Recent Advances in the Treatment of Hematologic Malignancies

Learning Objectives

Upon completion, participants should be able to:

• Describe recent clinical data supporting the use of novel agents that target FLT3 for the treatment of AML

• Identify aspects of current and emerging CAR T-cell therapies, including targets, activity, and toxicity
AML: Basic Facts

- Estimated new cases annually = 19,520\textsuperscript{a}
- Most patients diagnosed after age 60 years\textsuperscript{a}
- Heterogeneous based on disease- and patient-related features\textsuperscript{b}
- Therapy is adapted accordingly\textsuperscript{c}
- 5-year OS = 27\%\textsuperscript{a}
- Outcomes have improved in younger patients but remain suboptimal
- Outcomes have not improved as much for older patients; 5-year OS for AML patients older than 65 years = 5\%\textsuperscript{a}

The Molecular Heterogeneity of AML

**Patient Clusters**

- FLT3 mutations in AML
  - Three types of FLT3 mutation:
    - ITD
      - 20%-30%
      - Disrupts the auto-inhibitory function of the JM region
      - The receptor is still dependent on the presence of FLT3 ligand for complete activation
    - TKD point mutation
      - 5%-10%
      - Activates FLT3 kinase directly
    - JM domain point mutation (1%)

Characteristics of FLT3 Mutation–Positive AML

Higher incidence of NPM1 and DNMT3A mutations


Karyotype characteristics

<table>
<thead>
<tr>
<th></th>
<th>ITD neg/TKD wt (%)</th>
<th>ITD pos/TKD wt (%)</th>
<th>TKD mut/TKD wt (%)</th>
<th>ITD pos + TKD mut/TKD wt (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>721 (73.6)</td>
<td>183 (18.7)</td>
<td>58 (5.9)</td>
<td>17 (1.7)</td>
</tr>
<tr>
<td>Karyotype not available</td>
<td>59 (8.2)</td>
<td>22 (12.0)</td>
<td>2 (3.4)</td>
<td>0 (0)</td>
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<tr>
<td>Normal (XX,XY)</td>
<td>282 (59.1)</td>
<td>119 (65.5)</td>
<td>35 (80.3)</td>
<td>15 (61.8)</td>
</tr>
<tr>
<td>Aberrant</td>
<td>380 (52.7)</td>
<td>42 (33.3)</td>
<td>21 (34.3)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Individual aberrations (6;21)</td>
<td>38 (5.3)</td>
<td>2 (1.3)</td>
<td>1 (1.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>t(15;17)</td>
<td>16 (5.6)</td>
<td>13 (7.1)</td>
<td>4 (8.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>inv(16)(16;16)</td>
<td>38 (5.0)</td>
<td>1 (0.6)</td>
<td>5 (8.6)</td>
<td>1 (4.6)</td>
</tr>
<tr>
<td>t(9;22)</td>
<td>5 (0.1)</td>
<td>9 (4.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>t(3;3), inv(3q)</td>
<td>10 (1.4)</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>+8</td>
<td>59 (8.6)</td>
<td>6 (1.2)</td>
<td>9 (1.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>+8/11/13/9;22</td>
<td>54 (9.9)</td>
<td>9 (0.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>t(11;19)/22</td>
<td>26 (3.6)</td>
<td>13 (7.1)</td>
<td>4 (8.9)</td>
<td>1 (4.6)</td>
</tr>
<tr>
<td>-5/5q</td>
<td>70 (10.4)</td>
<td>2 (1.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>-7/7q</td>
<td>86 (11.9)</td>
<td>8 (0.0)</td>
<td>5 (8.6)</td>
<td>0 (0)</td>
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<tr>
<td>Other monosomies</td>
<td>94 (13.3)</td>
<td>3 (1.6)</td>
<td>1 (1.7)</td>
<td>0 (0)</td>
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<tr>
<td>Multiple aberrations</td>
<td>132 (18.3)</td>
<td>13 (1.6)</td>
<td>5 (8.6)</td>
<td>1 (4.8)</td>
</tr>
</tbody>
</table>

Effect of FLT3-ITD Mutation on Outcome (UK NCRI AML 10 and AML 12)

283/1,135 (25%) non-APL AML are FLT3-ITD pos

FLT3-ITD pos: CR 86%
FLT3-ITD neg: CR 85%

Outcome of FLT3-ITD–Positive AML Following Allogeneic HSCT

The prognosis for patients with FLT3-ITD–positive AML remains poor following allogeneic HSCT due to higher risk of relapse.

