Novel Agents in Hematology: Newly FDA approved and Investigational Drugs in Benign and Malignant Hematology

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Mayo Clinic Hospital
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Topic Objectives

• Describe common hematological malignancies, standard of care, and the landscape of evolving therapies

• Review the safety and efficacy data of the landmark clinical trials of select novel agents in benign and malignant hematology

• Discuss novel therapeutic approaches of investigation drugs currently in clinical trials
Advancements in Cancer Treatment

- National Cancer Act of 1971 effort to eradicate cancer as a leading cause of death
- Remarkable progress over several decades
  - Understanding molecular biology, clonal evolution
  - Identifying and targeting genetic mutations
  - Recognizing role of immunosurveillance
- Targeted/Immunotherapy + chemotherapy
  - Monoclonal antibodies, small molecule inhibitors
  - Check point inhibitors, CAR-T cell
Challenges of Resistance

- Cancer ability evolve and adapt to become resistant to therapy
  - Targeted therapy select for resistant clones leading to refractory or recurrent (r/r) disease

- Overcoming resistance
  - Novel therapies, targets identified
  - 2nd-gen improved selectivity and toxicity profile
  - Multi-drug protocols combining chemotherapy with mAb and small molecule inhibitors

- Cancer 2nd leading cause of death

2017 Drug approvals

• 49 novel Agents FDA approved drugs in 2017
  • 19 Heme/Onc 19 (38.8%), 6 ID (12.5%), 21 Other (43.8%)

• Novel Agents in clinical practice
  • Monoclonal antibodies (bi-specific, antibody-drug conjugates, check point inhibitors, novel targets)
  • Small molecule inhibitors (TKIs)
  • CAR-T cells
2017 FDA Approved in Hematology

- Midostaurin (FLT3+ AML)
- Inotuzumab (r/r pre-B ALL)
- Tisagenlecleucel (r/r pre-B ALL)
- AxicabtageneCiloleucil (r/r large B-cell Lymphoma)
- Emicizumab (Hemophilia A)
- Obinutuzumab (untreated FL)
- Lenalidomide (maintenance post-auto HCST MM)
- Rituximab SQ (FL, DLBCL, CLL)
- Gemtuzumab Ozogamicin (CD33+ AML)
- Tociluzumab (CAR T-Cell CRS)
- Obinutuzumab (untreated FL)
- AxicabtageneCiloleucil (r/r large B-cell Lymphoma)
- Lenalidomide (maintenance post-auto HCST MM)
- Pembrolizumab (refractory cHL s/p ≥ 3lines of therapy)
- Pembrolizumab (refractory cHL s/p ≥ 3lines of therapy)
- Liposomal daunorubicin and cytarabine (tAML/AML-MRC)
- Ibrutinib (cGVHD)
- Brentuximab vedotin (pALCL CD20+ MF)

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# Novel Agents 2017

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism</th>
<th>Indication</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copanlisib (Aliqopa)</td>
<td>Phosphatidylinositol-3-kinase (PI3K) Inhibitor</td>
<td>Follicular Lymphoma</td>
<td>Sept 4&lt;sup&gt;th&lt;/sup&gt; 2017</td>
</tr>
<tr>
<td>Acalabrutinib (Calquence)</td>
<td>Bruton Tyrosine Kinase (BTK) Inhibitor</td>
<td>Mantle Cell Lymphoma</td>
<td>Oct 31&lt;sup&gt;st&lt;/sup&gt; 2017</td>
</tr>
<tr>
<td>Emicizumab-kxwh (Hemlibra)</td>
<td>Bispecific factor IXa- and factor X-directed antibody</td>
<td>Hemophilia A</td>
<td>Nov 16&lt;sup&gt;th&lt;/sup&gt; 2017</td>
</tr>
<tr>
<td>Axicabtagne ciloleucel (Yescarta)</td>
<td>CAR T-cell</td>
<td>Aggressive Lymphoma</td>
<td>Oct 18&lt;sup&gt;th&lt;/sup&gt; 2017</td>
</tr>
</tbody>
</table>
Assessment Question 1

• What novel therapeutic approach for the treatment of cancer was first approved in 2017?

