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Blood 142 (2023) 1697–1698

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

624.HODGKIN LYMPHOMAS AND T/NK CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

The Combination of Nivolumab and CC-486 Is Active in Hodgkin Lymphoma Refractory to PD-1 Blockade

Matthew G. Mei, MD[1], Lu Chen, PhD[2], Sandrine Puverel, PhD[3], L. Elizabeth Budde, MD PhD[3], Swetha Kambhampati, MD[3], Shari Daniels[1], Bev Dunning[1], Melissa Banez, CCR[4], Larry W. Kwak[3], Alex F. Herrera, MD[5]

[1] City of Hope National Medical Center, Duarte, CA
[2] Department of Computational and Quantitative Medicine, City of Hope National Medical Center, Duarte, CA
[3] Department of Hematology and HCT, City of Hope National Medical Center, Duarte, CA
[4] Clinical Trials Office, City of Hope National Medical Center, Duarte, CA
[5] City of Hope, Duarte, CA

Introduction: PD1 blockade is highly active in patients (pts) with relapsed/refractory (RR) Hodgkin lymphoma (HL); however, most patients ultimately progress on therapy, and HL that is refractory to PD1 blockade remains an unmet need. Furthermore, as PD-1 directed therapies are being administered in earlier lines, it is anticipated that pts with RR HL will be increasingly refractory to PD-1 directed therapies. Hypomethylating agents (HMA) have been shown to increase T-cell infiltration and upregulate PD-1 and CTLA-4 expression in tumors, as well as suppress myeloid-derived suppressor cells. We hypothesized that HMA might restore the sentivity of HL to PD-1 directed therapies. Therefore, we conducted a phase I study evaluating the safety and efficacy of nivolumab and CC-486, an oral HMA, in pts with RR HL refractory to PD-1 blockade.
Methods:Adult pts with RR HL who had progressed after at least 1 prior line of therapy and were refractory to PD-1 therapy were enrolled to receive oral CC-486 and nivolumab IV in 28-day cycles. PD-1 refractoriness was defined as progressive disease (PD) as best response, or PD while receiving or within 12 weeks of the last anti-PD-1 directed therapy. Pts were treated in a dose-finding cohort at 2 dose levels (DL) using a Rolling 6 design and then in a dose expansion cohort at the recommended phase 2 dose (RP2D). In DL1, CC-486 was administered at 200 mg PO daily on days 1-7, and in DL2 CC-486 was dosed at 300 mg PO daily on days 1-7; nivolumab 480 mg IV was given on day 8 in both DLs. Treatment could be continued for up to 2 years. Primary endpoints were determination of the RP2D and overall response rate (ORR) defined as the proportion of patients with a complete response (CR) or partial response (PR). Responses were assessed by investigators using PET-CT according to the 2014 Lugano Classification.
Results: As of July 7, 2023, 21 pts have been enrolled including 3 at DL1 and 18 at DL2 (RP2D). At baseline, 57% were male with a median age of 40 years (range 25-71), 95% had stage III-IV disease, and 71% had primary refractory disease, defined as lack of a complete remission (CR) or relapse within 3 months of frontline treatment. The median number of prior therapies was 6 (range 2-14), and 90% had prior brentuximab vedotin (BV). 76% of pts had received pembrolizumab, 67% had received nivolumab, and 43% had received both agents previously. 52% had undergone autologous stem cell transplant and 5% had had prior allogeneic stem cell transplant. Baseline characteristics are shown in Table 1.
The median number of cycles was 7 (range: 3-17). Among 19 pts evaluable for response (2 pending), ORR was 63% and CR rate was 10%. An additional 32% had SD as their best response; only one pt had PD as the best response. The median follow-up time was 9 months (range 2.8-16.3), and 71% of pts remain on treatment with an estimated median PFS of 11.3 months (95% CI: 7.1-N/A). 6 pts stopped therapy, including 4 for disease progression, 1 at treating physician's discretion and 1 due to patient preference.
The most common adverse events (AEs), any grade (Gr), were nausea (86%), diarrhea (71%), vomiting (48%), headache (33%), fatigue (29%), neutropenia (19%), and anemia (19%). Only two Gr 3+ AEs were recorded: one patient experienced Gr 3 anemia and another Gr 4 hypercalcemia. Notably, the hypercalcemia fully resolved with supportive care and did not recur with subsequent cycles. The only immune-related AE was grade 1 hypophysitis in a single pt.
Conclusions: Nivolumab combined with CC-486 is tolerable and elicits a high response rate in a PD-1 refractory cohort. At this time, the study has been amended to enroll 10 more patients at DL2 to provide a better estimation of the efficacy.

Disclosures Mei: *CTI:* Ended employment in the past 24 months, Honoraria; *Novartis:* Ended employment in the past 24 months, Honoraria; *Seagen:* Honoraria, Speakers Bureau; *BMS:* Research Funding; *Incyte:* Research Funding, Speakers Bu-

reau; *Beigene:* Research Funding; *Incyte:* Research Funding. **Budde:** *Amgen:* Research Funding; *Merck:* Research Funding; *AstraZeneca:* Consultancy, Research Funding; *MustangBio:* Research Funding; *Novartis, Gilead, F. Hoffmann-La Roche Ltd, BeiGene, Genentech, Inc.:* Consultancy; *Roche:* Consultancy; *ADC Therapeutics:* Consultancy. **Kwak:** *PeproMene Bio. Inc:* Consultancy, Current equity holder in private company. **Herrera:** *Caribou Biosciences:* Consultancy; *Adicet Bio:* Consultancy; *Genmab:* Consultancy; *AbbVie:* Consultancy; *Pfizer:* Consultancy; *Regeneron:* Consultancy; *Tubulis GmbH:* Consultancy; *Takeda:* Consultancy; *ADC Therapeutics:* Consultancy, Research Funding; *Karyopharm Therapeutics:* Consultancy; *AstraZeneca/MedImmune:* Consultancy; *Kite, a Gilead Company:* Research Funding; *Merck:* Consultancy, Research Funding; *Genentech/Roche:* Consultancy, Research Funding; *BMS:* Consultancy, Other: Travel/Accommodations/Expenses, Research Funding; *Allogene Therapeutics:* Consultancy; *Seattle Genetics:* Consultancy, Research Funding; *Gilead Sciences:* Research Funding; *AstraZeneca:* Research Funding.

OffLabel Disclosure: CC-486 (oral azacitidine) for use in relapsed/refractory Hodgkin lymphoma

Table 1: Baseline Characteristics

Baseline Characteristics	N (%)
Total	21 (100)
Stage I-II	1 (5)
Stage III-IV	20 (95)
Bulky disease (> 5cm)	3 (14)
Prior autologous transplant	11 (52)
Primary refractory	15 (71)
Prior BV	19 (90)
Prior pembrolizumab	16 (76)
Prior nivolumab	14 (67)
Previously received both nivolumab and pembrolizumab	9 (43)

Figure 1

https://doi.org/10.1182/blood-2023-190753