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Review

Brentuximab vedotin in relapsed/refractory Hodgkin lymphoma: An updated review of published data from the named patient program

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ABSTRACT

Brentuximab vedotin was available via named patient program (NPP) to patients with relapsed/refractory (R/R) Hodgkin lymphoma (HL) or systemic anaplastic large-cell lymphoma in ~60 non-US/Canadian countries, before local approval. Published results were examined recently; through systematic literature review, we identified 12 new NPP publications. Most (10/12) publications included new NPP data describing 8 unique cohorts (N = 480; all R/R HL) and new participating countries. Overall response rates were 58–80%, and complete remission rates were 10–40%. With median follow-up of 9.5–26 months, median progression-free survival was 5–10.5 months and median overall survival (OS) had not been reached in most cohorts; 1- and 2-year OS was 67–76% and 58–67%, respectively. Tolerability was as expected from previous reports. Despite intrinsic bias and heterogeneous cohorts, this update supports previous findings showing comparable efficacy and tolerability of brentuximab vedotin between real-world practice and phase 2 trial results in R/R HL.

1. Introduction

Prior to local regulatory approval, the CD30-targeted antibody-drug conjugate, brentuximab vedotin, was made available for compassionate use in approximately 60 non-US/Canadian countries via a Named Patient Program (NPP; Takeda Pharma-

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Table 1
Key characteristics of patients treated under the NPP.

Publication	N (n in NPP)	Country	Treatment dates	R/R HL, n	Median age, years (range)	Male, %	Median number of prior therapies, n (range)	Primary refractory/no response to last prior therapy, %	Prior ASCT/ prior alloSCT, %
Update (including new patients) to cohort included in original review of NPP data									
Erdem et al. (2014)	10 (NR)	Turkey	NR	10	26 (22–30)	80	4 (3–5)[a]	50/80	100/NR
Reports including new NPP patients with potential overlap[b] with cohorts included in original review of NPP data									
Perrot et al. (2014)	241 (241)	France	Jan 2011–Jan 2014	241	34 (17–79)	NR	3 (1–13)[c]	74/47[d]	61[e]/16
Viviani et al. (2015)[f]	45 (NR)	Italy	Jan 2011–Apr 2014	45	A: 38 (20–76) B: 39 (18–64)	40	A: 4 (2–12) B: 4 (2–9)	A: 75/NR B: 68/NR	A: 0/NR B: 100/NR
Salihoglu et al. (2015) (update of congress abstract, Ferhanoglu et al., 2014)	58 (58)	Turkey	Mar 2011–Jul 2013	58	26 (13–62)	64	4 (2–7)[c]	49/72	83/17[g]
Reports of new NPP cohorts not included in original review of NPP data									
Tsirigotis et al. (2015)	80 (NR)	Greece	Jun 2011–Aug 2014	80	32 (18–77)	54	4 (1–7)	67/65	79/3[h]
Carlo-Stella et al. (2015)[i] (update of congress abstract, Ricci et al., 2014[i])	16 (16)	Italy	Jun 2011–Jan 2014	16	29 (22–43)	81	8 (4–15)	31/88	100/100
Yang et al. (2014)	22 (22)	Asia	Oct 2011–Jun 2013	22	30 (16–57)	68	NR (91% had received ≥3 lines)	55/NR	77[j]
Zallio et al. (2014)[g]	8 (NR)	Italy	Aug 2011–Sep 2013	8	32 (21–61)	NR	5 (NR)	NR/NR	100/NR

AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; HL, Hodgkin lymphoma; NPP, named patient program; NR, not reported; R/R, relapsed/refractory.

