

# A Phase I Trial of the Anti-KIR Antibody IPH2101 and Lenalidomide in Patients with Relapsed/Refractory Multiple Myeloma

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## Abstract

**Purpose:** Natural killer (NK) cells may play an important role in the immune response to multiple myeloma; however, multiple myeloma cells express killer immunoglobulin-like receptor (KIR) ligands to prevent NK cell cytotoxicity. Lenalidomide can expand and activate NK cells in parallel with its direct effects against multiple myeloma; however, dexamethasone may impair these favorable immunomodulatory properties. IPH2101, a first-in-class antiinhibitory KIR antibody, has acceptable safety and tolerability in multiple myeloma as a single agent. The present work sought to characterize lenalidomide and IPH2101 as a novel, steroid-sparing, dual immune therapy for multiple myeloma.

**Experimental Design:** A phase I trial enrolled 15 patients in three cohorts. Lenalidomide was administered *per os* at 10 mg on cohort 1 and 25 mg on cohorts 2 and 3 days 1 to 21 on a 28-day cycle with IPH2101 given intravenously on day 1 of each cycle at

0.2 mg/kg in cohort 1, 1 mg/kg in cohort 2, and 2 mg/kg in cohort 3. No corticosteroids were utilized. The primary endpoint was safety, and secondary endpoints included clinical activity, pharmacokinetics (PK), and pharmacodynamics (PD).

**Results:** The biologic endpoint of full KIR occupancy was achieved across the IPH2101 dosing interval. PD and PK of IPH2101 with lenalidomide were similar to data from a prior single-agent IPH2101 trial. Five serious adverse events (SAE) were reported. Five objective responses occurred. No autoimmunity was seen.

**Conclusions:** These findings suggest that lenalidomide in combination with antiinhibitory KIR therapy warrants further investigation in multiple myeloma as a steroid-sparing, dual immune therapy. This trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (reference: NCT01217203). *Clin Cancer Res*; 21(18):4055–61. ©2015 AACR.

## Introduction

Novel therapies including immunomodulating agents (e.g., thalidomide, lenalidomide, pomalidomide) and proteasome inhibitors (bortezomib, carfilzomib) have significantly improved patient outcomes with multiple myeloma (1). Immunomodulatory agents such as lenalidomide may exert anti-multiple myeloma efficacy, in part, through expansion and activation of natural killer (NK) cells, which have been shown to play an important role in the immune response against multiple myeloma (2–9). However, multiple myeloma cells utilize specific immunoevasive strategies to reduce NK cell recognition and cytotoxicity (10–13).

Presently, lenalidomide is administered in combination with dexamethasone, which may attenuate its favorable immunomod-

ulatory properties (14, 15). Corticosteroids are the backbone of virtually every effective therapy for multiple myeloma, yet these agents also confer substantial risk of toxicities (e.g., hypertension, glucose intolerance, osteoporosis, and psychiatric effects in addition to immune suppression). A prior study of lenalidomide plus high-dose dexamethasone (40 mg PO days 1–4, 9–12, and 17–20 on a 28-day cycle) versus lenalidomide plus low-dose dexamethasone (40 mg PO days 1, 8, 15, and 22 on a 28-day cycle) in newly diagnosed multiple myeloma showed that although response rates were higher with high-dose dexamethasone, overall survival was superior and less toxicity was observed with low-dose dexamethasone (16). An effective lenalidomide combination therapy, devoid of corticosteroids, would represent a significant advance in the treatment options for multiple myeloma (17).

