Lymphoma: New Approaches – Better Outcomes

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Disclosures: Michael E. Williams, MD, ScM

• Clinical trial grant support (PI) to University of Virginia:
  – Allos, Celgene, Gilead, Janssen, Pharmacyclics, TG Therapeutics

• Data Safety Monitoring Committee:
  – Celgene

• Consultant:
  – Abbvie, Astra-Zeneca, Kite, Juno, Janssen, TG Therapeutics, Gilead Sciences, Verastem, Seattle Genetics, Sandoz

• Scientific Advisory Board:
  – Lymphoma Research Foundation
Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial


- 132 sites, 17 countries
- Previously untreated, CD30+ PTCL
- Randomized 1:1 to CHOP (with placebo for BV) vs CHP-BV (CHOP minus vincristine, with placebo) x 6 cycles

- BV 1.8 mg/kg day 1

- Primary endpoint: PFS, blinded central review, by intent to treat
Median PFS: 48 vs 21 m; HR 0.71
Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial

Toxicity: CHOP vs CHP-BV

- Febrile neutropenia: 15% vs 18%
- Peripheral neuropathy: 55% vs 52%
- Fatal AE: 4% vs 3%

Conclusions:

- Front-line CHP-BV led to superior PFS and OS
Diffuse Large B-cell Lymphoma
DIFFUSE LARGE B CELL LYMPHOMA

R-CHOP is standard of care for most DLBCL

Stage I, II:
- **ASH 0781**: R-CHOP x 4 + R x 2 (18-60 y, aaIPI 0)

Stage III, IV:
- **ASH 0783** (analysis from GOYA study): 6 vs 8 cycles
  RCHOP – no significant difference in outcomes, less toxicity with 6 cycles → **R-CHOP-21 x 6 plus Rx 2 is standard of care**
DA-R-EPOCH vs R-CHOP
CALGB 50303
Advanced stage DLBCL

EFS

OS

Median follow-up 5.0 y
HR=1.14 (0.82-1.61)
p = 0.4386

Median follow-up 5.0 y
HR=1.18 (0.79-1.77)
p = 0.42

Bartlett N ASH 2016
Problems with this study

• Increased ratio of lower-risk IPI patients on this study
  • Required repeat biopsy for fresh frozen tissue
  • As a result, patients with higher risk presentations and in need of immediate therapy were less represented

• Patients in R-CHOP arm did better than expected

• If DA-R-EPOCH is going to move forward, it will need to be in subtypes where R-CHOP doesn’t work

Bartlett N, et al. ASH 2016
### Biology of DLBCL

#### Targeting disease subsets

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Cohort</th>
<th>Enrolling?</th>
</tr>
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<tbody>
<tr>
<td>E1411</td>
<td>R2 [Lenalidomide] -CHOP vs. RCHOP</td>
<td>All DLBCL</td>
<td>Enrolled, pending report</td>
</tr>
<tr>
<td>ROBUST</td>
<td>R2CHOP vs. RCHOP</td>
<td>ABC by Lymph2Cx</td>
<td>Enrolled, pending report</td>
</tr>
<tr>
<td>Jansen study</td>
<td>Ibrutinib RCHOP vs. RCHOP</td>
<td>Non-GCB by IHC</td>
<td>Enrolled pending report</td>
</tr>
<tr>
<td>PYRAMID</td>
<td>Bortezomib- RCHOP vs. RCHOP</td>
<td>Non-GCB by IHC</td>
<td>Reported, negative</td>
</tr>
<tr>
<td>GOYA</td>
<td>G[Obinutuzumab]-CHOP vs. RCHOP</td>
<td>All DLBCL</td>
<td>Reported, negative</td>
</tr>
<tr>
<td>PRELUDE</td>
<td>RCHOP vs. RCHOP + Enzastaurin maintenance</td>
<td>High risk DLBCL</td>
<td>Reported, negative</td>
</tr>
<tr>
<td>RAD-001</td>
<td>RCHOP vs. RCHOP + everolimus maintenance</td>
<td>High risk DLBCL</td>
<td>Reported, negative</td>
</tr>
<tr>
<td>REMARC</td>
<td>RCHOP vs. RCHOP + Len maintenance</td>
<td>Elderly DLBCL</td>
<td>Reported, negative</td>
</tr>
</tbody>
</table>

Goy A, JCO 2017 35:3519-3522
What targeted therapies should be considered now for DLBCL?