![Graph showing estimated event rate at 3 years for relapse risk, NRM, DFS, and OS for FLT3-ITD+ and FLT3-ITD- patients.](image)

P < .001, P < .05, P = .065, P = .334

Selectivity of FLT3 Inhibitors

<table>
<thead>
<tr>
<th>FLT3 Inhibitor</th>
<th>Kd (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lestaurtinibb</td>
<td>NA</td>
</tr>
<tr>
<td>Midostaurin</td>
<td></td>
</tr>
<tr>
<td>Sorafenibb</td>
<td></td>
</tr>
<tr>
<td>Tandutinibb</td>
<td></td>
</tr>
<tr>
<td>Quizartinibb</td>
<td></td>
</tr>
<tr>
<td>Crenolanibb</td>
<td></td>
</tr>
<tr>
<td>Gilteritinibb</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lestaurtinib</td>
<td>&quot;Investigational.&quot;</td>
</tr>
<tr>
<td>Midostaurin</td>
<td>&quot;Off-label use.&quot;</td>
</tr>
</tbody>
</table>

Lestaurtinib in First-Line Chemotherapy for FLT3-Mutated AML

AEs included nausea, emesis, constipation, diarrhea, and elevated alkaline phosphatase.


AML 15 and 17

<table>
<thead>
<tr>
<th></th>
<th>Lestaurtinib</th>
<th>Standard</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT3-ITD alone, n (%)</td>
<td>220 (73)</td>
<td>150 (75)</td>
<td></td>
</tr>
<tr>
<td>CR/CRI, %</td>
<td>92</td>
<td>94</td>
<td>.4</td>
</tr>
<tr>
<td>Survival at 5 y</td>
<td>51</td>
<td>56</td>
<td>.4</td>
</tr>
</tbody>
</table>

AML 17

<table>
<thead>
<tr>
<th></th>
<th>Lestaurtinib</th>
<th>Standard</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-y OS: No azole</td>
<td>60</td>
<td>55</td>
<td>.03</td>
</tr>
<tr>
<td>5-y OS: Azole</td>
<td>40</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>By FLT3 inhibition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 83)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 85%</td>
<td>60</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>≤ 85%</td>
<td>33</td>
<td></td>
<td></td>
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</tbody>
</table>

RATIFY (CALGB 10603): Chemotherapy + Midostaurin or Placebo in Newly Diagnosed Patients < 60 Years With FLT3-Mutated AML

Collaboration with 13 international cooperative groups; 225 sites from 17 countries
- Alliance, SWOG, ECOG, NCIC, NCCTG, GIMEMA, EORTC, AMLSG, SAL, OSHO, PETHEMA, CETLAM, ALSG
- 9 academic FLT3 screening laboratories worldwide

RATIFY (CALGB 10603): OS

Median OS

OS Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value (one-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>717</td>
<td>0.78 (0.63-0.96)</td>
<td>.009</td>
</tr>
<tr>
<td>ITD (high)</td>
<td>214</td>
<td>0.80 (0.57-1.12)</td>
<td>.19 (two-sided)</td>
</tr>
<tr>
<td>ITD (low)</td>
<td>341</td>
<td>0.81 (0.60-1.11)</td>
<td>.19 (two-sided)</td>
</tr>
<tr>
<td>TKD</td>
<td>162</td>
<td>0.85 (0.59-1.18)</td>
<td>.10 (two-sided)</td>
</tr>
</tbody>
</table>

Probability of Survival, %

Gilteritinib in FLT3-Mutated R/R AML Phase 1/2 Study (CHRYSALIS)

- ≥ 18 years with FLT3-ITD R/R AML, ≥ 10 patients/dose level (N = 252 total; 194 FLT3-ITD+)
- Induction failure or relapsed AML
- 7 dose escalation (n = 23) or expansion (n = 229) cohorts
- Primary endpoints: safety, tolerability, PK
- Doses of 80 mg/day or higher led to 90% phosphorylation inhibition by day 8
Gilteritinib in FLT3-Mutated R/R AML: Clinical Response by Dose

- **Proportion of Patients Achieving Response, %**
  - **20 mg (n = 14)**
  - **40 mg (n = 8)**
  - **80 mg (n = 12)**
  - **120 mg (n = 56)**
  - **200 mg (n = 89)**
  - **300 mg (n = 10)**
  - **450 mg (n = 2)**

Common AEs included diarrhea, fatigue, and abnormal liver enzyme tests.


