Global manufacturing experience with idecabtagene vicleucel in patients with relapsed and refractory multiple myeloma

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Introduction

- Idecabtagene vicleucel (ide-cel), a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR) T cell therapy, is currently approved in the USA, Europe, and Japan for patients with relapsed and refractory multiple myeloma (RRMM) after ≥ 2 prior lines of therapy[1]
- In the pivotal KarMMa-3 study (NCT03651128), ide-cel significantly improved median progression-free survival (13.8 vs 4.4 months; HR, 0.49; 95% CI, 0.38–0.63; $P < 0.001$) and overall response rate (71% vs 42%; $P < 0.001$) versus standard regimens in patients with triple-class–exposed RRMM who had disease refractory to the last regimen[1]
  - In KarMMa-3, the manufacturing success rate (MSR) for ide-cel was 98.8%[1]
- With CAR T cell therapies, including ide-cel, timely and reliable delivery of the product in both commercial and clinical trial settings is essential for optimizing timing of treatment, patient experience, and outcomes in RRMM therapy[2,3]
  - Low MSR can delay or prevent access to timely treatment, potentially impacting patient outcomes[2]
- Turnaround time (TAT) for CAR T cell manufacturing can vary due to differences in logistical processes, which are more pronounced when the manufacturing location and target market are geographically distant from one another. During this period, patients may benefit from bridging therapy to manage the risk of disease progression[3]
- A reliable and predictable TAT is crucial for effective planning for bridging therapy and ensuring patients can benefit from CAR T cell therapy[3]

Objective

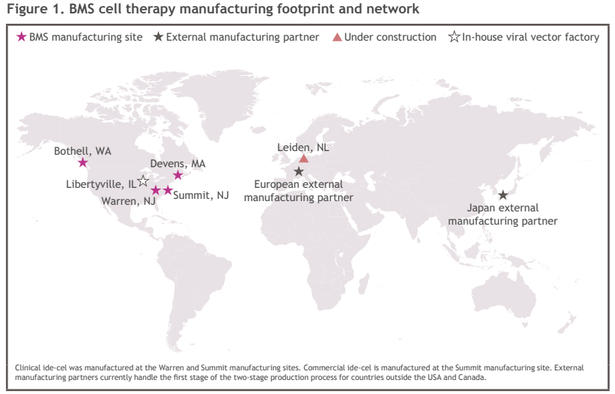
- In this analysis, we report the manufacturing capability, reliability, and timely delivery of ide-cel globally over more than 3 years since its initial market entry

Methods

Inclusion criteria

- This analysis included patients with RRMM, as captured on the Cell Therapy 360® portal, who underwent leukapheresis for ide-cel treatment after ≥ 2 prior lines of therapy between February 23, 2021 and May 1, 2024, and had final manufacturing outcomes available
  - The Cell Therapy 360® portal provides healthcare professionals with real-time access to key information throughout the CAR T cell therapy process, ensures efficient communication between treatment centers and manufacturers, timely delivery of product, and effective patient care[4]
- Globally, 245 centers are currently qualified for treating patients with commercially available ide-cel; 113 in the USA, 106 in European Union (EU; including Switzerland), and 26 in Japan
- A global network of manufacturing sites is used to supply these centers (**Figure 1**)
- The analysis also included clinically manufactured ide-cel for patients in the KarMMa-3 trial. The latest clinical data cutoff date was April 28, 2023

Figure 1. BMS cell therapy manufacturing footprint and network



Clinical ide-cel was manufactured at the Warren and Summit manufacturing sites. Commercial ide-cel is manufactured at the Summit manufacturing site. External manufacturing partners currently handle the first stage of the two-stage production process for countries outside the USA and Canada.