• Front-line: RR-CHOP? (stay tuned)

• Relapsed/Refractory, non-SCT eligible or relapse post-ASCT, not a trial candidate:
  – CAR-T-cell therapy
  – R²: Lenalidomide/Rituximab
  – Ibrutinib: in non-GCB and CNS
  – Copanlisib: in GCB and transformed FL
  – Brentuximab vedotin: If CD30+ (how + is +?)
Cooperative Group Strategies

- Identify patient with DLBCL
- Submit tissue to a “pre-study” to determine COO and double hit
- Give a cycle of RCHOP

For C2, enroll in another study with information from “pre-study”

- High risk, Double hit - EPOCH based trial
- Standard risk - RCHOP based study
- Frail/Elderly - mini-R-CHOP based study
- Others?

Problems with this strategy:
- TISSUE!!
R/R DLBCL: Recent Advances

• Anti-CD19-CAR-T
  - Axicabtagene ciloleucel [axi-cell; Yescarta]
  - Tisagenlecleucel [CTL-019; Kymriah]
• >95% success in generating CAR-T
• ORR 50-80%, CR 43-54%
• Most CR patients disease-free at >6 mo
• CRS, neurotoxicity can be severe

Neelapu et al, ZUMA trial, n = 111, multinational phase 2; Schuster et al, UPenn, n = 14; Tran et al, Editorial. NEJM 2017; 12/28/17
Original Article

Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Stephen J. Schuster, M.D., Michael R. Bishop, M.D., Constantine S. Tam, M.D., Edmund K. Waller, M.D., Ph.D., Peter Borchmann, M.D., Joseph P. McGuirk, D.O., Ulrich Jäger, M.D., Samantha Jaglowski, M.D., Charalambos Andreadis, M.D., Jason R. Westin, M.D., Isabelle Fleury, M.D., Veronika Bachanova, M.D., Ph.D., S. Ronan Foley, M.D., P. Joy Ho, M.B., B.S., D.Phil., Stephan Mielke, M.D., John M. Magenau, M.D., Harald Holte, M.D., Ph.D., Serafino Pantano, Ph.D., Lida B. Pacaud, M.D., Rakesh Awasthi, Ph.D., Jufen Chu, Ph.D., Özlem Anak, M.D., Gilles Salles, M.D., Ph.D., Richard T. Maziarz, M.D., for the JULIET Investigators

N Engl J Med
Volume 380(1):45-56
January 3, 2019
Screening, Enrollment, and Treatment

238 Patients were screened for eligibility

71 Were excluded during screening
  2 Were still undergoing screening at data cutoff

165 Enrolled in the study

50 Discontinued study before infusion
  12 Could not have CAR T cells manufactured
  38 Had other reasons
  4 Were awaiting infusion at data cutoff

111 Received an infusion

95 Received an infusion in the main cohort
  93 Received an infusion ≥3 mo before cutoff date
  2 Received an infusion <3 mo before cutoff date

16 Received an infusion in cohort A
  13 Received an infusion ≥3 mo before cutoff date
  3 Received an infusion <3 mo before cutoff date
Duration of Response, Progression-free Survival, and Overall Survival

A. Duration of Response

- Patients with complete response
- All patients

Probability of Maintaining Response

Median duration among all patients not reached
(95% CI, 10.0 months to not reached)

No. at Risk

<table>
<thead>
<tr>
<th>Months since First Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>37</td>
</tr>
</tbody>
</table>

B. Progression-free Survival

- Patients with complete response
- All patients

Probability of Remaining Progression-free

No. at Risk

<table>
<thead>
<tr>
<th>Months since Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>40</td>
</tr>
</tbody>
</table>

