2020 Year in Review: Diffuse large B-cell lymphoma and Hodgkin lymphoma

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Overview: Five parts

• **Diffuse large B-cell lymphoma (high-risk, relapsed/refractory)**
  – Shifting role of CAR-T
  – Management options for non-transplant/non-CAR-T patients

• **Hodgkin lymphoma**
  – Frontline management for advanced stage disease
  – Post-transplant consolidation
  – Relapsed/refractory disease
HIGH-RISK OR R/R DLBCL
Many subsets of DLBCL are not cured with R-CHOP

Key challenges:
- Increase number of patients cured with 1L treatment
- Improve options for patients 2L+

Low IPI
Low stage
GC phenotype

High IPI
Elderly
Non-GC phenotype
Double hit lymphoma
Dual protein overexpression

R-CHOP
Expected survival for R/R DLBCL Treated with Salvage Chemotherapy

Patients unable to undergo autologous stem cell transplant have median survivals < 1 year


Courtesy of Sonali M Smith, MD
CD19 Directed CAR T Cell Products in Clinical Development

Adapted from van der Steeg et al. Nat Rev Drug Discov, 2015

Axi-cel
Tisa-cel
Liso-cel
Liso-cel (TRANSCEND NHL-001)

Key patient features:
269 of 344 pts received product
42% over age 65y
67% chemo-refractory
7 pts with secondary CNSL

Abramson JS et al. Lancet. 2020 Sep 19;396(10254):839-852

Courtesy of Sonali M Smith, MD
Matching-Adjusted Indirect Comparison (MAIC) of Liso-cel vs Axi-cel and Tisagenlecleucel in R/R Large B-Cell Lymphoma

Is there a “best-in-class” CAR-T product?

Cartron G et al. ASH 2020; Abstract 2116

Courtesy of Sonali M Smith, MD
Liso-cel vs. Axi-cel and Liso-cel vs. Tisa-cel

- Pairwise matching-adjusted comparison study with matching and then adjustment of ZUMA-1, TRANSCEND, JULIET
- Better safety and comparable efficacy: liso-cel versus axi-cel
- Better efficacy and comparable safety: liso-cel versus tisa-cel
Can we identify non-responders vs. responders?

Multivariate analyses of JULIET trial:

- high levels of pre-infusion LDH associated with NRs at month 3 as well as worse PFS and OS
- Pre-infusion Grade 3/4 thrombocytopenia
- analyses suggest that a subset of pts with aggressive disease at infusion and/or pts with severe CRS/NE had poorer outcomes in the JULIET trial
Interim Analysis of ZUMA-12 Trial of Axi-cel as First-Line Therapy for Patients with High-Risk Large B-Cell Lymphoma

Moving CAR T-cell therapy earlier: high-risk DLBCL

Are CAR-T cells “better” if utilized earlier?

- Higher frequency of CCR7+CD45RA+ T-cells
- Greater CAR-T cell expansion

Med f/u 9.5m

Neelapu SS et al. ASH 2020; Abstract 405
Impact of CAR-T in high-risk and R/R DLBCL

Impact on Patient Care and Treatment Algorithm

• There soon will be three anti-CD19 CAR-T products available: axi-cel, liso-cel, and tisa-cel, with an approximately 30-40% rate of durable remissions in 3L DLBCL
• Liso-cel appears to have more favorable toxicity profile
• Identifying predictors of response/non-response is key

Implications for Future Research

• If toxicity can be minimized, is outpatient CAR-T coming soon? Can CAR-T be safely delivered in the community?
• Early identification of chemoresistance may allow CAR-T to be utilized earlier in the treatment paradigm
OPTIONS FOR NON-CAR-T/NON-TRANSPLANT CANDIDATES
Selinexor: oral XPO1 inhibitor

Selinexor: Mechanism of Action

Exportin 1 (XPO1 or CRM1) mediates the nuclear export of proteins, mRNAs, rRNAs, snRNAs and impacts

- Tumor suppressor proteins (p53, IκB, FOXO etc.)
- eIF4E (Translational initiation factor) bound oncogenic mRNAs (c-Myc, Bcl-xL, cyclins etc.)

