How to sequence non-CAR T-cell therapy for relapsed/refractory DLBCL

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Disclosures

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• Advisory Board member: Morphosys/Incyte, Epizyme, ADC Therapeutics, Calithera
Overview

• Recently FDA-approved therapies for R/R DLBCL
  • Polatuzumab vedotin (+rituximab/bendamustine) (June 2019)
  • Selinexor (June 2020)
  • Tafasitamab (+lenalidomide) (July 2020)
  • Loncastuximab teserine (April 2021)

• Sequencing of therapies
  • Line of therapy (2\textsuperscript{nd} vs 3\textsuperscript{rd} and beyond)
  • Candidacy for cellular therapies (CART19, ASCT)
  • Other factors – disease progression rate, patient preference
Polatuzumab vedotin

- MOA: anti-CD79B ADC linked to MMAE
- Design: phase 2 randomized (pola-BR vs BR), n=40 each arm
- Inclusion criteria: non-transformed DLBCL, ≥1 line prior therapy, ASCT ineligible
- Dosing: IV q3 weeks x6 cycles
- Toxicity: cytopenias, infection, low-grade PN (pola)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pola-BR</th>
<th>BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>45%</td>
<td>17.5%</td>
</tr>
<tr>
<td>CRR</td>
<td>40%</td>
<td>17.5%</td>
</tr>
<tr>
<td>mPFS</td>
<td>9.5 mo</td>
<td>3.7 mo</td>
</tr>
<tr>
<td>mDOR</td>
<td>12.6 mo</td>
<td>7.7 mo</td>
</tr>
<tr>
<td>mOS</td>
<td>12.4 mo</td>
<td>4.7 mo</td>
</tr>
</tbody>
</table>
Selinexor

- MOA: selective inhibitor of XPO1-mediated nuclear export
- Design: phase 2, n=127 (SADAL)
- Inclusion criteria: DLBCL (incl transformed), 2-5 lines prior therapy, ASCT ineligible, 60-98 days since last lymphoma therapy
- Dosing: PO 60 mg or 100 mg twice weekly (100 mg dose discontinued)
- Toxicity: cytopenias (thrombocytopenia), fatigue, nausea

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>28%</td>
</tr>
<tr>
<td>CRR</td>
<td>12%</td>
</tr>
<tr>
<td>mPFS</td>
<td>2.6 mo</td>
</tr>
<tr>
<td>mDOR</td>
<td>9.3 mo</td>
</tr>
<tr>
<td>mOS</td>
<td>9.1 mo</td>
</tr>
</tbody>
</table>

Lancet Haematol. 2020 Jul;7(7):e511-e522
Tafasitamab

- MOA: FC-enhanced humanized anti-CD19 mAb
- Design: phase 2 combination with lenalidomide, n=81 (L-MIND)
- Inclusion criteria: DLBCL (incl transformed), 1-3 lines prior therapy, ASCT ineligible, non-DHL, non-primary refractory
- Dosing: tafa: IV qwk x4 mo then q2wk until progression, len 25 mg d1-21 x12 mo
- Toxicity: cytopenias, infection, rash, diarrhea

**Outcome**

<table>
<thead>
<tr>
<th></th>
<th>All pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>60%</td>
</tr>
<tr>
<td>CRR</td>
<td>43%</td>
</tr>
<tr>
<td>mPFS</td>
<td>11.6 mo</td>
</tr>
<tr>
<td>mDOR</td>
<td>43.9 mo</td>
</tr>
<tr>
<td>mOS</td>
<td>33.5 mo</td>
</tr>
</tbody>
</table>

Haematologica. 2021 Sep 1;106(9):2417-2426
Loncastuximab teserine

- **MOA:** anti-CD19 ADC linked to SG3199
- **Design:** phase 2, n=145 (LOTIS-2)
- **Inclusion criteria:** DLBCL (incl transformed), ≥2 lines prior therapy
- **Dosing:** IV q3wk dosing x1 year (higher dose for C1-2)
- **Toxicity:** cytopenias, GI, edema, elevated LFTs (including GGT)

