AT THE FOREFRONT
UChicago Medicine

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

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Overview: Five parts

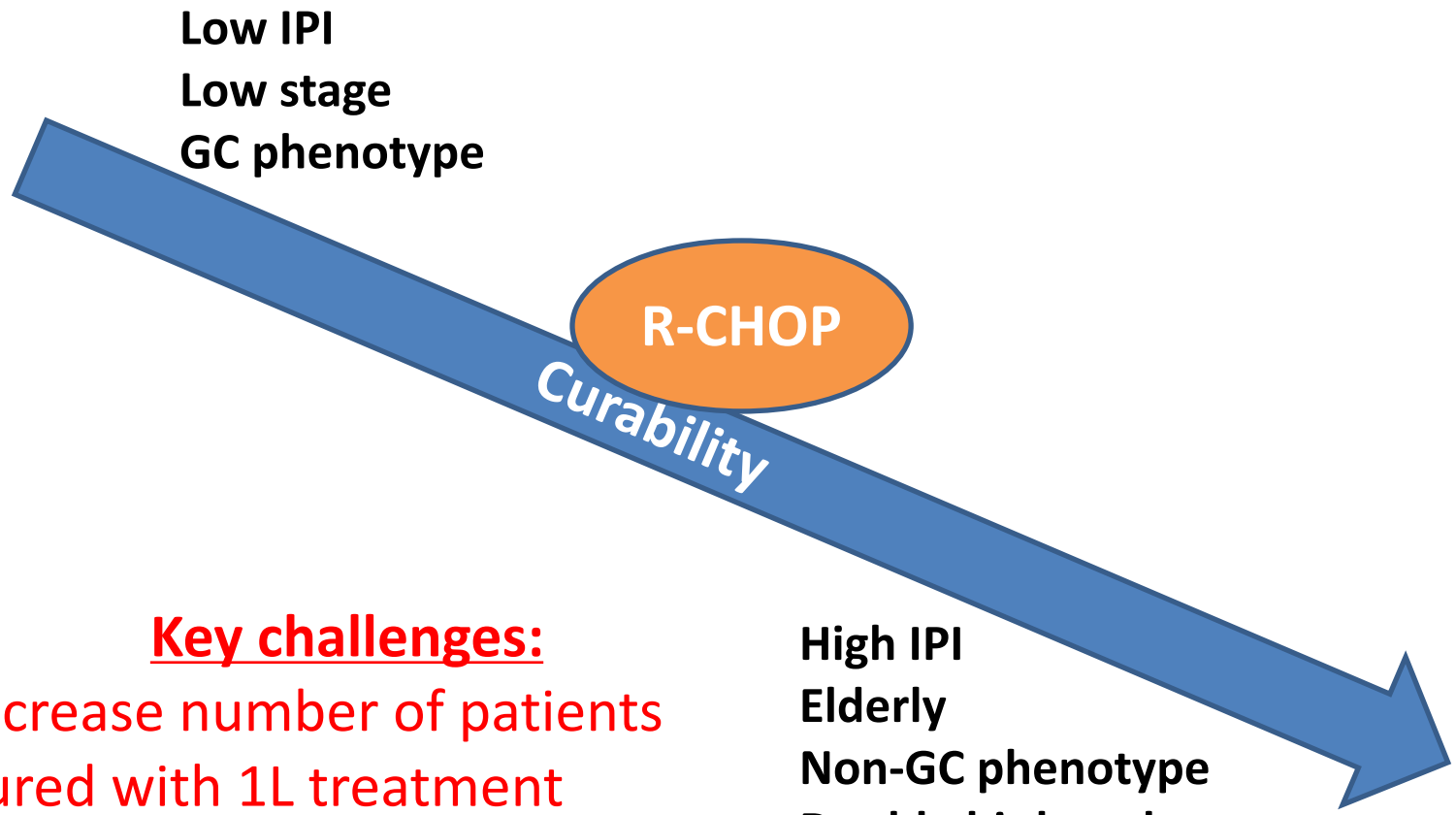
- **Diffuse large B-cell lymphoma (high-risk, relapsed/refractory)**
  - Shifting role of CAR-T
  - Management options for non-transplant/non-CAR-T patients
- **Hodgkin lymphoma**
  - Frontline management for advanced stage disease
  - Post-transplant consolidation
  - Relapsed/refractory disease

Courtesty of Sonali M Smith, MD

HIGH-RISK OR R/R DLBCL

Courtesy of Sonali M Smith, MD

Many subsets of DLBCL are not cured with R-CHOP

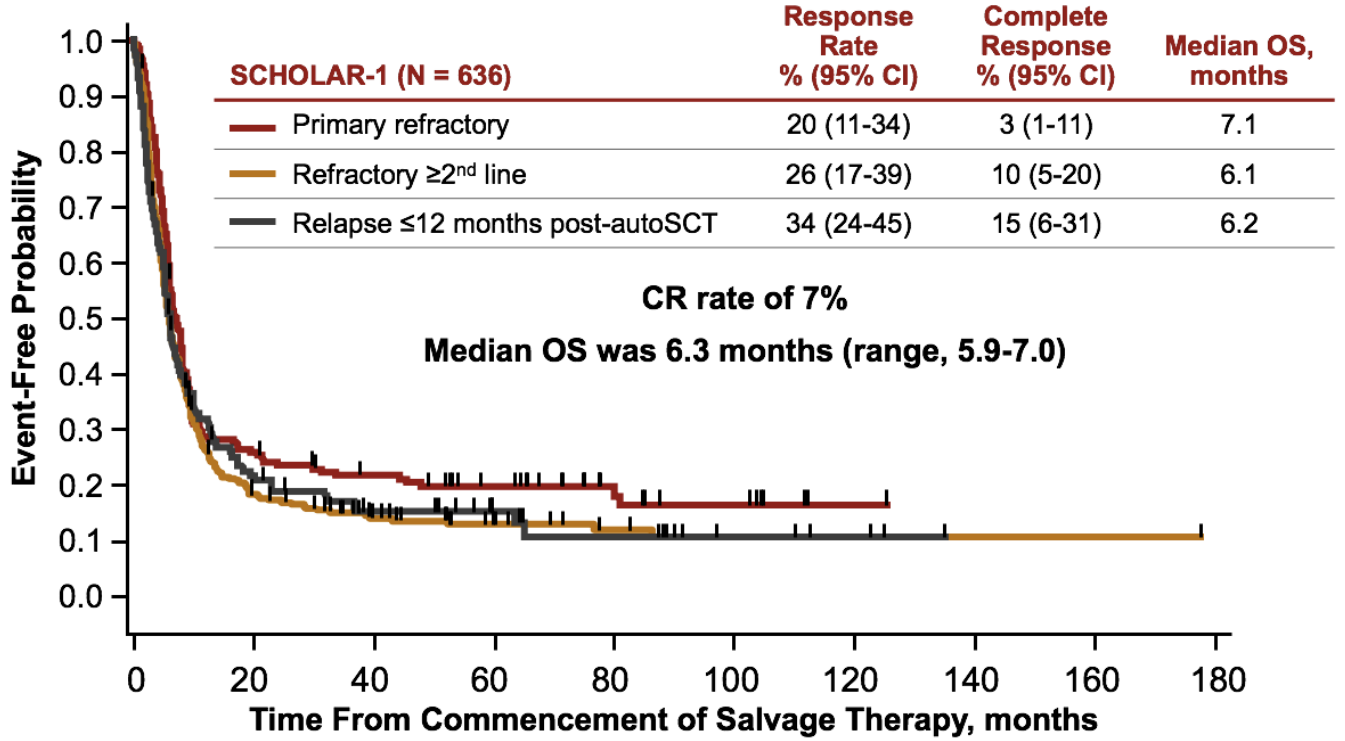


Key challenges:

