A Canadian Cancer Trials Group phase IB study of durvalumab with or without tremelimumab + standard platinum-doublet chemotherapy in patients with advanced, incurable solid malignancies (IND.226)

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ABSTRACT # 289

BACKGROUND: Immune checkpoint inhibitors are now established therapies in many advanced cancers. Preliminary studies suggest combining immune checkpoint inhibitors with platinum-based chemotherapy may enhance anti-tumour activity. The primary objective of this multicentre study was to evaluate the safety and tolerability durvalumab (Du), a PD-L1 inhibitor, ± tremelimumab (Tr), a CTLA-4 inhibitor, in combination with one of four standard platinum-doublet regimens (pemetrexed (pem), gemcitabine (gem), etoposide (each with cisplatin) or nab-paclitaxel (nabP, with carboplatin)), in order to establish a recommended phase II dose (R2PD) for each combination. **METHODS:** Patients (pts) with advanced solid tumours, regardless of tumour PDL-1 status or number of prior therapies, were enrolled into one of four cohorts. Dose level (DL) 0 added Du 15 mg/kg IV q3wks, DL1=Du 15mg/kg q3wk + Tr 1mg/kg x1; DL2a=Du 15mg/kg q3wk + Tr 1 mg/kg q6wk x multiple doses; DL2b=Du 15mg/kg q3wk + Tr 3 mg/kg q6wk x multiple doses. **RESULTS:** Seventy-eight pts (median age=60 (range 30-80); 51% male, 99% ECOG PS≤1) were enrolled of which 63% were chemonaïve. Thus far 285 cycles have been administered. Across dose levels, the majority of drug-related adverse events (AEs) were ≤Grade 2. Most AEs were attributable to chemotherapy though attribution of some AEs could be either chemotherapy or immune-related (renal, hepatic, skin and pulmonary toxicity). AEs that were considered by the investigator related to either Du or Tr were mainly ≤Grade 2 and manageable, the most common of which were fatigue (45%), nausea (20%), rash (14%) and anorexia (12%). Four patients had possible, but reversible DLTs, including hepatitis (1 each at DL0 (nabP) and DL2a (gem)), pneumonitis (1 pt each at DL1 (etoposide) and DL2a (pem). Accrual is ongoing and expansion cohorts are planned at the RP2D. **CONCLUSIONS:** In this PDL-1 unselected patient population, Du 15mg/kg q3w and T 3mg/kg q6w has to date been safely combined platinum-doublet chemotherapy. Updated safety data and clinical activity will be presented.

BACKGROUND

- Immune checkpoint inhibitors are now established therapies in various cancers including melanoma and non-small cell lung cancer.
- Combinations of PD-L1/PD-1 blocking agents with CTLA4 inhibitors are particularly promising and may result in more durable clinical benefit.
- Results of early trials with durvalumab ± tremelimumab in advanced cancers are consistent with a class effect of early and sustained tumour control that has been observed previously with other inhibitors of the immune checkpoint pathway.
- Preliminary studies suggest combining immune checkpoint inhibitors with platinum-based chemotherapy may enhance anti-tumour activity.
  - In preclinical models, conventional platinum-based chemotherapy has been shown to induce T-cell activation through the release of tumour-specific antigens during cancer cell death.[1,2]
  - Results of two randomized phase II trials in patients with stage IIIB/IV NSCLC and extensive stage SCLC treated with carboplatin-paclitaxel chemotherapy +/- ipilimumab showed promising efficacy of combination treatment with phased dosing of ipilimumab.[3,4]
- Combinations with PD1/PDL1- agent and platinum based chemotherapy have also been reported and appear tolerable.[5]

[1]Apetoh L, Tesniere A, Ghiringhelli F et al. Molecular interactions between dying tumor cells and the innate immune system determine the efficacy of conventional anticancer therapies. Cancer Res 2008; 68: 4026-4030.
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[3] Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol 2012 Jun 10;30(17):2046-54.
[4] Reck M, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol 2013;24:75-83.
[5] Antonia SJ, Goldberg SB, Balmanoukian AS et al. Phase Ib study of MEDI4736, a programmed cell death ligand-1 (PD-L1) antibody, in combination with tremelimumab, a cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibody, in patients (pts) with advanced NSCLC. J Clin Oncol 33, 2015 (suppl; abstr 3014).

OBJECTIVES

- The primary objective of this multicentre study was to evaluate the safety and tolerability durvalumab (Du), a PD-L1 inhibitor, ± tremelimumab (Tr), a CTLA-4 inhibitor, in combination with one of four standard q21day platinum-doublet regimens:
  - ✓Pemetrexed (pem) 500 mg/m^2
  - ✓Gemcitabine (gem) 1250 mg/m^2 d1,8
  - ✓Etoposide (etop) 100 mg/m^2 d1-3

  } + cisplatin 70-75mg/m^2
  - ✓Nab-paclitaxel (nabP) 100 mg/m^2 d1,8,15 + carboplatin AUC=6

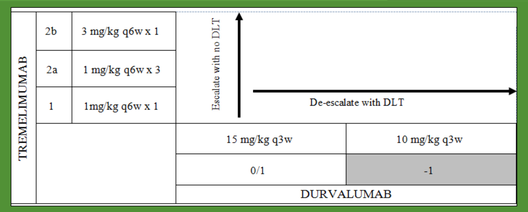
  in order to establish a recommended phase II dose (R2PD) for each combination.

  * *For patients with bladder cancer, cisplatin could be given as 35 mg/m^2 on day 1 and day 8 if indicated .*

METHODS

- Patients (pts) with advanced solid tumours, regardless of tumour PDL-1 status or number of prior therapies, were enrolled into one of four cohorts.
- Durvalumab & tremelimumab will be escalated/de-escalated as outlined in Figure 1 below.