[a] Excluding ASCT.
[b] Determined based on review of treatment dates for each report versus other reports from the same country included in the original review.
[c] Chemotherapy only.
[d] Patients progressive to last chemotherapy.
[e] Patients who received ≥1 transplant (type not specified).
[f] Data for some parameters only available by group (A, patients ineligible for ASCT [n = 20]; B, patients who had failed prior ASCT [n = 25]).
[g] 49 patients in total (85%) had prior transplantation, 9 of whom had both prior ASCT and alloSCT.
[h] 76% of patients had relapsed/progressed after ASCT and 3% had failed both ASCT and alloSCT.
[i] Based on review of treatment dates and other information within each publication these reports describe unique NPP patient series versus Italian reports included in the original literature review.
[j] ASCT and/or alloSCT (no breakdown by transplant type).

ceuticals International Co., Cambridge, MA, USA). Patients with relapsed/refractory (R/R), CD30-positive Hodgkin lymphoma (HL) or systemic anaplastic large cell lymphoma (sALCL) who met the US label criteria were eligible to participate. Clinical NPP data from 21 publications (identified by systematic literature review) have since been evaluated (Zinzani et al., 2015); efficacy and tolerability of brentuximab vedotin in real-world practice were similar to those reported in the registrational phase 2 trials in R/R HL and sALCL (Pro et al., 2012; Younes et al., 2012). As additional data are now available, we have evaluated new reports of NPP outcomes with brentuximab vedotin to assess how they compare with the previous NPP findings and pivotal phase 2 data.

2. Methodology

Details of the systematic literature review used to identify NPP publications have been published previously (Zinzani et al., 2015). Employing this methodology, search results (PubMed and pre-specified congress abstract books) were updated for the period, December 13, 2013 (data cut-off in the original review) to June 11, 2015 (to include abstracts presented at the International Congress on Malignant Lymphoma 2015). Search results were reviewed manually to identify original references reporting NPP data. Baseline data, together with efficacy and safety outcomes are reported.

3. Update of NPP efficacy and safety data

3.1. Studies identified

Since December 13, 2013 (Zinzani et al., 2015), an additional 12 publications reporting NPP data were identified (Carlo-Stella et al., 2015; Erdem et al., 2014; Ferhanoglu et al., 2014; Kahraman et al., 2014; Monjanel et al., 2014; Perrot et al., 2014; Ricci et al., 2014; Salihoglu et al., 2015; Tsirigotis et al., 2015; Viviani et al., 2015; Yang et al., 2014; Zallio et al., 2014). Two publications (Erdem et al., 2014; Monjanel et al., 2014) were updates to studies described in our previous review (Zinzani et al., 2015; Erdem et al., 2012; Monjanel et al., 2013); as one of these studies (describing a Turkish cohort of 10 patients) included five additional patients, it has been included in this analysis (Erdem et al., 2014). Another publication (Kahraman et al., 2014) evaluated the role of 18-fluorodeoxyglucose positron emission tomography/computed tomography for monitoring response to brentuximab vedotin; this paper was excluded as the clinical data for this cohort had been

Table 2
Brentuximab vedotin treatment and subsequent transplantation in patients with R/R HL treated under the NPP.

NPP cohort	Brentuximab vedotin		Transplantation post-brentuximab vedotin, n (%)
	Dose (mg/kg), frequency	Median number of cycles (range)	
Erdem et al. (2014)	1.8, Q3wk	NR (up to 16 cycles)	ASCT: NR alloSCT: 6 (60)
Perrot et al. (2014)	1.8, Q3wk	6 (1–16)	ASCT: 29 (12)alloSCT: 27 (11)
Viviani et al. (2015)	1.8, Q3wk	6 (3–19)	A: 7 (35)[a,b] B: 15 (60)[a,b]
Salihoglu et al. (2015)Ferhanoglu et al. (2014)	1.8, Q3wk	7 (2–18)	ASCT: 2 (3.5) alloSCT: 12 (21)
Tsirigotis et al. (2015)	1.8, Q3wk	6 (1–6)	NR
Carlo-Stella et al. (2015) Ricci et al. (2014)	1.8, Q3wk	8 (1–17)	ASCT: NR alloSCT: 1 (6)[c]
Yang et al. (2014)	1.8, Q3wk	5 (1–18)	NR
Zallio et al. (2014)	NR, Q3wk	6 (4–7)	ASCT: NRRIC alloSCT: 8 (100)

AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; HL, Hodgkin lymphoma; NPP, named patient program; NR, not reported; Q3wk, every 3 weeks; RIC, reduced-intensity conditioning; R/R, relapsed/refractory.
[a] Data for some parameters only available by group (A, patients ineligible for ASCT [n = 20]; B, patients who had failed prior ASCT [n = 25]).
[b] Transplant type not specified.
[c] One patient discontinued treatment with brentuximab vedotin due to availability of a donor for a second alloSCT (no further information is provided regarding whether this transplant went ahead).