IPH2101 (formerly 1-7F9) is a first-in-class, humanized IgG<sub>4</sub> monoclonal antibody against common inhibitory killer immunoglobulin-like receptors (KIR) that disrupts inhibitory KIR-ligand interaction to promote NK cell recognition and lysis of tumor cells seeking to recapitulate the effects of KIR-ligand mismatch that mediate NK cell alloreactivity in haploidentical allogeneic stem cell transplantation (18, 19). Multiple myeloma cells upregulate surface expression of HLA class I molecules (which serve as inhibitory KIR ligands) making this receptor-ligand axis a provocative target for NK-cell mediated therapeutics (5). A single-agent, dose-escalation, phase I trial of IPH2101 in relapsed/refractory multiple myeloma reached the biologic endpoint of full KIR blockade over dosing interval, with correlative

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### Translational Relevance

In addition to directly inducing apoptosis of multiple myeloma cells, lenalidomide modulates expansion and activation of natural killer (NK) cells. NK cells appear to play an important role in the immune response to multiple myeloma; however, multiple myeloma cells utilize NK cell-specific immunoevasive strategies, including expression of inhibitory killer immunoglobulin-like receptor (KIR) ligands that prevent NK cell recognition and lysis. IPH2101, a nondepleting, IgG<sub>4</sub> antibody against common inhibitory KIR, was shown to be a safe and well-tolerated agent in relapsed/refractory multiple myeloma, with evidence of disease stabilization in 34% of patients as a single agent. The present findings suggest that the use of lenalidomide for NK cell stimulation and IPH2101 to release NK cells from inhibitory signaling is safe, tolerable, and associated with signs of clinical efficacy. These results justify further research into combinatory, innate immune therapy for multiple myeloma devoid of corticosteroid use.

evidence of NK cell activation and enhanced function, but without dose-limiting toxicity (20). In that trial, stable disease was observed in 34% of treated patients (20). Preclinical data suggest that the combination of lenalidomide and IPH2101 confer anti-multiple myeloma effects through complementary mechanisms modulating the NK cell versus multiple myeloma effect (21). With lenalidomide to augment NK cell function and IPH2101 to release NK cells from inhibition, the present phase I dose-escalation trial of this combination was conducted in patients with relapsed/refractory multiple myeloma. No corticosteroids were utilized.

## Materials and Methods

### Study objectives

The primary objective of the trial was to determine the safety and tolerability of IPH2101 in combination with lenalidomide by NCI CTC Version 4.0 of May 2009. The secondary objectives were to evaluate the anti-multiple myeloma activity, the pharmacokinetics and pharmacodynamics of IPH2101 in combination with lenalidomide, and to confirm the absence of immunogenicity of IPH2101.

### Study population

Adult patients (ages 18–80 years) with relapsed/refractory multiple myeloma according to International Myeloma Working Group (IMWG) definition after one or two prior lines of treatment were eligible for inclusion with measurable disease, Eastern Cooperative Oncology Group performance status of 0–2, adequate renal (calculated creatinine clearance  $\geq 60$  mL/min), hepatic (bilirubin  $< 1.5 \times$  institutional upper limit of normal, ALT/AST  $< 3 \times$  institutional upper limit of normal), and bone marrow function (absolute neutrophil count  $> 1 \times 10^9/L$  and platelet  $\geq 75 \times 10^9/L$  for patients with  $< 50\%$  bone marrow plasma cells and  $\geq 30 \times 10^9/L$  for patients with  $> 50\%$  bone marrow plasma cells). Eligibility also included meeting satisfactory conditions outlined in the mandatory RevAssist program for lenalidomide dispensing. Patients could have had prior lenalidomide but had to have achieved at least partial response for 6 months and not have discontinued lenalido-

mid previously due to toxicity or intolerance. Patients with history of autoimmune disease, HIV, chronic hepatitis, or history of allogeneic transplantation were excluded. Concomitant use of corticosteroids was prohibited. The study was approved by Institutional Review Boards before initiation and was conducted in accordance with the Declaration of Helsinki. All subjects provided informed consent before participation.

### Study design

IPH2101 was administered intravenously on day 1 of a 28-day cycle over three cohorts of escalating doses: 0.2 mg/kg (with 10 mg lenalidomide orally days 1–21), 0.2 mg/kg (with 25 mg lenalidomide), and 1 mg/kg (with 25 mg lenalidomide). A standard 3+3 trial design was utilized with dosing cohorts added sequentially following interim safety and tolerability data review.