C. Progression-free Survival among Patients with a Response

- Patients with complete response at month 3
- Patients with partial response at month 3

Probability of Remaining Progression-free

No. at Risk

<table>
<thead>
<tr>
<th>Months since Infusion</th>
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</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>32</td>
</tr>
</tbody>
</table>

D. Overall Survival

- Patients with complete response
- All patients

Probability of Survival

No. at Risk

<table>
<thead>
<tr>
<th>Months since Infusion</th>
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</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>40</td>
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</table>

No. at Risk

<table>
<thead>
<tr>
<th>All patients</th>
</tr>
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<tbody>
<tr>
<td>111</td>
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</tbody>
</table>

Conclusion

• In this study, 40% of patients with relapsed or refractory diffuse large B-cell lymphoma have had durable complete responses with cells manufactured in a central commercial laboratory.
Axicabtagene Ciloleucel (Axi-cel) CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: Real World Experience

Nastoupil LJ, et al
ASH 2018
Axi-cel in R/R DLBCL

- DLBCL, PMBCL, transformed FL, and high-grade B-cell lymphoma
- Failed at least 2 prior lines of therapy
- In ZUMA-1 trial: ORR 82%, CR 58%, 42% with ongoing remissions > 6 mo *(NEJM 2017)*
- Pooled multicenter data from 17 US sites
- 211 pts leukapheresed, 165 infused (78%); 7% died of disease before infusion

Nastoupil et al. ASH 2018
Table 1. Patient characteristics and outcomes: comparison between ZUMA-1 (Neelapu and Locke et al. NEJM 2017) and commercial standard of care axi-cel treatment at 17 US centers.

<table>
<thead>
<tr>
<th></th>
<th>ZUMA-1</th>
<th>This Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>N infused pts</td>
<td>108</td>
<td>165</td>
</tr>
<tr>
<td>% meeting ZUMA-1 eligibility criteria</td>
<td>100%</td>
<td>51%</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>58 (23-76)</td>
<td>59 (21 – 82)</td>
</tr>
<tr>
<td>ECOG 0 or 1</td>
<td>100%</td>
<td>84%</td>
</tr>
<tr>
<td>Prior autologous transplant</td>
<td>23%</td>
<td>31%</td>
</tr>
<tr>
<td>DLBCL including HGBCL, not tFL or PMBCL</td>
<td>78%</td>
<td>61%</td>
</tr>
<tr>
<td>ORR/CR</td>
<td>82%/58% (Best)</td>
<td>79%/50% (Day 30)</td>
</tr>
<tr>
<td>Grade 3 or higher toxicity</td>
<td>CRS 13%/NEs 31%</td>
<td>CRS 7%/NEs 31%</td>
</tr>
</tbody>
</table>


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Axi-cel in R/R DLBCL: Conclusions

• Multicenter, retrospective study
• Comparable outcomes to ZUMA-1, including safety, even though half of these pts wouldn’t have qualified for ZUMA-1
• Bridging therapy can be a challenge

Nastoupil et al. ASH 2018
Follicular Lymphoma
**FOLLICULAR LYMPHOMA**

Who needs therapy?

Who needs chemotherapy?

When and how do we combine agents?

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Disease Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>Grade I/II</td>
</tr>
<tr>
<td>Low Burden</td>
<td>Symptomatic High FL Burden</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Grade IIIA</td>
</tr>
<tr>
<td>Low Burden</td>
<td>Asymptomatic High FL Burden</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Grade IIIB</td>
</tr>
</tbody>
</table>

Leonard, Nastoupil, Flowers. ASH 2018 Hematology Education Program
ABSTRACT 445

AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R²) vs Rituximab/Placebo in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

John P. Leonard,¹ Marek Trneny,² Koji Izutsu,³ Nathan H. Fowler,⁴ Xiaonan Hong,⁵ Jun Zhu,⁶ Huilai Zhang⁷ Fritz Offner,⁸ Adriana Scheliga,⁹ Grzegorz Nowakowski,¹⁰ Antonio Pinto,¹¹ Francesca Re,¹² Laura Maria Fogliatto,¹³ Philip Scheinberg,¹⁴ Ian Flinn,¹⁵ Claudia Moreira,¹⁶ David Liu,¹⁷ Stacey Kalambakas,¹⁷ Chengqing Wu,¹⁷ Pierre Fustier,¹⁸ and John G Gribben,¹⁹ on behalf of the AUGMENT study investigators

