Immune Therapy in Clear Cell Ovarian Cancer (ITICC)

Hal Hirte

Canadian Cancer Clinical Trials Group

GYNECOLOGIC CANCER INTERGROUP

An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Results of Phase II Study of Durvalumab and Tremelimumab in recurrent clear cell ovarian cancer

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IND. 228: A PHASE II STUDY OF DURVALUMAB AND TREMELIMUMAB IN PATIENTS WITH ADVANCED RARE TUMOURS

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Supported by:	AstraZeneca

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Trial Schema

Patients cohorts:

1. Salivary carcinoma *(excluding adenoid cystic carcinoma histology*)
2. Carcinoma of unknown primary with *tumour infiltrating lymphocytes (TILs) and/or expressing PD-L1*
3. Mucosal melanoma
4. Acral melanoma
5. Osteosarcoma
6. Undifferentiated pleomorphic sarcoma
7. Clear Cell Carcinoma of the Ovary
8. Squamous cell carcinoma of the anal canal (SCCA)

This is a multi-centre, non-blinded, open-label single arm phase II study of durvalumab in combination with tremelimumab in patients with rare tumours. A minimum of 70, and a maximum of 140 patients will be enrolled.

TILs present and/or positive expression of PD-L1 for **cohort 2** ONLY

Registration

2-stage design - each cohort

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Clear Cell Ovarian Ca Results

- This arm has completed the 2nd stage of accrual (20 patients total accrued)
- Responses seen in a number of patients on the clear cell arm to date
- response data from stage II now available
- We would accept the drug combination as active if four or more responses are observed from 20 patients accrued
- This proposal is based on the clear cell ovarian ca arm demonstrating this level of activity

- Anecdotally:
  - Significant responses are being seen
  - Some are particularly “deep” with marked tumour regression
  - Some appear to be durable
    - Have patients on therapy > 6 mo
  - Toxicity – as expected with this combination of agents

Response - Clear Cell Cohort

- 20 eligible; 19 evaluable (1 symptomatic progression)
- 7/20 pts had partial responses; duration 3.1-10.3m
- 3/20 pts had stable disease as best response; duration 5.1- 6.9m
- ORR = 35% (95% CI, 15.4% to 59.2%),

Next Steps Ovarian Cohort

- AZ requested final analysis
  - To discuss expanding cohort further, evaluating single agent durvalumab or other combinations.
- Will be discussed at a November 2018 meeting.

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How can we build on this?

OCC is Chemoresistant

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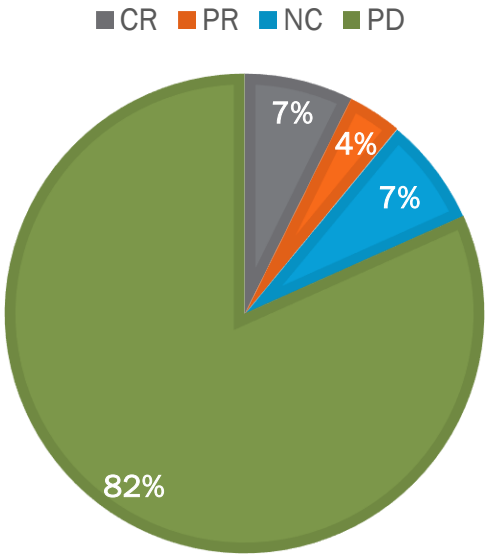
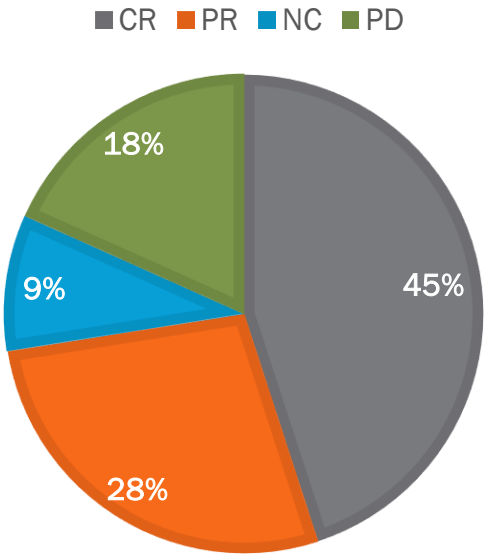
CLEAR CELL CARCINOMA