Patients were to receive four cycles of IPH2101 and lenalidomide and were eligible for an additional four cycles pending safety, tolerability, and evidence of clinical benefit. Thereafter, patients were maintained on single-agent lenalidomide. Dose modifications of IPH2101 were not permitted. Dose modifications for lenalidomide-related grade 3 or 4 hematologic adverse events (AE) followed standard dose adaptation rules. For other grade 4 AEs related to lenalidomide, treatment was held and restarted at next lower dose following resolution of toxicity if trial continuation was considered in the patient's best interest by the treating physician.

Dose-limiting toxicity (DLT) was defined as any of the following in cycle 1 of treatment: grade 4 neutropenia lasting  $\geq 7$  days or grade 3 neutropenia with fever  $> 38^\circ C$ , grade 4 thrombocytopenia for patients with baseline platelet count  $\geq 75 \times 10^9/L$  (or  $< 10 \times 10^9/L$ , or with bleeding, for patients with baseline  $> 50\%$  bone marrow plasma cells and platelet count  $30\text{--}75 \times 10^9/L$ ). Patients experiencing a lenalidomide-related hematologic DLT were able to continue on trial if considered in the patient's best interest by the treating physician and if patient qualified for next cycle of therapy with dose reduction (however, the event was still counted toward

**Table 1.** Demographics, disease, and prior treatment characteristics of patients ( $n = 15$ )

Demographics	Value
Sex, female, $n$ (%)	5 (33)
Median age, y (range)	60 (39–76)
Prior treatments, patients, $n$ (%)	
Corticosteroids	11 (73)
Anthracyclines	5 (33)
Alkylating agents	12 (80)
Bortezomib	11 (73)
Lenalidomide	10 (66)
Thalidomide	5 (33)
Other	4 (27)
Median time, diagnosis to enrollment, y (range)	3.5 (1.3–10.1)
International Staging System stage, $n$ (%)	
1	8 (53)
2	3 (20)
3	0 (0)
Unknown	4 (27)
Type of M-protein, patients, $n$ (%)	
IgG	6 (40)
IgA	3 (20)
Light chain	6 (40)
Cytogenetics (available on $n = 11$ ),%	
Standard risk	45
High risk	55

**Table 2.** Grade 3/4 AEs possibly/probably related to IPH2101 and/or lenalidomide

Category/event	Grade	Events	N	Relationship to study agents	
				IPH2101	Lenalidomide
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
Lymphopenia	3, 4	15	3	7	13
Thrombocytopenia	3	1	1		1
Infectious					
Eye infection	3	1	1		1
Metabolic					
Lipase elevation	3	1		1	1
Hypophosphatemia	3	1		1	1

establishment of a maximally tolerated dose). Any grade  $\geq 3$  nonhematologic toxicity possibly or probably related to the combination that did not resolve or decrease to grade 2 or less within 3 days was also considered a DLT.

**Response criteria**

Objective responses were assessed by uniform International Myeloma Working Group (IMWG) criteria and minor response by European Group for Blood and Marrow Transplant (EBMT) criteria. Time-to-event endpoints (time to progression, progression-free survival, and duration of response) were defined according to IMWG guidelines.

**Correlative studies**

Pharmacokinetics (PK) and pharmacodynamics (PD) were analyzed as described previously (20). PK and PD of IPH2101 were assessed in combination with lenalidomide and compared with historic data from a prior single-agent IPH2101 trial to assess any effects of concomitant administration of lenalidomide on the PK and PD of IPH2101. Cytokine profiles and lymphocyte subsets were serially analyzed over the course of the trial as described previously (20).