A. Conventional chemotherapy
B. Small molecule inhibitors
C. Monoclonal antibodies
D. CAR T-cells (Adaptive Cellular Therapy)
E. Hematopoietic Stem Cell Transplant
Non-Hodgkin’s Lymphoma (NHL)

• Most common blood cancer
  • Rising incidence, doubling in past 25-30 yrs
• Seventh leading site of new cancer cases
  • 4% of new cancers, 3% cancer-related deaths
• Heterogeneous group of lymphoproliferative disorders
• B-cells are the majority (85%) and T-cells (15%) and rarely NK cells
Non-Hodgkin’s Lymphoma

**Indolent Lymphoma**
- Follicular Lymphoma (FL) (17%)
- Small Lymphocytic Lymphoma (SLL)/ Chronic Lymphocytic Leukemia (CLL) (18.3%)
- Marginal Zone (MZL) (8.3%)
- Mantel Cell (MCL) (4.1%)

**Aggressive Lymphoma**
- Diffuse Large B-cell Lymphoma (DLBCL) (32.5%)
- Mantle Cell Lymphoma (MCL) (4.1%)
- Primary Mediastinal Large B-Cell Lymphoma (PMBCL) (2.4%)
- Burkitt Lymphoma (<1%)
Marginal Zone Lymphoma

Mantle Zone

Germinal Center

Naïve B Cell

GC B-Cell

Marginal Zone

DLBCL (ABC type) PMBCL

Memory B-Cell

Mantle Cell Lymphoma

Plasmablast

Plasma Cell

Follicular Lymphoma

Burkitt Lymphoma

DLBCL (GC type)

Lymphocyte-predominant HL

Multiple Myeloma

B-CLL

GC B-Cell

Mantle Cell Lymphoma

Multiple Myeloma
Therapeutic Approaches

• Wait and watch vs Immunochemotherapy vs Targeted Agents
• Immunotherapy
  • CD20+ mAb (rituximab, ofatumumab, obinutuzumab, ibritumomab-radioisotope)
  • CD30+ ADC (brentuximab vedotin)
• Chemotherapy
  • Alkylating Agents (Cyclophosphamide, Ifosfamide, bendamustine)
  • Purine/pyrimidine analogs (fludarabine, cladribine, cytarabine)
  • Other – anthracyclines, vinca alkaloids, etc
• Small molecule inhibitors
  • Ibrutunib, venetoclax, idelalisib, IMiDs
• Autologous HSCT
• CAR-T cells (CD19 directed)
Copanlisib (Aliqopa)

- 2nd generation small molecule inhibitor of Phosphatidylinositol-3-kinase (PI3K)
- FDA approved 9/14/17
- Indication: r/r FL s/p ≥ 2 previous treatments
- Dose: 60 mg IV on D1,8,15 Q 28 d cycle
- Idelalisib – 1st-generation PI3K-Inhibitor
  - Efficacy in r/r indolent lymphoma (CLL, FL, SLL)
  - BBW – autoimmune (hepatitis, pneumonitis, colitis), infections, GI perforation
PI3K/AKT/mTOR Pathway

Growth Factor – PDGF, IGF, TGF-α, VEGF

Receptor Tyrosine Kinase

PI3Kβ
PI3Kα
PI3Kδ

PI3K/akt/mTOR Pathway

Phosphate and tensin homolog – PIP₃ to PIP₂ -Tumor suppressor

Copanlisib

PTEN

Idelalisib – PI3K-δ

DNA Transcription/Protein Synthesis

Gene Expression: Proliferation, cell survival, Angiogenesis

RAS
B-RAF
MEK
ERK 1/2
### CHRONOS-1 Trial

#### Baseline

<table>
<thead>
<tr>
<th></th>
<th>N=104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>62</td>
</tr>
<tr>
<td>ECOG 0-1</td>
<td>96%</td>
</tr>
<tr>
<td>Presence of B symptoms</td>
<td>13%</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>21</td>
</tr>
<tr>
<td>III</td>
<td>28</td>
</tr>
<tr>
<td>IV</td>
<td>48</td>
</tr>
<tr>
<td>Median # of prior therapies</td>
<td>3 (2-8)</td>
</tr>
</tbody>
</table>

#### Refractory

- Anti-CD20 mab: 57%
- Alkylating Agent: 38%
- Combination: 41%

#### Response

<table>
<thead>
<tr>
<th></th>
<th>N=104</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>59% (49,68)</td>
</tr>
<tr>
<td>CR</td>
<td>14% (8,23)</td>
</tr>
<tr>
<td>PR</td>
<td>44% (35,54)</td>
</tr>
<tr>
<td>Median DOR</td>
<td>12.2 mo</td>
</tr>
</tbody>
</table>