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Gilteritinib in FLT3-Mutated R/R AML: OS

- **OS, %**
  - ≤ 40 mg/day
  - ≥ 80 mg/day

Common AEs included diarrhea, fatigue, and abnormal liver enzyme tests.

NDA filed 2018.

Quizartinib in FLT3-ITD–Positive R/R AML: Randomized Phase 2 Study

- FLT3-ITD–positive R/R AML after one second-line salvage or HSCT
- N = 76
- Prior FLT3 inhibitor allowed
- Primary objective: CR rate
- Secondary objectives: OS, duration of CRc, rate of bridging to HSCT, safety

![Diagram of FLT3-ITD+ R/R AML to second-line salvage chemotherapy or relapsed after HSCT (N = 76)](quizartinib_diagram)

Quizzartinib 30 mg/day
Quizzartinib 60 mg/day


Quizartinib in FLT3-ITD–Positive R/R AML: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>30-mg arm (n = 38)</th>
<th>60-mg arm (n = 38)</th>
<th>Total (N = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, CRc, and PR, %</td>
<td>60.5</td>
<td>71.1</td>
<td>65.8</td>
</tr>
<tr>
<td>CRc, %</td>
<td>47.4</td>
<td>47.4</td>
<td>47.4</td>
</tr>
<tr>
<td>Median duration CRc, wk</td>
<td>4.2</td>
<td>9.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Bridge to HSCT, %</td>
<td>32</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>Median OS, wk</td>
<td>20.9</td>
<td>27.3</td>
<td>22.6</td>
</tr>
</tbody>
</table>

AEs included febrile neutropenia, anemia, thrombocytopenia, neutropenia, pneumonia, increased bilirubin, and pyrexia.
Quizartinib significantly prolongs overall survival in patients with FLT3-ITD–mutated relapsed/refractory AML in the phase 3, randomized, controlled QuANTUM-R trial


Presented at the 23rd Congress of the European Hematology Association; June 16, 2018; Stockholm, Sweden. Abstract LB2600.

Quizartinib (AC220): A Highly Potent and Selective FLT3 Inhibitor

Quizartinib properties:
- Oral, highly potent, selective
- Nanomolar affinity (1.6 ± 0.7 nM) against FLT3 and complete suppression of FLT3 phosphorylation in ex vivo PIA assays
- Highly selective for FLT3 when screened against 402 human kinases (other kinases with Kd within 10-fold that of FLT3 were closely related RTKs [eg, KIT])

First-generation multikinase inhibitors
- Lestaurtinib
- Midostaurin
- Sorafenib

Second-generation FLT3 inhibitor
- Quizartinib

References:
QuANTUM-R Study Design

- Primary endpoint: OS (ITT population)
- Secondary endpoint: event-free survival (ITT population)
- Select exploratory endpoints: CRc rate, duration of CRc, and transplant rate
- Enrollment dates: May 2014 (first patient) to September 2017 (last patient); data cutoff: February 2018

- FLT3-ITD AML (N = 367)
  - Age ≥ 18 years
  - Refractory AML or relapse within 6 months of first remission (± HSCT)
  - ≥ 1 cycle of standard-dose anthracycline- or mitoxantrone-containing induction therapy
  - ≥ 3% FLT3-ITD allelic ratio

- Quizartinib (n = 245)
  - 30 mg × 15 days → 60 mg if QTcF ≤ 450 ms on day 16

- Salvage chemotherapy (n = 122)
  - LoDAC (n = 29)
  - MEC (n = 40) or FLAG-IDA (n = 53)

- HSCT

- Quizartinib continuation

- Long-term follow-up

Optional treatments

QuANTUM-R CONSORT Diagram

- Screened (N = 563)
  - Randomized 2:1 (N = 367)

Quizartinib (n = 245)
  - Treated (n = 241)
  - Not treated (n = 4)

Ongoing on initial treatment (n = 6)
Completed treatment (N/A)

Primary reason for treatment discontinuation:
  - HSCT (n = 78)
  - Relapse (n = 60)
  - Lack of response/PD (n = 47)
  - AEs (n = 24)
  - Death (n = 17)
  - Protocol violation (n = 1)
  - Withdrew consent (n = 3)
  - Other (n = 4)