### Outcome

<table>
<thead>
<tr>
<th></th>
<th>All pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>48%</td>
</tr>
<tr>
<td>CRR</td>
<td>24%</td>
</tr>
<tr>
<td>mPFS</td>
<td>4.9 mo</td>
</tr>
<tr>
<td>mDOR</td>
<td>10.3 mo</td>
</tr>
<tr>
<td>mOS</td>
<td>9.9 mo</td>
</tr>
</tbody>
</table>
## Summary – R/R DLBCL therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Prior therapy</th>
<th>Relevant exclusion criteria</th>
<th>ORR</th>
<th>CRR</th>
<th>Median PFS</th>
<th>Median OS</th>
<th>Median DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polatuzumab (+bendamustine/rituximab)</td>
<td>≥ 1 line</td>
<td>Transformed indolent lymphoma</td>
<td>45%</td>
<td>40%</td>
<td>9.5 months</td>
<td>12.4 months</td>
<td>12.6 months</td>
</tr>
<tr>
<td>Selinexor</td>
<td>2-5 lines</td>
<td>Treatment within prior 60-98 days</td>
<td>28%</td>
<td>12%</td>
<td>2.6 months</td>
<td>9.1 months</td>
<td>9.3 months</td>
</tr>
<tr>
<td>Tafasitamab (+lenalidomide)</td>
<td>1-3 lines</td>
<td>DHL, primary refractory</td>
<td>58%</td>
<td>40%</td>
<td>11.6 months</td>
<td>33.5 months</td>
<td>43.9 months</td>
</tr>
<tr>
<td>Loncastuximab</td>
<td>≥ 2 lines</td>
<td></td>
<td>48%</td>
<td>24%</td>
<td>4.9 months</td>
<td>9.9 months</td>
<td>10.3 months</td>
</tr>
</tbody>
</table>
### Summary – R/R DLBCL therapies (continued)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Median time to response</th>
<th>ORR ≥3&lt;sup&gt;rd&lt;/sup&gt; line setting</th>
<th>ORR de novo/primary refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polatuzumab (+bendamustine/rituximab)</td>
<td>NR</td>
<td>50%</td>
<td>45%/NR</td>
</tr>
<tr>
<td>Selinexor</td>
<td>2 months</td>
<td>28%</td>
<td>24%/39%</td>
</tr>
<tr>
<td>Tafasitamab (+lenalidomide)</td>
<td>2 months</td>
<td>50%</td>
<td>~58%/99%</td>
</tr>
<tr>
<td>Loncastuximab</td>
<td>1.5 months</td>
<td>48%</td>
<td>49%/49%</td>
</tr>
</tbody>
</table>

- **Outcome All pts**
  - mClinresp: 21.5 d
  - mRadresp: 64 d
  - mEarlresp: 22 d

- **Design**: retrospective, n=50
- **Inclusion**: R/R DLBCL/HGBL, bridging tx prior to CART19
- **Dosing**: 48% pola monotherapy, 30% benda

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*Leuk Lymphoma. 2022 Jan;63(1):243-246*
CD19 expression/CD19-targeted therapy response following CD19-directed antibodies

Tafasitamab

- Case series of 8 lymph node biopsies taken from patients with progression on tafa-len treated on L-MIND
  - All had CD19 expression by IHC
  - 3/8 <85 days post-last dose of tafa (window of potential residual exposure)

- Case series of 2 patients with serial lymph node biopsies after progression on tafa-len who received CART19
  - Patient #1 – CD19 expression negative on days 4, 14, 26 but positive on day 32. NE for CART19 response
  - Patient #2 - CD19 expression negative on day 7, positive on day 25. Response to CART19

