EBMT

Out-of-Specification products and manufacturing failures in European CAR-T cell centers

Cellular Therapy & Immunobiology Working Party

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Disclosure statement

Research grants:	Sanofi Genzyme, Therakos Malinckrodt
Advisory Boards:	BMS Celgene, Sanofi Genzyme
Speaker’s fees:	BMS Celgene, Kite Gilead, Miltenyi Biotec, Novartis, Pierre Fabre, Sanofi Genzyme, Therakos Malinckrodt
Travel Support:	Kite Gilead, Pierre Fabre, Therakos Malinckrodt

Introduction

- CAR-T cell therapy significantly changed the treatment landscape for relapsed/refractory $CD19^+$ B-cell malignancies and multiple myeloma.
- Approved CAR-T cell products utilize patient's leukocytes (autologous MNCs) as starting material for the manufacturing.
- CAR-T cell product specifications are predefined attributes set to ensure manufacturing of consistent, safe, viable, and potent products approved by regulatory authorities as part of MA.

CAR=chimeric antigen receptor; MA=marketing authorization

Background manufacturing problems

- Not always possible to manufacture CAR-T cells from the provided starting material “autologous leukocytes” or to achieve CAR-T cell product specifications:
  - Manufacturing failure: CAR-T cell production is **not** possible
  - Out-of-Specification: one or more specifications for final product release are **not** met
  - Microbiologically contaminated starting materials

Rate of CAR-T manufacturing problems

- In pivotal trials manufacturing failure rates:
  - in anti-CD19 trials: 4 to 14%
  - in anti-BCMA CAR-T cell trials: 0 to 1%
- Real world evidence:
  - manufacturing failure rates: ~2-14%
  - OOS: ~4-7%
- EU: supply of non-conforming ATMPs by MAH justified under exceptional circumstances upon request of the treating physician.

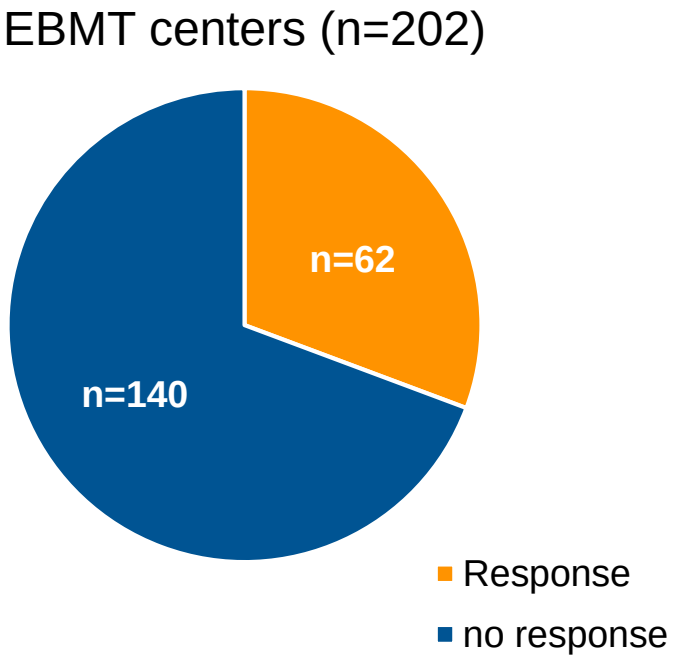
BCMA=B-cell maturation antigen, MAH=marketing authorization holder, OOS=Out-of-Specification

EBMT Survey on commercial CAR-Ts

- Identify centers that experienced manufacturing failures and/or had OOS CAR-T cell products.
- Collect information on the numbers of manufacturing failures, OOS products and microbiologically contaminated starting materials.
- In a 2nd survey we currently evaluate possible risk factors for unsuccessful CAR-T cell manufacturing and outcome of patients (infused/not infused).

EBMT Survey on commercial CAR-Ts

- 22-item survey
- Disseminated in September 2023, open until December 2023.
- 31% of 202 centres responded.
- Majority of centers (81%) started their activity between 2019 - 2021.