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

Courtesy of Sonali M Smith, MD

Expected survival for R/R DLBCL Treated with Salvage Chemotherapy



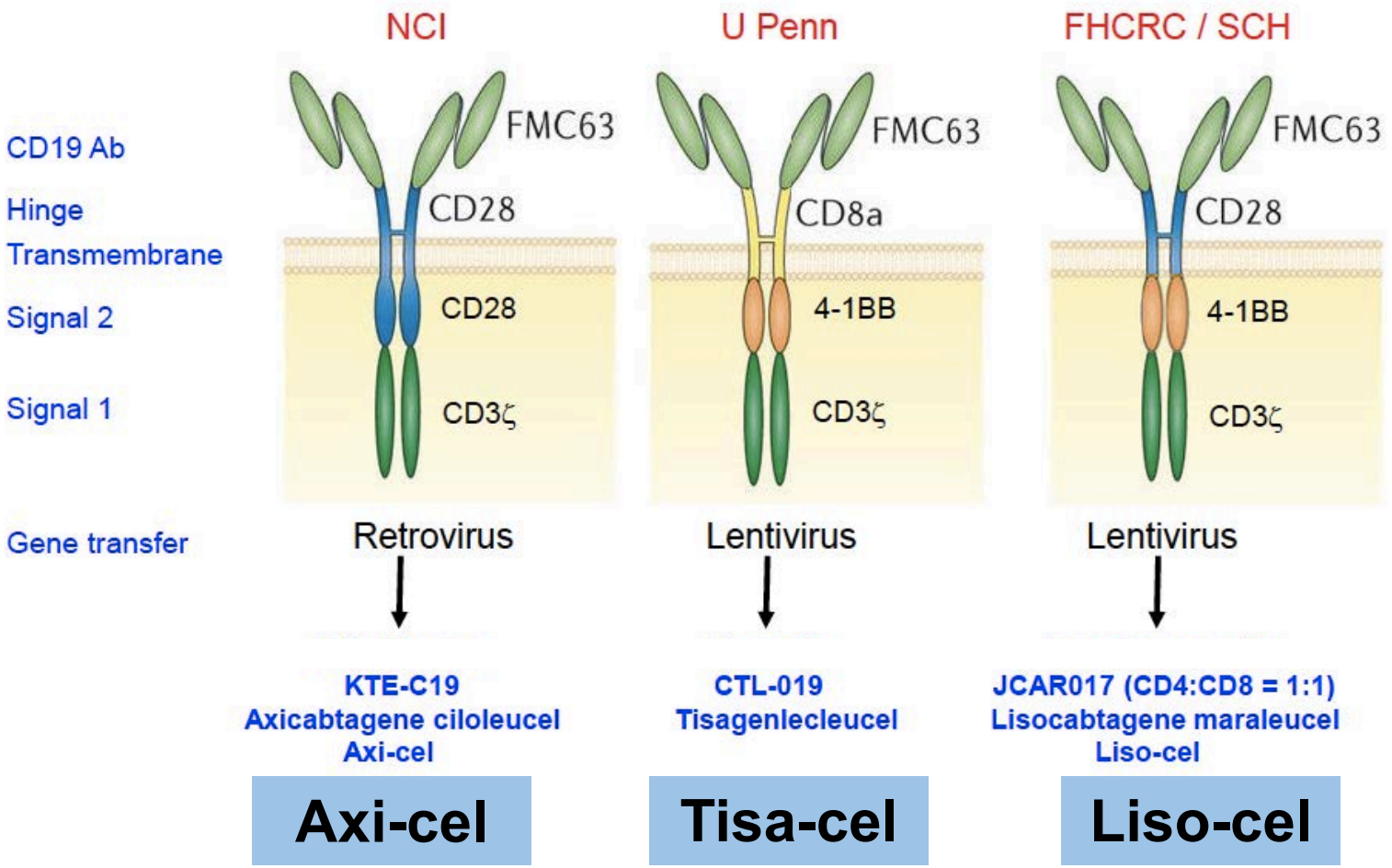
SCHOLAR-1 (N = 636)	Response Rate % (95% CI)	Complete Response % (95% CI)	Median OS, months
Primary refractory	20 (11-34)	3 (1-11)	7.1
Refractory ≥2nd line	26 (17-39)	10 (5-20)	6.1
Relapse ≤12 months post-autoSCT	34 (24-45)	15 (6-31)	6.2

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

Crump M, et al. *Blood*. 2017;130:1800-1808

Courtesty of Sonali M Smith, MD

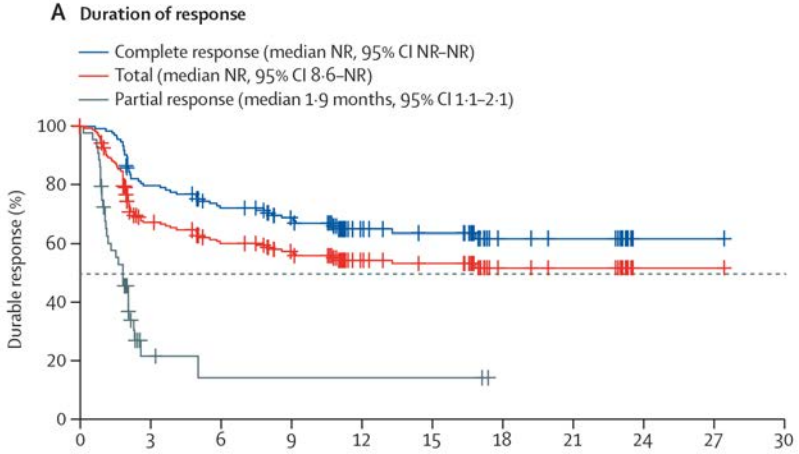
CD19 Directed CAR T Cell Products in Clinical Development



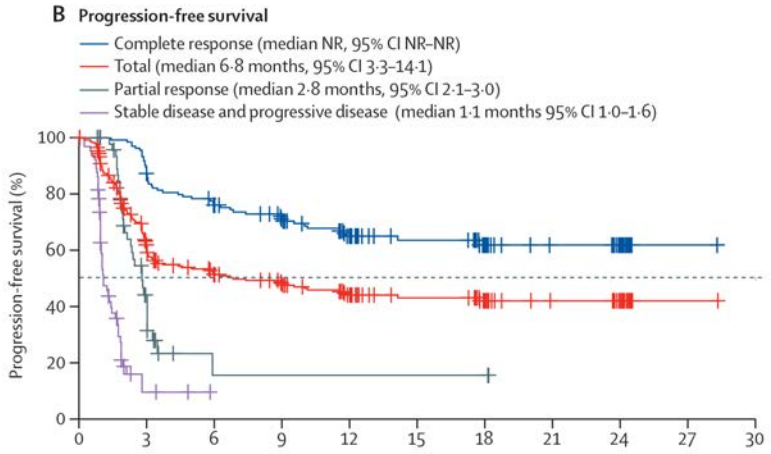
Adapted from van der Steegan et al. Nat Rev Drug Discov, 2015

Courtesty of Sonali M Smith, MD

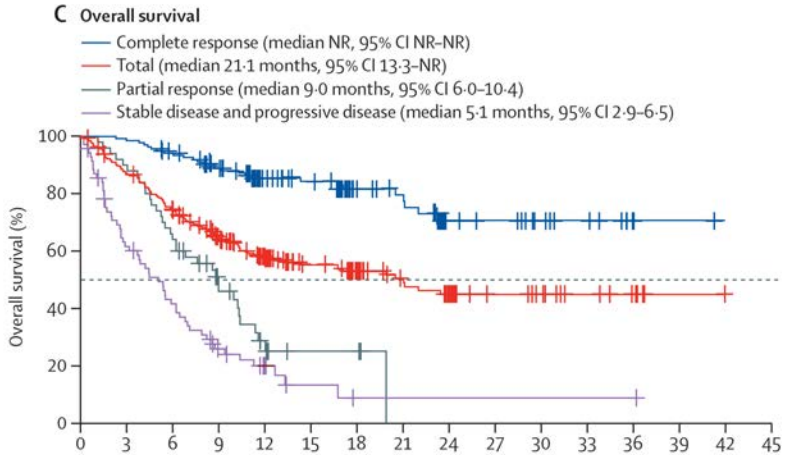
Liso-cel (TRANSCEND NHL-001)



Duration of Response



Overall Survival



Progression-free survival

<u>Key patient features</u>:

