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Phase I study of PF-03446962, a fully human monoclonal antibody against activin receptor-like kinase-1, in patients with hepatocellular carcinoma†

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Background: This expansion cohort of a multicenter, dose-escalation, phase I study (NCT00557856) evaluated safety, tolerability, antitumor activity, pharmacokinetics, and pharmacodynamic effects of the anti-activin receptor-like kinase-1 (ALK-1) monoclonal antibody PF-03446962 in advanced hepatocellular carcinoma (HCC).

Patients and methods: Patients with HCC and disease progression after prior antiangiogenic therapy or intolerance to treatment received PF-03446962 7 mg/kg intravenously biweekly, as recommended in the dose-escalation part of the study.

Results: Twenty-four patients received PF-03446962. The most frequent treatment-related adverse events (AEs) were thrombocytopenia (33.3%), asthenia (29.2), and chills (16.7%). Two patients experienced treatment-related telangiectasia, suggesting an *in vivo* knockout of ALK-1 function through ALK-1 pathway inhibition. Overall, treatment-related grade 3–4 AEs were reported in eight patients (33.3%). Treatment-related grade 3–4 thrombocytopenia was noted in four patients. No complete or partial responses were reported. Twelve (50%) patients achieved stable disease, which lasted ≥12 weeks in seven (29.2%) patients. The median time to progression was 3 months. Biomarker analyses showed higher mean tumor expression of c-tumor mesenchymal–epithelial transition factor and higher mean serum levels of bone morphogenetic protein-9 in patients with disease control (DC) for ≥12 weeks versus patients with disease progression. Conversely, lower mean serum transforming growth factor-β and vascular endothelial growth factor receptor-3 levels were detected in patients with DC versus patients with progression.

Conclusions: The observed safety, tolerability, pharmacokinetic profile, and clinical activity support further evaluation of PF-03446962 in patients with HCC and other solid malignancies, as single agent or in combination with other antiangiogenic, chemotherapeutic, or immunotherapeutic agents.

Trial registration number: NCT00557856.

Key words: PF-03446962, activin-receptor-like kinase-1, ALK-1, TGF-β receptor, angiogenesis, hepatocellular carcinoma

introduction

Hepatocellular carcinoma (HCC) is often diagnosed at an unresectable, advanced stage that ultimately requires systemic treatment. To date, the only agent shown to provide survival benefit in this setting is the multi-kinase inhibitor sorafenib, which exerts antiangiogenic effects by inhibiting the vascular endothelial growth factor (VEGF) receptor (VEGFR)-2, VEGFR-3, and

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platelet-derived growth factor receptor-β [1]. There is no standard second-line therapy for patients with HCC who are intolerant to or experience disease progression after sorafenib treatment, and the results of clinical trials with several targeted therapies have so far been disappointing [2].

Activin receptor-like kinase-1 (ALK-1) is a type-I transforming growth factor (TGF)-β receptor preferentially expressed on proliferating vascular endothelial cells. It has distinct expression and functional properties compared with other TGF-β receptor superfamily members. Upon binding of bone morphogenetic proteins (BMP) 9 and 10, ALK-1 forms a complex with TGF-β and its type II receptor endoglin, leading to intracellular signaling by phosphorylation; activation of SMADs 1, 5, and 8; and gene expression modulation [3–5].

Results from studies in experimental animal models harboring a loss-of-function mutation demonstrated that ALK-1 plays a key role in vascular development, particularly in vessel maturation, and in vessel organization and patency during neoangiogenesis [6, 7]. Importantly, the ALK-1 pathway is expressed to a varying extent in the vasculature of most human tumors, and its activation may contribute to tumor-associated angiogenesis and resistance to the inhibitory effects of VEGF-targeted agents, pointing to ALK-1 inhibition as a potential, novel anticancer treatment strategy [8, 9].