- Multicenter, single-arm trial
- 104 pt r/r FL (Grade 1-2 or 3a)
- Failed ≥2 therapies
  - Include RTX+Alkylating Agent
  - Copanlisib 60 mg IV D1,8,15 Q28d
  - Dose reductions 45mg & 30mg
- Primary End Point ORR
  - Assessed Q 2cycles
CHRONOS-1: Toxicity

Adverse effects (all Grades; Grade≥3):

- **Hyperglycemia** (54%; 39%) diarrhea(36%,5%), fatigue(36%,4%), **hypertension** (35%;27%), neutropenia(32%;25%), nausea(36%,<1%), lower respiratory infection(21%; 14%), and thrombocytopenia(22%, 8 %)
- Transient during infusion, occurred greater frequency on D1

<table>
<thead>
<tr>
<th>Hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak blood glucose</td>
</tr>
<tr>
<td>Mean change BG</td>
</tr>
<tr>
<td>Grade 3-4</td>
</tr>
<tr>
<td>TEAE HbA1c &gt;6.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak systolic BP</td>
</tr>
<tr>
<td>Mean change BP</td>
</tr>
<tr>
<td>Grade 3 AE</td>
</tr>
</tbody>
</table>

Dose reduction due to AE 21%; Discontinuation due to AE 16%
## PI3K: Efficacy Data

<table>
<thead>
<tr>
<th>Response Rates</th>
<th>Copanlisib N=104</th>
<th>Copanlisib N=142</th>
<th>Idelalisib (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>59% (61)</td>
<td>58.5%</td>
<td>54% (39)</td>
</tr>
<tr>
<td>CR</td>
<td>14% (15)</td>
<td>16.4%</td>
<td>8% (6)</td>
</tr>
<tr>
<td>PR</td>
<td>44% (46)</td>
<td>42%</td>
<td>46% (33)</td>
</tr>
<tr>
<td>Median DOR (range)</td>
<td>12.2 (0+,22.6)</td>
<td>20 mo</td>
<td>NE(0-14.8)</td>
</tr>
<tr>
<td>Time to response</td>
<td>1.7 mo (1.3-9.7mo)</td>
<td>--</td>
<td>1.9 mo (1.6-8.3)</td>
</tr>
</tbody>
</table>

## PI3K: Toxicity Data

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Idelalisib</th>
<th>Copanlisib (6/16)</th>
<th>Copanlisib(2/17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>----</td>
<td>48.3%</td>
<td>49.3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>----</td>
<td>29.6%</td>
<td>29.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47%</td>
<td>33.8%</td>
<td>33.8%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>25%</td>
<td>25.4%</td>
<td>27.4%</td>
</tr>
<tr>
<td>Hepatotoxicity (Grade 3/4)</td>
<td>18%</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4%</td>
<td>4.2%</td>
<td>4.2%</td>
</tr>
<tr>
<td>D/C d/t AE</td>
<td>17%</td>
<td>16%</td>
<td>18.3%</td>
</tr>
</tbody>
</table>
PI3K-Inhibitors

• PI3K-I class includes Idelalisib and Copanlisib
  • Similar ORR between groups in r/r FL
• Copanlisib broader specificity than Idelalisib
  • PI3K-α inhibition may overcome resistance
• Toxicity profiles differ d/t route, frequency, PI3K target

Copanlisib
• Hyperglycemia and hypertension
• Less autoimmune and infectious toxicities

Idelalisib
• BBW - Autoimmune hepatitis, pneumonitis, colitis
• GI perforation
Future Direction

• CHRONOS-3*
  • Combination with Rituximab vs placebo in relapsed indolent NHL (≥1 prior therapy)

• CHRONOS-4**
  • Combination with immuno-chemotherapy (R-CHOP or R-bendamustine) + copanlisib or placebo in relapsed indolent NHL (1-3 prior lines of therapy)

• PI3K/mTOR pathway targeted in solid tumor
  • Breast cancer (+trastuzumab/AI), glioblastoma, NSCLC, HNSCC (+cetuximab)

* Excluding pts w/prior PI3K resistance; **Excludes Rituximab resistant disease
Acalabrutinib (Calquence)

- Small molecule inhibitor of Bruton T- Kinase (BTK)
- FDA approved October 31, 2017
- Treatment of mantle cell lymphoma (MCL) who have received at least one prior therapy