269 of 344 pts received product

42% over age 65y

67% chemo-refractory

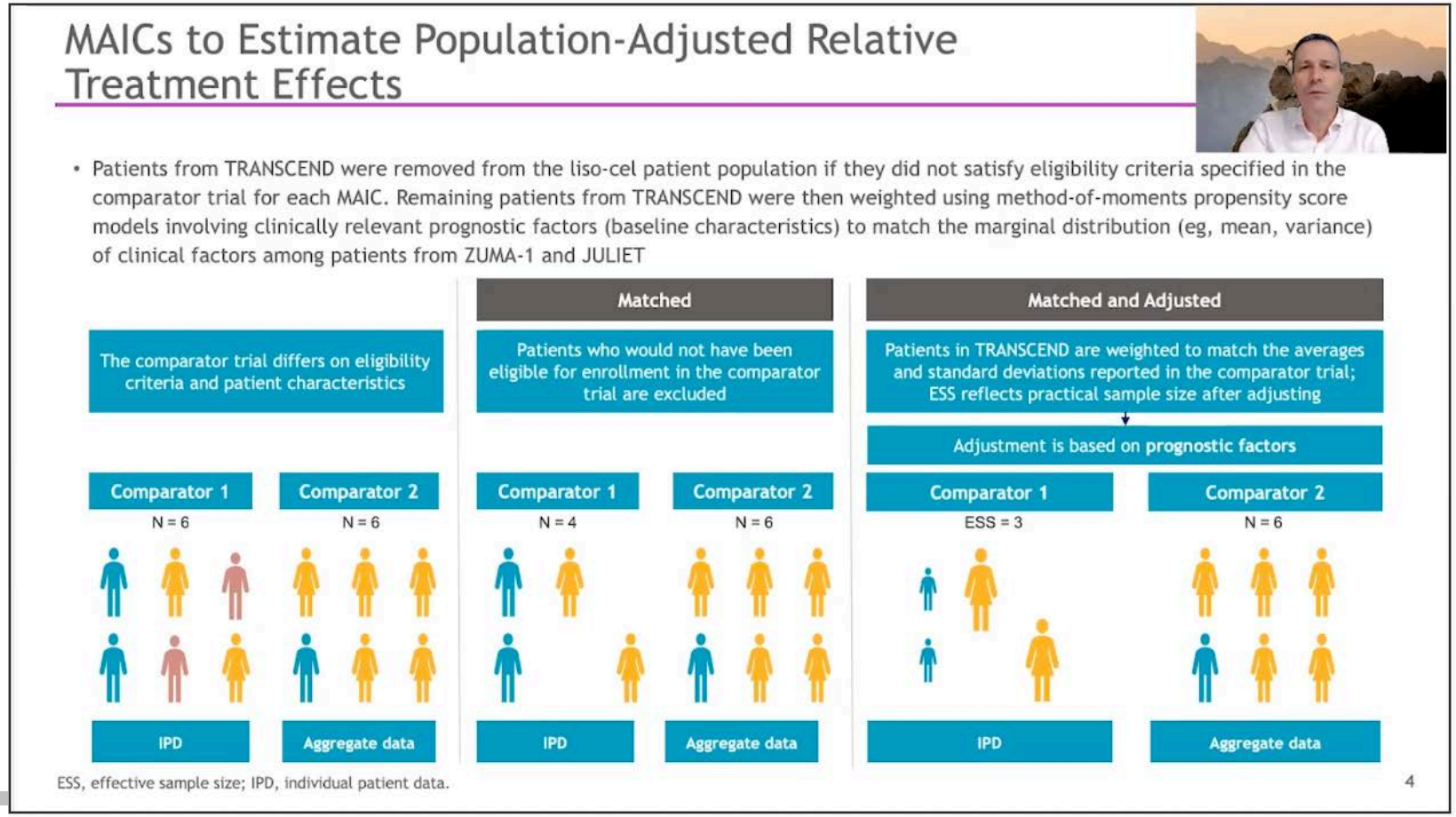
7 pts with secondary CNSL

	Patients (n=269)
Cytokine release syndrome, neurological events, or both	127 (47%)
Cytokine release syndrome*	
Any grade	113 (42%)
Grade 3	4 (1%)
Grade 4	2 (1%)
Time to onset, days	5 (1–14)
Time to resolution, days	5 (1–17)
Neurological events†	
Any grade	80 (30%)
Grade 3	23 (9%)
Grade 4	4 (1%)
Time to onset, days	9 (1–66)
Time to resolution, days	11 (1–86)

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

Courtesty 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?



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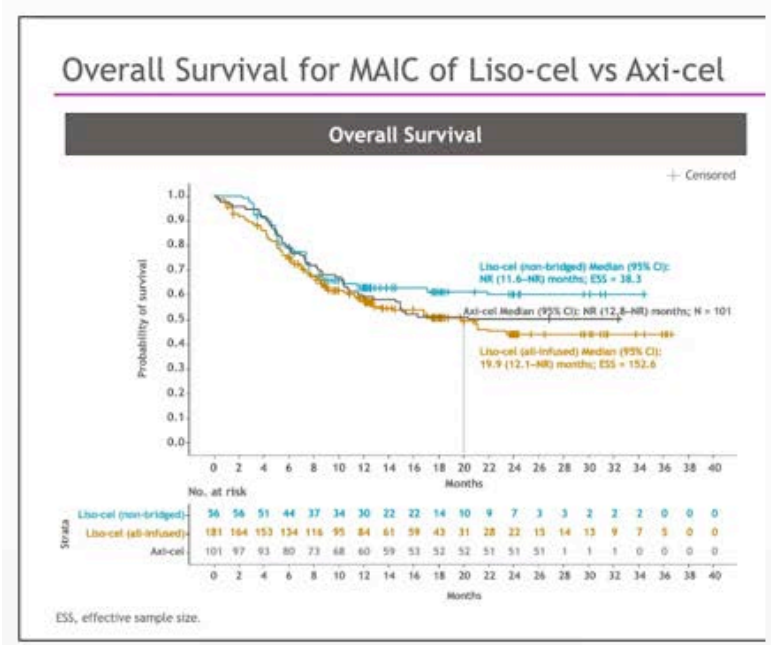
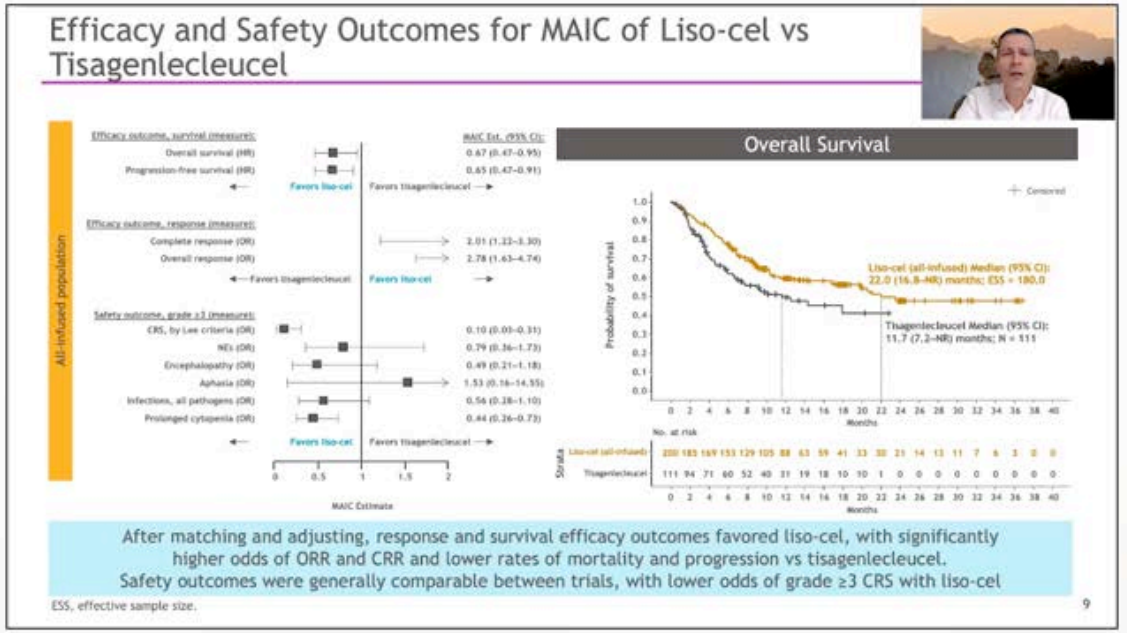
Cartron G et al. ASH 2020; Abstract 2116

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

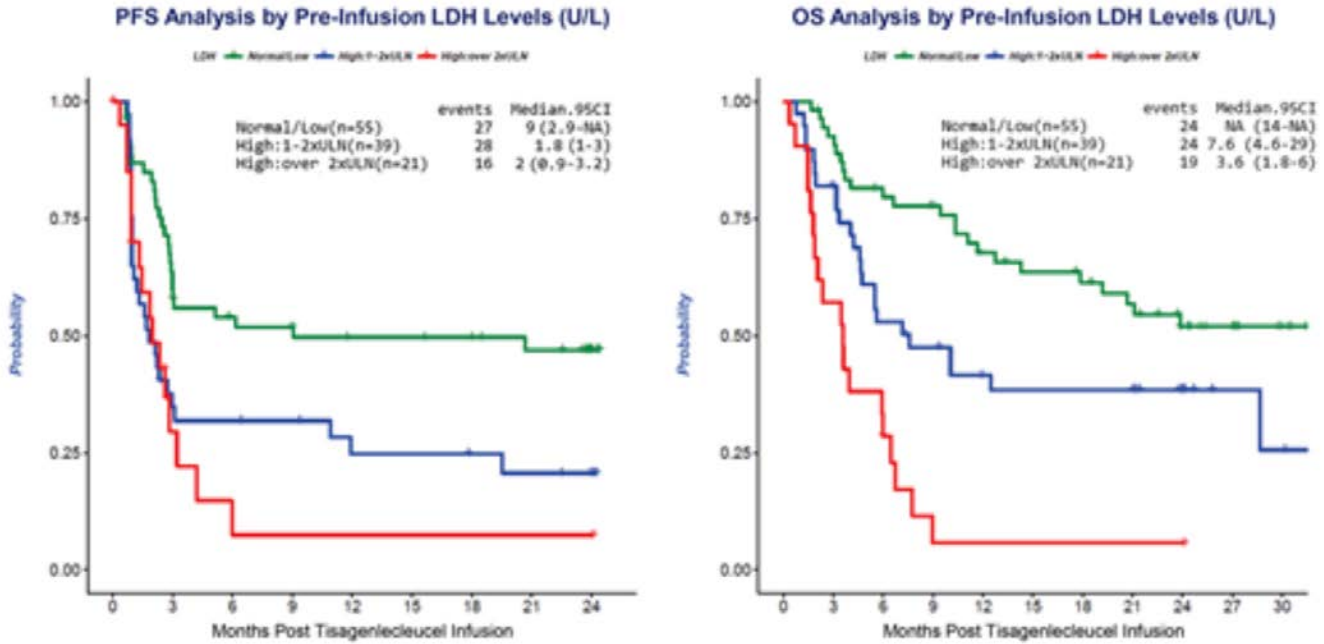
Cartron G et al. ASH 2020; Abstract 2116

Courtesty of Sonali M Smith, MD

Can we identify non-responders vs. responders?