Loncastuximab

- 15 patients treated on LOTIS-2 received subsequent CART19 therapy
  - 7/15 achieved response
  - 6/15 achieved CR
  - No mention of CD19 expression

Leuk Lymphoma. 2022 Feb;63(2):468-472
Leuk Lymphoma. 2022 Mar;63(3):751-754
Sequencing of R/R DLBCL therapies

• Patient “buckets”
  • 2nd line, ASCT eligible
  • 2nd line, non-ASCT eligible, CART19 eligible
  • 2nd line, non-ASCT/non-CART19 eligible
  • ≥3rd line, CART19 eligible
  • ≥3rd line, non-CART19 eligible

• Patient factors
  • Comorbidities
  • Toxicity from prior therapy
  • Preference for IV and/or oral therapy
  • Willingness to travel to infusion center
Sequencing of R/R DLBCL therapies

2\textsuperscript{nd} line, ASCT eligible

- Commerical axi-cel if R/R ≤1yr from dx (bridge with polatuzumab +/- rituximab, obinutuzumab, ibrutinib, radiation therapy)
- Salvage immunochemotherapy (R-ICE, R-DHAC, R-GDP)

If CR or very good PR:
- HDT/ASCT

If Modest PR/SD/PD:
- Commercial CART19 (bridge with polatuzumab +/- rituximab, obinutuzumab, ibrutinib, radiation therapy)
Sequencing of R/R DLBCL therapies

2\textsuperscript{nd} line, non-ASCT eligible, CART19 eligible

Polatuzumab +/- rituximab, gemcitabine-containing palliative regimen

- CR or very good PR
  - Continue current therapy or active observation
- Modest PR/SD/PD
  - Commercial CART19 (bridge with polatuzumab +/- rituximab, obinutuzumab, ibrutinib, radiation therapy)
Sequencing of R/R DLBCL therapies

2\textsuperscript{nd} line, non-ASCT/non-CART19 eligible

Tafasitamab/lenalidomide, polatuzumab +/- rituximab, gemcitabine-containing palliative regimen

- CR or very good PR
  - Continue current therapy or active observation
- Modest PR/SD/PD
  - Therapies in step 1 not given before, loncastuximib, selinexor, clinical trial
Sequencing of R/R DLBCL therapies

≥3rd line, CART19 eligible

Commercial CART19 (bridge with polatuzumab +/- rituximab, obinutuzumab, ibrutinib, radiation therapy)
Sequencing of R/R DLBCL therapies

≥3rd line, non-CART19 eligible

Tafasitamab/lenalidomide (CD19+), polatuzumab +/- rituximab, loncastuximab (CD19+), selinexor, gemcitabine-containing palliative regimen, salvage immunochemotherapy (if ASCT candidate and not previously received), clinical trial

- CR or very good PR
  - Continue current therapy or active observation
- Modest PR/SD/PD
  - Therapies in step 1 not given before
Conclusions

• Recently FDA-approved therapies for R/R DLBCL are efficacious and tolerable

• No optimal standard sequencing of therapies for all patients

• Consider individual patient factors
  • Eligible for CART19 – consider avoiding prior use of CD19-directed therapies
  • Post-CART19 – test for CD19 expression prior to using CD19-directed therapies
  • Rapid disease progression – polatuzumab, cytotoxic chemo
  • Willing to receive frequent infusion therapy – tafasitamab/lenalidomide
  • Oral therapy only - selinexor
Non-FDA-approved R/R DLBCL therapies

Ibrutinib

- MOA: BTK inhibitor
- Design: phase 2, n=80, dose 560 mg daily

Obintuzumab

- MOA: type II glycoengineered anti-CD20 mAb
- Design: phase 2, n=25 R/R DLBCL (GAUGUIN)

ARS Question

• When should CD19-directed therapies be used for a R/R DLBCL patient relative to treatment with CART19

A. Before CART19
B. After CART19
C. After CART only if tumor cells express CD19
D. Never
E. A and B
F. A and C