A Phase I Trial Of Anti-KIR Monoclonal Antibody IPH2101 and Lenalidomide For Multiple Myeloma

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Introduction & Methods

Multiple myeloma (MM) cells upregulate MHC class I serving as ligands to inhibitory Killer Immunoglobulin-like Receptors (KIR) to evade natural killer (NK) cell immunity. IPH2101 is a human, IgG_4 monoclonal antibody against common inhibitory KIR that prevents KIR-ligand interaction and augments NK cell cytotoxicity against tumors **(1)**. A single-agent, phase I trial of IPH2101 demonstrated acceptable safety and tolerability with 34% of heavily pre-treated patients (pts) achieving disease stabilization **(2)**. Lenalidomide (LEN) expands and activates NK cells. Our preclinical data suggest IPH2101 and LEN combine to enhance NK cell function against MM **(3)**. We present results of a phase I clinical trial of IPH2101 and LEN in MM.

The primary objective is to evaluate the safety of IPH2101 and LEN with the following secondary endpoints: to evaluate the pharmacokinetics (PK) of IPH2101 with LEN , to evaluate the biological activity of IPH2101 on KIR occupancy, NK cell phenotype and function, cytokine/chemokine release, and to evaluate anti-MM activity as determined by response rate, duration of response, progression-free survival (PFS) and time to progression.

Subjects:

- Adult pts with relapsed MM following 1 or 2 prior lines of therapy are eligible. Pts must have measurable disease, ECOG performance status 0-2, standard organ-system function and bone marrow reserve. Prior LEN is permitted unless resistance or intolerance to therapy (Tx) was observed.

Study Design:

A 3+3 dose escalation is being conducted with IPH2101 administered intravenously q28 days and LEN administered orally days 1-21 on a 28d cycle for 4 cycles. Responding pts may continue an additional 4 cycles after which LEN alone is continued. Pts completing all 8 cycles were maintained on LEN thereafter. No administration of dexamethasone or other systemic corticosteroids was permitted. Dose reductions of LEN were permitted per prescribing information.

Definition of Dose Limiting Toxicity (DLT):

- Any non-hematologic, grade (Gr) 3 or greater toxicity at least possibly related to Tx that does not resolve to ≤Gr 2 within 3 days
- Gr 4 neutropenia >7 days, or Gr 3 neutropenia with fever
- Gr 4 thrombocytopenia (for pts with baseline platelets > $75x10^9$/L) or with bleeding
- Platelet count </= 10×10^9/L (for pts with baseline platelets > $30x10^9$/L and > 50% BM plasma cells)

Pts that experience LEN-related hematologic DLT may continue on therapy if event resolves and investigator considers this in the best interest of the patient, and patient qualifies for initiation of next cycle of therapy with appropriate dose reduction (note: event still qualifies towards MTD however).

Subjects: 15 pts (10 M, 5 F, median age 60) [Table 1] have been treated, 10 pts received 1 previous line of Tx and 5 received 2 previous lines. 10 had prior LEN exposure. The median number of cycles of the combination received is 4 (range 1-8). 5 pts received 8 cycles of the combination.

Table 1. Study Design and subject treatment :

Cohort:	IPH2101 (mg/kg)	Lenalidomide (mg/day)	Subjects:
1	0.2	10	6*
2	0.2	25	3
3	1.0	25	6*

**= cohorts expanded to n=6 each due to Dose Limiting Toxicity*

Results

Safety and tolerability:

As of October 31, 2013, 46 AEs (12%) of Gr 3 or 4 in severity possibly or probably related to IPH2101 and/or LEN have been observed in n=8 pts [Table 2]. Five Serious Adverse Events (SAE) have been reported, of which 4 were possibly or probably related to IPH2101 and/or LEN .

After the end of the study, one pt experienced therapy-related myeloid neoplasm, t-MDS, classified as refractory cytopenia with multilineage dysplasia related to LEN . This patient received LEN + DEX and autologous hematopoietic stem cells transplant before relapsing and entering the study (cohort 1). The pt received LEN 10 mg/day during 28 months, Tx was held transiently due to neutropenia.

DLT description:

Two DLTs (infusion-related toxicities) have been observed (cohorts 1 and 3). Two pts experienced infusion-related reactions with first dose of IPH2101 characterized by fever and cytokine release (Figure1). Both pts subsequently developed severe, transient leucopenia which resolved without intervention. These cohorts were expanded without recurrence of DLT, and both pts were subsequently re-treated without recurrence of DLT.