PF-03446962 is a fully human, anti-ALK-1 monoclonal antibody with antiangiogenic activity in human xenograft tumor models [10, 11]. Treatment with PF-03446962 had a manageable safety profile and showed preliminary evidence of antitumor activity in the dose-finding part of a phase I study conducted in patients with advanced, solid tumors [12]. During dose escalation in this trial, a patient with metastatic HCC previously treated with sorafenib developed a durable partial response (PR) after treatment with PF-03446962 2 mg/kg [12]. Doses between 4.5 and 15 mg/kg were associated with exposures steadily above the projected efficacious concentration level. The recommended phase II dose (RP2D) for PF-03446962 was set at 7 mg/kg biweekly in patients with advanced solid tumors, including HCC [12]. In an identical study conducted in Asia, four of nine patients with HCC continued PF-03446962 treatment for >12 weeks; three patients who experienced telangiectasia showed reductions in α-fetoprotein levels [13]. We report here the safety, antitumor activity, pharmacokinetics, and pharmacodynamic results obtained in the exploratory part of the study, conducted in patients with HCC.

patients and methods

study design, patients, and treatment

This report presents part 2 of a phase I study conducted in HCC patients who had disease progression after prior treatment with VEGFR–tyrosine kinase inhibitors (TKIs), such as sorafenib, or who were intolerant to treatment.

Patients with HCC were eligible for this expansion cohort if they had Child–Pugh classification scores A–B7 [14], had archival, diagnostic tumor samples obtained before treatment with VEGFR TKIs, and *de novo* biopsy samples after VEGFR TKI treatment before PF-03446962 administration. In addition, patients had to have adequate bone marrow, renal, and liver function, and Eastern Cooperative Oncology Group performance status 0 or 1.

Patients were excluded if they had an active bleeding disorder, QT interval corrected for heart rate prolongation >470 ms, or active brain metastases. Furthermore, patients were excluded if they had a history of hereditary hemorrhagic telangiectasia or required anticoagulant therapy (with the exception of low-dose, prophylactic anticoagulants).

The institutional review boards of participating institutions approved the protocol. Patients provided signed informed consent. The study was conducted in compliance with the Declaration of Helsinki and the International Congress of Harmonization Good Clinical Practices guidelines, and registered at ClinicalTrials.gov (NCT00557856).

PF-03446962 was administered as a 1 h intravenous infusion on days 1 and 29 and biweekly thereafter, at the RP2D of 7 mg/kg. Treatment was continued until disease progression, patient withdrawal, or unacceptable toxicity.

assessments

safety. Adverse events (AEs) were graded by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

antitumor activity. Tumor responses were assessed by computed tomography or magnetic resonance imaging at screening every 6 weeks after the first dose of PF-03446962, based on the Response Evaluation Criteria in Solid Tumors version 1.0. End points included complete response (CR) or PR and disease control (DC), defined as CR + PR + stable disease lasting ≥12 weeks from the first dose of PF-03446962. Disease control rate (DCR) was calculated as the number of patients achieving DC/number of response-evaluable patients.

pharmacokinetics. Serial blood samples were collected pre-dose, on days 1–22 after first dose, and pre- and post-dose during treatment cycles 2–12. Serum PF-03446962 concentrations were determined by a validated enzyme-linked immunoassay.

pharmacodynamics. Tumor biospecimens were collected before treatment with previous antiangiogenic agents (archival biospecimen) and at screening before PF-03446962 treatment (*de novo* biospecimen). Protein expression levels of c-MET were evaluated in tumor tissues by immunohistochemistry (Mosaic Laboratories, Lake Forest, CA). Analysis included cellular/subcellular staining localization, staining intensity, and percentage of stained cells. *H*-score calculation: 3× (3^+-stained cell percentage) + 2× (2^+-stained cell percentage) + 1× (1^+-stained cell percentage). The Aushon SearchLight® multiplex-analysis platform-A (Aushon BioSystems, Billerica, MA) was used to evaluate serum soluble biomarker proteins [i.e. BMP-9, TGF-β1, VEGF-R1, VEGF-R2, VEGFR-3, endoglin, angiopoietin-2, VEGF-A, VEGF-C, VEGF-D, CD54, CD106, and chemokine (C–C motif) ligand 2/MCP-1]. Blood samples were collected at screening, on cycle 1 day 1 before infusion, and 6 h after PF-03446962 infusion, cycle 1 day 22, cycles 2 and 3 before infusion, and at the end of study.

statistical analysis

A cohort size of ∼20 patients was selected to provide a DCR estimate at ≥12 weeks with a 90% confidence interval (CI) of approximately ±20%. Data from the tumor tissue immunochemistry and serum soluble protein analyses were summarized to include mean and median values, and plotted to include 1.5× inter-quartile ranges. Descriptive statistics (without *P* value generation) were used throughout the study.