SEROUS CARCINOMA



Sugiyama et al. Cancer 2000

Studies of PD-1/PD-L1 Inhibitors in OCC

regimen	target	phase	trial	CTG ID
Durvalumab vs chemo	PD-L1	RCT II (N=46)	MOCCA (Singapore)	NCT03405454
Nivolumab +/- ipilimumab	PD-L1 +/- CTLA-4	RCT II (N=62)	BrUOG354 (Brown University)	NCT03355976
Pembrolizumab + epacadostat	PD-1 + IDO	II (N=23)	NIH (NRG-016)	NCT03602586

Oda et al. Gynecol Oncol 2018 in press

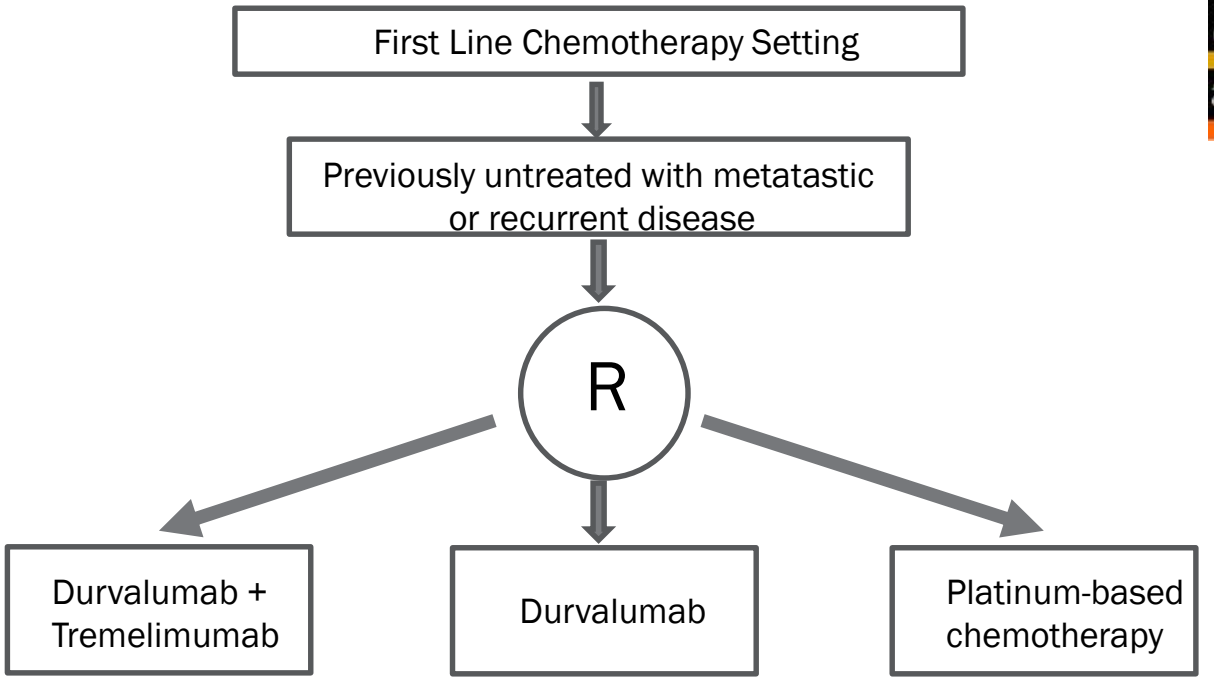
IND228 – What next?

- Next steps now that response data from stage II available?
  - Expand to a large single cohort study
    - Could be practice changing, but would need ~120 pts, and would require involvement of other GCIC partners. AZ has to be on board
  - Randomized phase 2/(3) compared to standard chemo
    - Cross over at progression on chemo?
  - Include other gynecologic clear cells cancers (endometrial, cervix)?
- Interest in participation in such a trial?