¹Meyer Cancer Center, Weill Cornell Medicine and New York Presbyterian Hospital, New York, NY; ²Charles University Hospital, Prague, Czech Republic; ³National Cancer Center Hospital, Tokyo, Japan; ⁴The University of Texas MD Anderson Cancer Center, Houston, TX; ⁵Fudan University Shanghai Cancer Center, Shanghai, China; ⁶Beijing Cancer Hospital, Beijing, China; ⁷Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; ⁸UZ Gent, Gent, Belgium; ⁹INCA Instituto Nacional De Cancer, Rio de Janeiro, Brazil; ¹⁰Mayo Clinic, Rochester, MN; ¹¹Istituto Nazionale Per Lo Studio E La Cura Dei Tumori Fondazione Giovanni Pascale, Napoli, Italy; ¹²Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; ¹³Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; ¹⁴Division of Hematology, Hospital A Beneficência Portuguesa, São Paulo, Brazil; ¹⁵SCRI Tennessee Oncology Nashville, Nashville, TN; ¹⁶Instituto Português de Oncologia Do Porto Francisco Gentil Epe, Porto, Portugal; ¹⁷Celgene Corporation, Summit, NJ; ¹⁸Celgene Corporation, Boudry, Switzerland; ¹⁹Centre for Haematology-Oncology, Barts Cancer Institute, London, United Kingdom
**STUDY DESIGN: RANDOMIZED DOUBLE BLIND PHASE III TRIAL**

**Primary endpoint:** PFS by IRC (2007 IWG criteria w/o PET)

**R-lenalidomide (R²)**
- Rituximab: 375 mg/m² d1, 8, 15, 22 of cycle 1; d1 of cycles 2-5
- Lenalidomide: 20 mg/d*, d1-21/28 (12 cycles)
  
  *10 mg if CrCl between 30 to 59 mL/min.

**R-placebo**
- Rituximab: 375 mg/m² d1, 8, 15, 22 of cycle 1; d1 of cycles 2-5
- Placebo: matched capsules (12 cycles)

- Prophylactic anticoagulation / antiplatelet Rx recommended for at risk patients
- Growth factor use was allowed per ASCO/ESMO guidelines
- Primary endpoint: PFS by IRC (2007 IWG criteria w/o PET)

5-year follow-up for OS, SPMs, subsequent treatment, and histological transformation

**Stratification**
- Prior rituximab (yes vs no)
- Time since last therapy (≤ 2 vs > 2 y)
- Histology (FL vs MZL)

**Key eligibility criteria**
- MZL or FL (grades 1-3a) in need of treatment
- ≥ 1 prior chemotherapy, immunotherapy or chemoimmunotherapy
- Not rituximab refractory

**PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL (ITT, IRC)**

*Median follow up: 28.3 months

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>R² (n = 178)</th>
<th>R-placebo (n = 180)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By IRC, mo (95% CI)</strong></td>
<td>39.4 (22.9-NE)</td>
<td>14.1 (11.4-16.7)</td>
<td>0.46 (0.34-0.62)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>By investigator, mo (95% CI)</strong></td>
<td>25.3 (21.2-NE)</td>
<td>14.3 (12.4-17.7)</td>
<td>0.51 (0.38-0.69)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Censoring rules based on FDA guidance.

Data cutoff June 22, 2018.
OVERALL SURVIVAL IN PATIENTS WITH FL (PRESPECIFIED SUBGROUP ANALYSIS)

Data cutoff June 22, 2018.

