3. RELAPSED/REFRACTORY MULTIPLE MYELOMA

CILTACABTAGENE AUTOLEUCEL OUT-OF-SPECIFICATION MANUFACTURING OUTCOMES IMPROVE WITH EARLIER LINES OF THERAPY

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Introduction. Cilta-cel is manufactured using autologous T cells, whose quality attributes are the main driver of out-of-specification (OOS) manufacturing results. Previous reports show naive and central memory T cell enrichment correlates with greater in-specification product manufacturing; enrichment is more frequent when patients have fewer prior lines of therapy (pLOTs). Here, we report cilta-cel manufacturing results across multiple pLOTs.

Methods. Cilta-cel manufacturing data were analysed to discern manufacturing outcome determinants, define biomarkers predictive of manufacturing success, and assess outcomes following OOS-driven remanufacturing.

Results. T cells from patients with fewer pLOTs yielded improved rates of first-time manufacturing success (≥1 pLOT, 93% vs ≥4 pLOTs, 89%; N=~3000). CD3+ cell recovery at manufacturing initiation was less favourable in patients with ≥4 vs fewer pLOTs. The initial cellular CD4:CD8 ratio improved by 54% with fewer pLOTs (average ratio: 1 pLOT, 1.0 vs ≥4 pLOTs, 0.65), indicating a CD4:CD8 ratio >0.5 may contribute to better in-specification, first-time manufacturing. Recovery of viable cells before lentiviral vector transduction and cumulative population doubling level of cells improved up to 7% with relatively fewer pLOTs ($P<0.05$ for both). Metabolic activity markers were significantly improved with fewer pLOTs (average improvement of 10% with 1 vs more pLOTs). Across OOS outcomes from all pLOTs (n=317), 63% were released through an expanded access program without remanufacturing. Of the remaining 37%, 8.6% were cancelled and 28.6% (n=90) underwent remanufacturing (54 resulted in OOS/cancellation, 36 generated within-specification results). Material from patients with ≥4 pLOTs undergoing remanufacturing led to the same or additional OOS outcomes or cancellations as the first manufacturing OOS outcome (67% attempts, n=36). Remanufacturing from recollection of new material was requested in 14% of initial OOS cases due to insufficient remaining material or concerns about the effect of prior therapies, indicating long-lasting impact of prior treatments and/or disease characteristics. Remanufacturing with new material (n=45) yielded similar/worse outcomes in 31% of cases, with 20% being cancelled. Remanufacturing cancellation and OOS outcome rates with ≥4 pLOTs were 39.5% and 35.5%, respectively (n=29). Manufacturing success rate improved to 99% using cells from ≥1 pLOT patients (6.5% received OOS product) vs 97% for ≥4 pLOTs (9.2% received OOS product).

Conclusions. Rates of first and overall manufacturing success were higher, and T cell attributes linked to manufacturing outcomes were improved, when using cells collected from patients with ≥1 vs ≥4 pLOTs. Remanufacture often leads to additional OOS outcomes, further delaying patient treatment.