Study Proposal

- Comparison of durvalumab + tremelimumab, versus durvalumab alone versus standard of care chemotherapy in recurrent/metastatic clear cell of ovary (?and endometrium, cervix)
  - Study 1 - First line metastatic or recurrence with no prior chemotherapy – comparator is platinum-based chemo
  - Study 2 - Recurrence after previous chemotherapy– physicians choice of chemotherapy (carboplatin +/- paclitaxel/gemcitabine/PLD, weekly paclitaxel, liposomal doxorubicin, topotecan)
    - Up to 3 prior chemotherapy treatments
  - PS 0,1,2
  - Normal marrow, kidney and liver function

Study Schema – First Line Trial



Phase II stage

Phase III Stage – continue accrual to best two arms and drop an experimental arm

Phase III stage

Patients on chemo control arm may cross-over to IO arm at progression

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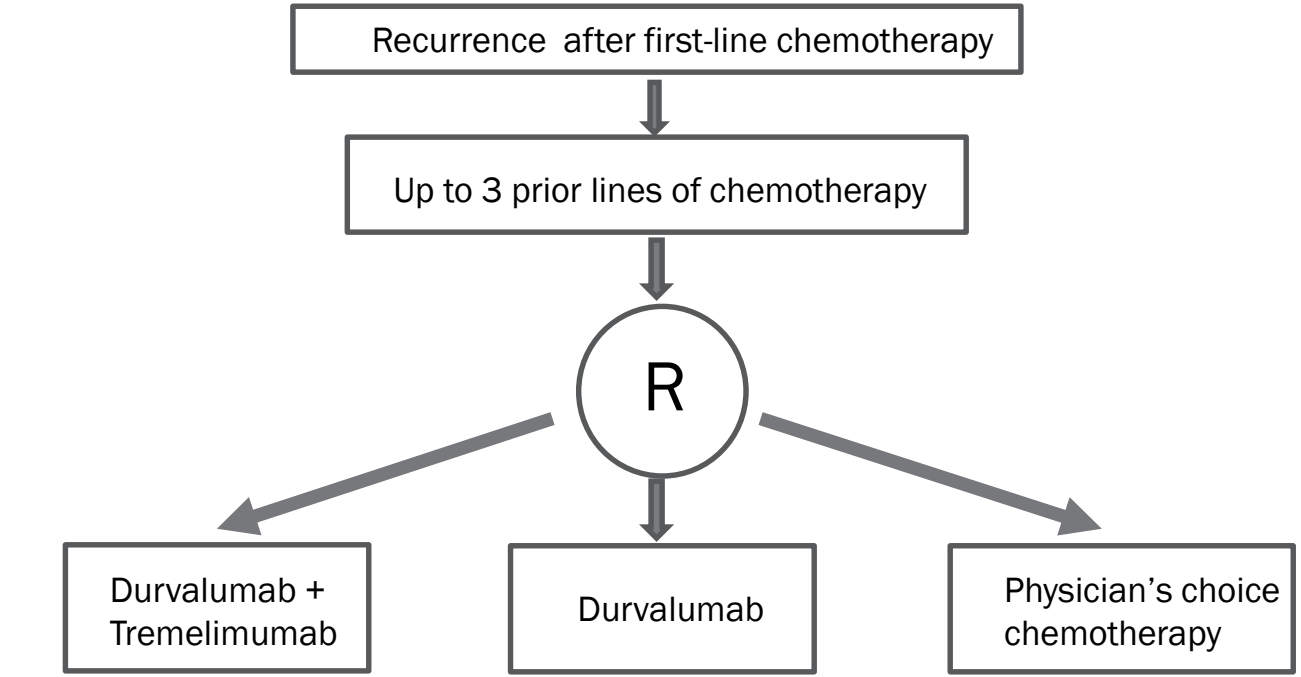
Study Schema – Previous chemotherapy



Patients on chemo control arm may cross-over to IO arm at progression

Study Endpoints

- Toxicity/QOL
- Response rate
  - Meaningful increase
    - from 10% in control arm to > 30% in IO arm for chemonaive
    - From 3% in control arm to > 20% in IO arm for previously treated
- Increase in PFS by 50%
- Increase in OS by 50%
  - Chemonaive
    - post carboplatin/paclitaxel PFS -10 mo, OS 21 mo
    - 50% increase in PFS from 10 to 15 mo, OS from 21 to 30 mo
  - Recurrence post chemo
    - PFS 8 mo, OS 18 mo
    - 50% increase in PFS from 8 to 12 mo, OS from 18 to 27 mo

Correlative studies

- Will require baseline and on-study tumour biopsy
- Optional biopsy at progression
- Ongoing discussions about broad correlative biomarker analysis

Sample Size Estimate

- Being reviewed with CCTG statistician

Feasibility

- Interest from other GCIG partners?
- Competing studies?
- Timelines