- 35 total deaths (11 R², 24 R-placebo)

- 2-year OS was 95% (95% CI, 90%-98%) for R² and 86% (95% CI, 79%-91%) for R-placebo
CONCLUSIONS: AUGMENT TRIAL

• Greater efficacy with manageable toxicity allowed more patients to complete R² compared to R-placebo
  
  – Disease progression (more frequent with R-placebo) was the most common cause of treatment discontinuation

• AEs differed between arms
  
  – Neutropenia, infections, tumor flare, and cutaneous reactions were more frequent with R²
  
  – Fewer cases of SPMs and histological transformations occurred with R²
Original Article

Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma

Franck Morschhauser, M.D., Ph.D., Nathan H. Fowler, M.D., Pierre Feugier, M.D., Reda Bouabdallah, M.D., Hervé Tilly, M.D., M. Lia Palomba, M.D., Christophe Fruchart, M.D., Edward N. Libby, M.D., Rene-Olivier Casasnovas, M.D., Ian W. Flinn, M.D., Ph.D., Corinne Haioun, M.D., Hervé Maisonneuve, M.D., Loic Ysebaert, M.D., Nancy L. Bartlett, M.D., Kamal Bouabdallah, M.D., Pauline Brice, M.D., Vincent Ribrag, M.D., Nicolas Daguindau, M.D., Steven Le Gouill, M.D., Gian M. Pica, M.D., Alejandro Martin Garcia-Sancho, M.D., Ph.D., Armando López-Guillermo, M.D., Jean-François Larouche, M.D., Kiyoshi Ando, M.D., Ph.D., Maria Gomes da Silva, M.D., Ph.D., Marc André, M.D., Pierre Zachée, M.D., Laurie H. Sehn, M.D., Kensei Tobinai, M.D., Guillaume Cartron, M.D., Ph.D., David Liu, M.D., Ph.D., Jianming Wang, Ph.D., Luc Xerri, M.D., Ph.D., Gilles A. Salles, M.D., Ph.D., for the RELEVANCE Trial Investigators

N Engl J Med
Volume 379(10):934-947
September 6, 2018
Study Overview

- Superiority phase 3 trial of Len/R vs R-Chemo
- Previously untreated FL, n = 1030
- At median f/u of 38 mo, CR for LenR 48% vs 53%, 3-year PFS 77% vs 78%, OS 94% for each arm

- The combination of rituximab and lenalidomide achieved results that were similar to those of rituximab plus chemotherapy in the treatment of previously untreated patients with advanced follicular lymphoma.
Progression-free Survival and Overall Survival in the Intention-to-Treat Population.

Mantle Cell Lymphoma
MCL Initial Therapy: 2019

• Watch/Wait low risk, asymptomatic
• Younger, fit patients
  - Rituximab plus a high-dose cytarabine - based regimen → ASCT → Maint Rituximab
• Older or serious coexisting illness
  - Rituximab - Bendamustine
  - R-CHOP → Maintenance R q 2 mo x 2-3 yr
  - R2 - (Lenalidomide plus Rituximab)
  - Moving targeted therapies to front-line
  - Clinical trial preferred
E1411 - Phase 2 Intergroup Trial: Initial Therapy of Mantle Cell Lymphoma

BR x 6 → Rituximab
BVR x 6 → Rituximab
BR x 6 → Lenalidomide + Rituximab
BVR x 6 → Lenalidomide + Rituximab

BR = Bendamustine, Rituximab
V = Bortezomib

M. Smith, Study PI; accrual completed September 2016
E1411 - Phase 2 Intergroup Trial: Initial Therapy of Mantle Cell Lymphoma

BR x 6 → Rituximab

BVR x 6 → Lenalidomide + Rituximab

Anticipated data analysis Fall 2019

BR = Bendamustine, Rituximab

V = Bortezomib

M. Smith, Study PI; accrual completed September 2016
EA4151: A Randomized Phase III Trial of Consolidation with Autologous Hematopoietic Cell Transplantation Followed by Maintenance Rituximab vs. Maintenance Rituximab Alone for Patients with Mantle Cell Lymphoma In Minimal Residual Disease-Negative First Complete Remission