JULIET Trial

Figure 1: PFS and OS by LDH at pre-infusion



Multivariate analyses of JULIET trial:

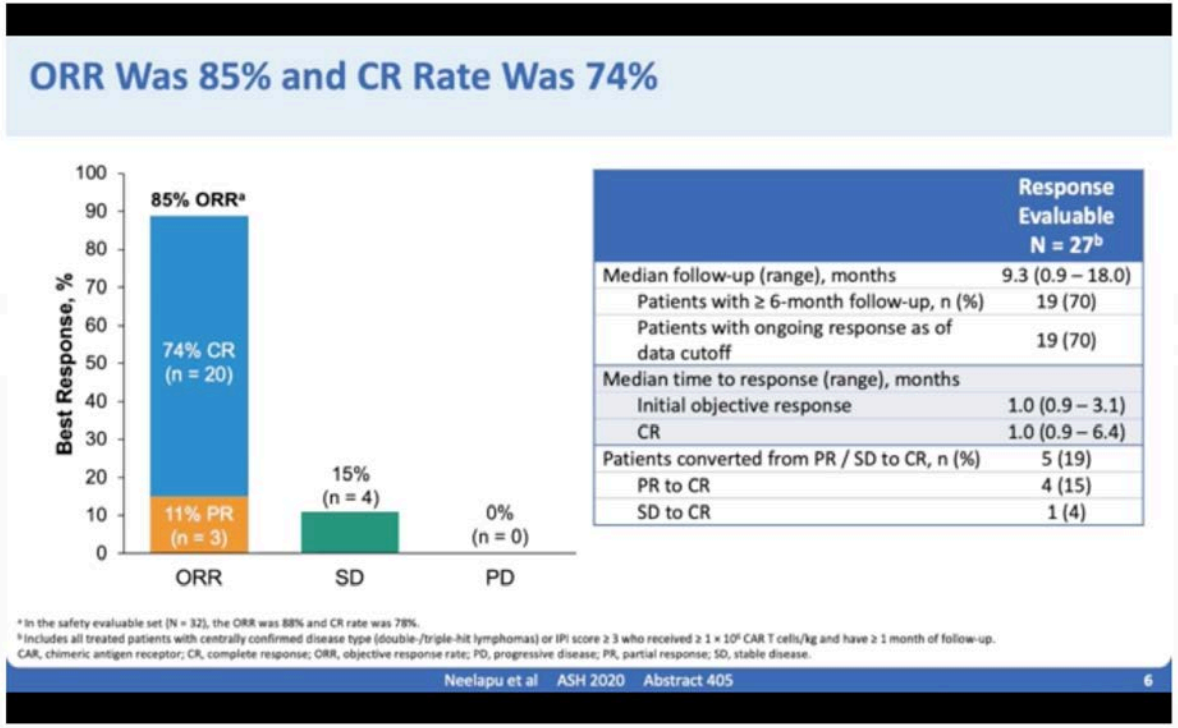
- high levels of pre-infusion LDH associated with NRs at month 3 as well as worse PFS and OS
- Pre-infusion Grade 3/4 thrombocytopenia
- analyses suggest that a subset of pts with aggressive disease at infusion and/or pts with severe CRS/NE had poorer outcomes in the JULIET trial

Westin JR et al. ASH 2019; Abstract 4103.
Schuster SJ et al. N Engl J Med. 2019 Jan 3;380(1):45-56

Courtesty of Sonali M Smith, MD

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



Med f/u 9.5m

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

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

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Neelapu SS et al. ASH 2020; Abstract 405

Courtesy of Sonali M Smith, MD

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

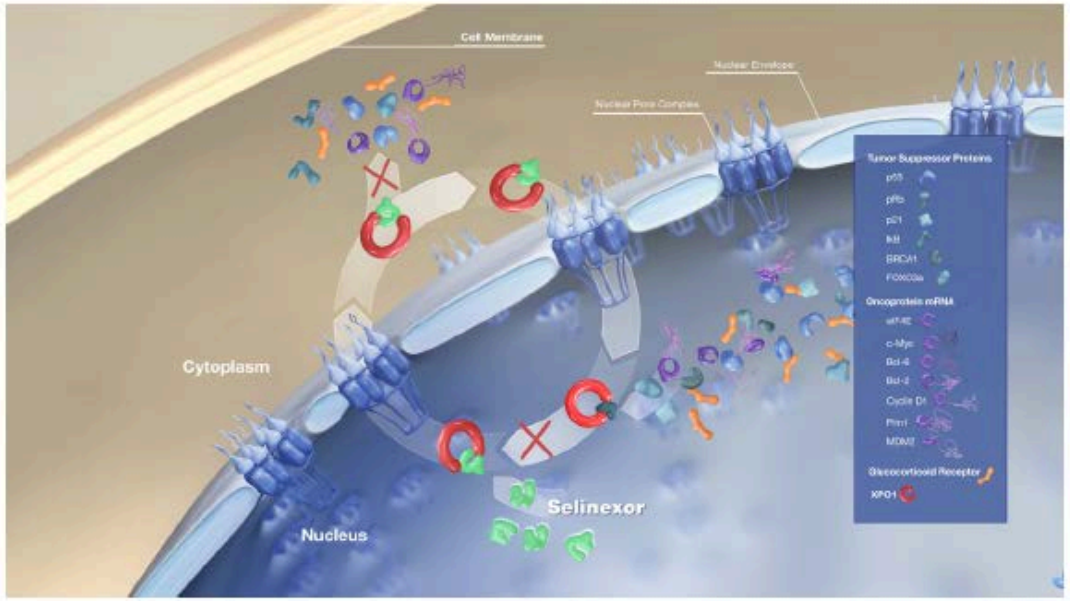
Courtesty of Sonali M Smith, MD

OPTIONS FOR NON-CAR-T/NON-TRANSPLANT CANDIDATES

Courtesy of Sonali M Smith, MD

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[1]
- Reduces c-Myc, Bcl-2, and Bcl-6 levels[2-3]

1. Kodali 2011 2. Kuruvilla 2014 3. Schmidt 2013

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%

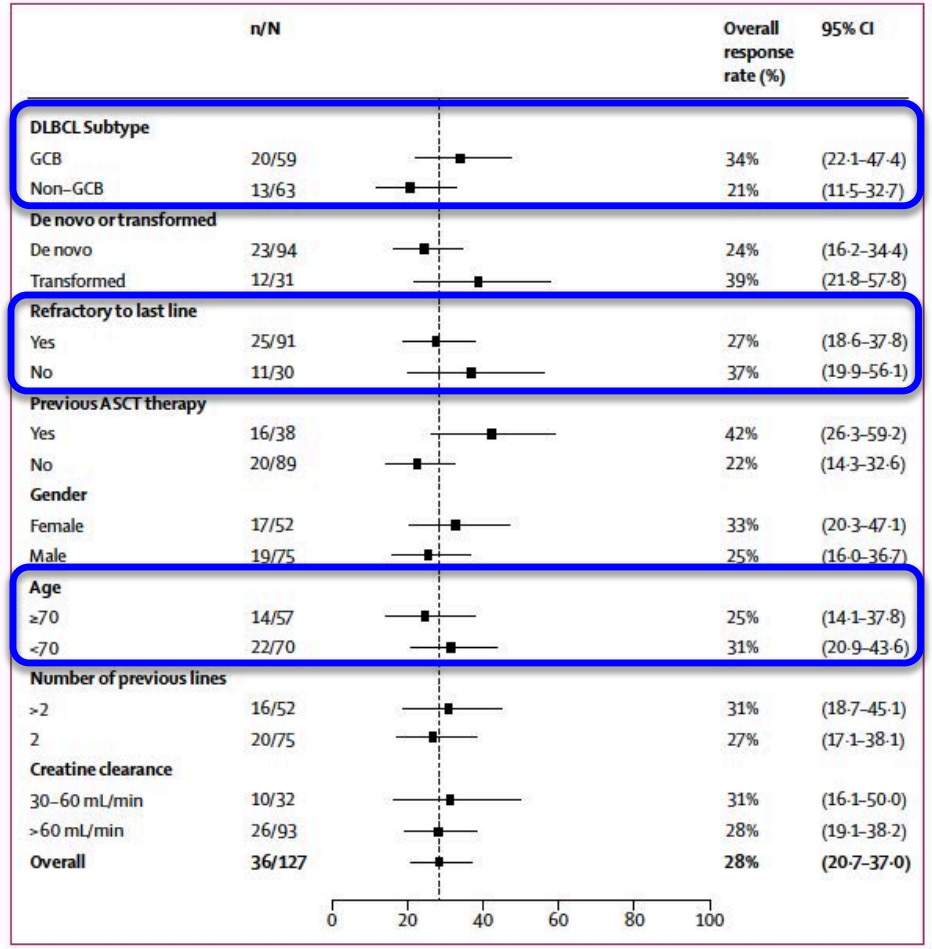
CR 12%

Med DR 9.3m

--med DR for CR pts 23m

--med DR for PR pts 4.4m

No impact of COO



Kalakonda N et al. *Lancet Haematol* 2020;7(7):e511-22.