EBMT Survey on commercial CAR-Ts

JACIE Accreditation

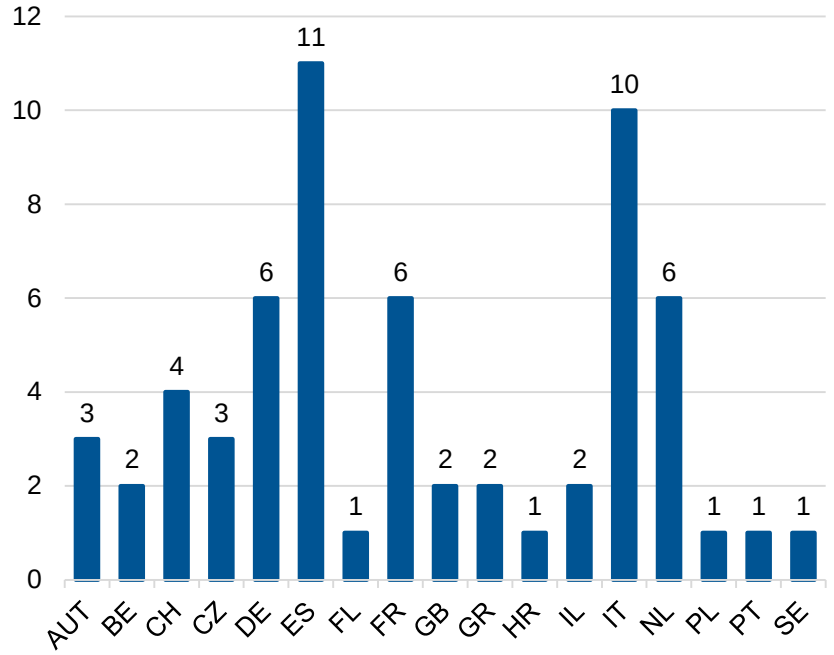
- Transplant + IEC program n=41 (66%)
- Transplant program only n=11 (18%)

Total n=52 (84%)

- Collection center n=52 (85%)
- Processing center n=50 (83%)

Serving a single IEC program n=41 (66%)

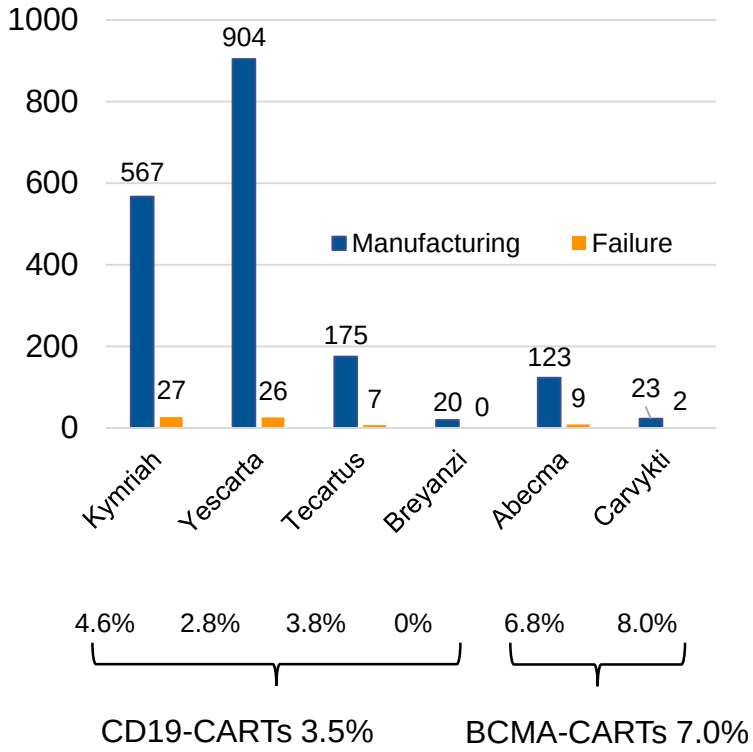
Serving multiple programs n=21 (34%)