ECOG-led Intergroup study in Mantle Cell Lymphoma

Timothy Fenske, MD; Medical College of Wisconsin (Study Chair)
Brian Till, MD University of Washington (SWOG Co-Chair)
Kristie Blum, MD; The Ohio State University (Alliance Co-Chair)
Brad Kahl, MD; Washington University (ECOG Lymphoma Chair)
Hillard Lazarus, MD; Case Western Reserve (ECOG BMT Chair)
Tom Witzig, MD; Mayo Clinic (ECOG Laboratory Co-chair)
Fangxin Hong, PhD (Study Statistician)
EA4151- Schema

Step 0
- Any induction regimen
- Enroll before, during, or after induction

PRE\_REGISTRATION
Submit diagnostic tissue for molecular testing

Clonal Marker Present?
- Yes
  - Post-induction restaging + Submission of blood for MRD assessment
  - MRD-neg CR
  - MRD-neg PR or MRD-pos CR
- No
  - No informative marker: MRD indeterminate

Step 1
- Arm A
  - Auto-HCT + Rituximab x 3 years
- Arm B
  - Rituximab x 3 years
- Arm C
  - Auto-HCT + Rituximab x 3 years
- Arm D
  - Auto-HCT + Rituximab x 3 years

Stratify:
- MIPI-c
- Intensive vs non-intensive induction

ECOG-ACRIN
cancer research group
Reshaping the future of patient care
BTK Inhibitors
PFS and OS by Prior Line of Therapy
Pooled analysis of 3 Ibrutinib studies in Relapsed/Refractory MCL (n=370)

Median PFS was nearly 3 years in patients with 1 prior line of therapy

Patients censored from OS analysis upon study discontinuation. CI, confidence interval; NE, not estimable.

Conclusions: Ibrutinib in R/R MCL

- In a mature pooled data set of 370 R/R MCL patients across 3 studies:
  - Median PFS was nearly 3 y for pts with 1 prior line of therapy
  - Median PFS was nearly 4 y for pts achieving CR, and median DOR was 55 months
- CR rate increases over time with continued ibrutinib therapy
- New onset grade ≥ 3 adverse events:
  - were most common in the first year
  - were less common in patients with 1 prior line of therapy

Acalabrutinib

- Second generation BTK inhibitor
  - FDA Approved in Mantle cell lymphoma with at least one prior therapy
  - Dose: 100 mg twice daily until unacceptable toxicity or progression
- More specific for BTK, fewer off target effects than ibrutinib
  - Less TEK kinase inhibition

Herman S, CCR 2017
Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, phase 2 trial

### Acalabrutinib in R/R MCL

Compared to ibrutinib (n=370, pooled data, 3 trials) more favorable patient population in the acalabrutinib trial (n=124)

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib 560 mg/day</th>
<th>Acalabrutinib 100 mg 2x/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med age</td>
<td>67.5</td>
<td>68 (61-75)</td>
</tr>
<tr>
<td>Median prior lines of therapy</td>
<td>2 (1-9)</td>
<td>2 (1-2)</td>
</tr>
<tr>
<td>sMIPI high</td>
<td>32%</td>
<td>17%</td>
</tr>
<tr>
<td>sMIPI int</td>
<td>45%</td>
<td>44%</td>
</tr>
<tr>
<td>sMIPI low</td>
<td>24%</td>
<td>39%</td>
</tr>
<tr>
<td>Blastoid</td>
<td>12%</td>
<td>NR</td>
</tr>
<tr>
<td>Prior SCT</td>
<td>34%</td>
<td>18%</td>
</tr>
<tr>
<td>Refractory</td>
<td>NR</td>
<td>24%</td>
</tr>
</tbody>
</table>

Acalabrutinib vs. Ibrutinib in MCL

- Acalabrutinib appears to have better safety profile
  - Very infrequent atrial fibrillation and bleeding events
  - More headache with acalabrutinib
- Acalabrutinib was used in less heavily pre-treated patients
  - Can’t say that it is more effective in MCL as yet
  - Head-to-head trial of ibrutinib vs acalabrutinib (ACE-CL-006) enrolled high-risk, relapsed CLL; results pending
- In MCL, both agents have efficacy, choose based on patient factors
- If a patient fails a BTK inhibitor, consider switch to venetoclax
- If a BTK inhibitor is stopped for toxicity, use the alternative BTK agent
- Acala plus BR, and other combinations, in current clinical trials
BCL2 Inhibitors
Venetoclax