reported previously in two publications captured in the original review (Rothe et al., 2012; Theurich et al., 2013). Four further publications described 344 patients in French (Perrot et al., 2014), Italian (Viviani et al., 2015), and Turkish (Ferhanoglu et al., 2014; Salihoglu et al., 2015) cohorts. These four publications were included in the present analysis as they reported additional patients to those identified in our original searches. However, based on review of treatment dates compared with other reports from the same countries, we could not discount that they also included patients who had been described previously. Lastly, five publications described 126 patients in four new cohorts not described in the original review. These patients cohorts were from Italy (two cohorts of 16 (Carlo-Stella et al., 2015; Ricci et al., 2014) and 8 patients, respectively (Zallio et al., 2014)), Greece (a single cohort of 80 patients (Tsirigotis et al., 2015)), and Asia (a single cohort of 22 patients (Yang et al., 2014)); one of the Asian patients may have been described previously in a case report (Cao et al., 2013)).

In total, 10 publications (Carlo-Stella et al., 2015; Erdem et al., 2014; Ferhanoglu et al., 2014; Perrot et al., 2014; Ricci et al., 2014; Salihoglu et al., 2015; Tsirigotis et al., 2015; Viviani et al., 2015; Yang et al., 2014; Zallio et al., 2014) included NPP data for eight unique cohorts and 480 patients (Table 1). As stated above, for several publications it has not been possible to determine the extent of overlap with previous reports of NPP data. Additionally, some publications included non-NPP data, but did not provide a breakdown of outcomes for the NPP and non-NPP cohorts.

3.2. Patient characteristics

All 480 patients had R/R HL (Table 1). The most common median number of prior therapies was 4. Overall, 31–75% of patients had primary refractory HL, and 47–88% had no response to their last prior therapy. Most patients (61–100%) had undergone prior ASCT, and (excluding one analysis looking specifically at patients who had failed allogeneic SCT [alloSCT] (Carlo-Stella et al., 2015; Ricci et al., 2014)), up to 17% of patients had received prior alloSCT.

3.3. Treatment exposure

Exposure to brentuximab vedotin and information regarding subsequent transplantation are presented in Table 2. In all cohorts where the dosing schedule was fully reported, brentuximab vedotin was administered intravenously at a dose of 1.8 mg/kg every 3 weeks. The median number of cycles of brentuximab vedotin received ranged from 5 to 8 (Table 2).

3.4. Response and survival outcomes

Where detailed methods were reported, response to brentuximab vedotin was assessed by computed tomography and/or positron-emission tomography (Carlo-Stella et al., 2015; Ferhanoglu et al., 2014; Ricci et al., 2014; Salihoglu et al., 2015; Yang et al., 2014). Best response data are shown in Table 3. Responses were seen within a median of 3–4 treatment cycles, and lasted for a median of 4–9 months. Overall response rates (ORR; complete remission [CR] + partial remission [PR]) were typically 58–80%, although lower ORRs were reported in two studies where response was assessed later in therapy (Ferhanoglu et al., 2014; Perrot et al., 2014; Salihoglu et al., 2015). CR rates were 10–40%.

Five publications describing four cohorts reported ORRs and CR rates in the subset of patients with prior SCT (Carlo-Stella et al., 2015; Erdem et al., 2014; Ricci et al., 2014; Viviani et al., 2015; Zallio et al., 2014): 32/43 patients (74%) with prior ASCT (Erdem et al., 2014; Viviani et al., 2015; Zallio et al., 2014), and 11/16 patients (69%) with prior ASCT and alloSCT (Carlo-Stella et al., 2015; Ricci et al., 2014) achieved an objective response. CRs were seen in 8/43 (19%) and 5/16 (31%) patients, respectively.

Most studies reported survival data; after a median follow-up of 9.5–26 months, median overall survival (OS) had not been reached in most cohorts, although values of 25 months and 31 months were reported in two studies (Carlo-Stella et al., 2015; Ricci et al., 2014; Tsirigotis et al., 2015). One- and 2-year OS was 67–76% and 58–67%, respectively. Median progression-free survival (PFS) was between 5 and 10.5 months (Table 3).

