LATE FAILURE OF AGGRESSIVE B-CELL LYMPHOMA FOLLOWING CAR T-CELL THERAPY: A LYSA STUDY FROM THE DESCAR-T REGISTRY

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Outcomes of R/R aggressive BCL after anti-CD19 CAR T-cells failure

- Relapsed/refractory (R/R) aggressive B-cell lymphomas (BCL) which fail anti-CD19 CAR T-cell therapy showed dismal outcomes, with a median Overall Survival (OS) of 3.2 – 8.6 months $^{1-5}$

- Most failures occur in the first 3 months after CAR T-cell infusion $^{1,4,6}$

- Progression in the first 30 days lead to worse prognosis, with median OS of 1.7 – 2.9 months $^{1,4}$

- Better Progression-Free Survival (PFS) and OS in patients presenting later failures $^{1,3,4,6}$

Endpoints of the study

Primary:
Outcomes (PFS2 and OS2) of the R/R aggressive BCL patients which relapse or progress after M3 from anti-CD19 CAR T-cell therapy (Late Failure)

Secondary:
• Baseline characteristics of the patients
• Patterns of treatments at CAR T-cells failure and responses
• Outcomes (PFS2 and OS2) according to time of failure
• Factors associated with late failures

DESCAR-T *
French Registry created in 2018
• Sponsor: LYSARC
• Collection of data of patients subsequently treated in France by commercial CAR T-cells

Total n= 1464
(Aggressive BCL n= 1129)
pts registered in October 2022

*DESCART = Dispositif d’ Evaluation et de Suivi des CAR-T
Study population

At the time of analysis, April 2022:
• 977 R/R aggressive BCL pts received Axi-cel or Tisa-cel were included in the DESCAR- T registry (treated set)
• Median F-Up: **12.4** months

- **Treated set**
  - 977 pts

- **Failure set**
  - 431 pts (44.1%)

- **Non progressive set**
  - 546 pts (55.9%)

- **Early Failure set (<M3)**
  - 286 pts (66.4%)

- **Late Failure set (≥M3)**
  - 145 pts (33.6%)

- Median time to failure **4.11 months (3-21.5)**
CARLATE: target population

- D0: CAR T injection
- Treatment of CAR T failure
- M3
- M6
- M9
- M12
- OS2
- PFS2
- Relapse or progression after treatment of failure
- Death or last F-Up

- Failure (start of F-Up)
- Treatment of failure
- Registered events: - Relapse/Progression after treatment of failure
    - Death or last F-Up
## Baseline features of the late failure set (n=145)

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>n=145 (100 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65yrs</td>
<td>58 (40%)</td>
</tr>
<tr>
<td>DLBCL</td>
<td>109 (75.2%)</td>
</tr>
<tr>
<td>tFL</td>
<td>15 (10.3%)</td>
</tr>
<tr>
<td>PMBL</td>
<td>6 (4.1%)</td>
</tr>
<tr>
<td>HGBCL</td>
<td>6 (4.1%)</td>
</tr>
<tr>
<td>Others ( PCNSL n=1, transformed MZL n=5, Richter syndrome n=1, unclassifiable aggressive lymphoma with features intermediate between DLBCL and chL n=2)</td>
<td>9 (6.2%)</td>
</tr>
</tbody>
</table>

### At registration:

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG PS 2</td>
<td>6 (4.1%)</td>
</tr>
<tr>
<td>aaIPI ≥2</td>
<td>78 (57.8%)</td>
</tr>
<tr>
<td>Stage III-IV</td>
<td>120 (85.1%)</td>
</tr>
<tr>
<td>&gt;3 previous treatment lines</td>
<td>74 (51%)</td>
</tr>
<tr>
<td>Prior autotransplant</td>
<td>34 (23.4%)</td>
</tr>
<tr>
<td>LDH &gt; normal</td>
<td>94 (64.8%)</td>
</tr>
</tbody>
</table>

### At lymphodepletion:

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Bridging therapy</td>
<td>120 (82.8%)</td>
</tr>
<tr>
<td>Progressive disease after bridging</td>
<td>66 (55%)</td>
</tr>
<tr>
<td>PS ECOG ≥2</td>
<td>12 (9.3%)</td>
</tr>
<tr>
<td>LDH elevated</td>
<td>72 (50.7%)</td>
</tr>
<tr>
<td>CRP &gt; 30 mg/l</td>
<td>24 (16.2%)</td>
</tr>
<tr>
<td>Bulky disease (&gt;5 cm)</td>
<td>34 (23.4%)</td>
</tr>
<tr>
<td>CAR T-cell product:</td>
<td></td>
</tr>
<tr>
<td>Axicabtagene ciloleucel</td>
<td>94 (64.8%)</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>51 (35.2%)</td>
</tr>
</tbody>
</table>
Progression-free survival-2 of late failure set

145 patients

Median PFS2= 4.2 months (95%CI, 3.4-6.0)
Progression-free survival-2 of late failure set

145 patients

At 6-months 41.3% (95%CI, 32.8-49.7) were progression-free

Median PFS2 = 4.2 months (95%CI, 3.4-6.0)
Overall survival-2 of late failure set

Median OS2 = **12.1 months** (95%CI, 6.9-15.7)

145 patients
Overall survival-2 of late failure set

145 patients

At 6-months 63.2% (95%CI, 54.2-70.9) were alive

Median OS2= **12.1 months** (95%CI, 6.9-15.7)
Progression-free survival-2 according to time of failure

145 pts
Failure ≥M3

- n =104 pts (72%)
  M3-M6
- n=21 pts (14%)
  M6-M9
- n=20 pts (14%)
  >M9

Median
PFS-2

2.9 months
(95%CI, 2.9-5.0)