Ibrutinib (Imbruvica)
- 1st-generation BTK inhibitor
- Activity against r/r MCL, CLL/SLL (+/- del17p), MZL (s/p CD20+mab), cGVHD 2017
- Toxicity profile: hemorrhage, Atrial fibrillation (A.Fib), cytopenias, infection, secondary malignancies
ACE-LY-004 Trial

- Phase 2, multi-center, single-arm
- 124 pt r/r MCL
- Failed ≥1 therapies
  - Excluded prior BTK-I
  - Concomitant warfarin
- Acalabrutinib 100 mg PO BID
- Primary End Point ORR

<table>
<thead>
<tr>
<th>Baseline</th>
<th>N=124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>68 (49-90)</td>
</tr>
<tr>
<td>Intermediate MIPI</td>
<td>44%</td>
</tr>
<tr>
<td>High risk MIPI</td>
<td>17%</td>
</tr>
<tr>
<td>Extranodal disease</td>
<td>73%</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>51%</td>
</tr>
<tr>
<td>Median # of prior therapies</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>Refractory to prior tx</td>
<td>24%</td>
</tr>
<tr>
<td>Prior HSCT</td>
<td>18%</td>
</tr>
</tbody>
</table>

## ACE-LY-004 Trial

<table>
<thead>
<tr>
<th>Response</th>
<th>Acalabrutinib* N=104</th>
<th>Ibrutinib N=111</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>81% (72,87)</td>
<td>66%</td>
</tr>
<tr>
<td>CR</td>
<td>40% (31,49)</td>
<td>17%</td>
</tr>
<tr>
<td>PR</td>
<td>41% (32,50)</td>
<td>49%</td>
</tr>
<tr>
<td>Median DOR</td>
<td>NR (13.5 mo-NR)</td>
<td>17.5 mo</td>
</tr>
<tr>
<td>Cont response 12 mo</td>
<td>73%</td>
<td>-----</td>
</tr>
<tr>
<td>Time to response</td>
<td>1.9 mo (1.5-4.4)</td>
<td>1.9 mo</td>
</tr>
</tbody>
</table>

*Median f/u 15.2 mo (0.3-23.7mo)
## ACE-LY-004: Toxicity

- **All Grade**: Anemia, thrombocytopenia, headache, neutropenia, Diarrhea, fatigue, myalgia
- **Common Grade 3**: Neutropenia (11%); Anemia (9%); Pneumonia (6%)

<table>
<thead>
<tr>
<th></th>
<th>Acalabrutinib (N=612)</th>
<th>Ibrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytosis</td>
<td>31%</td>
<td>33%</td>
</tr>
<tr>
<td>Onset (wks)</td>
<td>1.1</td>
<td>1-2</td>
</tr>
<tr>
<td>Duration (wks)</td>
<td>6.7</td>
<td>8</td>
</tr>
<tr>
<td>A.Fib/A.Flutter (Gr 3)</td>
<td>0 % (3%; 1%)</td>
<td>7% (2.8%)</td>
</tr>
<tr>
<td>Hemorrhage Major</td>
<td>32% (52%)</td>
<td>31%-51%</td>
</tr>
<tr>
<td></td>
<td>0.8% (2%)</td>
<td>6%</td>
</tr>
<tr>
<td>2nd Primary Malignancy</td>
<td>3% (5%)</td>
<td>3-16%</td>
</tr>
<tr>
<td>Grade $\geq$3 Infections</td>
<td>14% (18%)</td>
<td>14-29%</td>
</tr>
</tbody>
</table>

Acalabrutinib: Conclusions

• High RR and duration of response in r/r MCL
• More selective BTK-I than Ibrutinib
• Improved toxicity profile A.Fib/A.Flutter and hemorrhage, infections, secondary malignancies

• Activity in patients progressed on ibrutinib?
• Durable response with long term follow-up?
• Front-line with Benda/Rituxan?
  • Ongoing trial: BR + placebo or acalabrutinib
• Activity in other heme malignancies?
  • Phase 1 study in CLL
Emicizumab-kxwh (Hemlibra)

- First in class humanized bispecific mAb
  - Factor IXa and factor X
- FDA approved Nov 16\textsuperscript{th} 2017
- Indicated:
  - Adult and pediatric pt with hemophilia A \textit{with factor VIII inhibitors}
  - Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- Dose: 3 mg/kg by SQ weekly x4 weeks, followed by 1.5 mg/kg Q week
Hemophilia A

