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ORAL ABSTRACTS

905.OUTCOMES RESEARCH-LYMPHOID MALIGNANCIES

Risk Factors for CD19-Targeting CAR T Manufacturing Failure and Patient Outcomes: A Report from the UK National CAR T Panel

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CAR T manufacturing failure (MF) rates reported in literature range between 1-13%. In some cases the manufacturing process fails to yield a product and in others results in one which does not meet pre-specified criteria for release and labelled an out of specification (OOS) product. We conducted a multicentre retrospective review of factors contributing to MF and its impact on patient outcomes.

Patients with relapsed or refractory large B cell lymphoma (LBCL), mantle cell lymphoma (MCL) or B acute lymphoblastic leukemia (B-ALL) approved for CAR T therapy with axicabtagene ciloleucel (axi-cel), brexucabtagene autoleucel (brexu-cel) or tisagenlecleucel (tisa-cel) by the UK national CAR T panel between January 2019 and January 2023 were eligible. Patients with MF were identified from databases of the 11 participating CAR T centres and from the national OOS CAR T panel.

In total 1138 patients were approved for CAR T therapy (903 LBCL, 97 MCL and 138 B-ALL). We identified 58 patients who had at least 1 CAR T MF; 38 LBCL (LBCL-MF), 14 MCL and 6 B-ALL with inferred MF frequency of 4.20%, 14.43% and 4.34% respectively. Intended CAR T product was axi-cel in 28 and tisa-cel in 10 LBCL, brexu-cel for all MCL and tisa-cel for all B-ALL patients. Most frequent reasons for MF were poor growth in culture (n=12), low cell viability (n=12) and low T cell purity (n=6). Of the 58 patients with MF, OOS product was available and infused in 19 patients (OOS cohort: 14 LBCL, 2 MCL and 3 B-ALL). Repeat apheresis led to infusion of a product in-specification in 17 patients (MF-delayed-infusion cohort: 10 LBCL, 6 MCL and 1 B-ALL). Another 22 patients did not proceed to CAR T infusion (MF-no-infusion cohort: 14 LBCL, 6 MCL and 2 B-ALL), some despite attempts at remanufacture (n=9) or available OOS product (n=5). We included 25 randomly selected matched (for disease subtype and product) controls (all LBCL: 19 axi-cel and 6 tisa-cel) without MF, 18 of whom received infusion.

Univariable analysis of potential baseline clinical factors contributing to risk of MF did not reveal any significant impact of the number of lines of prior therapy, history of prior stem cell transplant or a need for holding therapy prior to apheresis.

Bendamustine therapy was significantly associated with risk of MF for all lymphoma patients and the LBCL subset; prior exposure in 4% controls vs 32.7% of all lymphoma MF (p=0.004) and 26.3% of LBCL-MF (p=0.039). This was largely due to therapy within 6 months; 0% of controls vs 19.2% of all lymphoma MF (p=0.026) and 23.7% of LBCL-MF (p=0.009). Factors at apheresis including white cell count, neutrophil count, platelet count, absolute lymphocyte count, CD3 count, CRP, LDH and volume of blood processed had no impact on the risk of MF.

With a median follow up of 11.6 months, the 12-month overall survival (OS) from date of approval for CAR T therapy was 45.0% (31.4 - 57.7) for all MF patients (n=58), 49% (24.7 - 69.5) for the OOS cohort (n=19), 64.2% (33.6 - 83.5) for the MF-delayed-infusion cohort (n=17) and 27.3% (11.1 - 46.4) for the MF-no-infusion cohort (n=22). Corresponding 12-month OS was 43.0% (26.7 - 58.3) for all LBCL-MF (n=38), 49.0% (21.6 - 71.7) for LBCL-OOS (n=14), 53.3% (17.3 - 79.8) for the LBCL-delayed-infusion cohort (n=10) and 28.6% (8.8 - 52.4) for the no-infusion cohort (n=14). The 12-month OS for LBCL controls (n=25) was 51.2% (30.3-68.7) for all and 65.5% (38.6 - 82.8) for infused patients (n=18). There was no significant difference between OS for LBCL-MF and LBCL controls (HR 1.38, p=0.31). Though OS was numerically lower for LBCL-OOS compared to infused LBCL controls, it was not statistically different (HR 1.82, p=0.21).

