New clinical data from the DeCidE[1] trial: Results on DPX-Survivac, low dose cyclophosphamide (CPA), and epacadostat (INCB024360) in subjects with advanced recurrent epithelial ovarian cancer

ABSTRACT #262

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Background

Every year, ovarian cancer afflicts approximately 22,000 women in the US and approximately 14,000 will die from the disease. Primary treatment consists of debulking surgery followed by systemic chemotherapy with or without the addition of targeted therapies. Despite achieving initial benefits, a significant number of these women will experience recurrence after their 1st or 2nd line therapy.

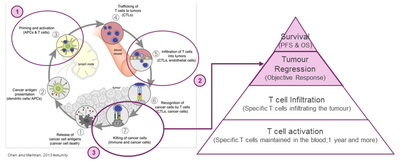
The introduction of immunotherapies and their known success in several indications was thought to bring a revolution for the treatment of ovarian cancer; unfortunately this revolution has yet to be realised. There remains a significant unmet medical need for novel therapies that will help ovarian cancer patients live better and longer. Consequently, there is also a pressing need to identify biomarkers or clinical features that are predictive of response, thus providing substantial benefits to the patients.

DPX-Survivac is a novel and unique T cell activation therapy that generates de novo T cells against survivin. In maintenance Phase 1 and 1b studies in ovarian cancer, it was shown that DPX-Survivac can generate a strong and specific T cell response against survivin expressed on the surface of the tumour and long progression free interval have been observed in subjects (> 7 years). DPX-Survivac showed a well-tolerated safety profile with majority of events being grade 1 and 2 local site reactions.

Epacadostat is an IDO1 inhibitor that prevents the oxidation of tryptophan into kynurenine. This inhibition has been shown to increase and restore the proliferation and activation of immune cells.

The combination of DPX-Survivac and epacadostat was thought to lead to a synergistic effect on the tumour microenvironment and on the immune response directed against the tumour cells, and potentially lead to clinical benefits. Preclinical studies with these molecules supported the investigation of this treatment in ovarian cancer.

This combination is investigated in the current Phase 1b/2 study in patients with advanced and recurrent ovarian cancer. The results of the Phase 1b are presented here.



Study Design

- Multicenter study, ongoing in Canada and the United States
- Phase 1b: Non-randomized, open label, uncontrolled study
  - Dosing Group 1 subjects received DPX-Survivac (2 × 0.25 mL q3w, up to 6 × 0.1 mL q8w), low dose cyclophosphamide (CPA, 50 mg BID, alternating weeks), and epacadostat up to 100 mg BID
  - Dosing Group 2 subjects received DPX-Survivac, low dose, and epacadostat 300 mg BID
- Phase 2 original design: Randomized double arm study treating with DPX-Survivac and CPA with and without epacadostat
- Primary objectives: safety, cell mediated immunity, changes in immune cell infiltration of tumour
- Secondary objectives: ORR, DCR, DoR using RECIST v1.1, time to progression, overall survival, CA-125 response and progression

Results

Table 1: Baseline subject demographics and disposition (N=53)

Parameter	Statistic	All Subjects n (%)	Group 1 (N=14) n (%)	Group 2 (N=39) n (%)
Age (years)	0	63 (10)	65 (11)	62 (10)
	Min, Max	35, 87	35, 79	36, 87
Race n (%)	White	47 (88.7)	14 (100)	33 (84.6)
	Black or African American	3 (5.7)	0 (0.0)	3 (7.7)
	Other	3 (5.7)	0 (0.0)	3 (7.7)
ECOG	0	29 (54.7)	11 (78.6)	18 (46.2)
	1	24 (42.3)	3 (21.4)	21 (53.8)
Cancer type	Epithelial Ovarian	39 (73.6)	8 (57.1)	31 (79.5)
	Fallopian Tube	6 (11.3)	3 (21.4)	3 (7.7)
	Peritoneal	8 (15.1)	3 (21.4)	5 (12.8)
Number of Previous Treatments	1	7 (13.2)	4 (28.6)	4 (10.3)
	2	12 (22.6)	3 (21.4)	8 (20.5)
	3	6 (11.3)	1 (7.1)	5 (12.8)
	4	10 (18.9)	3 (21.4)	7 (17.9)
	≥5	18 (34.0)	3 (21.4)	15 (38.5)
Sensitivity to Most Recent Platinum	Sensitive	19 (35.8)	6 (42.8)	13 (33.3)
	Resistant/ Refractory	34 (64.2)	8 (57.1)	26 (66.7)
Best response to Most Recent Platinum	unknown	9 (17.0)	3 (21.4)	6 (15.4)
	Progressive disease	5 (9.4)	0 (0.0)	5 (12.8)
	Stable disease	11 (20.1)	2 (14.3)	9 (23.1)
	Partial response	13 (24.5)	3 (21.4)	10 (25.6)
	Complete response	15 (28.3)	6 (42.9)	9 (23.1)
Evaluable	D56 scan/biopsy complete	32 (60.4)	10 (71.4)	22 (56.4)
Early Withdrawal*	Disease progression	24 (45.3)	6 (42.9)	18 (46.1)
	Adverse event	10 (18.8)	2 (14.3)	8 (20.5)
	Withdrawal of consent	6 (11.3)	2 (14.3)	4 (10.3)
	Investigator judgement	3 (5.7)	1 (7.1)	2 (5.1)
	Other	3 (5.7)	1 (7.1)	2 (5.1)

