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651 Nivolumab for Newly Diagnosed Advanced-Stage Classical Hodgkin Lymphoma (cHL): Results from the Phase 2 Checkmate 205 Study

Program: Oral and Poster Abstracts
Type: Oral
Session: 624. Hodgkin Lymphoma and T/NK Cell Lymphoma—Clinical Studies: Hodgkin Lymphoma Immunotherapy Studies; nodular lymphocyte predominant Hodgkin lymphoma clinical studies

Monday, December 11, 2017: 11:00 AM
Bldg A, Lvl 4, Marcus Aud. (Georgia World Congress Center)

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Introduction: Nivolumab (nivo), an immune checkpoint inhibitor targeting the programmed death-1 (PD-1) receptor, augments T-cell activation and restores antitumor T-cell function. In the phase 2 CheckMate 205 study (NCT02181738), nivo demonstrated frequent (65-73%) and durable objective responses across 3 cohorts of patients (pts) with relapsed/refractory (R/R) cHL after failure of autologous hematopoietic cell transplantation (Fanale M et al. ICML 2017 [oral 125]). While most pts with cHL are cured with first-line therapy, those with advanced-stage disease are more likely to relapse or progress. More aggressive regimens (eg, BEACOPPesc., Borchmann P et al. *Lancet Oncol* 2017) are associated with improved progression-free survival (PFS) but are hampered by excessive toxicities and have limited applicability in elderly pts. PD-1 ligand gene amplification has been linked to poorer outcomes in cHL pts treated with standard induction regimens (Roemer MG et al. *J Clin Oncol* 2016) but is associated with improved responses to nivo in R/R cHL (Younes A et al. *Lancet Oncol* 2016), suggesting that PD-1 blockade may benefit pts in the frontline setting. We therefore assessed the safety and efficacy of nivo as a single-agent lead-in treatment followed by nivo in combination with chemotherapy, excluding bleomycin due to potential overlapping pulmonary toxicity, for pts with previously untreated advanced-stage cHL.

Methods: Cohort D of CheckMate 205 enrolled untreated pts (aged ≥18 y) with advanced-stage newly diagnosed cHL (stage III, IV, or II with B symptoms and extranodal or bulky disease) and ECOG score 0-1. Pts received 4 biweekly doses of nivo monotherapy (240 mg IV flat dose) followed by nivo plus chemotherapy (nivo 240 mg IV, doxorubicin, vinblastine, dacarbazine [N-AVD]) for 6 cycles (12 doses). The primary endpoint was safety and tolerability: proportion of pts with ≥1 grade (G) 3-5 treatment-related adverse event (TRAE) ≤30 d after last dose. Additional endpoints included rates of discontinuation and of independent radiologic review committee-assessed complete remission (CR).

Results: At database lock (June 2017), 51 pts had been treated, with a median (range) follow-up of 8 (1-11) mo. Median (range) age was 37 (18-87) y; 29 (57%) pts had stage IV disease, and 41 (80%) had B symptoms. At baseline, 7 (14%) pts had bulky disease and 17 (33%) had extranodal involvement. International prognostic score was ≥3 in 25 (49%) pts. At analysis, 49 (96%) pts had completed nivo monotherapy treatment, receiving all 4 doses; 1 pt discontinued due to disease progression and 1 due to study drug toxicity (G1-2 hyperthyroidism), subsequently receiving AVD only. TRAEs for both treatment phases are shown in the Table. During nivo monotherapy, 2 pts had 1 dose delay each due to an AE; 2 (4%) pts had serious AEs (SAEs; 1 G1-2 hyperthyroidism; 1 G1-2 polyneuropathy); an immune-mediated AE (IMAE), G1-2 hyperthyroidism, was reported in 2 (4%) pts. Fifty pts started combination therapy; at database lock, 35 (70%) had completed therapy, with 34 (69%) receiving 12 N-AVD doses. With N-AVD, 10 (20%) pts had SAEs, 6 G3-4; the most common G3-4 SAE was febrile neutropenia in 2 (4%) pts; IMAEs occurring in >1 pt were hypothyroidism in 8 (16%) pts and increased ALT in 2 (4%). AEs leading to discontinuation of N-AVD occurred in 2 pts: G1-2 hepatic abnormality, and G3-4 febrile neutropenia (FN) and Klebsiella bacteremia. The pt who developed FN and Klebsiella bacteremia died 38 d after the first dose of his fifth cycle of N-AVD due to study drug toxicity of acute respiratory insufficiency. Important primary, secondary, and exploratory endpoints (including CR and objective response rates at end of monotherapy, after 2 combocycles and end of therapy, and PFS) will be presented at the meeting.

Conclusions: Nivo monotherapy followed by N-AVD combination therapy was well-tolerated in pts with newly diagnosed, untreated, advanced-stage cHL. Nearly all pts completed nivo monotherapy treatment and started combination therapy with N-AVD. The safety profile was consistent with historical experience of nivo and AVD separately, with no new safety signals. Nivo followed by N-AVD may provide a tolerable alternative treatment option to standard-of-care multi-agent chemotherapy for pts with newly diagnosed advanced-stage cHL.

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Table. Treatment-related adverse events (≥5%)

Event	Any grade	Grade 3–4
Nivo monotherapy (n=51)		
Total patients with an event	36 (70.6)	0
Infusion-related reaction	11 (21.6)	0
Pyrexia	5 (9.8)	0
Pruritus	4 (7.8)	0
Rash	4 (7.8)	0
Fatigue	3 (5.9)	0
Arthralgia	3 (5.9)	0
N-AVD (n=50)		
Total patients with an event	43 (86.0)	26 (52.0)
Neutropenia	28 (56.0)	24 (48.0)
Nausea	17 (34.0)	1 (2.0)
Fatigue	8 (16.0)	0
Constipation	7 (14.0)	0
Vomiting	6 (12.0)	0
Hypothyroidism	6 (12.0)	0
Stomatitis	6 (12.0)	0
Diarrhea	3 (6.0)	0
Pruritus	3 (6.0)	0
Rash	3 (6.0)	0
Febrile neutropenia	5 (10.0)	5 (10.0)
White blood cell count decreased	5 (10.0)	0
Asthenia	4 (8.0)	1 (2.0)
Alopecia	4 (8.0)	1 (2.0)

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