Dose ranging study of monalizumab (IPH2201) in patients with gynecologic malignancies: A trial of the Canadian Cancer Trials Group (CCTG): IND221

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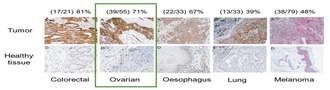
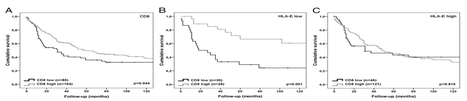
Abstract # 296

BACKGROUND

- HLA-E is a non-classical major histocompatibility complex class I molecule
- HLA-E is over expressed in several malignancies, including ovarian cancers



- HLA-E expression is associated with a poor prognosis in ovarian cancers, abrogating the positive effects of CD8 expression



- HLA-E is a ligand for CD94/NKG2A
- CD94/NKG2A is a checkpoint receptor on a subset of NK and CD8+, NKT, and γδ T-cells
- Monalizumab (IPH2201) is a humanized (IgG4s241P) version of mouse anti-human NKG2A mAb that targets the CD94/NKG2A receptor with high affinity
- Targeting the CD94 and HLA-E interaction could impact cancer outcomes
- A phase I study of monalizumab in patients with Rheumatoid Arthritis demonstrated minimal toxicity with IV and SC dosing of up to 10 mg/kg IV (no DLTs and MTD not reached)

Objectives

Primary: Dose ranging study to confirm the RP2D of single agent monalizumab in patients with advanced/metastatic/recurrent gynecologic malignancies

Secondary:

- To assess the safety, toxicity, and pharmacokinetics
- To assess pharmacodynamics
- To assess correlation of tumour and stromal biomarkers with outcomes (TIL (CD8, Nkp46), HLA-E, PDL-1 and CD94)
- To explore the efficacy of monalizumab in gynecologic malignancies

METHODS

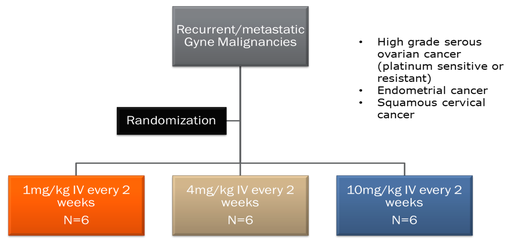


Figure 1. Study design: Dose-ranging, Part 1.

METHODS

- **Key Eligibility Criteria**:
  - Advanced, metastatic, or recurrent high grade serous ovarian cancer, epithelial endometrial cancer or squamous cervical cancer
    - platinum sensitive or platinum resistant
  - RECIST evaluable disease
  - ECOG PS <3
  - At least one prior regimen of platinum-based cytotoxic chemotherapy for advanced, metastatic or recurrent disease (no more than 3 prior cytotoxic regimens)
  - Availability of formalin fixed paraffin embedded tissue block
- **Planned Correlative Studies:**
  - Drug Pharmacokinetics
  - Archival tumour for immunohistochemical studies
    - Lymphocyte infiltration (TIL, stromal and intra tumoral CD8)
    - HLA-E expression (tumour, lymphocytes, endothelium)
    - Tumour PDL-1
    - Nkp46 (stromal and intra-tumoral)
  - Plasma and serum
  - Whole blood for circulating tumour cell studies
  - Receptor occupancy studies
  - Anti-drug antibody studies

RESULTS

Table 1. Baseline Patient Characteristics

		1 mg/kg N=6	4 mg/kg N=6	10 mg/kg N=6
Age	Median	59 (50-74)	62 (51-71)	63 (36-74)
Prior Rx	Chemo Hormone Radiation Other	6 1 1 4	6 1 2	6 1 1
N prior regimens	<3 ≥3	4 2	3 3	6 0
N sites of disease	<4 ≥4	1 5	2 4	3 3

Table 2. Treatment Delivered

	1 mg/kg N=6	4 mg/kg N=6	10 mg/kg N=6
Total and Median # cycles	33 6	35 6	41 6
90% of Planned dose intensity	100%	66.7%	66.7%

Table 3. Related Adverse Events (%)

	1 mg/kg N=6		4 mg/kg N=6		10 mg/kg N=6	
	All	≥ G3	All	≥ G3	All	≥ G3
Fatigue	17%	17%	50%	17%		
Headache			50%		50%	
Dry mouth			33%			
Nausea			33%	17%	17%	17%
Vomiting	17%		33%		17%	17%
Dry eye			17%			
Constipation			17%			
Sweating			17%			
Rash (maculo-papular)			17%			
Hot flashes			17%		33%	
Abdo pain					17%	
Vaginal discharge					17%	
Dehydration					17%	17%
Arthromyalgia					33%	