* Two group 1 and one Group 2 subjects completed treatment. Three Group 3 subjects remain on study.

Table 2: Treatment-related adverse events occurring in three or more subjects

Toxicity	Total n(%)	Group 1				Group 2			
		G1	G2	G3	G4	G1	G2	G3	G4
Nausea	29 (54.7)	4	3	0	0	17	5	0	0
Injection site induration	27 (50.9)	10	0	0	0	13	4	0	0
Fatigue	25 (47.2)	3	2	2	0	14	2	2	0
Injection site erythema	23 (43.4)	9	0	0	0	12	2	0	0
Diarrhoea	7 (13.2)	2	2	0	0	1	2	0	0
Injection site warmth	7 (13.2)	4	0	0	0	2	1	0	0
Injection site pruritus	7 (13.2)	4	0	0	0	2	1	0	0
Abdominal pain	6 (11.3)	0	0	0	0	2	3	1	0
Lipodystrophy acquired	6 (11.3)	2	1	0	0	2	1	0	0
WBC count decreased	5 (9.4)	1	1	0	0	1	2	0	0
Vomiting	5 (9.4)	3	0	0	0	0	2	0	0
Injection site pain	5 (9.4)	3	0	0	0	1	1	0	0
Rash maculo-popular	4 (7.5)	0	0	1	0	0	1	2	0
Anaemia	4 (7.5)	0	0	1	0	0	1	2	0
Pruritus	4 (7.5)	1	0	0	0	1	1	1	0
Abdominal distension	4 (7.5)	0	0	0	0	2	2	0	0
Pyrexia	4 (7.5)	1	0	0	0	3	0	0	0
Lipase increased	3 (5.7)	0	0	1	1	0	0	1	0
Rash	3 (5.7)	0	1	1	0	0	1	0	0
Injection site rash	3 (5.7)	1	0	0	0	1	1	0	0
Decreased appetite	3 (5.7)	3	0	0	0	0	0	0	0
Dizziness	3 (5.7)	1	0	0	0	2	0	0	0

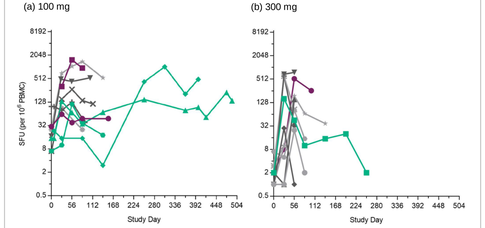


Figure 1: Antigen-specific T cells were detected in PBMCs of all evaluable subjects by *ex vivo* IFN-γ ELISPOT (a) Dosing Group 1 (up to 100 mg BID epacadostat) (b) Dosing Group 2 (300 mg BID epacadostat). IFN-γ ELISPOT responses to survivin peptide stimulation; each point is the average SFU per 1x10^6 PBMCs per duplicate wells.

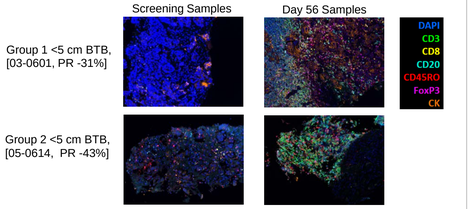


Figure 2: Increases in tumour immune infiltration are demonstrated by multiplex IHC in 2 subjects who achieved a PR. Analysis was conducted by PerkinElmer. A pre-treatment biopsy was taken before study enrollment and an on-treatment biopsy between D56 and D70. Unmixed composite fluorescence IHC images are shown. BTB = baseline tumour burden (sum of target lesions by RECISTS 1.1)

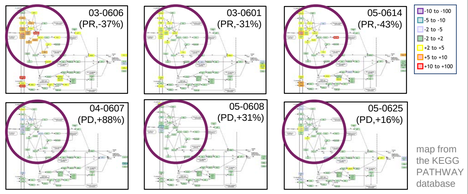
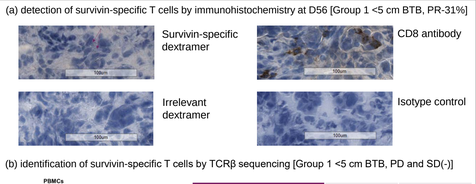


Figure 3: Changes in CD8 T cell activation induced in tumours of 6 subjects. Activation of T cell receptor signaling pathway correlates with objective clinical responses to study treatment. Analysis is performed at the RNA level using whole exome sequencing of tumour biopsy samples. Fold-changes in the expression of each transcript were calculated relative to baseline levels. Fold-changes in the expression induced by treatment are color-coded.