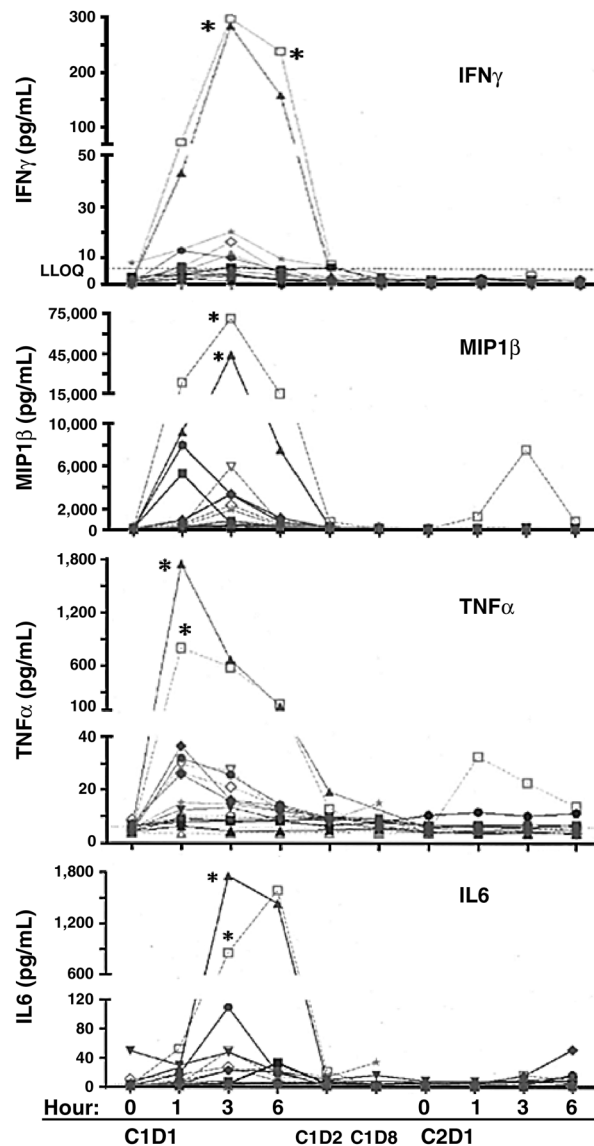
**Statistical considerations**

Descriptive statistics were used to summarize continuous data and categorical data were summarized by number/percentage of events. Progression-free survival was calculated using the Kaplan-Meier method.

