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Randomized, phase 3 trial of inotuzumab ozogamicin plus rituximab versus chemotherapy plus rituximab for relapsed/refractory aggressive B-cell non-Hodgkin lymphoma

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Inotuzumab ozogamicin (InO), a humanized anti-CD22 antibody–calicheamicin conjugate, demonstrated preliminary antitumour activity and manageable toxicity in phase 1/2 trials for the treatment of relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL), as a single-agent (Advani *et al*, 2010; Ogura *et al*, 2010) and in combination with rituximab (R-InO) (Advani *et al*, 2010; Fayad *et al*, 2013; Ogura *et al*, 2012; Ogura *et al*, 2010). Given this preliminary evidence, a 2-arm, randomized, open-label, phase 3 study (NCT01232556) was conducted to compare the efficacy and safety of R-InO with investigator's choice (IC) of rituximab plus bendamustine (R-B) or rituximab plus gemcitabine (R-G), in adults with R/R CD20+/CD22+ aggressive B-NHL who were not candidates for high-dose chemotherapy, with or without transplant (see Supplemental Methods and Table SI for eligibility criteria, dose regimens and dose-delay/-reduction criteria).

The primary endpoint was overall survival (OS); 2 interim analyses (IAs) were planned when 40% and 70% of OS events were reached (see Supplemental Methods for details of assessments and statistical methods). The trial was to be terminated for futility if $P>0.29$ (hazard ratio [HR]>0.9) or $P>0.10$ (HR>0.82) at the first or second IA, respectively, or if $P<0.0073$ for efficacy at the second analysis. The planned IA based on ~40% of OS events (108 events) conducted in May 2013 yielded an estimated HR>0.9 for OS in the R-InO versus IC arm; enrollment was thus stopped for futility. Reported here are the final data from this trial (locked on 24 July 2014) to inform future research and potential clinical studies in this difficult-to-treat patient population.

Patient enrollment occurred between February 2011 and May 2013; 338 patients were randomized (R-InO, n=166; IC, n=172 [R-B, n=137; R-G, n=35]; Fig S1). Nearly all patients (91%) had diffuse large B-cell lymphoma (DLBCL) at baseline; 68% were aged ≥65 years **(**Table SII**)**. Age was the primary reason why enrolled patients were not candidates for high-dose chemotherapy (R-InO, 77%; IC, 67%; Table SIII). Threehundred and thirty-two patients received ≥1 dose of study drug [median (range) number of treatment cycles: 3.0 (1.0–6.0) for R-InO and R-G, 3.5 (1.0–6.0) for R-B; Table SIV**]**. Ninety-four patients completed treatment. Common reasons for discontinuing were progressive disease/relapse (R-InO, 50% vs IC, 57%) and adverse events (AEs; R-InO, 32% vs IC, 17%; Table SV).

Median (range) duration of follow-up among surviving patients was 14.9 (0.4–32.8) months for R-InO and 15.9 (0.1–31.2) months for IC.

Overall survival was not significantly different for R-InO versus IC (*P*=0.708; HR [95% confidence interval (CI)]=1.1 [0.8–1.4]; Fig S2); Kaplan-Meier estimated median (95% CI) OS was 9.5 (7.0–14.5) and 9.5 (7.7–14.1) months (estimated probabilities of OS [95% CI] at 18 months, 35% [27%–43%] and 37% [29%–45%]). Progression-free survival (PFS) was also not significantly different for R-InO versus IC (*P*=0.27; HR [95% CI)]=0.9 [0.7–1.2]; Fig S2). Median (95% CI) PFS with R-InO and IC were 3.7 (2.9–5.0) and 3.5 (2.8–4.9) months (estimated probabilities of PFS [95% CI] at 18 months, 19% [13%–26%] and 17% [12%–24%]). Notably, survival among patients receiving R-InO was prolonged for those with higher versus lower baseline CD22 expression levels **(**Fig S3**)**. Among all randomized patients, the objective response rate (ORR; 95% CI) was 41% (33%–49%) for R-InO and 44% (36%–51%) for IC (arm difference, 3% [–8% to 13%]; *P*=0.714; Table I); Kaplan-Meier estimated median (95% CI) duration of response (DOR) for R-InO versus IC was 11.6 (7.8–not reached [NR]) versus 6.9 (5.5–10.8) months (HR=0.76 [0.47–1.25]; *P*=0.142).

Median OS and PFS with R-InO were 9.5 [95% CI, 7.0–14.5] and 3.7 [2.9–5.0] months, respectively; ORR and DOR were 41% and 11.6 months. Although comparisons across studies require caution due to differences in design and patient characteristics, median OS and PFS with R-InO in the previous study with refractory aggressive B-NHL (n=30) are shorter (OS, 8.8 [3.9–NR] months; PFS, 1.9 [1.0–4.8] months), the ORR is lower (20%), and the DOR is shorter (6.1 months) (Fayad *et al*, 2013). Conversely, the median OS and PFS with R-InO in the relapsed DLBCL cohort in the previous study (n=47) are longer (OS, NR [34.7–NR] months; PFS, 17.1 [7.8–NR] months), the ORR is higher (74%), and the DOR is longer (17.7 months) (Fayad *et al*, 2013).

