Nivolumab and brentuximab vedotin-based, response-adapted treatment in children, adolescents, and young adults with standard-risk relapsed/refractory classical Hodgkin lymphoma: Primary analysis

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Introduction

- Outcomes for younger patients with relapsed/refractory classical Hodgkin lymphoma (R/R cHL) are poor, particularly for those without complete metabolic response (CMR) before autologous hematopoietic cell transplantation (auto-HCT)[1,2]
- Management of R/R cHL must balance efficacy with the risk of long-term toxicity of treatment, particularly in younger patients
  - In a retrospective analysis of patients 15-39 years old, non-relapse events accounted for 53% of deaths in cHL[3]
- New strategies are needed in the first salvage setting, with high rates of CMR and a low incidence of long-term toxicity
- Nivolumab, a fully human immunoglobulin G4 anti-programmed cell death (PD)-1 immune checkpoint inhibitor monoclonal antibody, has demonstrated durable and frequent responses with a favorable safety profile as a monotherapy in adult patients with R/R cHL[4]
  - The combination of nivolumab + brentuximab vedotin (BV) has shown a CMR rate of 67% and a 2-year progression-free survival (PFS) rate of 78% as first salvage in adults with R/R cHL[5]
- CheckMate 744 (NCT02927769) is an ongoing phase 2 study for children, adolescents, and young adults (CAYA) with R/R cHL, evaluating a risk-stratified, response-adapted approach using nivolumab + BV and, for patients with a suboptimal response, BV + bendamustine intensification
  - In the initial analysis of the standard-risk (R2) cohort, the regimen was well tolerated with high CMR rates before consolidation with high-dose chemotherapy plus auto-HCT[6]

Objective

- To evaluate the safety and efficacy of nivolumab + BV induction with response-adapted BV + bendamustine intensification as first salvage in CAYA with R/R cHL in the primary analysis of the R2 cohort

Methods

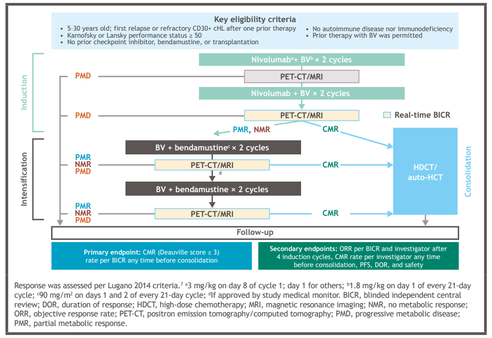
- The clinical criteria for assignment to the R2 cohort are outlined in **Table 1**; the study design and endpoints are shown in **Figure 1**

Table 1. Clinical criteria for assignment to the R2 cohort

Stage at diagnosis	Time to relapse from end of therapy (months)	B symptoms/extranodal disease at relapse, extensive disease where radiotherapy was contraindicated at relapse, or relapse in a prior radiation field
Any	< 3	Yes/No
IA, IIA	3-12 > 3 cycles and/or radiotherapy	Yes/No
IB, IIB, IIIA	< 12	
IIIB, IV	Any	
Any	Any	Yes

- Patients who had none of the risk factors listed (advanced disease stage at diagnosis, short time to relapse, B symptoms, extranodal disease, or relapse in a prior radiation field [or extensive disease if radiotherapy contraindicated]) were assigned to a separate, low-risk cohort

Figure 1. CheckMate 744 R2 study design



Response was assessed per Lugano 2014 criteria.[7] [a]3 mg/kg on day 8 of cycle 1; day 1 for others; [b]1.8 mg/kg on day 1 of every 21-day cycle; [c]90 mg/m^2 on days 1 and 2 of every 21-day cycle; [d]If approved by study medical monitor. BICR, blinded independent central review; DOR, duration of response; HDCT, high-dose chemotherapy; MRI, magnetic resonance imaging; NMR, no metabolic response; ORR, objective response rate; PET-CT, positron emission tomography/computed tomography; PMD, progressive metabolic disease; PMR, partial metabolic response.

- For the primary endpoint, response-evaluable patients were defined as all treated patients with one of: CMR at any time, PMR at any time, or completion of 6 cycles of therapy (nivolumab + BV × 4 and BV + bendamustine × 2)
  - Patients who came off study early due to toxicity without CMR or PMR were considered evaluable for response
- For ORR after 4 cycles, patients were considered evaluable for response after 4 cycles of nivolumab + BV
- Assessment of tumor reduction was exploratory, and based on BICR- and investigator-determined best reduction from baseline in maximum standardized uptake value (SUVmax) for the reference fluorodeoxyglucose (FDG)-avid lesion

Results

Patients

- At database lock, 44 patients were treated in the R2 cohort; baseline characteristics are shown in **Table 2**