results

patients

In all, 24 patients with HCC were enrolled and treated with PF-03446962. Patient demographics and disease characteristics are presented in Table 1. All patients had mild (compensated)

Table 1. Patient baseline demographics and clinical characteristics

	Patients ($n = 24$)
Gender, *n* (%)	
Male	19 (79)
Female	5 (21)
Age, median (range), years	64.0 (21–81)
ECOG PS at baseline, *n* (%)	
0	10 (42)
1	14 (58)
Disease stage, *n* (%)	
III	3 (13)
IV	20 (83)
Other	1 (4)
Medical history related to primary diagnosis, *n* (%)	
Liver cirrhosis	11 (46)
Hepatitis C	7 (29)
Hepatitis B	6 (25)
Alcohol abuse	5 (21)
Portal vein thrombosis	4 (17)
Esophageal varices	3 (13)
Hepatitis, non-specific	1 (4)
None	1 (4)
Child–Pugh classification A, *n* (%)	24 (100)
Prior treatment regimens, *n* (%)	
1	10 (42)
2	13 (54)
3	1 (4)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Treatment-emergent adverse events in three or more patients (all cause and treatment-related) ($n = 24$)

	All cause, *n* (%)	Treatment-related, *n* (%)
Asthenia	9 (38)	7 (29)
Pyrexia	9 (38)	3 (13)
Decreased appetite	8 (33)	2 (8)
Thrombocytopenia	8 (33)	8 (33)
Fatigue	7 (29)	2 (8)
Nausea	6 (25)	2 (8)
Cough	5 (21)	1 (4)
Epistaxis	5 (21)	3 (13)
Edema peripheral	5 (21)	1 (4)
Anemia	4 (17)	3 (13)
Chills	4 (17)	4 (17)
Dizziness	4 (17)	1 (4)
Pruritus	4 (17)	3 (13)
Vomiting	4 (17)	1 (4)
Abdominal pain	3 (13)	1 (4)
Abdominal pain, upper	3 (13)	0
Back pain	3 (13)	1 (4)
Blood creatinine increased	3 (13)	2 (8)
Constipation	3 (13)	2 (8)
Dyspnea	3 (13)	0
Hyperbilirubinemia	3 (13)	0
Hyperglycemia	3 (13)	0
Hypotension	3 (13)	2 (8)

Treatment-related grade 3–4 AEs were noted in eight (33%) patients: grade 3–4 thrombocytopenia ($n = 4$); grade 4 abdominal pain ($n = 1$); and grade 3 elevation of aspartate aminotransferase ($n = 1$), increased lipase ($n = 1$), and tumor necrosis ($n = 1$).

chronic liver disease, as defined by Child–Pugh classification score A5 or A6 [15]. Twenty-three patients had medical histories related to their primary cancer diagnosis.

Twenty (83%) patients had stage IV disease and all had measurable disease with adequate baseline assessment. The most frequently involved disease sites were liver (67% of patients) and lung (38%). All patients had received prior systemic treatment, 14 (58%) had been treated with 2–3 regimens. The vast majority ($n = 21$) had received prior systemic treatment with sorafenib for advanced disease and one patient each had received sorafenib in the adjuvant or neoadjuvant setting. Other prior systemic treatments are listed in supplementary Table S1, available at *Annals of Oncology* online.

safety

All patients experienced treatment-emergent AEs. Twenty (83.3%) patients had treatment-related AEs (Table 2); the most frequent included thrombocytopenia (33%), asthenia (29%), and chills (17%). Treatment-related telangiectasia, an on-target effect, was observed in two patients (grade 1).

All-cause grade 3–4 AEs were noted in 13 (54%) patients. One death reported on study was due to respiratory failure in a patient with disease progression and deemed unrelated to treatment. Treatment-related grade 3–4 AEs were reported in eight (33%) patients, including grade 3–4 thrombocytopenia ($n = 4$); grade 4 abdominal pain ($n = 1$); and grade 3 elevation of aspartate aminotransferase, increased lipase, and tumor necrosis ($n = 1$ each).