The observed toxicity profile of R-InO is generally consistent with that reported previously for InO alone (Advani *et al*, 2010; Ogura *et al*, 2010) and for R-InO (Fayad *et al*, 2013; Ogura *et al*, 2012).Treatment-related grade ≥3 treatment-emergent AEs (TEAEs) differing by ≥10% of patients between treatment arms were hematologic **(**Table II**)**. All-cause TEAEs followed a similar pattern **(**Table SVI**)**. Most common serious AEs (>5 patients in either arm) included febrile neutropenia (n=5 vs 7) and pneumonia (n=8 vs 1). Two treatment-related deaths occurred between treatment start and 56 days after last dose (R-InO, pneumonia [n=1]; IC, fungal pneumonia, febrile neutropenia and septicaemia [n=1]). Permanent discontinuations due to AEs were more frequent with R-InO versus IC (25% vs 18%), most commonly due to thrombocytopenia in the R-InO arm **(**Table SVII**)**.

Treatment-related hepatic TEAEs were more frequent with R-InO versus IC, with hyperbilirubinaemia occurring in 8% versus 2% of patients **(**Table II**)**. Two patients had grade 3 veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) during R-InO treatment (1 after the maximum 6 R-InO cycles; 1 after 3 cycles, resulting in treatment discontinuation). One additional patient developed VOD/SOS approximately 13 months after receiving a single R-InO dose and multiple subsequent therapies, including allogeneic stem cell transplantation after the single R-InO dose and before VOD/SOS onset. No VOD/SOS events occurred in the IC arm.

Rituximab-InO treatment was associated with antitumour activity in patients with R/R aggressive B-NHL who were not candidates for high-dose chemotherapy, with or without transplant, for whom treatment options are limited. However, R-InO was not superior to IC with respect to OS; estimates of ORR and median PFS and OS were similar for the 2 treatments. Nevertheless, the efficacy observed here and in other studies (Fayad *et al*, 2013; Ogura *et al*, 2016) suggests an examination of InO-containing combination therapies may be appropriate in certain patient populations. A study of InO plus rituximab, cyclophosphamide, vincristine and prednisolone in chemotherapy-naïve patients with DLBCL who are not candidates for anthracycline-based treatment is currently recruiting (NCT01679119).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I.

Response outcomes.

		IC		
Response	**R-InO (n=166)**	**R-B (n=137)**	**R-G (n=35)**	**Total (n=172)**
ORR, * n (%) [95% CI]	68 (41) [33–49]	66 (48) [40–57]	9 (26) [12–43]	75 (44) [36–51]
CR	21 (13)	23 (17)	0	23 (13)
unCR	5 (3)	5 (4)	0	5 (3)
PR	28 (17)	26 (19)	2 (6)	28 (16)
unPR	14 (8)	12 (9)	7 (20)	19 (11)
SD	18 (11)	7 (5)	5 (14)	12 (7)
PD	64 (39)	46 (34)	16 (46)	62 (36)
Missing †	15 (9)	17 (12)	5 (14)	22 (13)
Median (95% CI) DOR, ‡ months	11.6 (7.8–NR)	7.2 (6.5–10.8)	3.0 (0.9–NR)	6.9 (5.5–10.8)

CI=confidence interval; CR=complete response; DOR=duration of response; IC=investigator's choice (rituximab plus bendamustine [R-B] or rituximab plus gemcitabine [R-G]); NR=not reported; ORR=objective response rate; PD=disease progression; PR=partial response; R-InO=inotuzumab plus rituximab; SD=stable disease; unCR=unconfirmed complete response; unPR=unconfirmed partial response.

*ORR=CR+unCR+PR+unPR; difference in response between R-InO and IC arms (*P*=0.714 for ORR based on the Cochran-Mantel-Haenszel test).

†1 patient in the R-InO and 1 patient in the R-B group had an indeterminate response.

‡Confirmed and unconfirmed CR/PR; HR=0.76 (0.47–1.25); *P*=0.142 for difference in DOR between arms.

Table II.

Treatment-related, treatment-emergent AEs occurring in >10% of patients in either R-InO or IC arm.

	R-InO (n=164)		IC (n=167)	
	Any grade	**Grade ≥3**	**Any grade**	**Grade 3/4**
Any AE, n (%)	148 (90)	102 (62)	146 (87)	107 (64)
Thrombocytopenia	99 (60)	78 (48)	59 (35)	26 (16)
Neutropenia	57 (35)	40 (24)	79 (47)	67 (40)
Fatigue	38 (23)	5 (3)	31 (19)	1 (1)
Nausea	39 (24)	0	25 (27)	0
AST increased	43 (26)	7 (4)	15 (9)	4 (2)
Pyrexia	16 (10)	1 (1)	20 (12)	2 (1)
Constipation	18 (11)	0	14 (8)	0
GGT increased	31 (19)	7 (4)	8 (5)	0
Leucopenia	35 (21)	13 (8)	52 (31)	39 (23)
ALT increased	28 (17)	7 (4)	13 (8)	2 (1)
Decreased appetite	20 (12)	2 (1)	24 (14)	0
Lymphopenia	26 (16)	15 (9)	38 (23)	37 (22)
Anaemia	17 (10)	7 (4)	39 (23)	12 (7)
Blood ALP increased	22 (13)	1 (1)	9 (5)	1 (1)
Cough	4 (2)	0	5 (3)	1 (1)
Vomiting	14 (9)	0	22 (13)	0
Diarrhoea	10 (6)	0	17 (10)	1 (1)

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyl transferase; IC=investigator's choice (rituximab plus bendamustine or rituximab plus gemcitabine); R-InO=inotuzumab plus rituximab.