**Results**

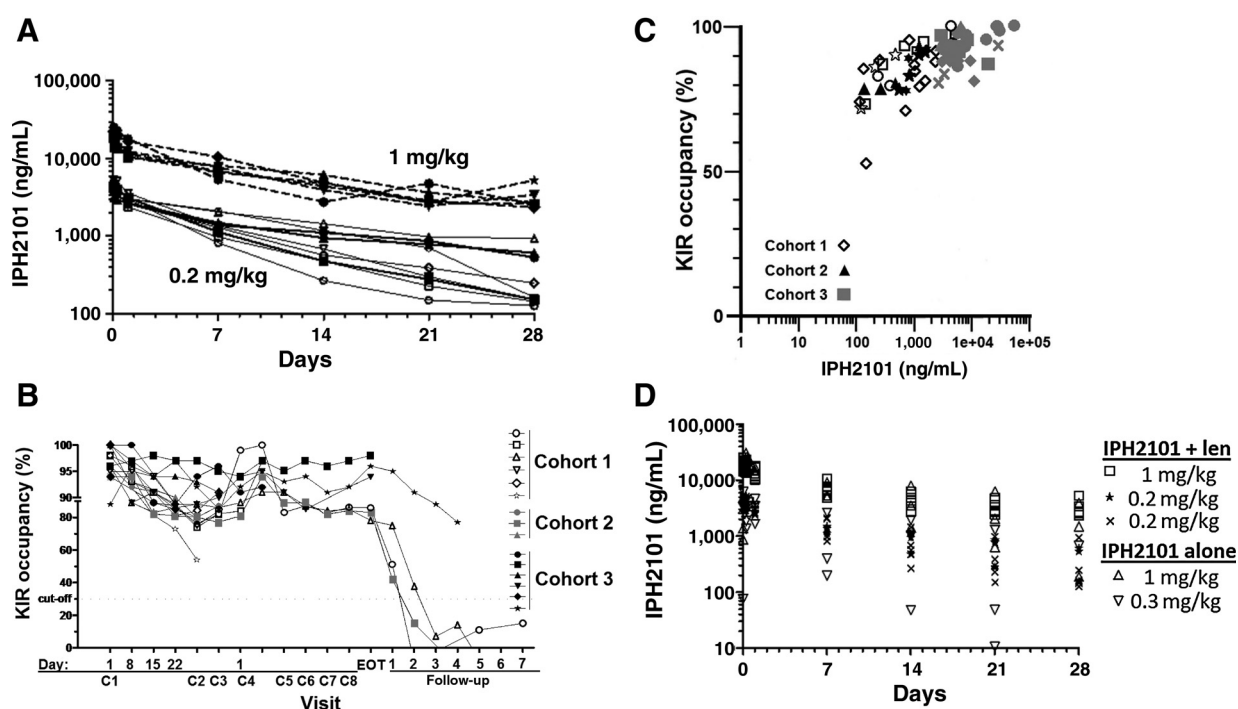
**Patient characteristics**

In total, 15 patients (10 male, 5 female; median age, 60 years; range, 39–76) were enrolled between February 2011 and December 2013 and received at least one dose of IPH2101 and lenalidomide. Cohorts 1 and 3 were expanded to  $n = 6$  patients resulting from potential DLTs described in detail below. There was an average of 3.5 years (range, 1.25–10.1) from diagnosis to enrollment on the trial. Ten patients had one prior line of therapy, 5 patients had two prior lines. Twelve had had prior high-dose therapy with autologous stem cell transplantation. Ten had received prior lenalidomide (prior exposure to lenalidomide was mean of  $6.8 \pm 6.5$  months, and time from lenalidomide exposure to first dose of IPH2101 and lenalidomide on study was average of  $2 \pm 1$  years). Patient demographics, disease, and prior treatment characteristics are summarized in Table 1.



**Figure 1.** Changes in proinflammatory cytokines observed in cycles 1 and 2. The 2 patients who experienced a potential DLT of clinically evident, infusion-related, cytokine release syndrome are marked (\*).

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**Figure 2.** A, PK data demonstrate the IPH2101 serum concentration over time is associated with dose. B, PD data suggest that KIR occupancy is a function of IPH2101 dose and time. Most patients treated at 1 mg/kg dosage achieved full KIR occupancy over the dosing interval of 28 days. C, IPH2101 dose correlates with KIR occupancy. D, coadministration of lenalidomide with IPH2101 does not appear to affect serum concentration of IPH2101 as compared with data from a prior single-agent IPH2101 study.

**Treatment, safety, and toxicity**

Eight patients (53%) completed four planned cycles of therapy. Five patients (33%) completed eight cycles of therapy of which, 4 went onto maintenance therapy. Four patients (27%) received reduced doses of lenalidomide, mainly related to neutropenia. In total, 46 treatment emergent AEs of grade 3/4 severity were observed in  $n = 8$  patients and considered "possibly" or "probably" related to IPH2101 and/or lenalidomide (summarized in Table 2). Of five serious AEs, three were "possibly" or "probably" related to IPH2101 and/or lenalidomide. No patients permanently discontinued treatment for safety related to IPH2101.

Potential DLTs were experienced by 1 patient in cohort 1 and 1 patient in cohort 3. These two events were similar in nature and timing, characterized by fever and cytokine release on cycle 1, day 1 following administration of IPH2101 and lenalidomide. Both patients subsequently developed grade 4 leucopenia and neutropenia, which resolved without growth factor support or other intervention within 72 hours. Cohorts 1 and 3 were both expanded without recurrence of the potential DLT. Both patients remained on study and did not experience similar reactions during subsequent cycles of therapy; however, neither experienced an objective response. Both patients with this DLT demonstrated profound increases in proinflammatory cytokines (IFN $\gamma$ , IL6, TNF $\alpha$ , and MIP1 $\beta$ ) as shown in Fig. 1) following infusion of IPH2101 as compared with other patients in the study. The trial was amended to include antipyretic and antihistamine prophylaxis, and no further infusion-related reactions were observed.