Received allogeneic HSCT (n = 78)

Salvage chemotherapy (n = 122)
  - Treated (n = 94)
  - Not treated (n = 28)

Ongoing on initial treatment (n = 0)
Completed treatment (n = 24)

Primary reason for treatment discontinuation:
  - HSCT (n = 3)
  - Relapse (n = 3)
  - Lack of response/PD (n = 49)
  - AEs (n = 1)
  - Death (n = 6)
  - Protocol violation (n = 2)
  - Withdrew consent (n = 2)
  - Lost to follow-up (n = 1)
  - Other (n = 3)

Received allogeneic HSCT (n = 14)
**QuANTUM-R Primary Endpoint:**
**OS by Kaplan-Meier Method**

- **Median OS:**
  - Quizartinib (n = 245): 6.2 months (95% CI, 5.3-7.2 months)
  - Salvage chemotherapy (n = 122): 4.7 months (95% CI, 4.0-5.5 months)

- **Median follow-up:** 23.5 months

- **HR, 0.76 (95% CI, 0.58-0.98)**
  - *P* = .0177 (1-sided, stratified log-rank)

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**QuANTUM-R: Best Response**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quizartinib n = 245</th>
<th>Salvage chemotherapy n = 122</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best response</strong></td>
<td>Percentage (95% CI)</td>
<td></td>
</tr>
<tr>
<td>CRc*</td>
<td>48 (42-55)</td>
<td>27 (19-36)</td>
</tr>
<tr>
<td>CR</td>
<td>4 (2-7)</td>
<td>1 (0-5)</td>
</tr>
<tr>
<td>CRp</td>
<td>4 (2-7)</td>
<td>0 (0-3)</td>
</tr>
<tr>
<td>CRi</td>
<td>40 (34-47)</td>
<td>26 (19-35)</td>
</tr>
<tr>
<td>PR</td>
<td>21 (16-27)</td>
<td>3 (1-8)</td>
</tr>
<tr>
<td>ORR (CRc + PR)</td>
<td>69 (63-75)</td>
<td>30 (22-39)</td>
</tr>
<tr>
<td>No response</td>
<td>25 (20-31)</td>
<td>37 (28-46)</td>
</tr>
<tr>
<td>Nonevaluable</td>
<td>5 (3-9)</td>
<td>33 (25-42)</td>
</tr>
</tbody>
</table>

*Nominal *P* = .001 for between-group comparison of CRc.

QuANTUM-R: Duration of CRc and Transplant Rate

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quizartinib n = 245</th>
<th>Salvage Chemotherapy n = 122</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of CRc (95% CI), weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>12.1 (10.4-27.1)</td>
<td>5.0 (3.3-12.6)</td>
</tr>
<tr>
<td>Transplant, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant rate*</td>
<td>32</td>
<td>12</td>
</tr>
</tbody>
</table>

*Nominal P < .0001 for between-group comparison of transplant rate.

QuANTUM-R: Conclusions

- Single-agent quizartinib significantly prolonged OS of patients with FLT3-ITD–mutated R/R AML compared with salvage chemotherapy
  - OS: HR, 0.76 (95% CI, 0.58-0.98; P = .0177)
- Single-agent quizartinib was well tolerated
  - Grade ≥ 3 QTcF prolongation was uncommon
  - Investigator choice and quizartinib associated with similar rates of TEAE
- QuANTUM-R: first phase 3 trial to demonstrate that an FLT3 inhibitor improved OS compared with standard chemotherapy in patients with FLT3-ITD–mutated R/R AML
- QuANTUM-First: ongoing phase 3 study of standard chemotherapy plus placebo versus quizartinib in patients with newly diagnosed FLT3-ITD–mutated AML

Targeting FLT3 in AML: Closing Thoughts

1. Single-agent inhibitors of FLT3 are active in AML, but response rates are low despite the presence of the biomarker and inhibition of the target in all subjects
   - Predictors of response are needed
2. Combination of a kinase inhibitor with chemotherapy improves the survival of patients with FLT3-mutated AML
   - OS benefit with midostaurin is less than impressive
   - Biological basis of survival benefit is not certain (ie, inhibition of FLT3 or other kinases)
   - Will more specific inhibitors further improve outcome with chemotherapy?
3. FLT3 is a late event in leukemogenesis and is likely present only in a subclone
4. Combination of FLT3 inhibitors with agents that target cellular apoptosis (eg, BCL2 inhibitors, MDM2 inhibitors) or target the leukemic stem cell (eg, Hedgehog inhibitors, anti-CD123 antibody drug conjugates) may further improve efficacy of this class of drugs