For infused patients, the 3 months complete response (CR) rates were similar for the LBCL-OOS (38.5%), LBCL controls (40%) and MF-delayed infusion (53.3%) cohorts. The 3 months overall response rate (OR) was non-significantly lower in the LBCL-OOS (38.5%) compared to LBCL controls (60%) and MF-delayed infusion (53.3%) cohorts.

There was no difference between any grade or grade ≥3 CRS or ICANS between the LBCL-OOS, LBCL-control and MF-delayed-infusion cohorts.

In summary, outcomes for patients infused with an in-specification or OOS CAR T product following MF are comparable to those of controls. Prior bendamustine therapy within 6 months of apheresis is the only risk factor associated with risk of MF in lymphoma patients. Further analysis will be presented at the meeting.

Disclosures Kirkwood: *Kite-Gilead:* Honoraria. **Gautama:** *Gilead:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Sponsorship, Speakers Bureau. **Gabriel:** *Accord:* Consultancy; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Abbvie:* Honoraria, Speakers Bureau; *Kite-Gilead:* Consultancy. **Malladi:** *Gilead:* Honoraria, Other: travel support, Speakers Bureau; *Novartis:* Honoraria, Speakers Bureau. **Nicholson:** *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Kite-Gilead:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding. **Besley:** *Kite, Novartis, Janssen and Takeda:* Honoraria. **Ghorashian:** *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *UCLB:* Patents & Royalties. **Davies:** *Kite-Gilead:* Honoraria, Speakers Bureau. **Chappell:** *Abbvie:* Honoraria, Speakers Bureau; *Miltenyi Biotec:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Vertex:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Black:** *Pierre Fabre:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Kite-Gilead:* Honoraria, Speakers Bureau. **Menne:** *Kite/Gilead, Amgen, Novartis, Pfizer, Celgene/BMS, Daiichi Sankyo, Atara, Roche, Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Janssen, AstraZeneca, Novartis:* Research Funding; *Amgen, Jazz, Pfizer, Bayer, Kyowa Kirin, Celgene/BMS, Kite/Gilead, Janssen, Takeda:* Other: Travel grants; *Kite/Gilead, Takeda, Janssen, F. Hoffmann-La Roche Ltd, Servier, Novartis, Celgene/BMS, Pfizer, Incyte:* Speakers Bureau; *Kite/Gilead, Amgen, Novartis, Pfizer, Celgene/BMS, Daiichi Sankyo, Atara, F. Hoffmann-La Roche Ltd, Janssen, BMS, CTI BioPharma, Blueprint Medicines, Sanofi-Aventis, Spark Therapeutics:* Divested equity in a private or publicly-traded company in the past 24 months, Honoraria. **O'Reilly:** *Autolus:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Honoraria; *Novartis:* Honoraria, Other: Conference support; *Kite-Gilead:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Conference support. **Sanderson:** *Novartis:* Honoraria, Speakers Bureau; *Gilead:* Honoraria, Speakers Bureau. **Chaganti:** *Takeda, Kite/Gilead, Incyte, AbbVie, Pierre Fabre:* Speakers Bureau; *Takeda, Kite/Gilead, F. Hoffmann-La Roche Ltd, Atara Bio, Orion Pharma, Adicet Bio, Incyte, AbbVie, Novartis, Pierre-Fabre, Miltenyi Bio:* Honoraria; *Janssen, Kite/Gilead:* Research Funding; *Takeda, Kite-Gilead, Abbvie, Pierre Fabre:* Other: Meeting attendance support; *Takeda, Kite/Gilead, F. Hoffmann-La Roche Ltd, Atara Bio, Orion Pharma, Adicet Bio, Incyte, AbbVie, Pierre-Fabre, Miltenyi Bio, BMS-Celgene:* Consultancy.

OffLabel Disclosure: Use of axicabtagene ciloleucel (axi-cel), brexucabtagene autoleucel (brexu-cel) and tisagenlecleucel (tisa-cel) not meeting pre-specified criteria for release and labelled out of specification (OOS) CAR T product.