Four patients permanently discontinued treatment due to an AE, reported in two cases as treatment-related (grade 4 thrombocytopenia and grade 3 tumor necrosis resulting in bowel perforation and bleeding). Temporary discontinuations occurred in six (25%) patients, all due to treatment-related AEs (grade 1 chills, pyrexia, and hypertension; grade 1–2 thrombocytopenia; grade 2 anemia and pruritus; and grade 3 increased aspartate aminotransferase level). No AE-related dose reductions were reported. Patients received a median of four treatment cycles. The median duration of treatment with PF-03446962 was 74.5 (range, 28–350) days.

antitumor activity

All patients were evaluable for response. No CRs or PRs were observed. Twelve (50%) patients had stable disease and 10 (42%) had progressive disease (PD). Response was indeterminate in two patients. Stable disease lasted ≥12 weeks in seven patients resulting in a DCR of 29% (90% exact CI, 14.6–47.9). The median time to tumor progression was 3 months (90% exact CI, 1.4–4.7) (supplementary Figure S1, available at *Annals of Oncology* online).

pharmacokinetics

Serum PF-03446962 concentration–time profiles and pharmacokinetics characteristics observed in patients with HCC treated at 7 mg/kg (supplementary Table S2, available at *Annals of*

Oncology online) were similar to those of patients with other solid tumors treated with PF-03446962 at 6.75 mg/kg in the dose-escalation phase [16]. Serum PF-03446962 concentrations exceeded the projected efficacious concentration following a single 7 mg/kg dose.

biomarker evaluations

Higher c-MET expression by percentage of positive cells was detected in tumor biospecimens obtained from patients with DC at ≥12 weeks compared with patients with PD (21% versus 2% in archival biospecimens; 88% versus 53% in *de novo* biospecimens) (Table 3). Likewise, the mean c-MET *H*-scores were 29 versus 2 in archival biospecimens and 103 versus 60 in *de novo* biospecimens in patients with DC at ≥12 weeks compared with patients with PD. The mean ratio of the c-MET *H*-score to baseline was 5 in patients with DC at ≥12 weeks versus 18 in patients with PD.

Higher mean serum levels [standard deviation (SD)] of BMP-9 were detected at baseline [62 (43.7) versus 42 (53.6) pg/ml], and all subsequent time points, in patients with DC at ≥12 weeks compared with patients with PD. Conversely, lower mean serum levels (SD) of TGF-β1 [38 402 (16 395) versus 86 731 (7665) pg/ml] and VEGFR-3 [311 511 (96 120) versus 469 286 (149 252) pg/ml] were found at baseline; and all subsequent time points, in patients with DC at ≥12 weeks compared with patients with PD (Figure 1; supplementary Table S3, available at *Annals of Oncology* online).

Table 3. Tumor expression of c-MET by disease control at ≥12 weeks of treatment with PF-03446962 in patients with HCC[a]

	Disease control[b]	
Variable	Yes ($n = 6$)	No ($n = 16$)
% Cells expressing c-MET		
Archival sample (pre-sorafenib)	$n = 4$	$n = 11$
Mean	21	2
Standard deviation	29.82	2.93
%CV	143.7	161
Median	9	1
De novo sample (post-sorafenib)	$n = 4$	$n = 12$
Mean	88	53
Standard deviation	15.56	44.99
%CV	17.6	84.5
Median	95	60
H-score[c]		
Archival sample (pre-sorafenib)	$n = 4$	$n = 11$
Mean	29	2
Standard deviation	44.58	3.21
%CV	156.4	168.0
Median	10	1
De novo sample (post-sorafenib)	$n = 4$	$n = 12$
Mean	103	60
Standard deviation	10.23	53.07
%CV	9.9	87.8
Median	100	65

[a]Tissues from two patients were not analyzed owing to non-FFPE storage procedure.
[b]Yes = Patients with stable disease lasting ≥12 weeks; No = patients with early disease progression or with stable disease lasting <12 weeks.
[c]*H*-score = (3× percentage of cells staining at 3^+) + (2× percentage of cells staining at 2^+) + (1× percentage of cells staining at 1^+).
c-MET, mesenchymal–epithelial transition factor; HCC, hepatocellular carcinoma; CV, coefficient variation; FFPE, formalin-fixed, paraffin-embedded.

discussion

This expansion cohort study evaluated safety and antitumor activity of PF-03446962 in patients with advanced HCC who had progressed after prior systemic antiangiogenic therapy and explored possible correlations between DC and selected tumor or circulating biomarkers.