• Hemophilia A inherited, X-linked, recessive disorder
  • Deficiency of plasma clotting factor VIII (FVIII)
  • Most commonly presents as severe (FVIII<1%)

• FVIII essential to clotting cascade
  • Life threatening bleeds with trauma
  • Spontaneous bleeds (joints, muscles, ICH)
Hemophilia A

• Treatment replacement of recombinant FVIII
• Inhibitors to rFVIII can develop in 36%
  • Significant complication leading to treatment failure
• Bypassing Agents (FVII) are utilized in the setting with limited efficacy
• Emicizumab provides an alternative treatment in this setting
Intrinsic Pathway:
Vascular endothelial rupture
(collagen exposure)

Extrinsic Pathway:
Tissue Damage/trauma
Tissue thromboplastin (TF) + VII, Ca+

Common Pathway

FVIII + Ca+ + PL

Emicizumab

Prothrombin(II) → Thrombin(IIa)

Fibrinogen(I) → Fibrin monomers

Fibrin Gel

Crossed link Fibrin Clot

PL = platelet membrane phospholipid; TF = Tissue Factor
HAVEN-1 Trial

ABR with Emicizumab vs PPX Age ≥12yo

<table>
<thead>
<tr>
<th>End Point</th>
<th>Hemlibra (N=35)</th>
<th>No PPX (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated Bleeds: 87% Reduction (p&lt;0.0001)</td>
<td>2.9</td>
<td>23.3</td>
</tr>
<tr>
<td>All Bleeds: 80% Reduction (p&lt;0.0001)</td>
<td>5.5</td>
<td>28.3</td>
</tr>
<tr>
<td>Treated Spontaneous Bleeds: 92% reduction</td>
<td>1.3</td>
<td>16.8</td>
</tr>
<tr>
<td>(p&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABR</td>
<td>0.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Treated Joint Bleed 89% reduction (p=0.005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABR</td>
<td>0.1</td>
<td>3.0</td>
</tr>
<tr>
<td>Treated Target Joint Bleed: 95% reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p=0.0002)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABR</td>
<td></td>
<td></td>
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</table>

PPX= Prophylaxis

Intra-Pt comparison of ABR

<table>
<thead>
<tr>
<th></th>
<th>Hemlibra (N=24)</th>
<th>Prev. Bypassing Agent (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated Bleeds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABR</td>
<td>3.3</td>
<td>15.7</td>
</tr>
<tr>
<td>% reduction</td>
<td>79%</td>
<td>p=0.0003</td>
</tr>
<tr>
<td>% patients 0 bleeds</td>
<td>70.8%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Median ABR</td>
<td>0</td>
<td>12</td>
</tr>
</tbody>
</table>

Oldenburg et al. HAVEN-1. NEJM. 2017; 377:809-818

Phase III, multi-center, randomized, open-label study
• Hemophilia A with inhibitors to FVIII
• Emicizumab PPX vs No PPX (2:1)
• Outcome: Annualized bleed rate (ABR)
  • Number of bleeds over time
  • On demand bypassing agents allowed

Oldenburg et al. HAVEN-1. NEJM. 2017; 377:809-818

Intra-Pt comparison of ABR
Emicizumab: Toxicity

• Adverse Effects:
  • Injection site reaction(19%), pyrexia(7%), Headache(15%), Diarrhea(6%), Arthralgia(10%), Myalgia(5%)

• Black box warning:
  • Thrombic microangiopathy and thromboembolism (>100U/kg/d aPCC in ≥24h)

• Coagulation Tests Results affected
  • Activated partial thromboplastin time (aPTT)
  • aPTT-based activated Protein C Resistance(APC-R)
  • Activated Clotting Time (ACT)
Emicizumab

• Emicizumab is first in class bispecific mAb approved for Hemophilia A
• It significantly reduces the incidence of bleeds in patients with FVIII inhibitors
• Acceptable toxicity profile
  • BBW for TMA/TVE risk when used aPCC (>100U/kg/d ≥24h)
• Novel agent offers significant advancement in the standard of care for Hemophilia A
Monoclonal Antibodies: Future direction