CAR T-Cell Therapy for R/R DLBCL

Matthew McKinney, MD
Refractoriness and Relapses: The Fundamental Issue in DLBCL

- 15% to 25% are refractory to any chemotherapy
- 5% partial response patients
- 20% to 30% relapses
- 50% to 60% are already cured with previous chemotherapy (RCHOP)

We need randomized studies on these select groups of patients.
We will never improve those cured patients.

“Traditional” Salvage Chemotherapy in DLBCL

- Relapse < 12 Months (Post-CHOP)
  - Prior rituximab: No (n = 41)
  - Censored prior rituximab: No
  - Prior rituximab: Yes (n = 187)
  - Censored prior rituximab: Yes

- Relapse > 12 Months
  - Prior rituximab: No (n = 106)
  - Censored prior rituximab: No
  - Prior rituximab: Yes (n = 54)
  - Censored prior rituximab: Yes

P = .0010
P = .1124
SCHOLAR-1 Dataset

<table>
<thead>
<tr>
<th>MDACC (n = 165)</th>
<th>I/MC (n = 82)</th>
<th>LY-12 (n = 219)</th>
<th>CORAL (n = 170)</th>
<th>Pooled (N = 636)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients evaluated for survival, n</td>
<td>165</td>
<td>72</td>
<td>196</td>
<td>170</td>
</tr>
<tr>
<td>Survival from commencement of salvage therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Deaths</td>
<td>89</td>
<td>92</td>
<td>80</td>
<td>84</td>
</tr>
<tr>
<td>Median (95%, CI), mo</td>
<td>6.6</td>
<td>5.0</td>
<td>6.6</td>
<td>6.6</td>
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<tr>
<td>1-y survival rate</td>
<td>26</td>
<td>18</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>2-y survival rate</td>
<td>17</td>
<td>10</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Primary refractory</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Deaths</td>
<td>--</td>
<td>90</td>
<td>76</td>
<td>85</td>
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<tr>
<td>Median (95%, CI), mo</td>
<td>--</td>
<td>6.1</td>
<td>7.3</td>
<td>7.3</td>
</tr>
<tr>
<td>1-y survival rate</td>
<td>--</td>
<td>26</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>2-y survival rate</td>
<td>--</td>
<td>21</td>
<td>27</td>
<td>16</td>
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<tr>
<td>Refractory to second-line therapy</td>
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<td></td>
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<tr>
<td>Deaths</td>
<td>88</td>
<td>92</td>
<td>86</td>
<td>77</td>
</tr>
<tr>
<td>Median (95%, CI), mo</td>
<td>6.6</td>
<td>4.7</td>
<td>6.3</td>
<td>6.1</td>
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<tr>
<td>1-y survival rate</td>
<td>29</td>
<td>9</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>2-y survival rate</td>
<td>19</td>
<td>6</td>
<td>14</td>
<td>22</td>
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<tr>
<td>Relapsed ≤ 12-mo post-ASCT</td>
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<tr>
<td>Deaths</td>
<td>94</td>
<td>94</td>
<td>86</td>
<td>80</td>
</tr>
<tr>
<td>Median (95%, CI), mo</td>
<td>5.9</td>
<td>4.2</td>
<td>7.0</td>
<td>6.3</td>
</tr>
<tr>
<td>1-y survival rate</td>
<td>19</td>
<td>25</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>2-y survival rate</td>
<td>8</td>
<td>6</td>
<td>21</td>
<td>20</td>
</tr>
</tbody>
</table>

SCHOLAR-1 Long-Term Outcomes and ASCT

Outcomes are poor… how do you move the needle?

Rationale for Immunotherapy in DLBCL (and Other B-Cell NHLs)

• Chemorefractory DLBCL has a very poor outcome
• Immunotherapy of B-cell markers has already improved survival
• Acquired B-cell aplasia is remarkably well tolerated in adults

Molecular Aspects of CAR T-Cell Constructs

CARs are hybrid proteins consisting of an extracellular single chain fragment of variable region (scFv) fused to co-stimulatory signaling domains CD28 or 4-1BB (CD137), coupled with CD3ζ to mediate T-cell activation.