Single-agent treatment with PF-03446962 at the RP2D demonstrated a favorable safety profile in patients with HCC. The RP2 dose had been selected based on efficacy, safety, and pharmacokinetics profile and was considered adequate in this setting. The pharmacokinetics profile obtained with 7 mg/kg in patients with HCC, including those with underlying liver cirrhosis, was consistent with that previously observed in patients with other solid tumors treated at 6.75 mg/kg [12], but it is worthy to note that all subjects enrolled in this trial, as most of the other studies in this setting, were in Child–Pugh class A. Treatment-related AEs were mainly mild to moderate in severity and easily manageable; thrombocytopenia, asthenia, chills, pyrexia, epistaxis, and anemia were the most frequent AEs reported. Eight (33%) patients experienced severe toxicities; of which, four (17%) were grade 3–4 thrombocytopenia. However, platelet counts generally recovered before the next treatment cycle and thrombocytopenia was not associated with clinically significant bleeding. Permanent study drug discontinuations due to treatment-related AEs occurred only in two (8%) patients, whereas dose delays were observed in five cases (35%). No dose reductions were required. Occurrence of treatment-related telangiectasia suggests *in vivo* inhibition of ALK-1 function.

Overall, the activity of PF-03446962 was modest; no objective responses were reported. However, radiological evaluation of response remains challenging in HCC and many other molecularly targeted drugs have not yielded a significant level of objective responses when used as single agents. By comparison, sorafenib was approved as first-line standard treatment for advanced HCC based on the results of the SHARP trial showing a 2% response rate; in the second-line setting, three large randomized phase III trials with ramucirumab, brivanib, and everolimus produced a 7%, 10%, and 8% response rate, respectively [15–19]. Moreover, more than half of the patients ($n = 14$; 58%) entered the study after failure of two ($n = 13$) or more ($n = 1$) previous treatment lines. The median time to progression was 3 months and the DCR at 12 weeks 29%. These measures of clinical benefit are comparable to those obtained in the three second-line randomized studies mentioned above [15, 16, 18, 19]. For nine (38%) patients, duration of treatment with PF-03446962 exceeded duration of the last prior systemic therapy.

Higher mean archival and *de novo* tumor tissue c-MET expression, higher mean serum levels of BMP-9, and lower mean serum levels of TGF-β1 and VEGFR-3 were found in patients with DC at ≥12 weeks compared with patients with PD.

