes measuring <1.5 cm) and remains free of disease recurrence.

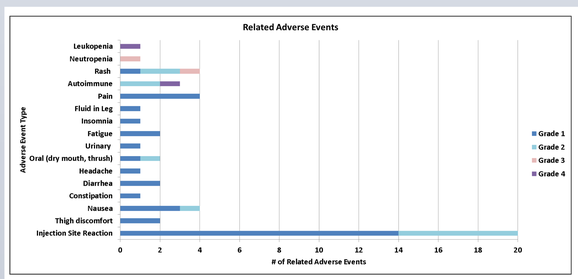


Figure 7: There were 50 Adverse Events (CTCAE 4.03 [10]), experienced amongst enrolled (N = 17) participants, that were deemed possibly (N = 20), probably (N = 8) or definitely (N = 23) related to one or more of the drugs of the combination therapy. The most common were Injection Site Reactions of which there were 20 (all grade 1 or 2), reported by 11 participants. Autoimmune (N = 3) includes; 1 neutropenia (grade 4), 1 hemolytic anemia (grade 3) and 1 pemphigus (grade 3), related to pembrolizumab with treatment held until resolution. Rash (N = 4) includes; 2 maculopapular (grade 2 = 1, grade 3 = 1), full body (N = 2). Pain (N = 4) includes; knee, skin, bone and general. No Adverse Events resulted in participant trial discontinuation. Serious Adverse Events (N = 4) were due to disease progression and deemed unrelated.

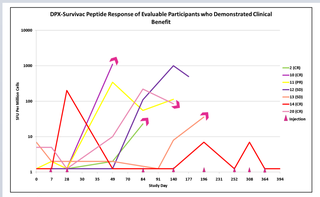
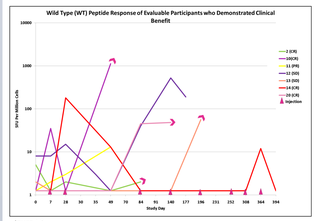


Figure 8



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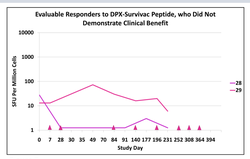


Figure 9

Figures 8 - 11: The peptides in DPX-Survivac include five peptides that are respectively restricted to HLA-A1, A2, A3, A24 and B7, with agonistic and heteroclytic modifications in some of them. The Wild Type (WT) peptides include the same peptides without any agonist or heteroclytic modifications. Immune responses were considered positive if the mean number of spots per time-point were greater than 2 x the mean standard deviation of the mean of the background and greater than 2 x the number of spots at baseline. Background negative control responses were subtracted from the peptides responses.

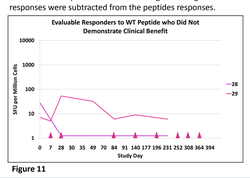
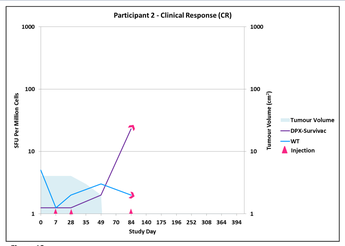


Figure 11

Figures 12 – 17: Shown are the immune responses to DPX-Survivac and the Wild Type (WT) peptides superimposed on tumour volume measurements at the various study days. The Y axis reflects both Spots per 1 x10[5] cells and tumour volume (cm[3]).



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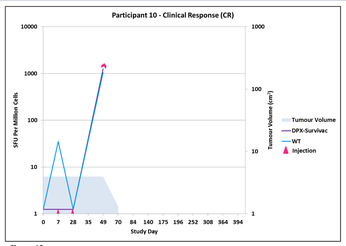

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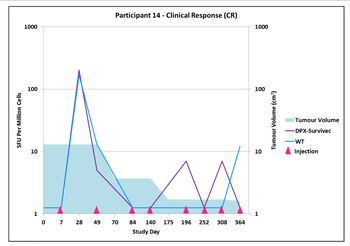

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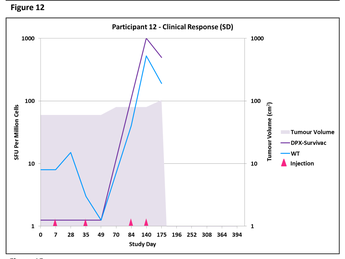

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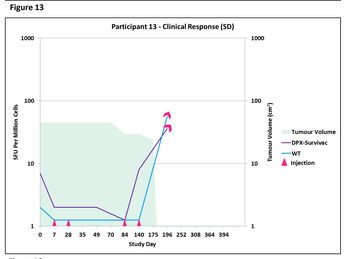

Figure 16

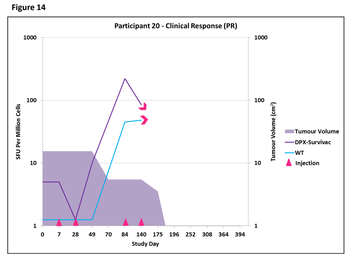

Figure 17

Conclusions

The SPiReL clinical trial is an ongoing trial and to date results suggest:

- Treatment of recurrent/refractory patients with DLBCL is feasible with a very favourable toxicity profile that is well suited for all patients, including older patients, or those with comorbidities.
- Survivin expression was demonstrated in samples tested, supporting the use of DPX-Survivac in recurrent/refractory DLBCL.
- Antigen specific immune responses were observed in the blood of 53% of participants (8/15 assayed participants). 8 of 9 evaluable participants showed immune responses, including immune activation in all 7 participants with clinical responses, thus establishing a relationship between clinical responses and immune activation.
- Further analyses are planned to determine the level of T cell tumour infiltration.
- Objective tumour regression/stabilization is observed in 7 of 9 evaluable participants, including 3 Complete Responses (CR), 2 Partial Responses (PR), and 2 Stable Disease (SD), in this difficult-to-treat recurrent/refractory patient population that included patients with Leg Lymphoma and post-ASCT.
- Additional follow-up and additional patients are needed to better describe and understand the clinical end-points.
- The promising clinical efficacy data emerging from this study suggests future studies evaluating this combination in recurrent/refractory DLBCL is a potential next step.

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Thank-you to our patients and families participating in our trial.

Conflict of Interest: N. Berinstein and D. Stewart; Merck – Consultant, Honoraria and Membership on an Entity's Board of Directors or Advisory Committee. The remaining authors have no conflicts of interest.

For more information about this project contact SPiReL@sunnybrook.ca