3.5. Subsequent stem cell transplant facilitated by brentuximab vedotin

SCT after brentuximab vedotin treatment was reported by transplant type in two cohorts (Table 2). Among 241 patients treated in French centers, 12% received subsequent ASCT and 11% underwent alloSCT (Perrot et al., 2014). A study of 58 patients in Turkey reported subsequent ASCT and alloSCT in 3% and 21% of patients, respectively. All five patients who received SCT in CR (1 ASCT; 4 alloSCT) were in continuous CR 1–12 months after transplantation, while 0/9 patients who received SCT while in stable or progressive disease obtained a remission post-SCT (Ferhanoglu et al., 2014; Salihoglu et al., 2015).

In a series of 10 patients in Turkey who had relapsed after ASCT, six went on to receive alloSCT after treatment with brentuximab vedotin (Erdem et al., 2014). In an Italian study, 7/20 patients (35%) who were ASCT-ineligible, and 15/25 patients (60%) who had failed

Table 3
Reported efficacy of brentuximab vedotin in patients with R/R HL treated under the NPP.

NPP cohort	Best response					Survival		
	n evaluable/N	ORR [CR + PR], %	CR, %	Median cycle number to best response (range)	Median DOR, months	Median follow-up, months (range)	Median OS, months	Median PFS, months
Erdem et al. (2014)	After 6 cycles: 10/10	After 6 cycles: 80	After 6 cycles: 10	NR	NR	NR	NR	NR
Perrot et al., 2014	223/241	58[a] (32[a] at end of treatment)	32[a] (23[a] at end of treatment)	4 (NR)	8	16 (NR)	Not reached (1-yr: 76%, 2-yr: 58%)	7
Viviani et al. (2015)[b]	A: 20/20 B: 25/25	A: 75 B: 64	A: 40 B: 20	3 (2–9)	NR	14 (1–36)	Not reached (2-yr: 60%[c])	5
Salihoglu et al. (2015)	Between 2–5 cycles: 49/58 After ≥6 cycles: 37/58	Between 2–5 cycles: 63 After ≥6 cycles: 32	Between 2–5 cycles: 27 After ≥6 cycles: 22	NR	9	NR	Not reached (1-yr: 71%)	7 (1-yr: 33%)
Ferhanoglu et al. (2014)	77/80	58	18	NR	NR	9.5 (1–35)	31	10.5
Tsirigotis et al. (2015)	16/16	69	31	4 (2–12)	5	26 (5–30)	25 (2-yr: 61%)	7 (2-yr: 20%)
Carlo-Stella et al. (2015) Ricci et al. (2014)	21/22[d]	73[d]	18[d]	NR Time to response in months: 0.9 (0.7–3.0)	4.4 (1.0–17.4)	NR	Not reached (1-yr: 67%)	5.7
Yang et al. (2014)	8/8	NR	25	NR	NR	12	NR	NR
Zallio et al. (2014)								

AlloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; CR, complete remission; CRu, unconfirmed; DOR, duration of response; HL, Hodgkin lymphoma; ITT, intention to treat; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial remission; NPP, named patient program; NR, not reported; R/R, relapsed/refractory; yr, year.

[a] Includes CRu.

[b] Data for some parameters only available by group (A, patients ineligible for ASCT [n = 20]; B, patients who had failed prior ASCT [n = 25]).

[c] 2-year OS was 70% in Group A and 53% in Group B.

[d] Although one patient was not evaluable for response, response rates are reported as an intention-to-treat analysis, i.e., n = 22.

prior ASCT went on to receive a transplant procedure following treatment with brentuximab vedotin (Viviani et al., 2015). Among a separate cohort of 12 patients from Italy who were undergoing reduced-intensity conditioning (RIC) alloSCT following a relapse after ASCT, eight had received brentuximab vedotin as a bridge to the allografting procedure. Seven of the eight patients (88%) engrafted; one patient relapsed at 8 months, and the others were alive and progression-free at 12 months (Zallio et al., 2014). In 16 patients from Italy who had failed both ASCT and alloSCT, one patient discontinued brentuximab vedotin due to availability of a donor for a second alloSCT (no further information is provided; (Carlo-Stella et al., 2015; Ricci et al., 2014)).