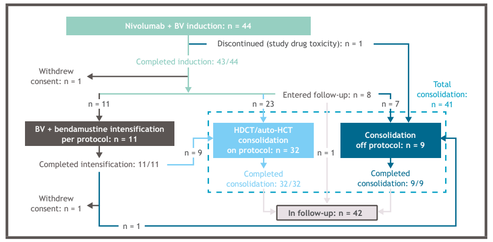
Table 2. Baseline demographics and clinical characteristics

Characteristic	R2 (n = 44)
Age, median (range), years	16 (9-30)
< 18 years of age	31 (70)
Male, n (%)	29 (66)
Performance status, median (range)	
Lansky,[a] n = 26	100 (70-100)
Karnofsky,[b] n = 18	100 (80-100)
Stage at initial diagnosis	
II	21 (48)
III	7 (16)
IV	16 (36)
Response to first-line therapy	
Refractory[c]	24 (55)
Relapsed[d]	20 (45)
3-12 months	14 (32)
≥ 12 months	6 (14)
Prior auto-HCT	0
Prior BV	0
B symptoms or extranodal disease at relapse	28 (64)
Bone marrow involvement	5 (11)
Stage IV at relapse	16 (36)

Data are n (%) unless otherwise stated.
[a]Patients ≤ 16 years; [b]Patients > 16 years; [c]Achieved CR to prior therapy, then experienced progression < 3 months after completion of that therapy, or never achieved CR; [d]Achieved CR to prior therapy, then experienced disease progression ≥ 3 months after completion of that therapy.
CR, complete response.

- At a minimum potential follow-up of 15.6 months (median observed follow-up of 20.9 months [range, 2.5-29.2]), 43 patients completed induction therapy and 11 received BV + bendamustine intensification (**Figure 2**)
  - One patient discontinued after induction cycle 2 due to grade 3 anaphylaxis considered related to BV; the patient subsequently proceeded to consolidation off protocol
  - Of the 11 patients who completed intensification, 9 proceeded to consolidation per protocol (1 withdrew consent and 1 received off-protocol consolidation before entering follow-up)

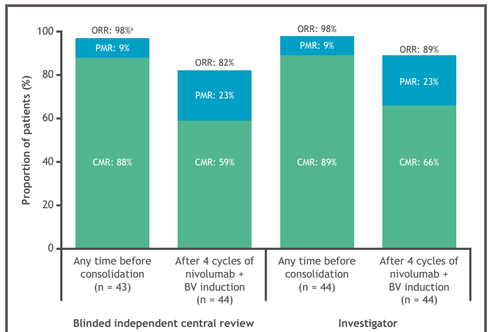
Figure 2. Patient disposition



Best metabolic response

- Primary endpoint: CMR rate per BICR in response-evaluable patients any time before consolidation was 88% (90% CI, 77-95)
- Among the 44 response-evaluable patients after 4 cycles of nivolumab + BV induction, the CMR rate per BICR was 59%
  - Nine of the 11 patients (82%) who proceeded to intensification achieved CMR per BICR prior to consolidation
- Other CMR and ORR secondary endpoints are shown in **Figure 3**

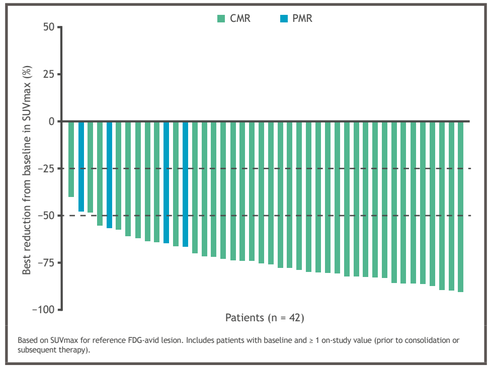
Figure 3. CMR and ORR in response-evaluable patients



CMR and PMR rates may not sum to ORR due to rounding. [a]43 patients were response evaluable for the primary endpoint and 42 achieved an objective response; 44 patients were response evaluable for ORR after 4 cycles.

- Among response-evaluable primary refractory patients (n = 23), 20 (87%; 90% CI, 70-96) patients achieved CMR per BICR any time before consolidation
  - 22 (96%) patients achieved an objective response per BICR
- Among response-evaluable pediatric patients (n = 30), 27 (90%; 90% CI, 76-97) patients achieved CMR per BICR any time before consolidation
  - All 30 patients achieved an objective response per BICR
- All patients evaluable for SUVmax (n = 42) achieved a ≥ 25% reduction, and the majority (93%) achieved a ≥ 50% reduction (**Figure 4**)

Figure 4. Reduction in SUVmax per BICR

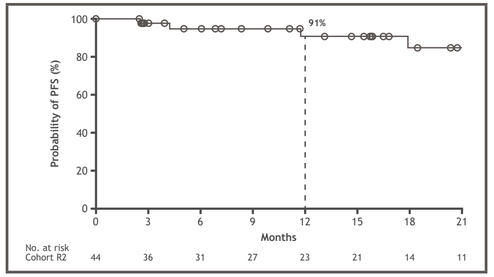


Based on SUVmax for reference FDG-avid lesion. Includes patients with baseline and ≥ 1 on-study value (prior to consolidation or subsequent therapy).