62 centers/17 countries

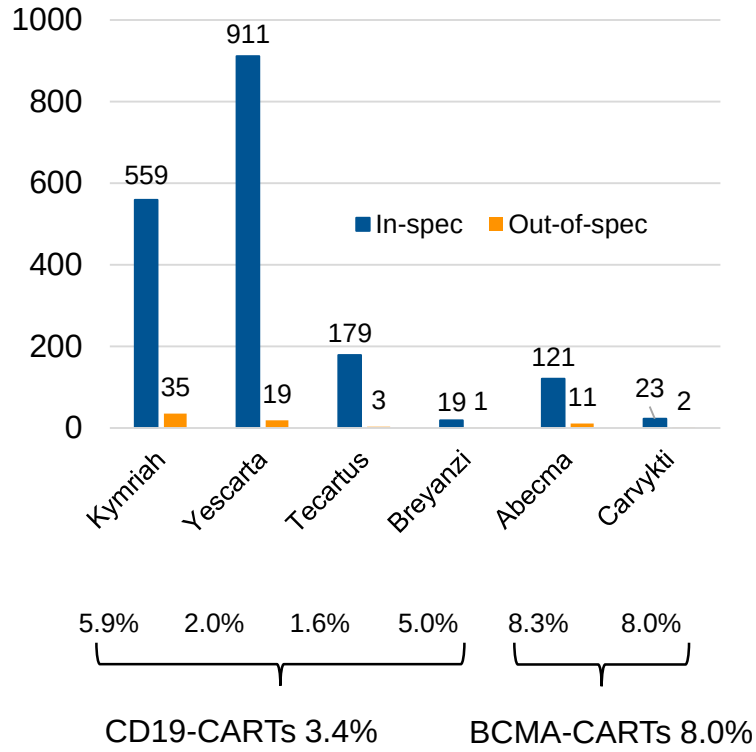
Results: Manufacturing failure (MF)

- MF has been observed in 71 out of 1883 patients (3.8%).
- For CD19-targeting CAR-T cells MF was 60 out of 1726 (3.5%).
- For BCMA-targeting CAR-T cells less patients have been reported and MF was higher with 11 out of 157 (7%).



Results: Out-of-Specification (OOS)

- OOS has been observed in 71 out of 1883 patients (3.8%).
- For CD19-targeting CAR-T cells OOS was 58 out of 1726 (3.4%).
- For BCMA-targeting CAR-T cells OOS was higher with 11 out of 157 (8%).



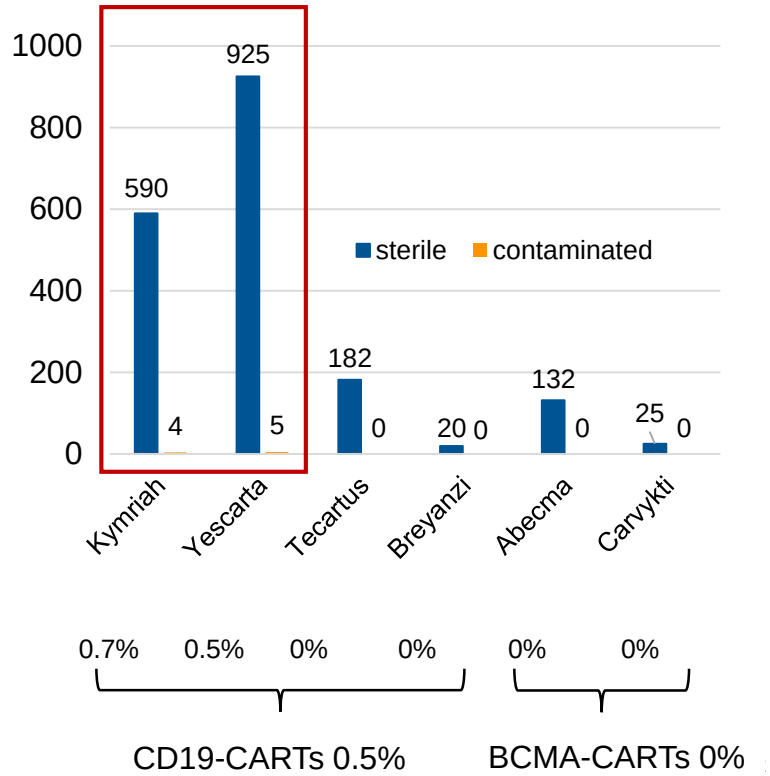
Results: Out-of-Specification (OOS)