First Generation
- CD4 / CD8 zeta CARs
- scFv CARs

Second Generation
- scFv CD28 CARs
- scFv CD137 CARs

Extracellular

Intracellular

Irving & Weiss, 1991
Letai et al., 1991
Romeo, 1991
Kowalski, 1987
Eshhar, 1993
Roberts, 1997
Finney, 1998
Maher, 2002
Finney, 2002
Imai, 2004
Mifune, 2009
Carpentor, 2009
**CTL019a** Is Designed to Hunt and Destroy CD19-Positive B-Cell Cancers in Patients

Aspects of Most Studied CD19 CAR T-Cell Constructs—The Models

<table>
<thead>
<tr>
<th>Academic Group</th>
<th>Company (Drug)</th>
<th>Costimulatory Domain</th>
<th>Vector Delivery</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPenn</td>
<td>Novartis (CTL019)</td>
<td>4-1BB</td>
<td>Lentiviral</td>
<td>ALL, CLL, DLBCL, FL</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Juno (JCAR 015)</td>
<td>CD28</td>
<td>Retroviral</td>
<td>ALL, CLL, various B-cell malignancies</td>
</tr>
<tr>
<td>Fred Hutchinson</td>
<td>Juno (JCAR 017)</td>
<td>4-1BB</td>
<td>Lentiviral</td>
<td></td>
</tr>
<tr>
<td>NCI (NIH)</td>
<td>Kite Pharma (KTE-C19)</td>
<td>CD28</td>
<td>Retroviral</td>
<td>DLBCL</td>
</tr>
<tr>
<td>Baylor</td>
<td>Bluebird/Celgene</td>
<td>CD28</td>
<td>Retroviral</td>
<td>ALL, CLL</td>
</tr>
<tr>
<td>MDACC</td>
<td>Ziopharm/Intrexon</td>
<td>CD28 → 4-1BB</td>
<td>Transposon/transposase</td>
<td>Adjuvant, pre-/post-transplant</td>
</tr>
<tr>
<td>Institut Pasteur</td>
<td>Cellcertis/Pfizer (UCART19a)</td>
<td>4-1BB</td>
<td>Lentiviral</td>
<td>ALL, CLL, AML, MM</td>
</tr>
<tr>
<td>Baylor</td>
<td>Bellicum (BPX-401a)</td>
<td>MyD88 + CD40</td>
<td>Retroviral</td>
<td>Various</td>
</tr>
<tr>
<td>Dartmouth</td>
<td>Cardio3</td>
<td>DAP-10 transmembrane</td>
<td>Retroviral</td>
<td>AML, MDS, MM</td>
</tr>
</tbody>
</table>

FDA-approved indication. *Off-label and investigational. www.clinicaltrials.gov*
Axicabtagene Ciloleucel (axi-cel) in R/R DLBCL

**Bar Chart**
- Axicabtagene Ciloleucel (axi-cel) in R/R DLBCL
- Best Response, %
  - Complete response
  - Partial response
  - Stable disease
  - Disease progression
  - Could not be evaluated

**Table**
- DLBCL (n = 77)
  - ORR: 49 (38)
  - SD: 12 (9)
  - PD: 5 (4)
  - NE: 1 (1)

- PMBCL or TFL (n = 24)
  - ORR: 71 (17)
  - SD: 8 (2)
  - PD: 4 (1)
  - NE: 4 (1)

- All Patients (N = 101)
  - ORR: 82 (85)
  - SD: 11 (11)
  - PD: 5 (5)
  - NE: 2 (2)

**Graph**
- 6-mo OS, ZUMA-1 vs SCHOLAR-1: 80% vs 55%
- Median OS (95% CI), mo
  - ZUMA-1: NR (10.5-NR)
  - SCHOLAR-1: 6.3 (6.1-7.5)