FIGURE1: Dose Escalation Schema for Du & Tr



† 1-2 doses of tremelimumab are given after doublet chemotherapy has been completed (pem maintenance may be ongoing).

‡ For the cisplatin + pem, gem and etoposide cohorts only, a final expansion cohort (dose level 3) will confirm the safety of the fixed ratio dose (Du + Tr).

Definition of Dose Limiting Toxicity (during cycle#1):

- Grade 3 or higher diarrhea/colitis or pneumonitis
- Liver transaminase elevation > 8 ×ULN or total bilirubin >5×ULN
- Other grade 3 toxicity (excluding fatigue, infusion reaction, endocrine disorder, inflammatory reaction, electrolyte abnormalities or myelosuppression) which does not resolve to grade 1 within 3 days with intensive management
- Any grade 4 immune related adverse event
- Toxicity requiring infliximab
- Other toxicities of concern to the trial committee including late toxicities, and excessively severe or frequent toxicities related to the standard chemotherapy regimen.

RESULTS

Table 1 Patient Demographics

Patient Characteristics	N=85
Age, median (range)	60 years (30-80)
Gender (M:F)	43:42
ECOG Performance Status	
0	29 (34%)
1	55 (65%)
Missing	1 (1%)
Tumour Type	
NSCLC	43 (51%)
SCLC	7 (8%)
Bladder, Pancreas, Unknown Primary	4 each (5% each)
Mesothelioma	3 (4%)
Other	20(24%)
No. of prior regimens	
0	57 (67%)
1	18 (21%)
2	6 (7%)
3	4 (5%)

Table 2 No. of Patient/Cycles per Dose Level

Dose Level	No. of patients	No. of cycles
0	24	156
1	16	97
2a	25	117
2b	17	75
3	7	1

- Centrally activated on 1-Oct-2015
  - First patient registered 16-Oct-2015
  - Currently 7 sites active
- 90 patients accrued as of 3-Oct-2016
  - 86 with baseline information entered
  - 1 patient ineligible; 42 patients off study

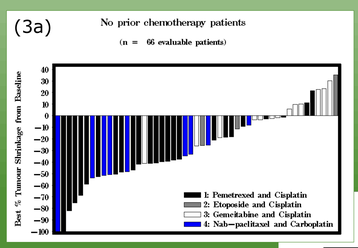
Table 3 Adverse Events - All Causality (% Related to Durvalumab ± Tremelimumab)

Dose Level	All N= 83		Durvalumab (DL0) N= 24		Durvalumab + Tremelimumab (1 mg/kg) (DL1, 2a,3) N= 42		Durvalumab + Tremelimumab (3 mg/kg) (DL2b) N= 17	
	All	>/=G3	All	>/=G3	All	>/=G3	All	>/=G3
Febrile neutropenia	5% (0%)	5% (0%)	4% (0%)	4% (0%)	5% (0%)	5% (0%)	6% (0%)	6% (0%)
Mucositis	12% (1%)	0%	17% (4%)	0%	14% (0%)	0%	-	-
Diarrhea	31% (12%)	8%(4%)	29% (8%)	4% (0%)	36% (12%)	10% (2%)	24%(18%)	12% (12%)
Rash	36% (23%)	4% (2%)	33% (17%)	0%	40% (33%)	2% (2%)	29% (6%)	12% (6%)
Pneumonitis	6% (5%)	2%(2%)	-	-	10% (10%)	5% (5%)	6% (0%)	0%
Hepatitis	1% (1%)	1% (1%)	-	-	2% (2%)	2% (2%)	-	-
Nephritis	1% (0%)	0%	4% (0%)	0%	-	-	-	-
Hypothyroidism	17% (12%)	0%	8% (8%)	0%	21% (14%)	0 %	18% (12%)	0%
Hyperthyroidism	7% (6%)	0%	-	-	12% (10%)	0%	6% (6%)	0%
Other endocrine	1% (0%)	0%	-	-	2%(0%)	0%	-	-

Table 4 All Causality Hematology / Laboratory Adverse Events

	N= 83	
	All	>/= G3
ANC	66%	36%
Platelets	47%	12%
Creatinine	27%	3%
Bilirubin	9%	1%
AST	28%	3%
Amylase	13%	4%
Lipase	21%	6%

(3a)



(3b)

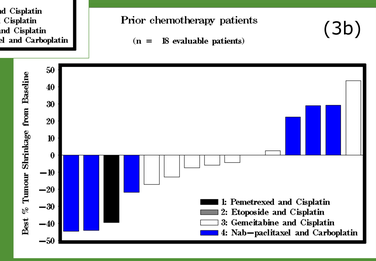


FIGURE 2:
Interim response by cohort
(3a) Patients with no prior chemotherapy and
(3b) Patients with prior chemotherapy

CONCLUSIONS

- In this PDL-1 unselected patient population, Du 15mg/kg q3w and T 3mg/kg q6w has to date been safely combined platinum-doublet chemotherapy.
- Most AEs were attributable to chemotherapy though attribution of some AEs could be either chemotherapy or immune-related (renal, hepatic, skin and pulmonary toxicity).
- AEs that were considered by the investigator related to either Du or Tr were mainly ≤Grade 2 and manageable.
- Patients treated tremelimumab appeared to have more immune related toxicity, but there was no clear dose response.
- Accrual is ongoing.
- Expansion cohorts are planned at the RP2D including expansion with carboplatin in place of cisplatin at the RP2D.

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