• Many monoclonal antibodies in clinical trials
• BCMA antibody drug conjugate (ADC) –
  • Humanized, afucosylated IgG1 anti-BCMA Monomethylauristatin F (MMAF)
    • MMAF- highly potent cytotoxic antimitotic
• DREAMM-1 Trial
  • r/r MM; BCMA+ DLBCL or FL
  • IV Q 3weeks x 1 yr

Hofland P. DREAMM-1 study. ADC Review. 2017
Axicabtagene ciloleucel (YESCARTA)

- FDA approved 10/2017
- Indication: Adult pt with r/r Large B-Cell Lymphoma ≥2 line of therapy
  - DLBCL not otherwise specified (NOS)
  - Primary Mediastinal lymphoma (PM-LBCL)
  - High-grade B-Cell lymphoma
  - DLBCL arising from FL
Mechanism of Action

- **Viral Vector**
  - CD19+ CAR
  - Infuse in patient

- **CD19+ B-Cell**

- **CAR T-Cell**
  - CD19 + CART
  - CD19 + CART
  - CD19 + CART

- **T-Cell**
  - CD19+ CAR
  - Infuse in patient

- **CAR T-cell activation and expansion**
Landmark Trial: ZUMA-1
Single arm phase 1/2 study (N=108)

• Inclusion Criteria
  • Aggressive B-Cell NHL
    • Primary refractory
    • Refractory ≥2 lines of therapy
    • Relapse ≤1 yr s/p auto HSCT

• Exclusion Criteria
  • ECOG PS ≥2
  • ALC <100/µL
  • CrCL <60 mL/min
  • AST, ALT >2.5 x ULN
  • Prior AlloHSCT
  • Prior CNS Lymphoma

• Lymphodepletion
  - Cyclophosphamide 500 mg/m²/d +
  - Fludarabine 30 mg/m²/d x 3d (D-5,-4,-3)

• Single infusion CAR-T target dose of 2x10⁶ cells/kg
• Mandatory 7 day stay in hospital
### ZUMA-1: Baseline

<table>
<thead>
<tr>
<th>Population: 91% Enrolled</th>
<th>N=101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median 58</td>
</tr>
<tr>
<td></td>
<td>≥65 24%</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>DLBCL 76%</td>
</tr>
<tr>
<td></td>
<td>Transformed FL 16%</td>
</tr>
<tr>
<td></td>
<td>PMBCL 8%</td>
</tr>
<tr>
<td>Prior Lines of Therapy</td>
<td>≥3 69%</td>
</tr>
<tr>
<td>Prior Treatments</td>
<td>Refractory ≥2 lines 77%</td>
</tr>
<tr>
<td></td>
<td>Relapse ≤1y s/p autoHSCT 21%</td>
</tr>
<tr>
<td></td>
<td>Primary refractory 2%</td>
</tr>
<tr>
<td>Days to CAR-T delivery</td>
<td>Median (range) 17 (14-51)</td>
</tr>
</tbody>
</table>

Locke & Neelapu et al. ZUMA-1 Trial. ASH/AACR 2017. #9986/7512
ZUMA-1: Efficacy Results

### Response Treated patients (N=101)

<table>
<thead>
<tr>
<th>Response</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>72% (62,81)</td>
</tr>
<tr>
<td>CR</td>
<td>52% (41, 62)</td>
</tr>
<tr>
<td>PR</td>
<td>21% (13.30)</td>
</tr>
</tbody>
</table>

### Duration of Response (DOR) (months)

#### # of responders
- 73 of 101

#### If achieved CR
- Median DOR (95% CI): NE (8.1; NE)

#### If achieved PR
- Median DOR (95% CI): 2.1 mo (1.3, 5.3)
- Median f/ for DOR: 7.9 mo

Is this response durable?

How does this improve our practice?

ITT: ORR 66% CR 47%

| ORR | 26% |
| CR  | 7%  |
| PR  | 19% |
| OS 6mo | 55% (vs 80%) |

Locke & Neelapu et al. ZUMA-1 Trial. AACR 2017. # 7512; Crump et al. SCHOLAR-1. Blood, 2017
# ZUMA-1: Safety

