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POSTER ABSTRACTS

705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALLY AVAILABLE THERAPIES

A Phase 2 Study of Nivolumab for Relapsed/Refractory Multiple Myeloma or Non-Hodgkin Lymphoma Following CAR-T Therapy

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Background: Treatment options are limited for patients with relapsed multiple myeloma (MM) or non-Hodgkin lymphoma (NHL) after CAR-T failure. While checkpoint inhibition may theoretically improve T-cell effector activity following CAR-T, a prospective trial of pembrolizumab (a monoclonal antibody targeting PD-1 on T-cells) following CD19 CAR-T in NHL showed an ORR of only 25% (Chong Blood 2022). In a recent multicenter NHL cohort (Major Blood Advances 2023), responses were similarly low with both pembrolizumab and nivolumab (nivo). However, nivo has not been studied prospectively in this setting, and the efficacy of checkpoint inhibition after CAR-T failure in MM has not been characterized.
Methods: We conducted a single-center phase 2 trial (NCT04205409) of nivo for MM or NHL pts with relapse following any CAR-T product (including investigational products) as their last line of therapy. Nivo monotherapy was dosed 480mg IV every 4 weeks until PD or toxicity. The primary endpoint was overall response rate (ORR) by IMWG or Lugano criteria. Secondary endpoints included safety data for AEs and immune-related AEs (irAEs) using CTCAE v5.0 as well as post-nivo CRS/ICANS using ASTCT criteria. Other endpoints included duration of response (DoR), PFS, CAR-T expansion following first nivo dose, and PD-L1/PD-1 IHC expression on tumor biopsies.
Results: We enrolled 20 pts (11 MM, 9 NHL) as detailed in Table 1. Prior to nivo, the best response to CAR-T had been CR in 64% of MM pts and 44% of NHL pts, while 1 MM pt and 1 NHL pt had experienced PD as best response. Median time between CAR-T infusion & C1D1 nivo was 624 days (range 59-1211) in MM and 149 days (range 34-506) in NHL. The ORR was 15% overall: 18% (2/11) for MM and 11% (1/9) for NHL. Characteristics of the 3 responders are detailed in Table 2. Both responders with MM had previously received fully human CAR-T therapies; in NHL, the sole response was in a patient who had received commercial axi-cel. In all 3 cases, clinical benefit was evident following a single nivo dose. Both MM patients achieved a VGPR by light chains (>95% reduction) within 4 weeks; in one patient, PET-CT showed complete resolution of a plasmacytoma that had measured 8.6cm one week before C1D1 nivo. DoR was 687 days for this patient and ≥198 days (ongoing) in the other responder with MM. In NHL, the responding patient - who had had a DS4 response at Day +30 then a DS5 response at Day +60 following axi-cel before starting nivo one month later - achieved a complete response (DS3) including resolution of hepatic and splenic lymphomatous lesions. Conversely, in all non-responders, PD was uniformly evident within a month of nivo as well. The most common Grade 3+ AEs were neutropenia (25%), anemia (15%), and sepsis (15%). One MM patient developed secondary MDS. Two irAEs (one Gr2 pneumonitis, one Gr2 rash) occurred, both in non-responders, and both resolved with brief courses of prednisone. CRS or ICANS did not occur following nivo in any pt. There were 3 deaths within 100 days of nivo initiation, all unrelated to treatment and, all in non-responders: two clearly due to PD and one due to

hypotensive cardiac arrest (no evidence of myocarditis). The results of ongoing correlative analyses will be presented at the meeting, including post-nivo CAR T-cell expansion data, nivolumab binding assays on T-cells, and PD-L1 tissue expression on tumor biopsies.

Conclusions: We found that responses to PD-1 blockade following CAR-T failure are uncommon, confirming prior studies in NHL which demonstrate poor activity in this setting. Our 18% ORR with post-CAR-T nivo in R/R MM (2/11 pts) is notably higher than the 4% ORR (1/27 pts) reported with nivo monotherapy in R/R MM (Lesokhin JCO 2016), although conclusions are difficult to draw with small *n*. Day +28 responses following a single dose of nivo 480mg were uniformly predictive of long-term efficacy. irAEs were relatively uncommon and manageable with steroids, while CRS and ICANS did not occur. To our knowledge, this is the first prospective evaluation of nivo following CAR-T failure. Given the non-curative nature of BCMA CAR-T, there may be certain pts with MM for whom checkpoint inhibition leads to a meaningful clinical benefit without unacceptable risks. Better tools to identify such patients are needed, and novel correlative data to help identify pre-nivolumab features of responders - particularly in MM - will be presented at the meeting.