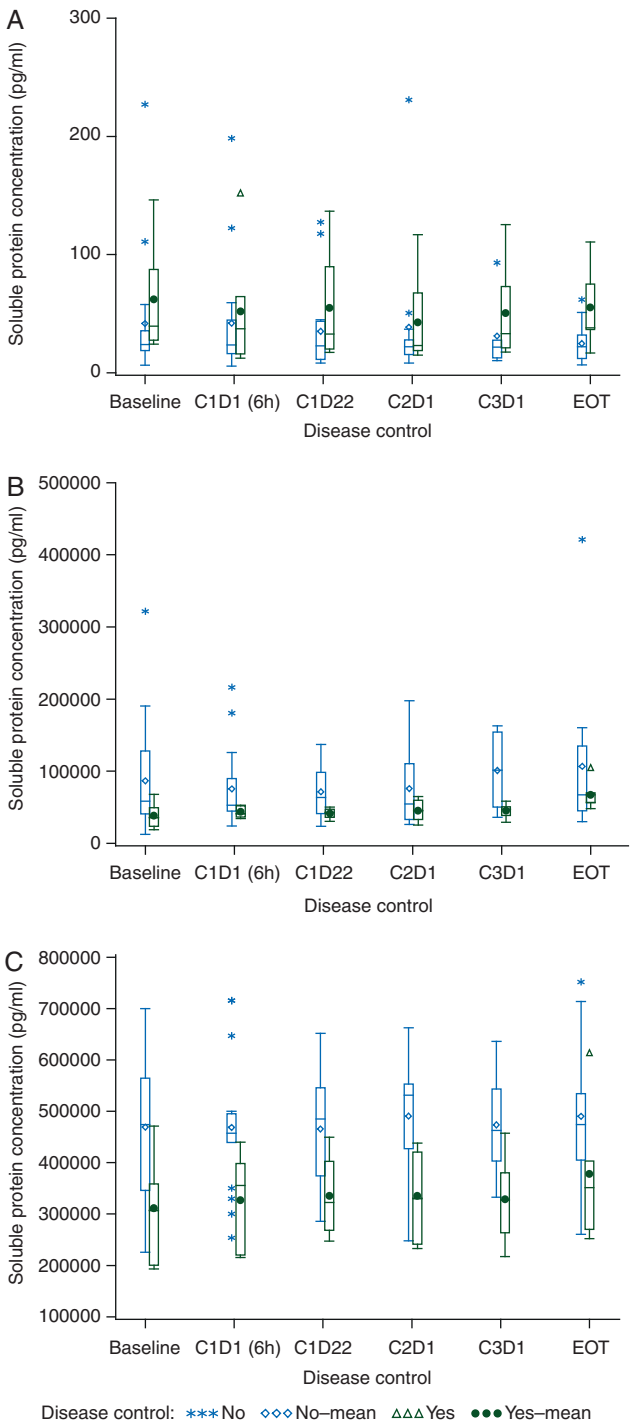

Figure 1. Soluble (A) BMP-9, (B) TGF-β1, and (C) VEGFR-3 protein concentrations at all time-points, by disease control at ≥12 weeks. Disease control: Yes = patients with stable disease ≥12 weeks; No = patients with disease progression or stable disease <12 weeks. Boxplot components include median (horizontal lines within boxes); whiskers extend vertically from the box to the most extreme point within 1.5 inter-quartile ranges. BMP, bone morphogenetic protein; C, cycle; D, day; EOT, end of treatment; TGF, transforming growth factor; VEGFR, vascular endothelial growth factor.

c-MET is a tyrosine kinase receptor bound by hepatocyte growth factor (HGF), and is implicated in tumor cell proliferation, survival, migration, invasion, angiogenesis, and metastasis. c-MET can be up-regulated via HGF-mediated autocrine, paracrine, amplification/mutation, transcriptional up-regulation or point mutations, and after sorafenib treatment. Activation and/or up-regulation of c-MET in HCC patients are associated with poor prognosis and prior clinical studies have suggested high tumor c-MET expression as a predictive marker of response to the HGF receptor c-MET inhibitor tivantinib in patients with HCC [19, 20]. The greater sensitivity to anti-ALK-1 treatment in patients with higher tumor c-MET may reflect the broad pro-tumorigenic potential of c-MET [21].

BMP-9 is a high-potency ligand for the ALK-1 receptor [22]. High circulating levels of BMP-9 may reflect higher tumor levels, which would be consistent with higher sensitivity to anti-ALK-1 therapy in patients with greater activation of the BMP-9/ALK-1 axis. Independently, the finding of lower TGF-β1 levels in patients with DC in this study suggests potential value for TGF-β as a prognostic marker. Separation of the predictive and prognostic value for the biomarker data reported here would require randomized trials versus placebo or agents with different mechanisms of action. Furthermore, additional assessments of the biomarker sensitivity and specificity in larger trials would be required to determine their implication for patient selection.

At vascular level, ALK1 pathway has a distinct, although complementary, role in promoting tumor angiogenesis compared with VEGF/VEGF-Rs signaling. Moreover, from preclinical models, we know that combination of VEGF blockade and ALK-1 inhibition results in marked vascular disruption and in a synergistic antitumor activity [10, 23].

The clinical benefit observed with PF-03446962 in this HCC population refractory to VEGF inhibition, albeit limited, suggests a role for ALK-1 in sustaining tumor growth in HCC. The manageable safety profile of PF-03446962 along with its distinctive mechanism of action support further evaluation of this novel compound, especially in the context of combination studies with other antiangiogenic, cytotoxic, or immunotherapeutic agents, for the treatment of advanced HCC.

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disclosure

MS has received travel support from Arqule and Pfizer. PZ has received consulting honoraria for advisory boards from Bayer, Janssen, Novartis, Pfizer, and Roche; and travel support from Janssen, Novartis, and Pfizer. FGB has received consulting honoraria from BMS, Eli Lilly, GSK, MSD, Merck Serono, Novartis, Servier; and research funding from BMS, Boehringer; Celgene, Genentech/Roche, GSK, Nerviano Medical Science, Novartis, Pfizer, Philogen, and Sanofi-Aventis. HB has received consulting honoraria from BMS, Celgene, Genentech, and Eli Lilly; research

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