After completion of the study, 1 patient developed therapy-related myelodysplasia. This patient had previously received

lenalidomide/dexamethasone induction therapy followed by intravenous melphalan 200 mg/m<sup>2</sup> with autologous stem cell transplantation before relapsing and entering cohort 1. The patient received lenalidomide 10 mg/day during 28 months while on study with treatment interruptions transiently for neutropenia.

**IPH2101 PK and PD are not affected by coadministration of lenalidomide**

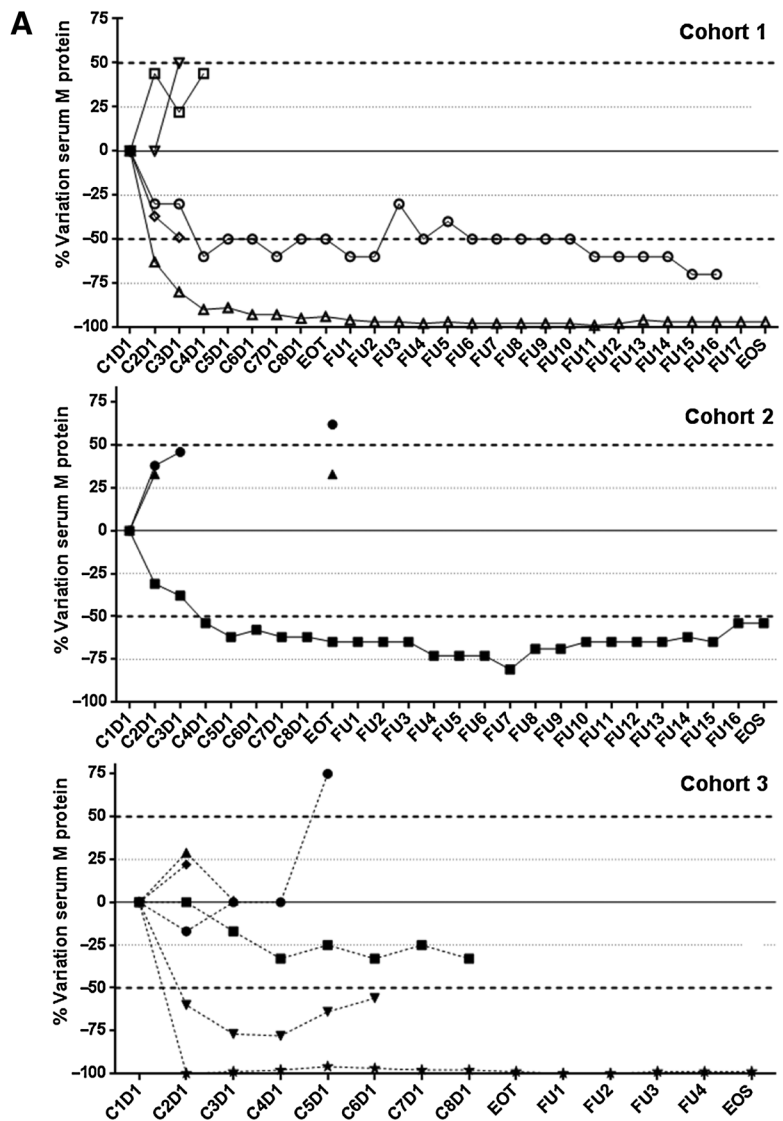
As in a prior single-agent trial, the dose of IPH2101 correlated with serum concentration over time (Fig. 2A). KIR occupancy was consistent across the 28-day dosing interval for most patients at the 1 mg/kg dose of IPH2101 (Fig. 2B). The administered dose of IPH2101 also correlated with the observed proportion of KIR occupancy (Fig. 2C). A direct comparison of IPH2101 serum concentrations as a function of dose (Fig. 2D) suggests that coadministration of lenalidomide did not significantly affect the PK of IPH2101 in the present study in comparison with data obtained in a prior single-agent trial (20).