Courtesty of Sonali M Smith, MD

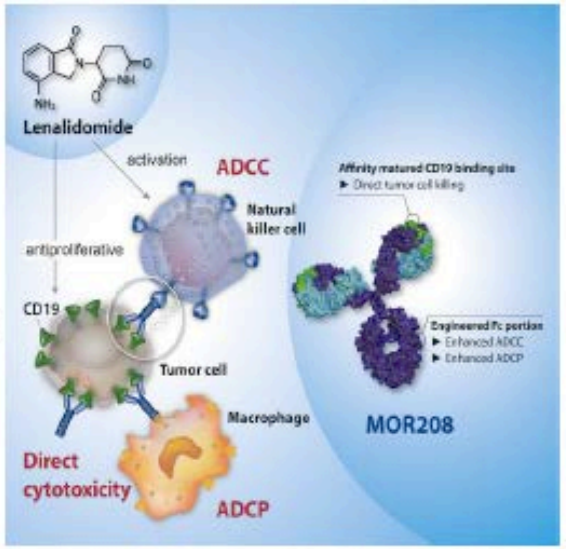
Tafasitamab MOA

Tafasitamab
Fc-enhanced, anti-CD19 mAb

+

Lenalidomide

- ADCC ↑
- ADCP ↑
- Direct Cell Death
- Encouraging single agent activity in NHL patients with long DoR in R/R DLBCL



- T and NK Cell Activation/Expansion
- Direct Cell Death
- Demonstrated activity as an anti-lymphoma agent, alone or in combination
- Approved for treatment of MCL and FL/MZL

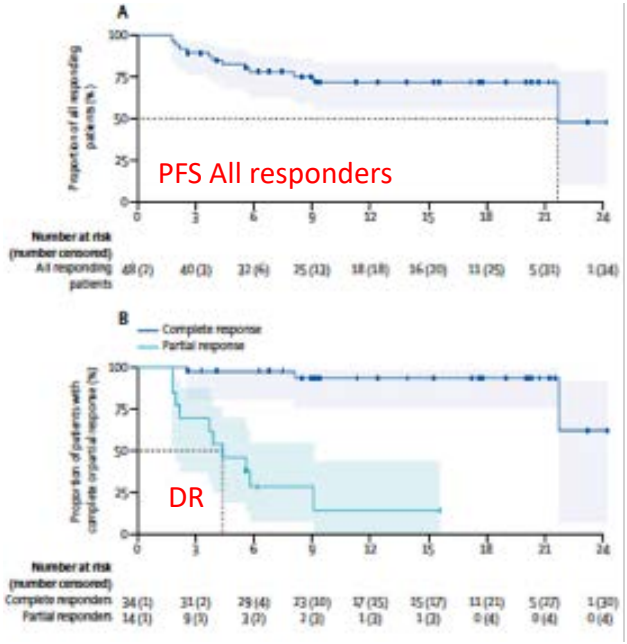
Potentiation of activity by combining Tafasitamab & LEN in vivo and in vitro

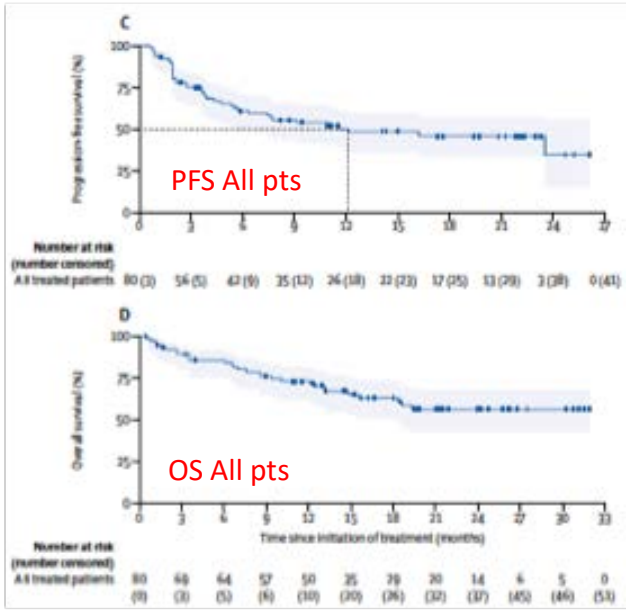
L-MIND trial: phase 2 trial of tafa-len x 12 cycles in R/R DLBCL

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

Salles G et al. Lancet Oncol. 2020 Jul;21(7):978-988

Courtesty 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

Courtesty of Sonali M Smith, MD

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

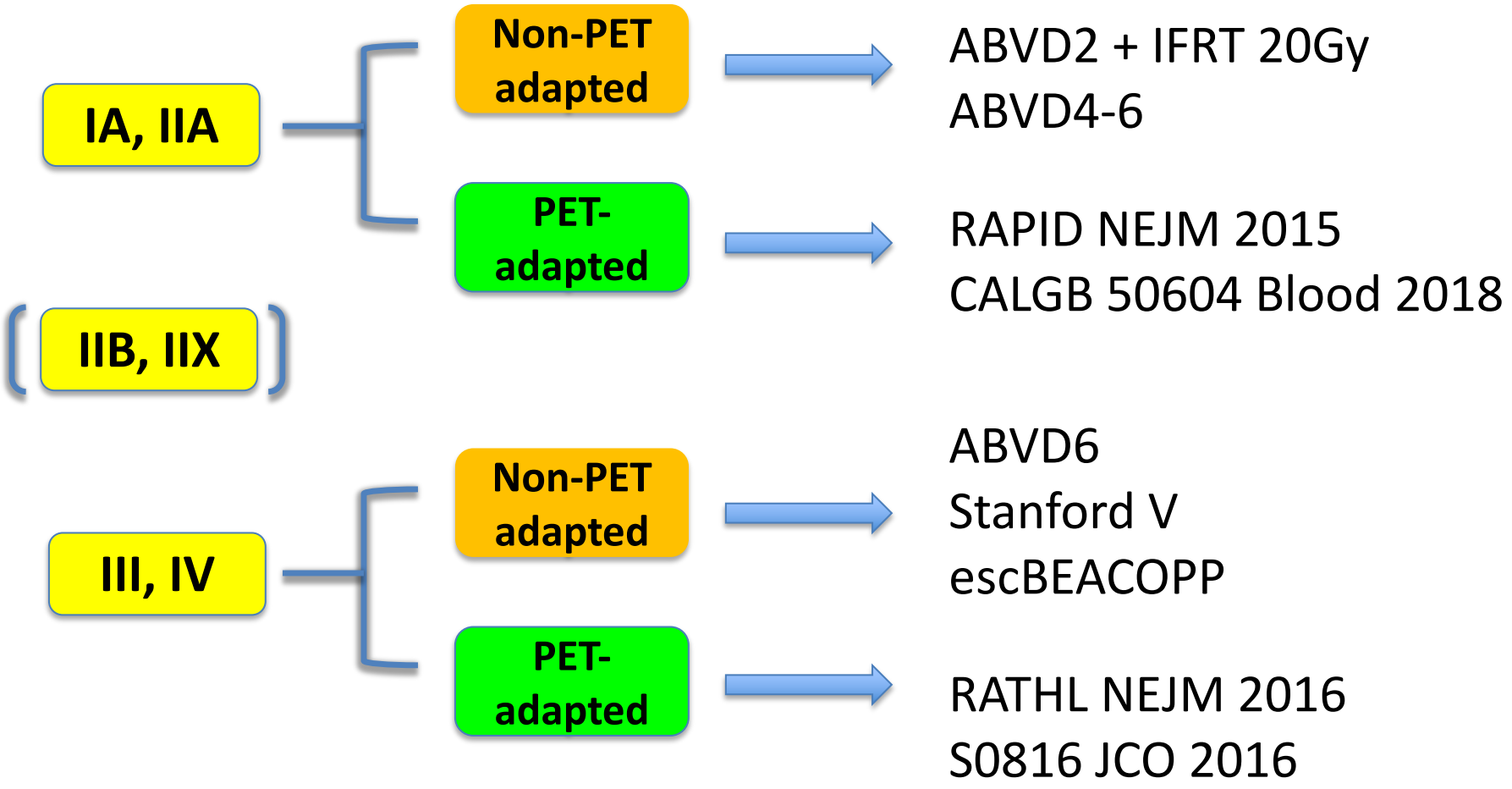
- Bispecifics are coming soon!
- Patient selection for “aggressive” vs. “non-aggressive” treatment is needed