<table>
<thead>
<tr>
<th>CRS</th>
<th>N=108</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>94%</td>
</tr>
<tr>
<td>≥ Grade 2</td>
<td>55%*</td>
</tr>
<tr>
<td>≥ Grade 3</td>
<td>13%**</td>
</tr>
<tr>
<td>Median Onset (range)</td>
<td>2 d (1-12)</td>
</tr>
<tr>
<td>Median Duration</td>
<td>7 d</td>
</tr>
<tr>
<td>Peak Prevalence</td>
<td>Day 5-6 (~80%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CNS Neurotoxicity</th>
<th>All Grades</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>65-87%</td>
<td>30-31%</td>
</tr>
<tr>
<td>Encephalopathy*</td>
<td>57%</td>
<td>29%</td>
</tr>
<tr>
<td>Delerium</td>
<td>17%</td>
<td>6%</td>
</tr>
<tr>
<td>Median Onset (range)</td>
<td>4 (0-16)</td>
<td>5 (1-10)</td>
</tr>
<tr>
<td>Median Duration</td>
<td>13 d</td>
<td>9 d</td>
</tr>
<tr>
<td>Peak Prevalence</td>
<td>Day 8 (57%)</td>
<td>Day 7 (26%)</td>
</tr>
</tbody>
</table>

*Encephalopathy includes cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor

*managed with tociluzumab per REMS
**managed with addition of steroids per REMS

Locke & Neelapu et al. ZUMA-1 Trial. ASH 2017. Abstract.#578
Summary: Axicabtagene ciloleucel

• FDA approved for r/r B-Cell Lymphomas
• REMS program to mitigate risk of CRS and Neurotoxicity
  • Training for health care providers
  • Ensuring tocilizumab availability
  • Grade specific management of toxicities
• No safety data for pt w/poor PS/organ dysfunction
• FDA mandated study characterize long term toxicity
Future Direction CAR T-Cells

• Adult Pre B-cell ALL
  • ROCKET Trial d/c to treatment deaths (Juno)

• Improve toxicity profile with CAR-T construct
  • Lisocbtagne maraleucel (Juno) preliminary improved CRS, neurotoxicity

• BCMA CAR T-cells in r/r MM
  • Improved efficacy with increase dosing
  • Toxicities CRS and neurotoxicity
  • Escape mechanism via decreased BCMA expression

ZUMA-1; Neelapu ASH 2017 and Locke ASH 2017; JULEIT; Schuster, ASH 2017; ASH 2017 (TRANSCEND; Abramson/Maloney; Group
Future Directions CAR T-Cells

- Overcoming CD19 Antigen receptor loss
  - 25% relapse CD19- disease w/median 10 f/u
  - Concern for pre-blinatumumumab relapse risk
  - Combination with PDL-1
  - Combination CAR T-Cells- CD19/22; CD19/BCMA

- How do we integrate with HSCT, mab?
- Role in CNS treatment or relapse?

ZUMA-1; Neelapu ASH 2017 and Locke ASH 2017; JULIEIT; Schuster, ASH 2017; ASH 2017 (TRANSCEND; Abramson/Maloney; Gru
Self Assessment Question 2

Which of the following statements is NOT true regarding select novel agents approved in 2017?

A. Copanlisib is a 2nd gen pan-PI3K inhibitor with increased autoimmune toxicity
B. Acalabrutinib is a 2nd gen BTK-I with ORR ~80% and improved toxicity (A.Fib/A.Flutter, hemorrhage, infections, secondary malignancies)
C. Emicizumab is a bispecific mAb approved for bleeding ppx in Hemophilia A patients with antibodies
D. Axicabtagne ciloleucel is a CD19+ CAR-T Cell approved with REMS program for CRS and neurotoxicity
Self Assessment Question 3

Which statement best describes approaches for novel hematology agents in clinical trials?

A. Novel agents are usually first approved in the 1st-line setting

B. Targeted agents (small molecule inhibitor and mab) are rarely active in more than one cancer

C. BCMA is a novel target in clinical trials for both antibody drug conjugates and CAR-T cells

D. Drugs first approved as monotherapy are rarely then studied in combination therapies
Summary

• Multiple advances in novel approach to the treatment of hematologic malignancies
  • Immunotherapy (mAb, ADC, BiTE)
  • Small molecule Inhibitors
  • CAR-T cell

• Challenges faced in clinical practice
  • Evaluate appropriate sequencing and safety/efficacy in combination
  • Unique characteristics and toxicity require vigilance in pharmacist’s continuing education
Novel Agents in Hematology: Newly FDA approved and Investigational Drugs in Benign and Malignant Hematology

Jilan Kubusek, PharmD, BCPS, BCOP
Mayo Clinic Hospital
Jan 2nd 2018