**Table 3.** Overall best response to therapy

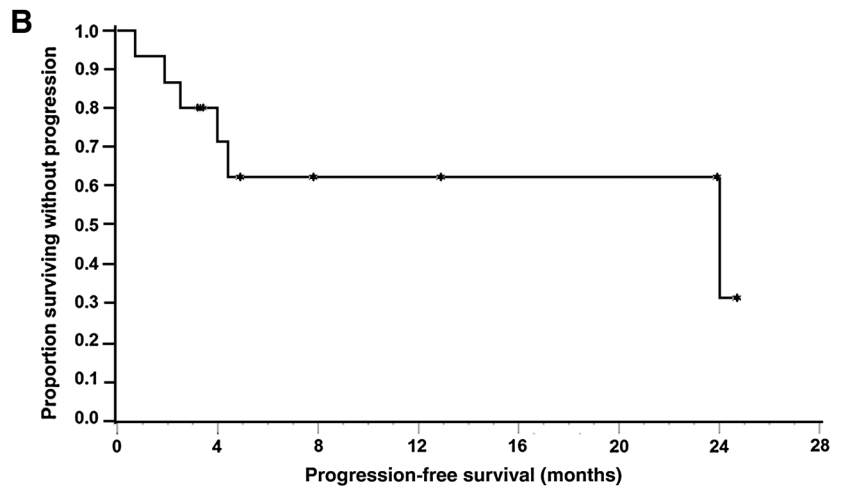
Response	Cohort <sup>a</sup>			Total
	1	2	3	
Objective response				
–VGPR	1	0	1	2 (13.3%)
–PR	1	1	1	3 (20%)
Minor response	0	0	1	1 (6.7%)
Stable disease	3	0	3	6 (40%)
Progressive disease	1	2	0	3 (20%)

<sup>a</sup>Cohort 1, 0.2 mg/kg IPH2101+ 10 mg lenalidomide; cohort 2, 0.2 mg/kg IPH2101+ 25 mg lenalidomide; cohort 3, 1 mg/kg IPH2101+ 25 mg lenalidomide.

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**Figure 3.** A, serial changes in individual subject multiple myeloma biomarkers per cohort. B, progression-free survival curve for enrolled subjects in the present trial.



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### Immunomodulatory correlates of IPH2101 and lenalidomide

No statistically significant changes were observed in proportions of lymphocyte subsets or expression of markers of activation on lymphocytes over the course of the trial (data not shown).

### Evaluation of clinical efficacy

Although safety and tolerability were the primary endpoints of the trial, patients were evaluated for best response to therapy. There were five objective responses (Table 3): two very good partial responses (VGPR) and three partial responses (PR); out of these, objective responses occurred in 3 patients who had received prior lenalidomide/dexamethasone. One patient achieved a minor response (MR) and 6 achieved stable disease. The median time to best response observed (VGPR, PR, or MR) was 2.8 cycles (range, 0.9–4.8; Fig. 3A). The median duration of response was 24 months [95% confidence intervals (CI), 2.5 to not reached]. The median progression-free survival was also 24 months (95% CI, 2.5 to not reached, Fig. 3B).

## Discussion

NK cells appear to play an important role in the immune response to multiple myeloma; however, the disease utilizes specific strategies to evade NK cell detection and cytotoxicity (22). Among these immunoevasive mechanisms, multiple myeloma cells may increase expression of inhibitory KIR ligands as the disease progresses (5). KIR-ligand mismatch has been shown to be a potential determinant of outcome in allogeneic stem cell transplantation in multiple myeloma as in other hematologic malignancies (19, 23). Based on these concepts, disrupting KIR–ligand interaction as a means to prevent inhibitory signaling in NK cells to augment the NK cell versus multiple myeloma effect has been a topic of ongoing investigation. An initial, single-agent, dose-escalation study showed acceptable safety and tolerability with the antiinhibitory KIR antibody, IPH2101, in patients with multiple myeloma achieving the biologic endpoint of full KIR occupancy over the dosing interval (20).