Courtesty of Sonali M Smith, MD

HODGKIN LYMPHOMA

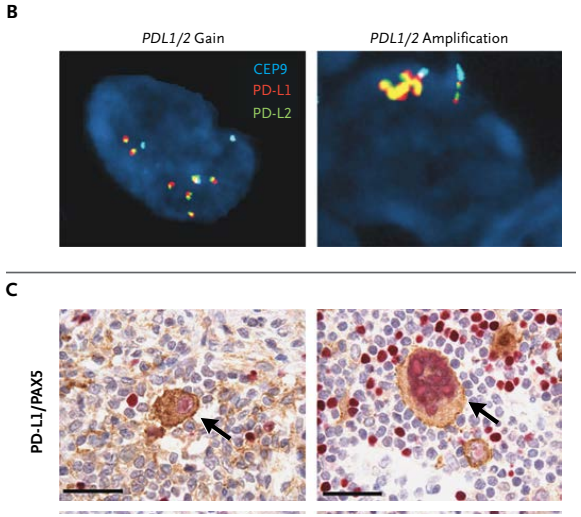
Courtesy of Sonali M Smith, MD

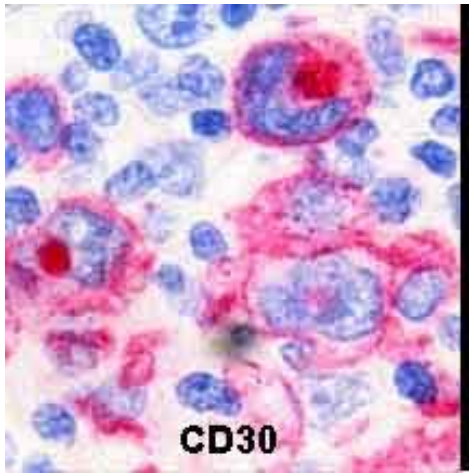
Snapshot of frontline standard treatment approach prior to targeted agents



Courtesty of Sonali M Smith, MD

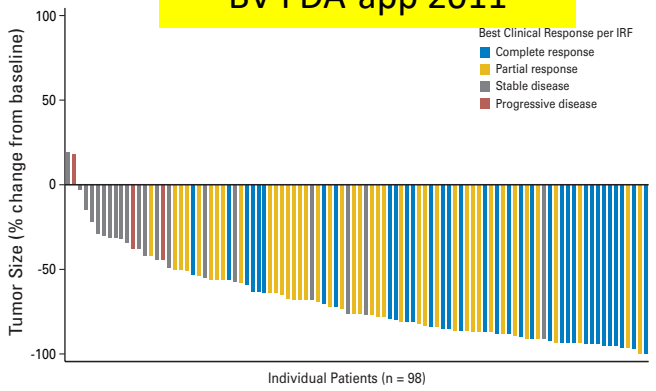
Evolution of care: two “new” targets



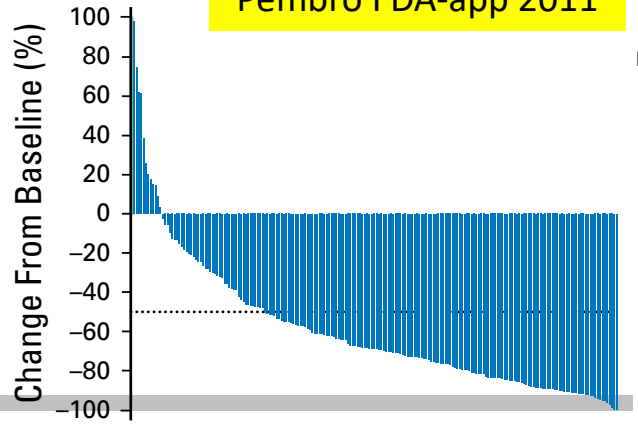


http://pleiad.umdnj.edu/~dweiss/hd_types/hdImmuno_img.html

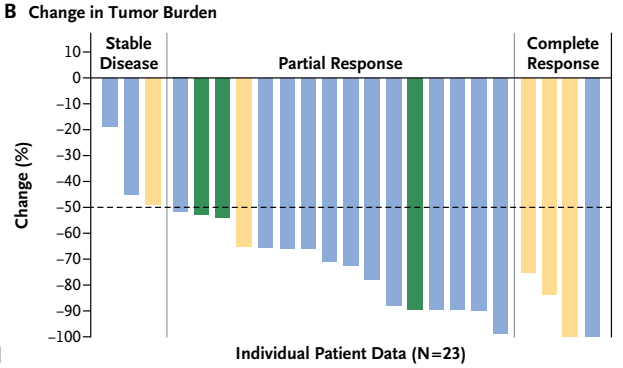
BV FDA-app 2011



Pembro FDA-app 2011



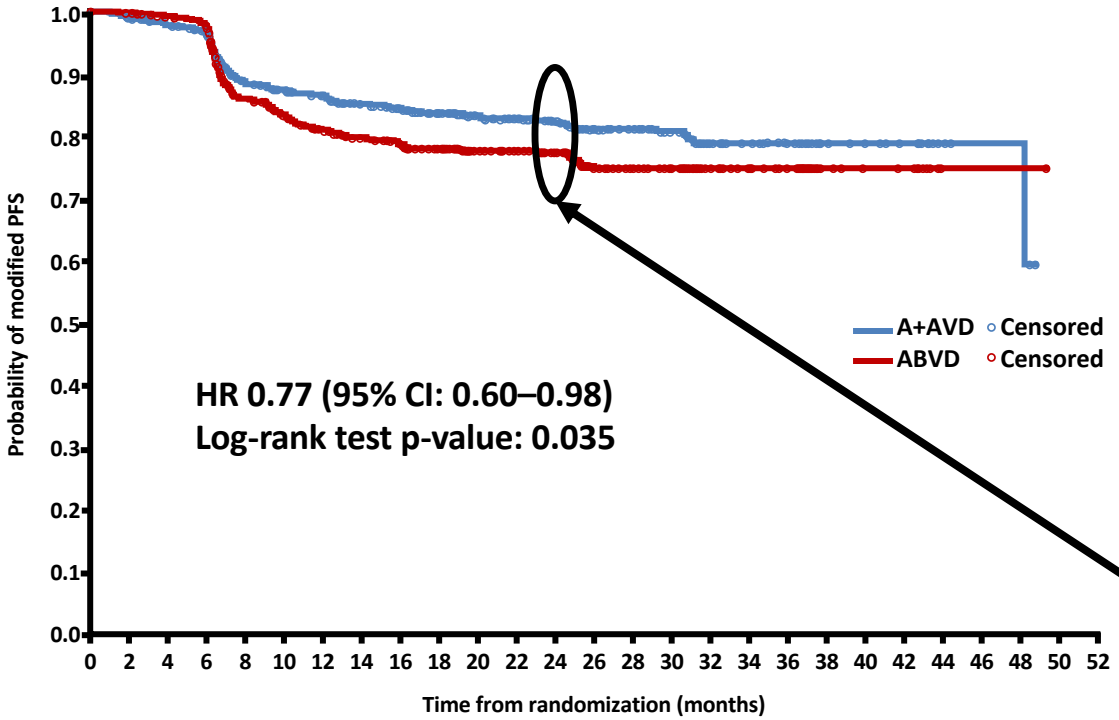
Nivo FDA-app 2016



Ansell et al. N Engl J Med. 2015 Jan 22;372(4):311-9; Younes et al. J Clin Oncol. 2012 Jun 20;30(18):2183-9; J Clin Oncol. 2017 Jul 1;35(19):2125-2132

Courtesty of Sonali M Smith, MD

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



Number of events

Category	A+AVD N=117	ABVD N=146
Progression	90	102
Death	18	22
Modified progression	9	22
Chemotherapy	7	15
Radiotherapy	2	7

Modified PFS estimates

Time	A+AVD (95% CI)	ABVD (95% CI)
2-year	82.1 (78.7–85.0)	77.2 (73.7–80.4)

Median follow-up (range): 24.9 months (0.0–49.3)

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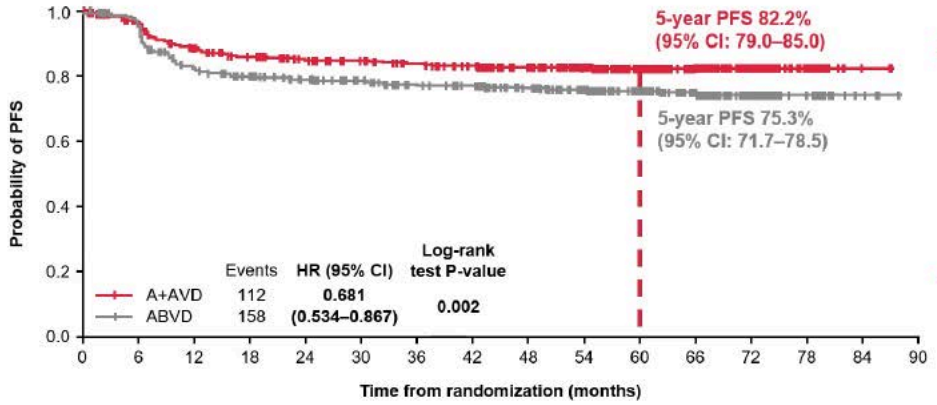
Connors et al. *NEJM* online 2017; slide courtesy of Alex Herrera

Courtesy of Sonali M Smith, MD

ASH 2020: 5-year follow up of ECHELON-1

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



- As of the 5-year follow-up, the prespecified number of events required to trigger an OS analysis have not been reached
- OS was a prespecified key secondary endpoint

Author Conclusions

- 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)

Courtesty of Sonali M Smith, MD

What about older patients with cHL?