- FDA-approved for CLL/SLL, with or without del 17p, with at least 1 prior therapy;
- Approved Nov. 2018 for AML pts > 75y in combination with aza, decitabine or AraC

1. An Increase in BCL-2 Expression Allows the Cancer Cell to Survive
2. Venetoclax Binds to and Inhibits Overexpressed BCL-2
3. Apoptosis is Initiated

Mitochondria

BH3-only family member proteins include BIM, BAD, PUMA, and NOXA

Courtesy of Dr. Sven deVos, UCLA
Venetoclax in NHL

Davids M, JCO 2017
Venetoclax safety

- Tumor lysis syndrome
  - Must use dosing ramp-up for venetoclax initiation
  - Be very cautious in CLL and MCL, especially if coexisting renal insufficiency
  - Highest risk is with lymphocytosis and bulky disease, or rapidly progressing disease

- Adverse events
  - GI: nausea/vomiting and diarrhea
  - Neutropenia and thrombocytopenia
  - Fatigue and headache

Davids M, et al. JCO 2017; Davids M, et al. JCO 2018
Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma


N Engl J Med
Volume 378(13):1211-1223
March 29, 2018
Ibrutinib plus venetoclax in MCL: Study Schema

24 patients; 23 relapsed or refractory; most high-risk including MIPI score and TP53 mutations

Kinetics of Response and Clearance of Minimal Residual Disease (MRD)

MCL: Ibrutinib plus venetoclax
n = 24

Complete response by PET/CT scan = 71%

3 non-responders

Toxicity mostly grade 1-2 diarrhea, fatigue

Grade 3-4:
33% neutropenia
12% diarrhea
4% bleeding
8% atrial fibrillation
8% tumor lysis

Tan et al, NEJM 2018
Phase I/Ib study of Ven and Ibr

Major inclusion/exclusion
- Ibrutinib naïve
- not high risk for TLS
- Relapsed to 1 prior chemotherapy containing regimen

<table>
<thead>
<tr>
<th>ABT-199 (mg per day)</th>
<th>Zone 2 / Arm C</th>
<th>Zone 3 / Arm E</th>
<th>Zone 4 / Arm F</th>
</tr>
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<tbody>
<tr>
<td>400 (week 3+)</td>
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<tr>
<td>200 (week 2)</td>
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<tr>
<td>100 (week 1)</td>
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<tr>
<td>200 (week 3+)</td>
<td>Zone 1 / Arm A</td>
<td>Zone 2 / Arm B</td>
<td>Zone 3 / Arm D</td>
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<tr>
<td>200 (week 2)</td>
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<tr>
<td>100 (week 1)</td>
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<tr>
<td>All subjects</td>
<td>280</td>
<td>420</td>
<td>560</td>
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<td>20-100 ABT (cycle 0)</td>
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Ibrutinib (week 1+) mg per day

Treatment Schema:

Venetoclax

Ibrutinib dosing per allocation
Ibrutinib Combined With Venetoclax in R/R Mantle Cell Lymphoma (SYMPATICO)

- Initiated May 2017
- Sponsor: Pharmacyclics
- Phase 3 multinational, randomized, double-blind study to compare the efficacy and safety of the combination of ibrutinib and venetoclax vs. ibrutinib and placebo in subjects with MCL
- R/R MCL, 1-5 prior treatments
Lymphoma Updates: ASH 2018

• Myriad new agents and treatment approaches
• Increasing recognition of clinical and biologic subtypes: ~ 100 unique entities in WHO 2017
• MRD testing of PB provides new insights into depth of remission, risk adapted therapy, and post-treatment monitoring
• Anti-CD19-CAR-T offering high responses and potential cures in R/R aggressive B-NHL