Selinexor is an oral selective XPO1 inhibitor; preclinical data support that XPO1 inhibition:

- Reactivates multiple TSPs relevant to NHL, (p53, p21, IκB, FOXO etc.)
- Disrupts localization of eIF4e (overexpressed in most B-cell lymphomas)
- Reduces c-Myc, Bcl-2, and Bcl-6 levels


Courtesy of Sonali M Smith, MD
## SADAL: phase 2 trial of selinexor monotherapy in R/R DLBCL

### Patient characteristics:
- N=127 with med age 67y
- 45% of pts ≥ 70y
- 72% refractory to last regimen

### Results:
- ORR 28%
- CR 12%
- Med DR 9.3m
  - med DR for CR pts 23m
  - med DR for PR pts 4.4m
- No impact of COO

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<th>DLBCL Subtype</th>
<th>n/N</th>
<th>Overall response rate (%)</th>
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<tr>
<td>GCB</td>
<td>20/59</td>
<td>24% (22.1-47.4)</td>
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<tr>
<td>Non-GCB</td>
<td>12/63</td>
<td>21% (11.5-32.7)</td>
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<tr>
<td>De novo or transformed</td>
<td>72/94</td>
<td>24% (16.2-34.4)</td>
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<td>Transformed</td>
<td>12/31</td>
<td>39% (22.8-57.8)</td>
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<th>Refractory to last line</th>
<th>ORR (%)</th>
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<tr>
<td>Yes</td>
<td>27% (18.6-35.8)</td>
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<tr>
<td>No</td>
<td>37% (19.9-55.1)</td>
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<th>Previous ASCT therapy</th>
<th>ORR (%)</th>
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<tr>
<td>Yes</td>
<td>42% (26.3-59.1)</td>
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<td>No</td>
<td>22% (14.3-32.6)</td>
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<table>
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<th>Gender</th>
<th>ORR (%)</th>
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<td>Female</td>
<td>33% (20.3-47.1)</td>
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<tr>
<td>Male</td>
<td>25% (16.0-36.7)</td>
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<tr>
<th>Age</th>
<th>ORR (%)</th>
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<tr>
<td>≥70</td>
<td>25% (14.1-38.4)</td>
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<td>&lt;70</td>
<td>31% (20.9-43.6)</td>
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<th>Number of previous lines</th>
<th>ORR (%)</th>
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<tr>
<td>≥2</td>
<td>31% (18.7-45.5)</td>
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<td>≥3</td>
<td>27% (17.3-38.1)</td>
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<th>Creatinine clearance</th>
<th>ORR (%)</th>
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<td>&gt;100 ml/min</td>
<td>31% (16.1-50.4)</td>
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<tr>
<td>60-99 ml/min</td>
<td>28% (19.1-38.2)</td>
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<tr>
<td>Overall</td>
<td>28% (20.7-37.0)</td>
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Tafasitamab MOA

L-MIND trial: phase 2 trial of tafa-len x 12 cycles in R/R DLBCL

Salles et al. ICML 2019. #124. Hortonet al., 2008; Awanet al., 2010; Richter et al., 2013; MorphoSys data on file; Wu et al., 2008; Lapalombella et al., 2008; Zhang et al., 2013, Wiernik et al., 2008; Witzig et al., 2011; Czuczman et al., 2017; Jurczak et al., 2018

Courtesy of Sonali M Smith, MD
L-MIND Results: very long response duration for CR pts

Patient characteristics:
N=81 with med age 72y
50% of pts 2L
42% R-ref, 44% ref

Results:
ORR 60%, CR 43%
Med DR 22m but NR for CR pts


Courtesy of Sonali M Smith, MD
ASH 2020: Advent of Bispecifics in Lymphoma

• CD20 x CD3
  • REGN1979 — Bannerji ASH 2020 #400
  • Mosunetuzumab — Olszewski ASH 2020 #401
  • Epcoritamab — Hutchings ASH 2020 #402
  • Glofitamab — Hutchings ASH 2020 #403

• CD19 x CD3
  • MB-CART2019.1 — Borchman ASH 2020 #404
Expanding options for non-CAR-T/non-transplant patients with R/R DLBCL

Impact on Patient Care and Treatment Algorithm
• There are now three new approved non-CAR-T regimens for R/R DLBCL
• There are no data on sequencing
• Responses seem durable

Implications for Future Research
• Bispecifics are coming soon!
• Patient selection for “aggressive” vs. “non-aggressive” treatment is needed
HODGKIN LYMPHOMA
Snapshot of frontline standard treatment approach prior to targeted agents