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)

Part A: BV monotherapy

Part B: BV (1.8mg/kg) + DTIC

Part C: BV + benda (70mg/m^2) ← Closed due to excess toxicity

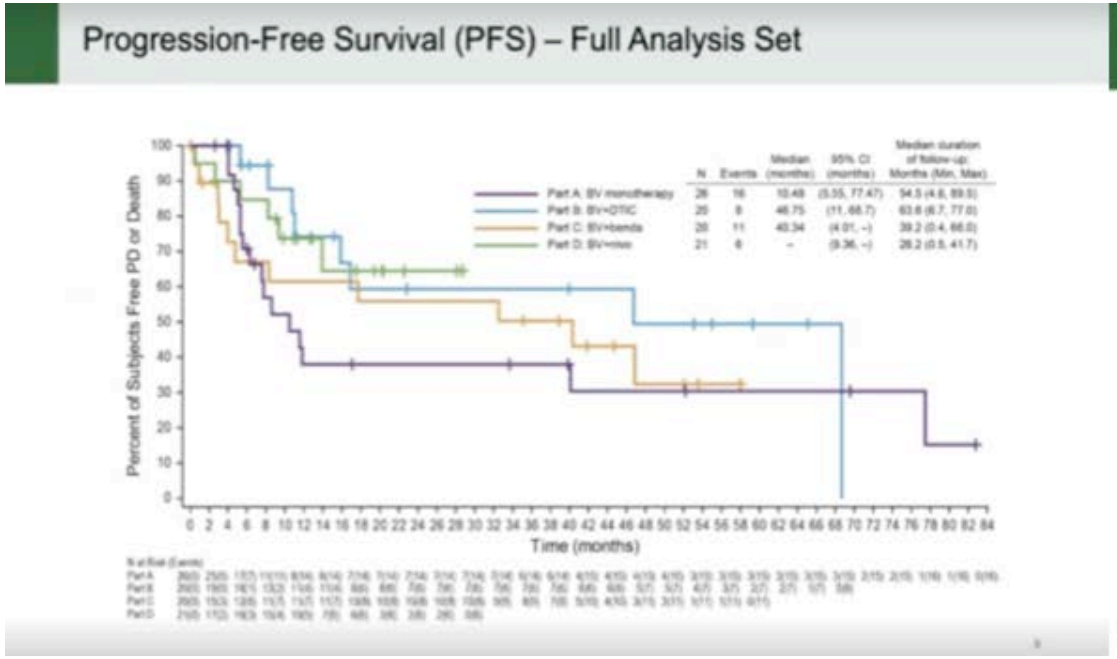
Part D: BV + nivo

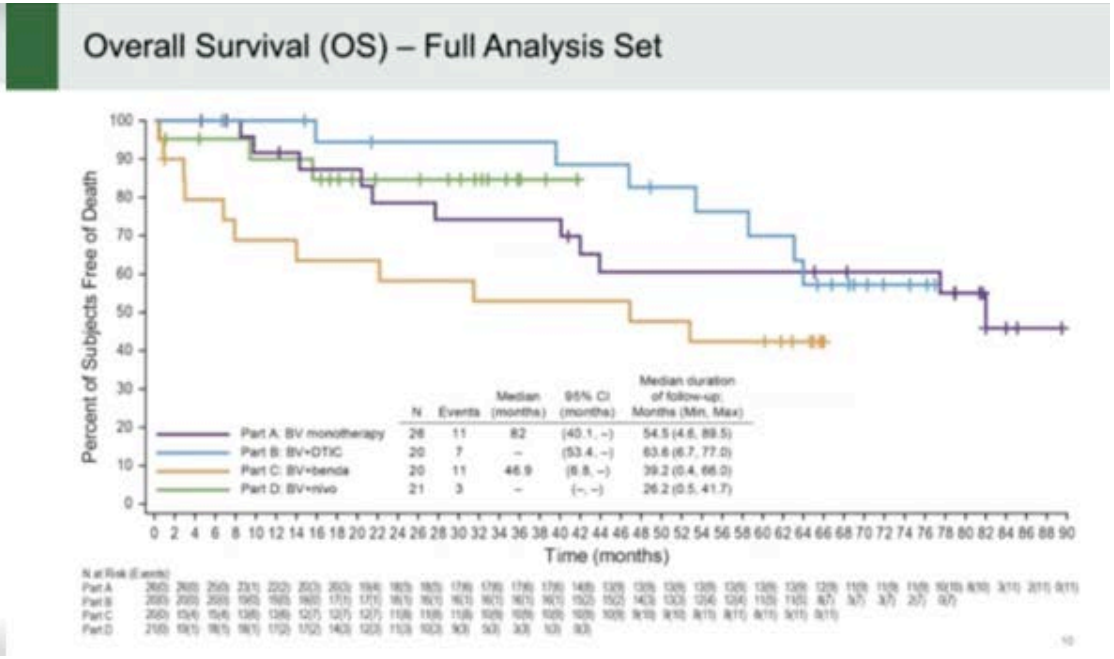
Full analysis set	Part A BV mono N=26	Part B BV+DTIC N=20	Part C BV+benda N=20	Part D BV+nivo N=21	Total N=87
Age in years, median (range)	78 (64-92)	69 (62-88)	75 (63-86)	72 (60-88)	74 (60-92)
Male, n (%)	14 (54)	14 (70)	10 (50)	15 (71)	53 (61)

Yasenchak CA et al. ASH 2020; Abstract 471

Courtesty 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

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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

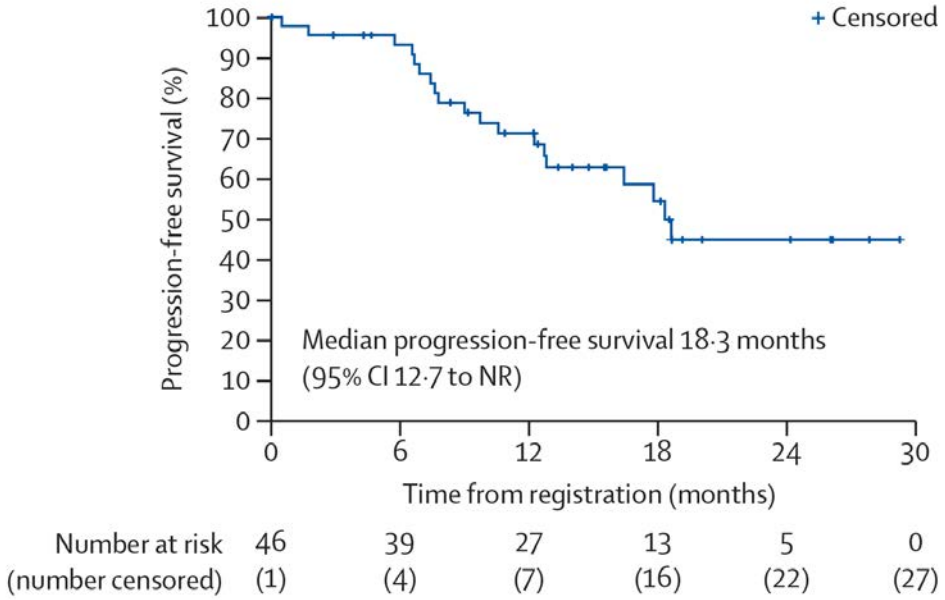
	Total (n=46)
Age	71·5 (64–77)
Sex	
Female	21 (46%)
Male	25 (54%)
ECOG performance status	
0	14 (30%)
1	26 (57%)
2	6 (13%)
Race	
White	39 (85%)
Black or African American	2 (4%)
Asian	2 (4%)
Not reported	3 (7%)
Clinical stage	
I	1 (2%)
II	15 (33%)
III	9 (20%)
IV	21 (46%)

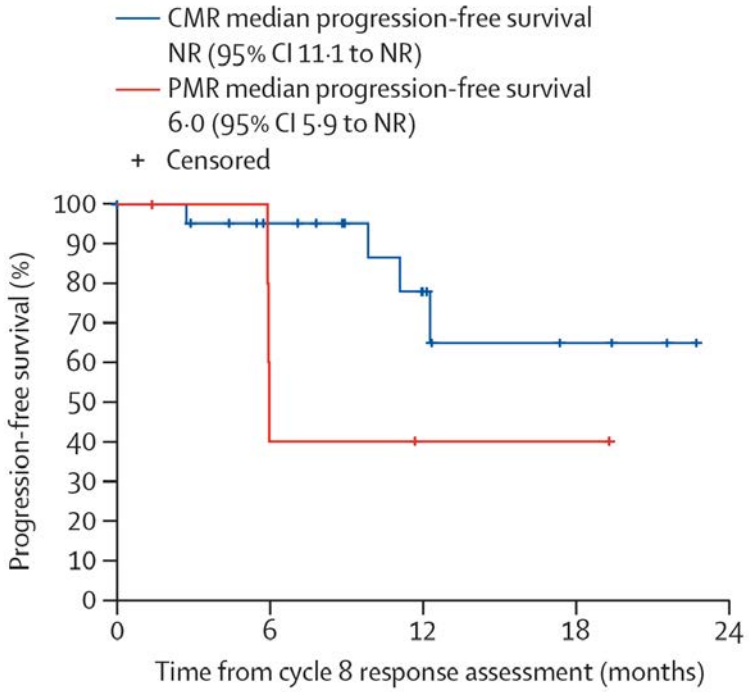
Med f/u 21.2m

Cheson BD et al. Lancet Haematol. 2020 Nov;7(11):e808-e815

Courtesty of Sonali M Smith, MD

BV plus nivo in TN older patients with cHL





Results:
CMR 65%
Med PFS 18m

A "negative" phase 2 trial?