Best overall response		PD	SD (-)
HLA type		HLA-A2	HLA-A2, A3
Tumour CD8$^+$ T cells D56 vs D0		Increase	No change
Frequency (N) of survivin-specific clones in tumour	D0	0% (0)	0% (0)
	D56	0% (0)	2.1% (18)

Figure 4: Infiltration of survivin-specific T cells into tumours correlates with clinical responses (a) *in situ* staining of on-treatment tumour; (b) detection of survivin-specific TCRβ clones in pre- and on-treatment tumour tissues using TCRβ sequencing

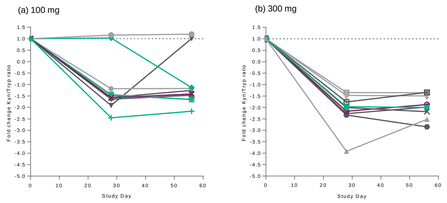


Figure 5: Most evaluable subjects demonstrated decreased kynurenine/ tryptophan levels in the blood. (a) Dosing Group 1 (up to 100 mg BID epacadostat) (b) Dosing Group 2 (300 mg BID epacadostat). Changes in plasma kyn/tryp ratio from the pre-treatment ratio are shown for each subject.

Table 3: Best on-study clinical response by RECIST v1.1 for evaluable study subjects (baseline tumour burden = sum of target lesions)

Efficacy Parameter	Baseline tumour burden < 5 cm			Baseline tumour burden ≥ 5 cm		
	All (N=12) N (%)	Group 1 (N=5)	Group 2 (N=7)	All (N=20) N (%)	Group 1 (N=5)	Group 2 (N=15)
Regression	8 (66.7)	5 (100)	3 (42.9)	3 (15.0)	0 (0)	3 (20.0)
PR	4 (33.3)	3 (60.0)	1 (14.3)	1 (5.0)	0 (0)	1 (6.7)
SD	6 (50.0)	2 (40.0)	4 (57.1)	12 (60.0)	2 (40.0)	10 (66.7)
DCR	10 (83.3)	5 (100)	5 (71.4)	13 (65.0)	2 (40.0)	11 (73.3)

Further Information

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ClinicalTrials.gov Identifier: NCT02785250
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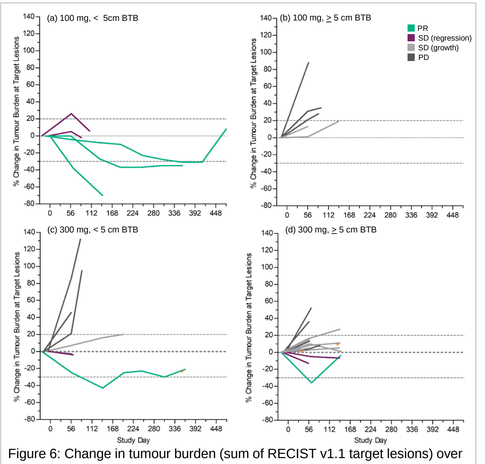

Figure 6: Change in tumour burden (sum of RECIST v1.1 target lesions) over time for evaluable study subjects (a) Group 1 dosing, < 5 cm BTB (b) Group 1 dosing, ≥ 5 cm BTB (c) Group 2 dosing, < 5 cm BTB (d) Group 2 dosing, ≥ 5 cm BTB (subjects still on treatment are marked with an *). For 3/5 subjects reaching PR the PFS interval from start of study treatment exceed that of the subject's last line of therapy.

Conclusions

- 53 recurrent ovarian cancer subjects were enrolled to receive DPX-Survivac, low dose cyclophosphamide, and up to 300 mg BID epacadostat
- Treatments have been well tolerated
- Robust systemic survivin-specific T cell responses
- Infiltration of T cells into tumours post treatment correlates with durable clinical responses
- Higher rates of clinical responses were observed in a subset of study subjects who began treatment with a lower baseline target tumour burden, consistent with recently reported findings[1,2]
- Inhibition of conversion of tryptophan into kynurenine has been observed as expected and is dose dependent
- Responders have shown prolonged duration of clinical benefits reaching up to more than 2 years, increasing the duration of clinical benefits to previous line of chemotherapy
- Phase 2 study is ongoing in subjects with baseline tumour burden (BTB) < 5 cm, treating with DPX-Survivac and low dose cyclophosphamide

[1] Huang et al, 2017 Nature [2] Zheng et al, 2018 Clin Pharmacol Ther