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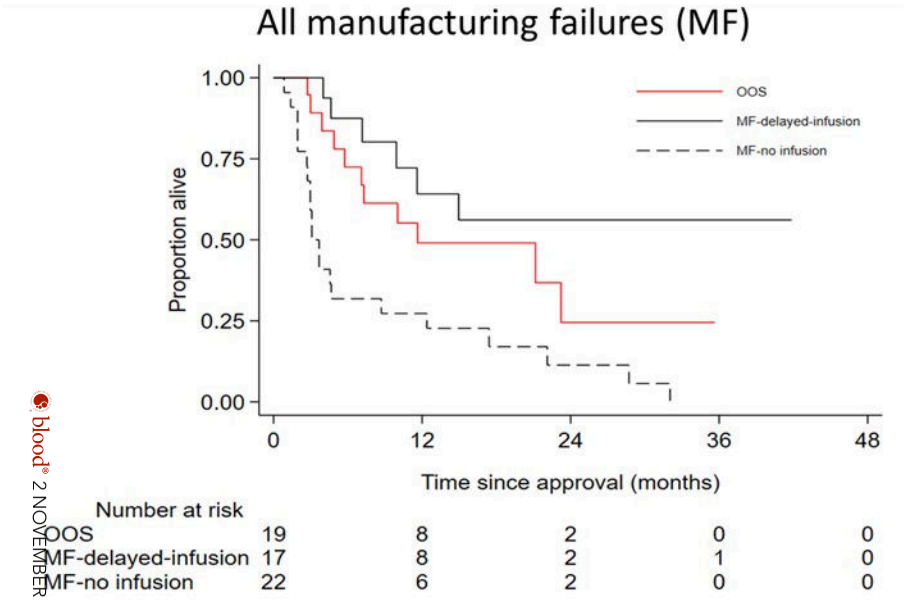

Figure 1A: Manufacturing failure by group. 12 month OS: OOS: 49% (24.7 – 69.5), MF-delayed infusion: 64.2% (33.6 – 83.5), MF-no-infusion: 27.3% (11.1 – 46.4)

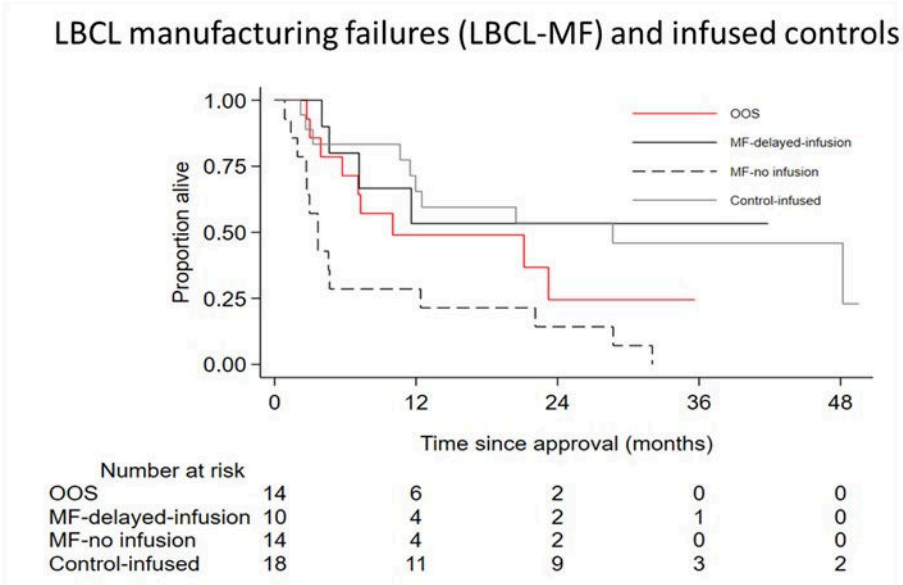

Figure 1B: Manufacturing failure by group and controls (infused only). 12 month OS: OOS: 49.0% (21.6 – 71.7), MF-delayed infusion: 53.3% (17.3 – 79.8), MF-no-infusion: 28.6% (8.8 – 52.4), Control-infused: 65.5% (38.6 – 82.8)

Figure 1