PFS and duration of response

- PFS rate by BICR at 12 months was 91% (90% CI, 77-96; **Figure 5**); in total, 4 events occurred
- Median duration of response was not reached

Figure 5. PFS per BICR



Stem cell mobilization

- Stem cell mobilization for auto-HCT was reported for a total of 40 patients
- The most common mobilization agents were granulocyte colony stimulating factor (22/40 patients [55%]) and plerixafor (4/40 patients [10%])
- Median time from the start of treatment to mobilization was 70 days (range, −173 to 209)
- The most common conditioning regimen prior to auto-HCT was carmustine, etoposide, cytarabine, and melphalan (BEAM) in 23 patients (52%)
- Each patient had a median (range) of 1 (1-5) apheresis session, in which a median (range) of 4.0 (0.3-268.0) × 10^6 CD34+ cells/kg were collected per session

Safety

- During nivolumab + BV induction, 31 (70%) patients experienced a treatment-related adverse event (AE); 8 (18%) patients experienced grade 3-4 treatment-related AEs (**Table 3**)
  - The most common any grade treatment-related AEs during induction were nausea (20%), hypersensitivity (20%), and diarrhea (14%), which were all grades 1-2

Table 3. Treatment-related AEs prior to consolidation

	Induction (n = 44)		Intensification (n = 11)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any treatment-related AE	31 (70)	8 (18)	8 (73)	3 (27)
Treatment-related AEs with ≥ 2 patients in either phase				
Hypersensitivity	9 (20)	0	1 (9)	0
Nausea	9 (20)	0	5 (45)	0
Diarrhea	6 (14)	0	1 (9)	0
Infusion-related reaction[a]	5 (11)	1 (2)	2 (18)	0
Abdominal pain	4 (9)	0	0	0
Pyrexia	4 (9)	0	1 (9)	0
Rash	4 (9)	0	0	0
Maculo-papular rash	3 (7)	0	0	0
Vomiting	3 (7)	0	6 (55)	1 (9)
Alopecia	2 (5)	0	0	0
Arthralgia	2 (5)	0	0	0
Fatigue	2 (5)	0	0	0
Increased AST	2 (5)	0	1 (9)	0
Pruritus	2 (5)	0	0	0
Upper abdominal pain	2 (5)	0	0	0
Headache	1 (2)	0	2 (18)	0

Data are n (%). [a]As preferred term.
AST, aspartate aminotransferase.

- Of the 11 patients who received BV + bendamustine intensification, 8 (73%) experienced a treatment-related AE of any grade and 3 (27%) experienced a grade 3-4 treatment-related AE
- Five (11%) patients experienced treatment-related serious AEs prior to consolidation (3 [7%] patients experienced grade 3-4 events)
- One treatment-related AE led to discontinuation (grade 3 anaphylaxis)
- There were no treatment-related deaths; 1 patient died due to disease progression

Other treatment-related AEs

- One patient experienced treatment-related neutropenia (grade 3) during induction and one did during intensification; there were no other treatment-related hematologic AEs
- Infusion-related reactions were reported in 8 patients during induction (6 grade 1-2 and 2 grade 3) and in 2 patients during intensification (both grade 1-2)
  - The majority of infusion-related reactions occurred during cycle 2
- Most treatment-related immune-mediated AEs were grade 1-2
  - One patient had 2 grade 3 infusion-related reactions
- Treatment-related peripheral sensory neuropathy was reported in 1 patient during induction with nivolumab + BV (grade 1)

Conclusions

- This risk-stratified, response-adapted approach using nivolumab + BV as first salvage therapy was well tolerated and showed high CMR rates for CAYA with R/R cHL
- The majority of patients did not require BV + bendamustine intensification
- There were no new safety signals during nivolumab + BV induction
  - Low rates of hematologic toxicity and peripheral neuropathy were reported
  - The incidence of treatment-related immune-mediated AEs was limited
- This approach did not appear to affect stem cell mobilization and collection
- Further follow-up is needed to confirm the durability of disease control

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Acknowledgments

- The patients and families who are making this study possible
- The clinical study teams who participated in the trial
- Study drugs provided by Bristol-Myers Squibb Company (Princeton, NJ, USA), ONO Pharmaceutical Company Ltd. (Osaka, Japan), and Seattle Genetics, Inc. (Bothell, WA, USA)
- This study was supported by Bristol-Myers Squibb Company, in collaboration with Seattle Genetics, the Children's Oncology Group and EuroNet-PHL
- All authors contributed to and approved the presentation; professional medical writing and editorial assistance were provided by Jane Cheung, Caudex, funded by Bristol-Myers Squibb Company

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