Manufacturing terms

- Ide-cel manufacturing terms and definitions used in this analysis are summarized in **Table 1**

Table 1. Ide-cel manufacturing terms

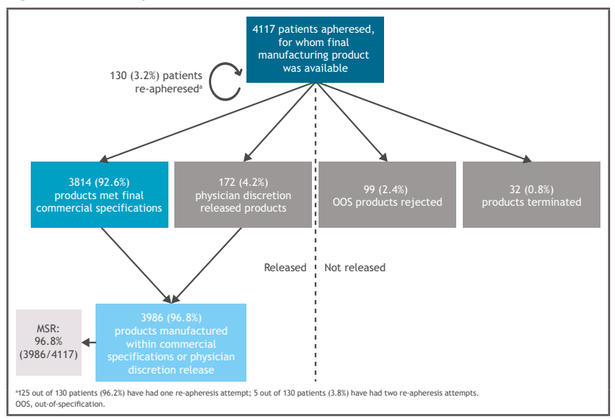
	Definition
Final manufacturing outcome	Meeting commercial specifications, or not meeting commercial specifications but released based on physician's request, or rejected, or terminated
Manufacturing success rate (MSR)	Percentage of patients for whom the product was released that either met commercial specifications, or through the expanded access protocol (EAP), single investigational new drug (sIND), or through the exceptional supply of advanced therapy medicinal products (ATMP; EU-Good Manufacturing Practice, Part IV, Section 11.5)[5]
Physician discretion release	Supply of the product upon physician request through enrolment into an EAP in the USA and Japan, supply under a sIND in the USA and exceptional supply according to the EU Guidelines on Good Manufacturing Practice specific to ATMP Part IV Section 11.5[5]
Rejected	Product not meeting commercial specifications and not requested by physician for use
Terminated	No drug product could be produced (eg, insufficient cells for harvest, insufficient cells to proceed manufacturing of intermediate product, contamination, or hardware malfunction)
Turnaround time (TAT)	Manufacturing TAT for commercial and clinical trial ide-cel was defined as the number of days from leukapheresis to product release

Results

Manufacturing success rate (MSR)

- Between February 2021 and May 2024 (data cutoff May 1, 2024), 4117 patients underwent leukapheresis for commercial ide-cel and had final manufacturing outcomes available (**Figure 2**)

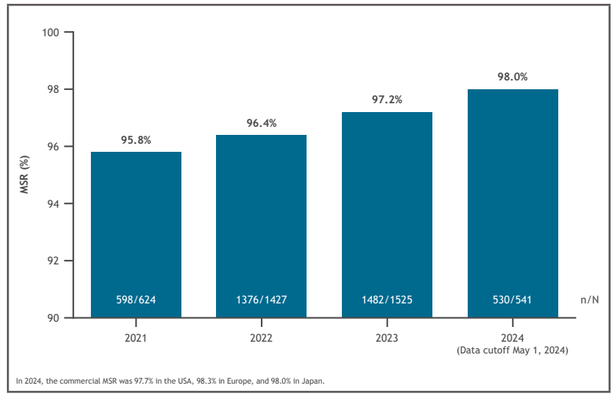
Figure 2. Product disposition and overall MSR



[a]125 out of 130 patients (96.2%) have had one re-apheresis attempt; 5 out of 130 patients (3.8%) have had two re-apheresis attempts.
OOS, out-of-specification.

- The MSR improved over 3 years; 95.8% in 2021, 96.4% in 2022, 97.2% in 2023, and 98.0% in 2024 (May 1, 2024; **Figure 3**)
  - In 2024 the commercial MSR was consistent between the USA (97.7%), Europe (98.3%), and Japan (98.0%)
- Of the 4117 patients, 271 (6.6%) products were OOS: 38/624 (6.1%) in 2021, 124/1427 (8.7%) in 2022, 84/1525 (5.5%) in 2023, and 25/541 (4.6%) in 2024 (**Table 2**)
  - In 2022, more patients had an OOS product (124/1427; 8.7%) compared with other years. However, most OOS products were supplied at the physician's discretion upon request (86/1427; 6.0%)

Figure 3. Overall MSR per year



In 2024, the commercial MSR was 97.7% in the USA, 98.3% in Europe, and 98.0% in Japan.