IA, IIA
- Non-PET adapted
  - ABVD2 + IFRT 20Gy
  - ABVD4-6

IIB, IIX

III, IV
- Non-PET adapted
- PET-adapted
  - ABVD6
  - Stanford V
eescBEACOPP
  - ABVD6 + IFRT 20Gy
  - RATHL NEJM 2016
  - S0816 JCO 2016

 Courtesy of Sonali M Smith, MD
Evolution of care: two “new” targets

http://pleiad.umdnj.edu/~dweiss/hd_types/hdImmuno_img.html


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Integration of targeted agents into frontline management of advanced stage cHL: ECHELON-1

HR 0.77 (95% CI: 0.60–0.98)
Log-rank test p-value: 0.035

Connors et al. NEJM online 2017; slide courtesy of Alex Herrera
ASH 2020: 5-year follow up of ECHELON-1

ECHELON-1: PFS per investigator at 5 years’ follow-up*

- At 5 years A+AVD continues to demonstrate a robust and durable treatment benefit independent of disease stage, risk factor score, and PET2 status, without requiring change of therapy based on interim PET assessment and without exposure to bleomycin.
- The sustained PFS benefit with A+AVD is coupled with:
  - A manageable long-term safety profile
  - A low rate of secondary malignancies
  - No observed impact on the rate of successful pregnancies compared with ABVD
  - A high rate of resolution and improvement of PN, with symptoms of PN resolving or improving over time.
- As most relapses in cHL occur within 5 years of frontline treatment, these long-term PFS data suggest that more patients may have been cured of their disease with A+AVD versus ABVD.
- A+AVD should be considered a preferred treatment option for all patients with previously untreated Stage III or IV cHL.

Strauss DJ et al. Brentuximab Vedotin with Chemotherapy for Patients with Previously Untreated, Stage III/IV Classical Hodgkin Lymphoma: 5-Year Update of the ECHELON-1 Study. ASH 2020; Abstract 2973. Poster

Courtesy of Sonali M Smith, MD
BV-AVD in frontline advanced stage cHL

Impact on Patient Care and Treatment Algorithm

• BV-AVD is a well-tolerated and effective option
• Avoids bleomycin AND avoids need for interim PET

Implications for Future Research

• Is this "the" or "a" new standard of care?
  – Will 5-year outcomes translate to a higher cure rate?
• BV-AVD is the control arm in S1826 US Intergroup trial compared to nivo-AVD (NCT03907488)

Courtesy of Sonali M Smith, MD
What about older patients with cHL?

Part A: BV monotherapy
Part B: BV (1.8mg/kg) + DTIC
Part C: BV + benda (70mg/m²)  
Part D: BV + nivo

Closed due to excess toxicity

SGN35-015 Study Design: Phase 2, Frontline Therapy in Older cHL Patients

- Eligible patients: ≥60 years of age with cHL, treatment naïve, considered unsuitable or unfit for conventional chemotherapy; fluorodeoxyglucose (FDG)-positron emission tomography (PET)-avid and measurable disease by computed tomography (CT)

Yasenchak CA et al. ASH 2020; Abstract 471

Courtesy of Sonali M Smith, MD
BV-based frontline treatment in older patients with cHL: BV + DTIC and BV-nivo promising

Part B: BV (1.8mg/kg) + DTIC
Med f/u 63m
Med PFS 46m

Part D: BV + nivo
Med f/u 26m

Yasenchak CA et al. ASH 2020; Abstract 471

Courtesy of Sonali M Smith, MD
BV plus nivo in TN older patients with cHL

- Phase II trial BV plus nivo q21d x 8 cycles

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<th>Total (n=46)</th>
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<td>21 (45%)</td>
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<td>25 (54%)</td>
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<td>26 (57%)</td>
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<td>2 (4%)</td>
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<td>3 (7%)</td>
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<td>I</td>
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<td>1 (2%)</td>
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<tr>
<td>II</td>
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<td>15 (33%)</td>
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<tr>
<td>III</td>
</tr>
<tr>
<td>9 (20%)</td>
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<tr>
<td>IV</td>
</tr>
<tr>
<td>21 (45%)</td>
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Med f/u 21.2m
Results:
CMR 65%
Med PFS 18m

Toxicity:
One-third needed dose adjustments
48% peripheral neuropathy (11% grade 3)
1 death from cardiac arrest

A “negative” phase 2 trial?
Treatment of older patients with treatment-naïve cHL

Impact on Patient Care and Treatment Algorithm

- Promising use of targeted agents in frontline setting that avoids bleomycin and reduces use of cytotoxic agents
- BV-benda is too toxic in older patients

Implications for Future Research

- There remains an unmet need for a less toxic treatment of older patients with cHL
- Should BV-nivo be further pursued?