**FDA approved axi-cel on October 18, 2017**
- Median follow-up: 8.7 mo

**Reference**
Durable Response Rates With FDA-Approved CAR T-Cell Therapy

**JULIET study in DLBCL shows strong Duration of Response**
74% of responders were relapse-free at 6 months

<table>
<thead>
<tr>
<th>r/r DLBCL responses to therapy</th>
<th>n</th>
<th>ORR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response</td>
<td>81</td>
<td>53%</td>
<td>40%</td>
</tr>
<tr>
<td>Month 3 response</td>
<td>81</td>
<td>38%</td>
<td>32%</td>
</tr>
<tr>
<td>Month 6 response</td>
<td>46</td>
<td>37%</td>
<td>30%</td>
</tr>
</tbody>
</table>

- 6-month probability of being relapse-free was 74%
- Median DOR and OS not reached
- 6-month probability of overall survival was 64.5%
- No patient who achieved a response (CR or PR) proceeded to allogeneic- or auto-SCT
CAR T Cells—Response at Cost of Toxicity

- Immunotherapy with CAR T cells with activation molecules not without collateral toxicity
- Cytokine release syndrome and neurologic toxicity can be severe/life-threatening
- Requires inpatient monitoring by dedicated expert staff

Patient Case

- 63-year-old with DLBCL
- Treated with:
  - Rituximab-EPOCH/MTX (complete response)
  - Rituximab-ICE (refractory)
  - 4/24/18 axi-cel infusion (post-collection/lymphodepletion)
Summary

- Outcomes in chemorefractory DLBCL have historically been dismal
- Current CAR modified T-cell technology offers new hope for R/R lymphomas and other B-cell malignancies
- Overcoming limitations associated with time to produce therapy, toxicity, and cost will be key to success of future therapies

Contact Information

Call (toll-free) 866 858 7434
Email info@med-iq.com

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Hematologic Malignancies: Abbreviations and Acronyms

AE = adverse event
ALL = acute lymphocytic leukemia
AML = acute myeloid leukemia
APC = antigen-presenting cell
APL = acute promyelocytic leukemia
ASCT = autologous stem cell transplantation
BCL2 = B-cell lymphoma 2
BM = bone marrow
CAR = chimeric antigen receptor
CBF = core-binding factor
CCTG = Canadian Cancer Trials Group
CLL = chronic lymphocytic leukemia
CR = complete remission
CRc = composite complete remission
CRI = complete remission with incomplete peripheral blood count recovery
CRp = complete remission with incomplete platelet recovery
CT = computed tomography
DFS = disease-free survival
DLBCL = diffuse large B-cell lymphoma
EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin
Exp = expected
FL = follicular lymphoma
FLAG-IDA = fludarabine, cytarabine, and idarubicin
FLT3 = fms-like tyrosine kinase-3
HSCT = hematopoietic stem cell transplantation
IA = Molecular Epidemiology Resource of the University of Iowa
ICE = ifosfamide, carboplatin, etoposide
ITD = internal tandem duplication
ITT = intention to treat
JM = juxtamembrane
LoDAC = low-dose cytarabine
LYSARC = Lymphoma Academic Research Organization
MC = Mayo Clinic Lymphoma Specialized Program of Research Excellence
MDACC = MD Anderson Cancer Center
MDS = myelodysplastic syndromes
MEC = mitoxantrone, etoposide, and cytarabine
MM = multiple myeloma
MSKCC = Memorial Sloan Kettering Cancer Center
MTD = maximum tolerated dose
MTX = methotrexate
NA = not available
N/A = not applicable
NCI = National Cancer Institute
NCRI = National Cancer Research Institute
ND = newly diagnosed
NDA = New Drug Application
NE = not evaluable
NHL = Non-Hodgkin lymphoma
NIH = National Institutes of Health
NR = not reached
NRM = nonrelapse mortality
Obs = observed
ORR = objective response rate
OS = overall survival
PD = progressive disease
PET = positron emission tomography
PIA = plasma inhibitory activity
PK = pharmacokinetics
PMBCL = primary mediastinal B-cell lymphoma
pMHC = peptide-major histocompatibility complex
PR = partial remission
QTcF = Fridericia-corrected QT interval
RCHOP = rituximab + cyclophosphamide/doxorubicin/vincristine/prednisone
R/R = relapsed or refractory
RTK = receptor tyrosine kinase
scFv = single-chain fragment of variable region
SD = stable disease
SEER = Surveillance, Epidemiology and End Results
TCR = T-cell receptor
TEAE = treatment-emergent adverse event
TFL = transformed follicular lymphoma
TIL = tumor-infiltrating lymphocyte
TKD = tyrosine kinase domain
WBC = white blood cell
wt = wild type