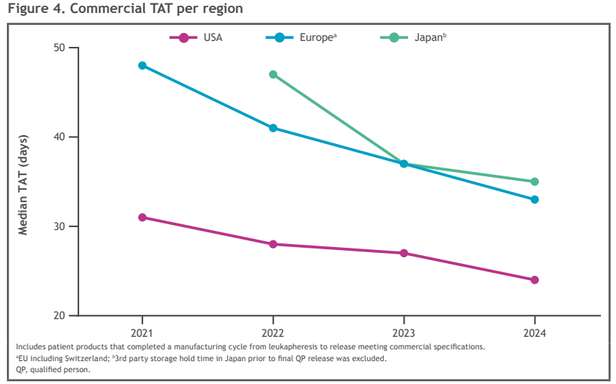
Table 2. Final manufacturing outcomes per patient per year

	2021	2022	2023	2024 (May 1, 2024)
Apheresed patients with final manufacturing outcome available, n	**624**	**1427**	**1525**	**541**
Re-apheresed patients, n (%)	29 (4.6)	63 (4.4)	32 (2.1)	6 (1.1)
Final manufacturing outcomes, n (%)				
Commercial product	579 (92.7)	1290 (90.4)	1433 (93.9)	512 (94.6)
Physician discretion release of OOS product	19 (3.0)	86 (6.0)	49 (3.2)	18 (3.3)
OOS product rejected	19 (3.0)	38 (2.7)	35 (2.3)	7 (1.3)
Terminated	7 (1.1)	13 (0.9)	8 (0.5)	4 (0.7)
MSR (commercial product + physician discretion release OOS product), n (%)	**598 (95.8)**	**1376 (96.4)**	**1482 (97.2)**	**530 (98.0)**

Turnaround time (TAT)

- The current commercial median (interquartile range [IQR]) TAT demonstrated year-on-year improvements from 2021 through 2024 (**Figure 4**)
  - USA: From 31 (28–35) days in 2021 to 24 (24–25) days in 2024
  - Europe: From 48 (46–53) days in 2021 to 33 (32–35) days in 2024
  - Japan: From 47 (40–48) days in 2022 to 35 (34–36) days in 2024
- In the KarMMa-3 clinical trial setting, the overall median (IQR) clinical TAT from 2019 through 2022 was 30 (28–35) days in the USA, 39 (34–46) days in EU (including Switzerland, United Kingdom, and Norway), and 45 (39–60) days in Japan

Figure 4. Commercial TAT per region



Includes patient products that completed a manufacturing cycle from leukapheresis to release meeting commercial specifications.
[a]EU including Switzerland; [b]3rd party storage hold time in Japan prior to final QP release was excluded.
QP, qualified person.

Discussion

- TAT for commercial ide-cel has been significantly reduced over the last 3 years across the USA, Europe, and Japan. Regional differences remain due to decentralized manufacturing processes
  - In the USA, where all manufacturing steps occur domestically, TAT is typically shorter, as evidenced by the median of 24 days for commercial ide-cel in 2024
  - In Europe and Japan, TAT is longer because a 2-step manufacturing process requires the product to be shipped to the USA for final manufacturing steps before it returns to treatment sites
  - Additionally, final products must meet the regulatory requirement of being EU quality released before re-entering the EU from the USA
- Compared to manufacturing CAR T cell products for clinical trials with a finite number of patients, commercial manufacturing must meet much higher demands, introducing a greater complexity and inherent challenges of scale
  - In 2024, the commercial MSR of ide-cel (98.0%) closely approached those of the KarMMa and KarMMa-3 clinical trials
  - The median commercial TAT for ide-cel in 2024 (USA: 24 days, Europe: 33 days, Japan: 35 days) was consistently shorter than the TAT from the KarMMa-3 clinical trial
  - Additionally, commercial ide-cel MSR and TAT are higher and shorter, respectively, than those reported for cilta-cel clinical trials; where 18% of patients experienced manufacturing failures in CARTITUDE-1, and the median TAT from leukapheresis to product release was 44 days in CARTITUDE-4[6]

Conclusions

- The timely and reliable delivery of CAR T cell products is essential for effective patient planning and optimizing treatment outcomes in RRMM
- The commercial manufacturing reliability of ide-cel has been notably high since 2021
- This analysis has revealed consistent year-on-year improvements in MSR and TAT for patients treated with ide-cel worldwide over the past 3 years
- These improvements have enabled the manufacturing of ide-cel to meet the increasing global patient demand effectively

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