Main reason in centers; n (%)	Kymriah n=16 (%)	Yescarta n=12 (%)	Tecartus n=3 (%)	Breyanzi n=1 (%)	Abecma n=4 (%)	Carvykti n=1 (%)
Low quantity viable CAR-T cell dose[1]	7 (47)	9 (74)	1 (33)	0	4 (100)	1 (100)
Low purity[2] viable CD3+	5 (33)	4 (33)	0	0	0	0
Potency[3] by IFN-y	7 (47)	3 (25)	0	1 (100)	0	0
Low/no expansion	0	3 (25)	2 (67)	0	0	0
Other	5 (33)	0	0	0	1 (25)	1 (100)

[1]including quantity assessed by other means; [2]including purity assessed by cell viability and other reasons; [3]including CAR expression

Results: Contaminated starting material (CSM)

- Observed in 9 out of 1883 patients (0.5%), only in MNCs for Kymriah and Yescarta.
- Kymriah: no manufacturing started
- Yescarta: in 3/5 (60%) cases manufacturing was performed and resulted in a sterile CAR-T cell product.



Percentage of OOS within centers

Centers n (%)	Kymriah n=49 (%)	Yescarta n=46 (%)	Tecartus n=31 (%)	Breyanzi n=5 (%)	Abecma n=7 (%)	Carvykti n=4 (%)
0%	27 (63)	30 (70)	25 (89)	3 (75)	2 (33)	3 (75)
>0-≤10%	7 (16)	9 (21)	3 (11)	0	1 (17)	0
>10-≤20%	3 (7)	1 (2.3)	0	0	3 (50)	0
>20-≤30%	3 (7)	1 (2.3)	0	0	0	1 (25)
>20-≤30%	2 (4.7)	2 (4.7)	0	0	0	0
>40%	1 (2.3)	0	0	1 (25)	0	0
missing	6	3	3	1	1	0

Percentage of MF within centers

Centers n (%)	Kymriah n=49 (%)	Yescarta n=46 (%)	Tecartus n=31 (%)	Breyanzi n=5 (%)	Abecma n=7 (%)	Carvykti n=4 (%)
0%	29 (66)	28 (65)	22 (79)	4 (100)	2 (40)	3 (75)
>0-≤10%	8 (18)	12 (28)	2 (7)	0	1 (20)	0
>10-≤20%	6 (14)	3 (7)	1 (3.6)	0	1 (20)	0
>20-≤30%	0	0	1 (3.6)	0	1 (20)	1 (25)
>20-≤30%	0	0	1 (3.6)	0	0	0
>40%	1 (2.3)	0	1 (3.6)	0	0	0
missing	5	3	3	1	2	0

Factors influencing MF and OOS

Currently we work on a 2nd survey to gather information on:

- Pretreatment (# of cycles and lines, concomitant medication)
- Time between last treatment and leukapheresis
- Peripheral blood counts and CD3 at day of leukapheresis
- Details on apheresis (e.g. processed blood volume) including collection results
- Outcome of patients **receiving or not receiving an OOS** product (ORR, OS, CRS, ICANS, etc.)

Published results of non-conforming CAR-Ts

- ZUMA-9 Study: Axi-cel in R/R LBCL for expanded access (C1) and commercial out-of-specification (C2) products

Jacobson CA; *Blood* 2020:136 suppl	**C1 (n=25)**	**C2 (n=36)**
ORR / CR (%)	76 / 64	53 / 36
median OS (95%CI), mo	23.8 (13.5-ne)	NR (3.4-ne)
12 mos OS (95% CI), %	76 (54-88)	62 (43-77)
Grade ≥3 CRS / NEs, %	0 / 36	3 / 19

Jacobson CA, *Blood* 2020

Conclusions

The rate of manufacturing failure in commercial CD19-directed CAR-T cells is similar to the study landscape.

Despite differences in total numbers of patients receiving CD19-targeting and BCMA-targeting CAR T cells, higher rates of manufacturing failure have been observed for BCMA-targeting CAR-T cells so far.

Possible factors influencing the manufacturing process in terms of out-of-specification and manufacturing success and outcome of these patients will be evaluated in a next step and is already underway.

Thanks!

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