Disclosures Banerjee: *BMS:* Consultancy; *Janssen:* Consultancy; *Genentech:* Consultancy; *Sanofi:* Consultancy; *SparkCures:* Consultancy; *Caribou:* Consultancy; *Pfizer:* Consultancy; *Pack Health:* Research Funding. **Lynch:** *TG Therapeutics:* Research Funding; *Incyte:* Research Funding; *Bayer:* Research Funding; *SeaGen:* Consultancy; *Genentech:* Research Funding; *Cyteir:* Research Funding; *Cancer Study Group:* Consultancy; *Foresight Diagnostics:* Consultancy; *Abbvie:* Consultancy; *Seagen Inc.:* Research Funding; *Rapt:* Research Funding; *Merck:* Research Funding. **Ujjani:** *Genentech:* Consultancy, Honoraria; *Pharmacyclics:* Consultancy, Honoraria, Research Funding; *PCYC:* Research Funding; *Epizyme:* Consultancy; *Beigene:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Lilly:* Consultancy, Honoraria, Research Funding; *Kite, a Gilead Company:* Consultancy, Other: Travel expenses , Research Funding; *Astrazeneca:* Consultancy, Honoraria, Research Funding; 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OffLabel Disclosure: Nivolumab for relapsed disease following CAR-T therapy in hematologic malignancies

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Table 1: Baseline characteristics of enrolled patients

R/R MM (n=11)		R/R NHL (n=9)	
Age at CAR-T	65 (46-75)	**Age at CAR-T**	57 (40-69)
% female	36% (n=4)	**% female**	22% (n=2)
# HRCA*		**Histology**	
0	36% (n=4)	DLBCL	78% (n=7)
1	45% (n=5)	HGBL	11% (n=1)
2	9% (n=1)	MCL	11% (n=1)
EMD	36% (n=4)	**Transformed disease**	33% (n=3)
# lines	6 (4-9)	**Extranodal disease**	44% (n=4)
CAR-T product (scFv type)		**# lines**	3 (2-4)
Murine BCMA CAR-T	45% (n=5)	**CAR-T product (scFv type)**	
Fully human BCMA CAR-T	54% (n=6)	Murine CD19 CAR-T	56% (n=5)
Best response to CAR-T		Fully human CD19 CAR-T	33% (n=3)
CR	64% (n=7)	Fully human CD20 CAR-T	11% (n=1)
VGPR	9% (n=1)	**Best response to CAR-T**	
PR	9% (n=1)	CR	44% (n=4)
MR	9% (n=1)	PR	44% (n=4)
PD	9% (n=1)	PD	11% (n=1)
CRS following CAR-T†	73% (n=8)	**CRS following CAR-T†**	56% (n=5)
ICANS following CAR-T†	27% (n=3)	**ICANS following CAR-T†**	44% (n=4)
CAR-T-nivo interval (days)	624 (59-1211)	**CAR-T-nivo interval (days)**	149 (34-506)

* HRCAs (high-risk cytogenetic abnormalities) included del(17p), t(4;14), t(14;16), gain(1q), and amp(1q). † Any-grade CRS or ICANS following ASTCT consensus criteria.

Table 2: Characteristics of responders to post-CAR-T nivolumab

Disease	CAR-T product (scFv type)	Best response to CAR-T	CAR-T DoR*	Interval between CAR-T and nivo	Nivo D+28 response	Nivo DoR*
MM	Fully human BCMA CAR-T	CR	549 days	624 days	VGPR	687 days
MM	Fully human BCMA CAR-T	CR	945 days	962 days	VGPR	≥198 days (ongoing)
DLBCL	Murine CD19 CAR-T	PR	70 days	87 days	CR	134 days

* DoR defined as interval between CAR-T infusion and documented progressive disease.

Figure 1