Courtesy of Sonali M Smith, MD
Treatment approach for relapsed cHL

- ASCT elig
- Salvage
- ASCT
- BV consol

R/R #1

ASCT inelig

Monotherapy with:
- Brentuximab vedotin
- Nivolumab
- Pembrolizumab

CR, PR
5-year follow up of post-ASCT BV (AETHERA TRIAL)

16 doses of BV
1.8mg/kg q21d post-ASCT

Is there a shorter, less toxic post-transplant option?

**Treatment:**
- 30-75 days post AHCT
- 1.8mg/kg BV and 3mg/kg nivo q21d x 8 doses
- Primary endpoint 18m PFS

**Patients:**
- N=59
- Med age 30 (18-72y)
- 32% primary refractory disease
- 39% EN disease
- 51% prior BV
- 42% prior PD-1 inhibitors

Herrera AF et al. ASH 2020; Abstract 472

Courtesy of Sonali M Smith, MD
Post-autologous stem cell transplant BV + nivo

Only 49% completed both agents
Most common AEs were neuropathy, neutropenia
27% had immune-related AE’s requiring steroids

PFS according to number of risk factors

19-month PFS in pts with:
1 risk factor (n=21) – 93%
(95 CI 59-99%)
2 risk factors (n=24) – 96%
(95 CI 73-99%)
3+ risk factors (n=14) – 83%
(95 CI 48-96%)

19m PFS is 92%
(med f/u is 18m)

Herrera AF et al. ASH 2020; Abstract 472
Courtesy of Sonali M Smith, MD
Post-transplant BV + nivo

Impact on Patient Care and Treatment Algorithm

- Shorter consolidation is appealing
- Intolerance rate seems high

Implications for Future Research

- Role of post-transplant consolidation will need to be refined
- What if patients receive BV and/or nivo in 1\textsuperscript{st} and 2\textsuperscript{nd} line settings?

Courtesy of Sonali M Smith, MD
KEYNOTE-204: Pembro vs. BV in R/R cHL

- Med PFS 13.2 vs. 8.3m favoring pembro
- Most pts BV-naive
Exploratory analysis of pembro vs. BV in R/R cHL by line of therapy (KEYNOTE-204)

Percent pts over 65y:
1L: 36-44%
2L+: 10-12%

Kuruvilla J et al. ASCO 2020; Abstract 8005. Oral, HoD
Zinzani P et al. EHA 2020; Abstract LB2600. Late Breaking
Kuruvilla J et al.. ASH 2020; Abstract 1158. Poster

Courtesy of Sonali M Smith, MD
Combination targeted therapy in R/R cHL

Sequential phase I trial with multiple groups (all 21d cycles)

Ipilimumab (1mg/kg or 3mg/kg) + BV 1.8mg/kg

Nivolumab 3mg/kg + BV (1.2mg/kg or 1.8mg/kg)

Ipilimumab (1mg/kg) + nivolumab (3mg/kg) + BV (1.2mg/kg or 1.8mg/kg)

Combination targeted therapy in R/R cHL

Grade 3-4 AE’s seen in all groups
    slightly higher in Ipi-groups
    (43% ipi vs. 50% in triplet vs. 16% in nivo groups)

Grade 5 toxicity
    2 deaths from pneumonitis (nivo group and triplet group)

Houot R, Merryman RW, Morschhauser F. Lancet Haematol. 2020
    Sep;7(9):e629-e630

Courtesy of Sonali M Smith, MD
Targeted therapy in R/R cHL

Impact on Patient Care and Treatment Algorithm

• Monotherapy with pembrolizumab has improved PFS compared to monotherapy with brentuximab vedotin

• Doublet and triplet therapy with immunotherapy has activity (but also toxicity)

Implications for Future Research

• Unclear impact of these agents if frontline standard of care changes

• There are no data on sequencing

• Combination regimens need further investigation regarding PFS and durability of response
Thank you