4.1 months
(95%CI, 2.5-NR)

6-months
PFS-2

36.2%
(95%CI, 26.6-45.8)

48.9%
(95%CI, 25.7-68.6)

p=0.06
### Progression-free survival-2 according to time of failure

**145 pts**  
Failure ≥M3

- **n = 104 pts (72%)**  
  M3-M6  
  **Median PFS-2**  
  2.9 months  
  (95%CI, 2.9-5.0)

- **n = 21 pts (14%)**  
  M3-M6  
  **4.1 months**  
  (95%CI, 2.5-NR)

- **n = 20 pts (14%)**  
  >M9  
  **21.8 months**  
  (95%CI, 4.8-21.8)

**6-months PFS-2**

- 36.2%  
  (95%CI, 26.6-45.8)

- 48.9%  
  (95%CI, 25.7-68.6)

- 62%  
  (95%CI, 33.8-81.1)

**HR = 0.46, 95%CI, 0.22 – 0.95, P=0.03**
Patterns of treatment after late CAR T failure and responses

<table>
<thead>
<tr>
<th>Responses (Cheson 2014)</th>
<th>Evaluable pts n= 74 (100%)</th>
</tr>
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<tr>
<td>ORR</td>
<td>16 (21.6%)</td>
</tr>
<tr>
<td>CR</td>
<td>11 (14.8%)</td>
</tr>
<tr>
<td>PR</td>
<td>5 (6.7%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>2 (2.7%)</td>
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<tr>
<td>Progressive disease</td>
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Systemic treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PD1</td>
<td>0%</td>
</tr>
<tr>
<td>Targeted drugs</td>
<td>30%</td>
</tr>
<tr>
<td>Bispecifics</td>
<td>37.5%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>20%</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>18.2%</td>
</tr>
<tr>
<td>Radiotherapy was proposed in 18 (14.5%) patients</td>
<td></td>
</tr>
</tbody>
</table>

Molecules were used alone or in combination.

*Bruton’s Tyrosine Kinase Inhibitors, Mucosa-Associated Lymphoid Tissue lymphoma translocation protein-1 inhibitors, anti-CD19, anti-CD38, second CAR T-cells infusion, etc. IMIDs: Immunomodulatory imide drugs; Abs: Antibodies; PD1: Programmed-death cell receptor-1.
Progression-free survival-2 according to treatment group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Subjects</th>
<th>Event % (N)</th>
<th>Censored % (N)</th>
<th>Median Survival (95%CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PD1</td>
<td>7</td>
<td>71.4 % (5)</td>
<td>28.6 % (2)</td>
<td>2.9 (0.1 ; NA)</td>
</tr>
<tr>
<td>Bispecific Abs</td>
<td>18</td>
<td>27.8 % (5)</td>
<td>72.2 % (13)</td>
<td>Not reached (5.8 ; NA)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>18</td>
<td>81.8 % (18)</td>
<td>18.2 % (4)</td>
<td>2.5 (1.6 ; 3.4)</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>41</td>
<td>85.4 % (35)</td>
<td>14.6 % (6)</td>
<td>3.9 (2.5 ; 5)</td>
</tr>
<tr>
<td>Targeted drug *</td>
<td>16</td>
<td>56.3 % (9)</td>
<td>43.8 % (7)</td>
<td>5.5 (1.9 ; NA)</td>
</tr>
</tbody>
</table>

*Bruton’s Tyrosine Kinase Inhibitors, Mucosa-Associated Lymphoid Tissue lymphoma translocation protein-1 inhibitors, anti-CD19, anti-CD38, second CAR T-cells infusion, etc.
Progression-free survival-2 according to treatment group

Bispecific Abs: 6-months PFS-2 77.5%, HR=0.188 (95% CI, 0.069–0.509), P=0.001

*Bruton’s Tyrosine Kinase Inhibitors, Mucosa-Associated Lymphoid Tissue lymphoma translocation protein-1 inhibitors, anti-CD19, anti-CD38, second CAR T-cells infusion, etc.
Overall survival-2 according to treatment group

*Bruton’s Tyrosine Kinase Inhibitors, Mucosa-Associated Lymphoid Tissue lymphoma translocation protein-1 inhibitors, anti-CD19, anti-CD38, second CAR T-cells infusion, etc.
Overall survival-2 according to treatment group

Bispecific Abs group: 6-months OS-2 92.9%, HR=0.167 (95% CI, 0.049–0.572), P=0.004;
Targeted drugs group: 6-months OS-2 76.6%, HR=0.278 (95% CI, 0.093–0.83), P=0.02

Bruton's Tyrosine Kinase Inhibitors, Mucosa-Associated Lymphoid Tissue lymphoma translocation protein-1 inhibitors, anti-CD19, anti-CD38, second CAR T-cells infusion, etc.
Multivariate analysis: predictive factors of late failure

**Compared to non progressive set:**

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Odds ratio [95%CI]</th>
<th>Pr&gt; Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP &gt;30 mg/l</td>
<td>1.984 [1.112-3.541]</td>
<td>0.02</td>
</tr>
<tr>
<td>No response to Bridging therapy</td>
<td>1.781 [1.103-2.875]</td>
<td>0.01</td>
</tr>
<tr>
<td>tFL histotype*</td>
<td>0.423 [0.214-0.838]</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* tFL: transformed Follicular Lymphoma
Conclusions

• Failure of CAR T-cells therapy lead to dismal outcomes even when it occurs after three months from infusion

• Bispecific Abs could be effective in improving outcomes in late failure population

• Mechanisms of CAR T-cells failure and new treatment strategies should be investigated to improve the outcomes of these patients
Acknowledgments

- All the patients and their families
- All participating centers, medical and paramedical teams
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- LYSA and LYSARC
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