Lenalidomide exerts direct anti-multiple myeloma effects but also appears to confer favorable immunomodulatory effects on NK cells (2–4). Although the addition of dexamethasone to lenalidomide appears to enhance direct anti-multiple myeloma activity, dexamethasone also appears to suppress lenalidomide's favorable immunomodulatory mechanisms particularly on NK cell function (14, 15). Thus, using lenalidomide as a means to augment NK cell number and function and IPH2101 to prevent inhibitory signaling, the present trial may be considered as the first "dual, innate immunotherapy" for multiple myeloma.

Overall, the combination of lenalidomide and IPH2101 was well tolerated. Infusion-related events observed on cohorts 1 and 3 were abrogated by premedication with antipyretic and antihistamine therapy. The PK and PD of IPH2101 did not appear to be affected by coadministration of lenalidomide and the prespecified biologic endpoint of full KIR occupancy over the 28-day dosing interval was achieved. Objective responses were observed in 33.3% of patients with and without prior lenalidomide exposure, and median PFS was 24 months. A prior study characterizing lenalidomide as a single agent in relapsed/refractory multiple myeloma demonstrated a relatively similar response rate (26%) to that observed in the present trial; however, median PFS was only 4.9 months with lenalidomide alone (24). Prior trials of

lenalidomide plus high-dose dexamethasone in the relapsed/refractory setting showed a 60% to 61% response rate with median PFS of 11.1 months (25, 26). It is important to note that the present study was small, and such comparisons to studies of lenalidomide alone or with dexamethasone are merely speculative in nature.

Therapeutic monoclonal antibodies (mAb) such as IPH2101 comprise just one dimension (27) of the promising, rapidly expanding field of immunotherapy for multiple myeloma, which also includes NK- and T-cellular therapies (28, 29), vaccines (29), and immunomodulating agents, among others. Tumor-directed mAbs (30, 31) as well as effector cell-targeted mAbs (20, 21, 32) provide an opportunity for increasing precision with which to modulate immunity against multiple myeloma, as well. The optimal combinations as well as the most appropriate clinical setting (e.g., smoldering, induction, maintenance, relapse) remain active areas of ongoing inquiry. The present data inform this process by demonstrating that the combination of anti-KIR blockade with IPH2101 as a release from inhibition with lenalidomide to augment NK cell function appears to be safe and tolerable with preliminary evidence of efficacy. These findings justify further research into combination immune therapies designed to complement one another in enhancing immunity against multiple myeloma as a therapeutic strategy.

### Disclosure of Potential Conflicts of Interest

D.M. Benson Jr reports receiving a commercial research grant from Innate Pharma. A.D. Cohen reports receiving a commercial research grant from Bristol-Myers Squibb and is a consultant/advisory board member for Bristol-Myers Squibb, Celgene, Janssen, and Onyx. S. Jagannath is a consultant/advisory board member for Bristol-Myers Squibb and Celgene. C.C. Hofmeister reports receiving speakers bureau honoraria from Celgene and is a consultant/advisory board member for Onyx. Y.A. Efebera reports receiving speakers bureau honoraria from Takeda. P. Andre and R. Zerbib hold ownership interest (including patents) in Innate Pharma. M.A. Caligiuri is a consultant/advisory board member for Innate Pharma. No potential conflicts of interest were disclosed by the other authors.

### Authors' Contributions

**Conception and design:** D.M. Benson Jr, S. Jagannath, M.A. Caligiuri  
**Development of methodology:** D.M. Benson Jr  
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** D.M. Benson Jr, A.D. Cohen, S. Jagannath, N.C. Munshi, G. Spitzer, C.C. Hofmeister  
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** D.M. Benson Jr, S. Jagannath, P. Andre, R. Zerbib, M.A. Caligiuri  
**Writing, review, and/or revision of the manuscript:** D.M. Benson Jr, A.D. Cohen, N.C. Munshi, G. Spitzer, Y.A. Efebera, R. Zerbib, M.A. Caligiuri  
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** D.M. Benson Jr, N.C. Munshi, R. Zerbib  
**Study supervision:** D.M. Benson Jr, S. Jagannath, G. Spitzer  
**Other (enrolled patients):** Y.A. Efebera

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