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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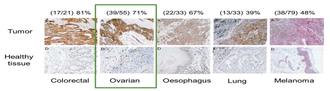
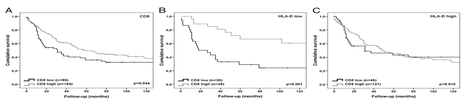
Abstract # 296

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

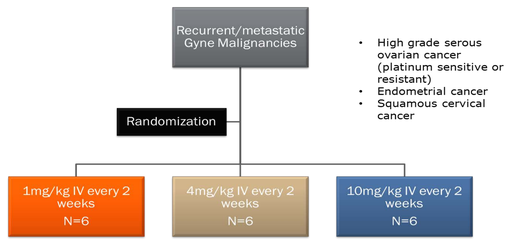


Figure 1. Study design: Dose-ranging, Part 1.

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

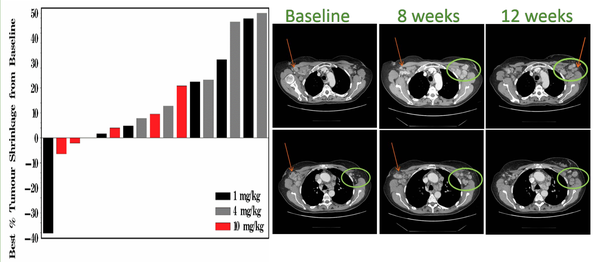
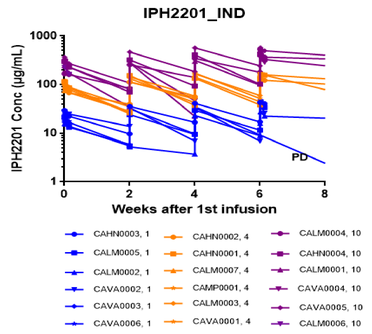


Figure 3. Concentration of monalizumab following infusion



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

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