3.6. *Safety of brentuximab vedotin*

Available adverse event (AE) data are summarized in Table 4. In the two largest cohorts (n = 299), any-grade neuropathy occurred in 28–31% of patients, and grade 3/4 neuropathy was reported in 2–3% of patients (Ferhanoglu et al., 2014; Perrot et al., 2014; Salihoglu et al., 2015). Any-grade hematologic toxicities reported in these cohorts included anemia, thrombocytopenia, and neutropenia; grade 3/4 neutropenia occurred in 2–7% of patients. Among the three smaller cohorts, reports of grade ≥3 hematologic AEs included neutropenia (13–32%), anemia (15%), and thrombocytopenia (12–14%) (Carlo-Stella et al., 2015; Ricci et al., 2014; Viviani et al., 2015; Yang et al., 2014). Other any-grade AEs for which incidence was reported in >1 cohort included nausea, pneumonia, myalgia/muscle pain, constipation, and pyrexia/fever.

Dose reductions were described for 9/80 patients (11%) in two cohorts (Ferhanoglu et al., 2014; Salihoglu et al., 2015; Yang et al., 2014), and 17% of patients in the French cohort (N = 241) required ≥1 dose adaptation (Perrot et al., 2014). Comprehensive discontinuation data were only available for the large French cohort, where 222 patients (92%) discontinued brentuximab vedotin, mainly because of progression (54%), but also to receive a transplant (25%) and due to AEs (5%) (Perrot et al., 2014). One Italian study (N = 45) reported that no patients discontinued treatment due to toxicity (Viviani et al., 2015), while in another, it was noted that 2/5 patients achieving CR discontinued due to toxicity (Carlo-Stella et al., 2015; Ricci et al., 2014).

Two studies reported that there were no deaths related to brentuximab vedotin (Carlo-Stella et al., 2015; Perrot et al., 2014; Ricci et al., 2014). One study reported the death of a patient who received a donor-lymphocyte infusion during treatment with brentuximab vedotin; the patient died after the development of stage IV pulmonary graft-versus-host-disease (GVHD) (Carlo-Stella et al., 2015; Ricci et al., 2014). Another study reported the death of a patient due to pneumonia after one cycle of brentuximab vedotin (Yang et al., 2014).

4. Discussion

In our previous review, pooled analysis of NPP data in R/R HL demonstrated similar efficacy and tolerability of brentuximab vedotin in the real-world setting to the pivotal phase 2 trial results (Zinzani et al., 2015; Younes et al., 2012). The pooled ORR and CR rate for all R/R HL cohorts was 67% and 26%, respectively, which compared with phase 2 rates of 75% and 34% (Zinzani et al., 2015; Younes et al., 2012). Among three NPP R/R HL cohorts, median PFS ranged from 6.8 to 9.0 months (Rothe et al., 2012; Sasse et al., 2013; Zinzani et al., 2013), which compared with a phase 2 report of 5.6 months (Younes et al., 2012). Median OS had not been reached in

Table 4
Reported tolerability of brentuximab vedotin in patients with R/R HL treated under the NPP.

NPP cohort[a]	N	Neurologic adverse events		Hematologic adverse events		Other adverse events	
		Any grade, %	Grade 3/4, %	Any grade, %	Grade 3/4, %	Any grade, %	Grade 3/4, %
Perrot et al., 2014	241	Peripheral sensory neuropathy: 28[b]	Peripheral sensory neuropathy: 2[b]	Anemia: 39[b] Thrombocytopenia: 27[b] Neutropenia: 23[b]	Neutropenia: 7[b]	Diarrhea: 14[b]	
Viviani et al. (2015)	45		Peripheral sensory neuropathy: 4[c]		Neutropenia: 13[c]		Pneumonia: 2[c]
Salihoglu et al. (2015) Ferhanoglu et al. (2014)	58	Neuropathy: 31 Oculomotor nerve palsy: 2 Generalized tonic convulsions: 3	Neuropathy: 3	Neutropenia: 28	Neutropenia: 2	Fatigue: 50 Nausea: 33 Vomiting; 26 Myalgia: 26 Alopecia: 21 Extremity pain: 21 Pyrexia: 14 Muscle spasm: 14 Constipation: 12 Pruritus: 12	Nausea: 3 Myalgia: 3 Extremity pain: 3 Vomiting: 2
Carlo-Stella et al. (2015) Ricci et al. (2014)	16	Peripheral sensory neuropathy: 31[c]	Peripheral sensory neuropathy: 6[d] Guillain-Barré syndrome: 6		Neutropenia: 18[c] Anemia: 15[c] Thrombocytopenia: 12[c]	Infections: 19 Fever (unknown origin): 13	
Yang et al. (2014)	22		Sensory neuropathy: 0[b]		Neutropenia: 32[b] Thrombocytopenia; 14[b]		Pneumonia: 5[b] Hemorrhagic cystitis: 5[b] Nausea: 5[b] Constipation: 5[b] Muscle pain: 5[b]

