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POSTER ABSTRACTS

711.CELL COLLECTION AND PROCESSING

Failure and out of Specification Manufacturing of Autologous CAR-T Cells Could be Associated with a High Concentration of Total Nucleated Cells, CD3 $^{+}$ Cells and Neutrophils in the Apheresis Product

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Manufacturing capacities of commercial autologous chimeric antigen receptor (CAR)-T cells have been significantly increased during the last years, allowing treatment of a larger patient cohort. However, this was associated with the emergence of several failures and out of specifications (OOS), resulting in treatment delay. The aim of our study was to identify early indicators related to apheresis products that can predict CAR-T cells manufacturing failure or OOS. To this end, we analyzed manipulation processes of cellular starting materials (conservation, freezing, cryopreservation) and quality controls (QC) including count and/or concentration of total nucleated cells (TNC), CD3 $^{+}$, CD4 $^{+}$, CD8 $^{+}$ cells, platelets, monocytes and neutrophils.
We analyzed 802 apheresis products that were collected for the manufacturing of axicabtagene ciloleucel (axi-cel, n=303), tisagenlecleucel (tisa-cel, n=403), brexucatagene autoleucel (brexu-cel, n=44) and idecabtagene vicleucel (ide-cel, n=52). This cohort was classified into 3 groups: failure (CAR-T cells not produced), OOS (CAR-T cells produced but non-compliant) and compliant.
We identified 21 failures and 24 OOS, resulting in either no treatment or a significant delay when the OOS were injected (57.6±17.5d *versus* 45.9±16.3d in compliant group, p=0.0405). Among each CAR-T cells product, 13 (4.3%) axi-cel, 30 (7.4%) tisa-cel, 1 (2.3%) brexu-cel and 1 (1.9%) ide-cel were concerned. The main causes of failures were low viability (33.3%), non-compliant dose (28.6%), microbiological contamination (23.8%) and formulation concerns (14.3%). In OOS, low viability (41.7%), low dose (29.2%), microbiological contamination (4.2%), formulation (12.5%) and safety concerns (8.3%; i.e high vector copy number) were identified. 17 products (13 failures and 4 OOS) were successfully remanufactured without an increased delay comparing to compliant products (47.5±15.9 and 47.3±15.1 respectively *versus* 45.9±16.3 d).
To identify risk factors of manufacturing failure or OOS due to non-compliant viability and/or dose, we analyzed processing and QC of collected cellular starting materials. OOS were associated with a high concentration of TNC (146.7±94.3 *vs* 61.6±36.1 x10 ^{6}/mL, p=0.009) and CD3 $^{+}$ cells (88.6±76.5 vs 26.0±21.9 x10 ^{6}/mL, p=0.0112) in cell collections, while failures were observed in apheresis with high neutrophils concentration (14.3±15.03 x10 ^{3}/µL *vs* 6.0±7.6 x10 ^{3}/µL, p=0.0195). Interestingly, neutrophils were significantly decreased in apheresis collected for CAR-T cells remanufacturing which succeed (p=0.0156).
This preliminary study showed that high TNC, CD3 $^{+}$ cells and neutrophils concentration in the apheresis product might be predictive factors of failures and/or OOS of commercial autologous CAR-T cells manufacturing.

Disclosures Cohet: *Kite/Gilead:* Consultancy. **Parquet:** *Kite/Gilead:* Honoraria; *Sanofi:* Honoraria; *Novartis:* Honoraria. **Brignier:** *Kite/Gilead:* Honoraria. **Menouche:** *Vertex:* Consultancy; *Sandoz:* Consultancy; *Sanofi:* Honoraria. **Azar:** *Janssen:* Con-

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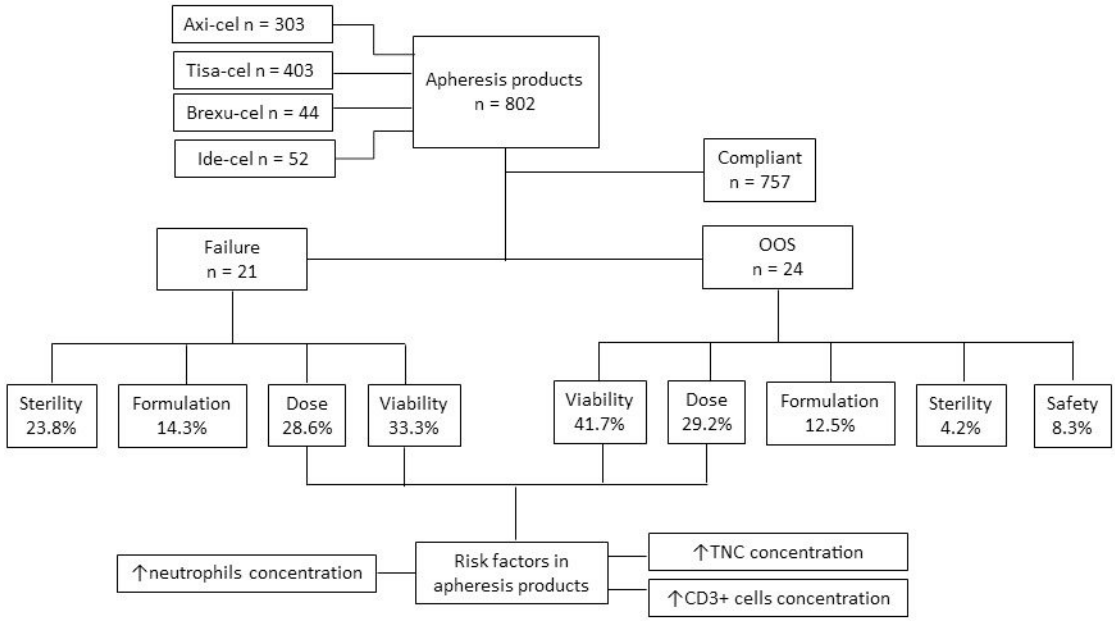

Figure 1

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