Table 2. Related Grade 3 and 4 Adverse Events (as of October 31 2013):

Category / Event:	Grade:	Events:	N:	Relationship to study agents:	
				IPH2101	LEN
Constitutional:					
- Cytokine release syndrome	3	1	1	1	
- Infusion reaction	3	1	1	1	1
- Febrile Neutropenia	3	2	2	2	1
Hematologic:					
- Neutropenia	3,4	23	7	9	20
- Leucopenia	3,4	13	3	5	11
- Lymphopenia	3,4	2	1	2	2
- Thrombocytopenia	3	1	1		1
Infectious:					
- Eye infection	3	1	1		1
Metabolic:					
- Lipase elevation	3	1	1	1	
- Hypophosphatemia	3	1	1	1	

Efficacy:

Table 3. Disease Responses and Duration of Response in month (as of October 31 2013):

Cohort:	Very Good Partial Response (VGPR)	Partial Response (PR)	Minimal Response (MR)	Stable Disease (SD)
1	1 (27+)	1 (21)		3 (3)*
2		1 (20+)		
3	1 (11+)	1 (3)	1 (5)**	1 (3)*

** = Consent withdrawal ** = LEN intolerance*

Figure 1 shows changes in pro-inflammatory cytokines (*patients who experienced the DLT of infusion reaction).

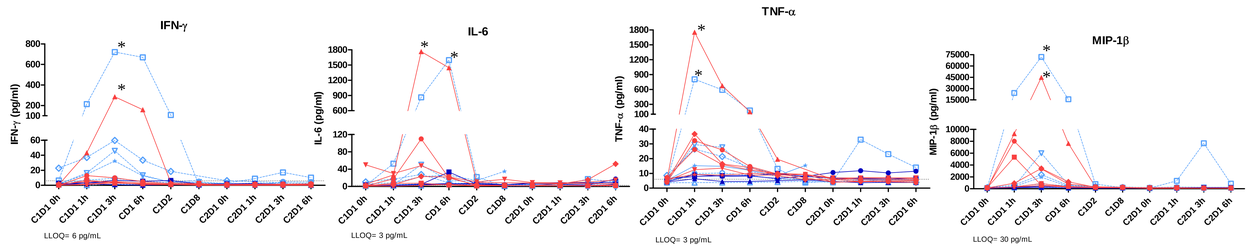

Figure 2 shows that IPH2101 pharmacodynamics (Receptor Saturation Assay) do not appear to be altered by co-administration of LEN (compared to single-agent IPH2101 PD data).

Discussion

- NK cells play an important role in the immune response to MM; however, the disease elicits specific immunoevasive strategies to attenuate NK cell surveillance and cytotoxicity. By blocking inhibitory KIR receptors, IPH2101 has been shown to increase NK cell cytotoxicity against MM. In addition to direct anti-MM effects, LEN has been shown to expand and activate NK cells providing a rationale for combining this agent with IPH2101.
- Treatment has been safe and generally well tolerated. MTD has not been reached. Most frequent Gr 3/4 adverse event was neutropenia related to LEN. Severe infusion reactions following the first dose of IPH2101 have not been observed since amending the trial to provide anti-pyretic and anti-histamine prophylaxis.
- IPH2101 PD do not appear to be altered by co-administration of LEN, and full KIR blockade over the dosing interval has been achieved. No evidence of autoimmunity has been observed.
- Although caution is warranted in interpreting early efficacy data, in this analysis by standard criteria, five pts achieved an objective response (2VGPR, 3 PR) with a median duration of 20+ months (3-27+). Three of these pts had prior LEN/DEX Tx.
- In summary, lenalidomide promotes NK cell expansion and activation. IPH2101 prevents inhibitory signaling in NK cells by blocking inhibitory KIR. Thus, this therapeutic combination may promote restoration and enhancement of the NK cell -vs. MM effect. Although the study is small, response rate and response duration are encouraging.
- These findings support further investigation of anti-KIR therapy with LEN as the first, steroid-sparing, dual immunotherapy for MM.

References

(1) Romagne F. et al, Blood 2009;114:2667-77 **; (2)** Benson D. et al, Blood 2012;120:4324-33; **(3)** Benson D. et al, Blood 2011;118: 6387-91

Disclosures:

Benson: Innate Pharma: Research Funding. Off Label Use: Lenalidomide without concomitant dexamethasone. Zerbib: Innate Pharma: Employment. Andre: Innate Pharma: Employment. Caligiuri: Innate Pharma: Membership on an entity's Board of Directors or advisory committees.