RESULTS

Table 4. Laboratory Abnormalities (%)

	1 mg/kg N=6		4 mg/kg N=6		10 mg/kg N=6	
	All	≥ G3	All	≥G3	All	≥G3
Neutropenia	17%		17%		17%	
Anemia	67%		83%		83%	
Lymphopenia	67%		83%	17%	50%	17%
Thrombocytopenia	17%					
↑ Creatinine	33%		33%		33%	
↑ AST/ALT	50%		50%		67%	
Hypoalbuminemia	67%	17%	83%		50%	33%

Table 5. RECIST Responses (N=17)

	# patients	Median Duration (mo)	Range (mo)
Complete response	0		
Partial response	0		
Stable disease	7	3.4	1.4- 5.5
Progressive disease	10		
In-evaluable	1		
Total	18		

Table 6. Baseline Characteristics: SD vs PD (N=17)

	Stable Disease	Progressive Disease
Median Age	54.6	59.9
Median # prior therapies	2	2.5
Median Duration on last systemic therapy	195 days	204 days
Platinum Resistant at study entry	5/7	6/10

Figure 2. Best Tumour shrinkage from baseline (N=17); Mixed response

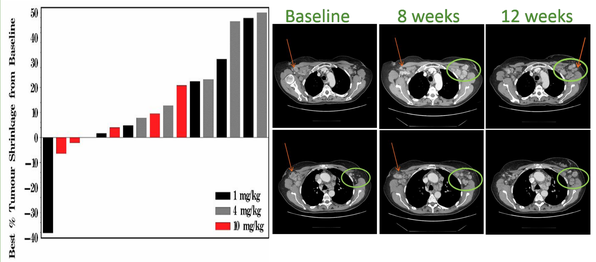
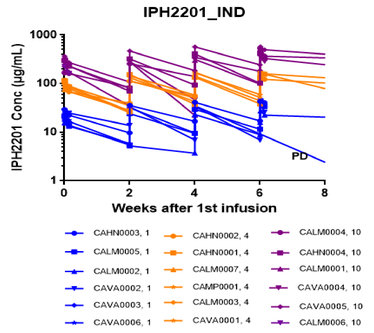


Figure 3. Concentration of monalizumab following infusion



RESULTS

Table 7. Pharmacokinetic Analysis

Dose_ Level		Tmax h	Cmax µg/ml	C_{trough} h*µg/ml	AUC_{336h} h*µg/ml	Cmax/Dose	AUC_{336h} /Dose
1	N	6	6	5	5	6	4
	Mean	**1.33**	**23.8**	**8.1**	**4573.8**	**23.8**	**4573.8**
	CV%	61.2	20.5	44.8	31.3	20.5	31.3
4	N	6	6	6	6	6	5
	Mean	**1.67**	**108.5**	**30.2**	**19277.0**	**27.1**	**4819.2**
	CV%	62.0	10.6	18.9	8.3	10.6	8.3
10	N	6	6	5	5	6	5
	Mean	**2.00**	**268.7**	**75.4**	**50667.3**	**26.9**	**5066.7**
	CV%	54.8	25.1	35.5	22.4	25.1	22.4

- **Biomarker Analysis**
  - The following immune markers were studied by IHC
    - CD8 stroma
    - CD8 intra-tumor
    - Nkp46 stroma
    - Nkp46 intra-tumor
    - PDL-1 tumor
    - HLA-E tumor
    - HLA-E lymphocytes
    - HLA-E endothelium
  - Trend in stromal CD8 expression: association with SD vs PD (p=0.2)
  - Intra-tumoral CD8 expression was not associated with outcome (median 3 vs 3, p=0.67)

CONCLUSIONS

- The RP2D of monalizumab is 10 mg/kg IV every 2 weeks
- Monalizumab as a single agent is well tolerated with no reported DLTs or SAEs
- Short term disease stabilization observed in 41% of evaluable patients in these heavily pretreated cohorts
- Trend in stromal CD8 expression and SD
- Part 2 of this study is ongoing: expanded cohorts (N=10) of
  - Platinum sensitive HGSC ovary/fallopian tube/peritoneum
  - Platinum resistant HGSC ovary/fallopian tube/peritoneum
  - Epithelial endometrial cancers
  - Squamous cervical cancer
- Future studies of monalizumab in combination with other immune therapies, or with standard treatments are warranted

ACKNOWLEDGEMENTS

The Canadian Cancer Trials Group is supported by the Canadian Cancer Society Research Institute.