HL, Hodgkin lymphoma; NPP, named patient program; R/R, relapsed/refractory.
[a] Specific details of adverse events were not available for 3 of the 8 patient cohorts.
[b] Treatment-related adverse events.
[c] Grade ≥3.
[d] Discrepancy in published report (abstract states two patients with grade 3 peripheral sensory neuropathy and results section states one patient with grade 3 peripheral sensory neuropathy; if n = 2 then percentages with any grade and grade 3/4 peripheral sensory neuropathy would be 38% and 13%, respectively).

the four HL cohorts that reported OS data (Rothe et al., 2012; Sasse et al., 2013; Zinzani et al., 2013; Garciaz et al., 2014). With regard to safety, the overall rate and intensity of toxicities reported in the NPP were similar to those seen in the registrational phase 2 trial (Younes et al., 2012), albeit with slightly lower rates of individual AEs, possibly due to under-reporting of AEs in the NPP or differences in the number of cycles administered (Zinzani et al., 2015).

The results of this updated NPP analysis (480 patients with R/R HL) support the previous NPP findings in R/R HL (207 patients with a specified diagnosis of R/R HL). Although it was not possible to determine the extent of overlap between the patient populations included in the two analyses, the current review includes at least 126 new patients versus our original review, in four new cohorts which were not previously described, as well as new participating countries. This represents a substantial increase in patient numbers, and these data add to the growing body of evidence demonstrating the efficacy and safety of brentuximab vedotin in real-world clinical practice. The observed response rates (ORR 58–80%; CR rate 10–40%) and median times to events (PFS 5–10.5 months; OS 25–31 months) are consistent with those reported in our original review and in the pivotal phase 2 trial (Zinzani et al., 2015; Younes et al., 2012). Interestingly, response rates and OS data for patients in the new cohorts from Asia and Turkey were comparable to those seen in Western patients treated within the NPP (Erdem et al., 2014; Ferhanoglu et al., 2014; Salihoglu et al., 2015; Yang et al., 2014). As reported previously (Zinzani et al., 2015), responses to brentuximab vedotin were rapid, typically occurring within the first 3–4 cycles. The speed of response illustrates the importance of assessing response soon after treatment is initiated and highlights a need to clarify optimal timing of first staging to ensure consistent evaluation in the real-world setting. Brentuximab vedotin's tolerability profile was as expected from the previous NPP report and clinical trial data (Zinzani et al., 2015; Younes et al., 2012; Moskowitz et al., 2015), with generally manageable toxicities.

As discussed in our original review, this type of analysis is associated with a number of intrinsic limitations, such as reporting/selection bias and heterogeneous reporting. While the strength of any conclusions that can be drawn is therefore limited, the data reviewed here are similar to those reported previously (Zinzani et al., 2015; Younes et al., 2012). In summary, this updated review of published NPP data supports the findings of our original literature review, which showed comparable efficacy and tolerability of brentuximab vedotin in real-world practice to phase 2 trial results in R/R HL.

Conflict of interest

Employment: AG, VB (Millennium Pharmaceuticals Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Ltd)

Consultancies: PLZ, JR (Millennium Pharmaceuticals Inc.)

Stock ownership: VB (Takeda Pharmaceutical Company Limited)

Honoraria: PLZ (Millennium Pharmaceuticals Inc.; Takeda); JR (Millennium Pharmaceuticals Inc.; Takeda; Seattle Genetics, Inc.)

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