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

Cheson BD et al. Lancet Haematol. 2020 Nov;7(11):e808-e815
Connors JM et al. Lancet Haematol. 2020 Nov;7(11):e776-e777

Courtesty of Sonali M Smith, MD

Treatment of older patients with treatment-naïve cHL

Impact on Patient Care and Treatment Algorithm

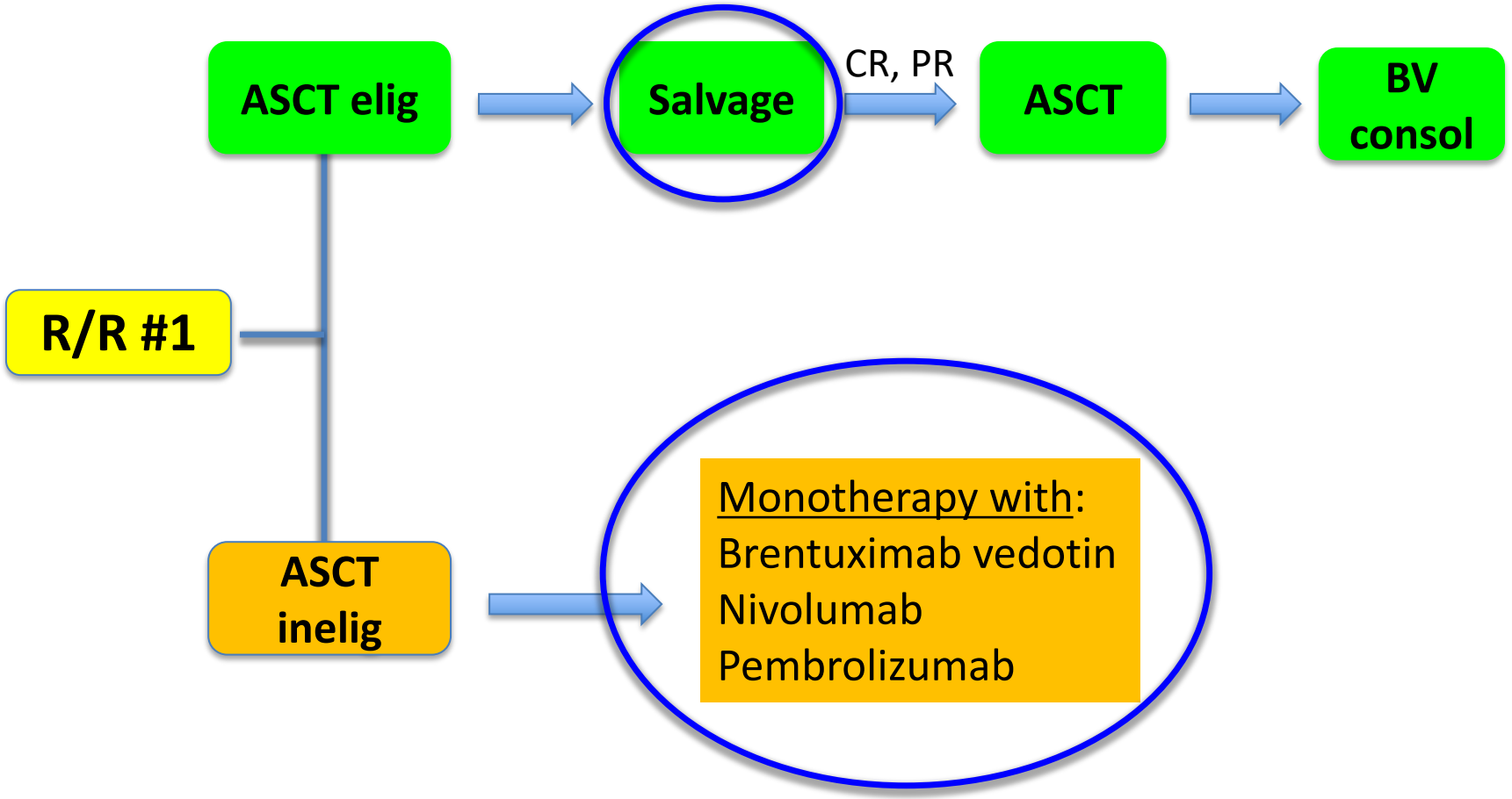
- Promising use of targeted agents in frontline setting that avoids bleomycin and reduces use of cytotoxic agents
- BV-benda is too toxic in older patients

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?

Courtesty of Sonali M Smith, MD

Treatment approach for relapsed cHL



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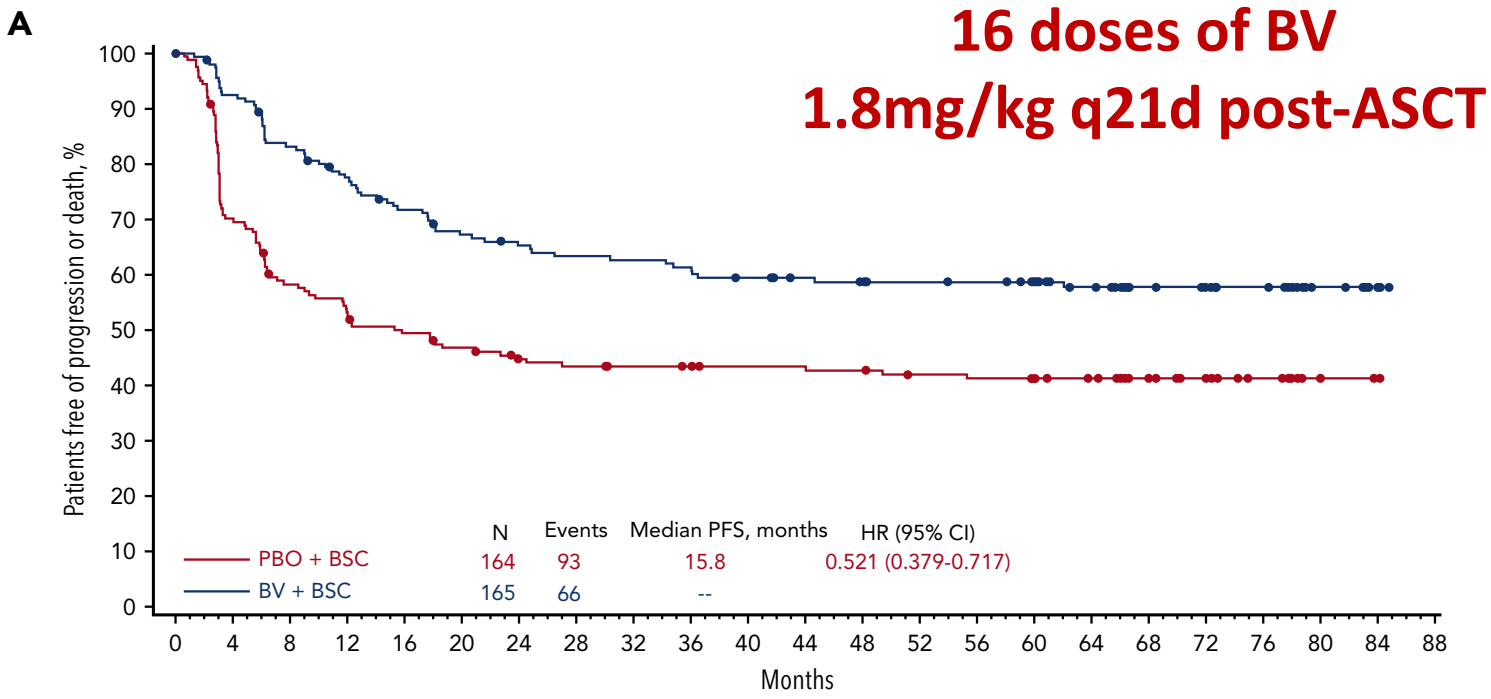
5-year follow up of post-ASCT BV (AETHERA TRIAL)



Moskowitz et al. Blood. 2018 Dec 20;132(25):2639-2642.

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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

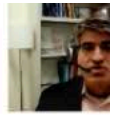
51% prior BV

42% prior PD-1 inhibitors

Herrera AF et al. ASH 2020; Abstract 472

Courtesty of Sonali M Smith, MD

Post-autologous stem cell transplant BV + nivo



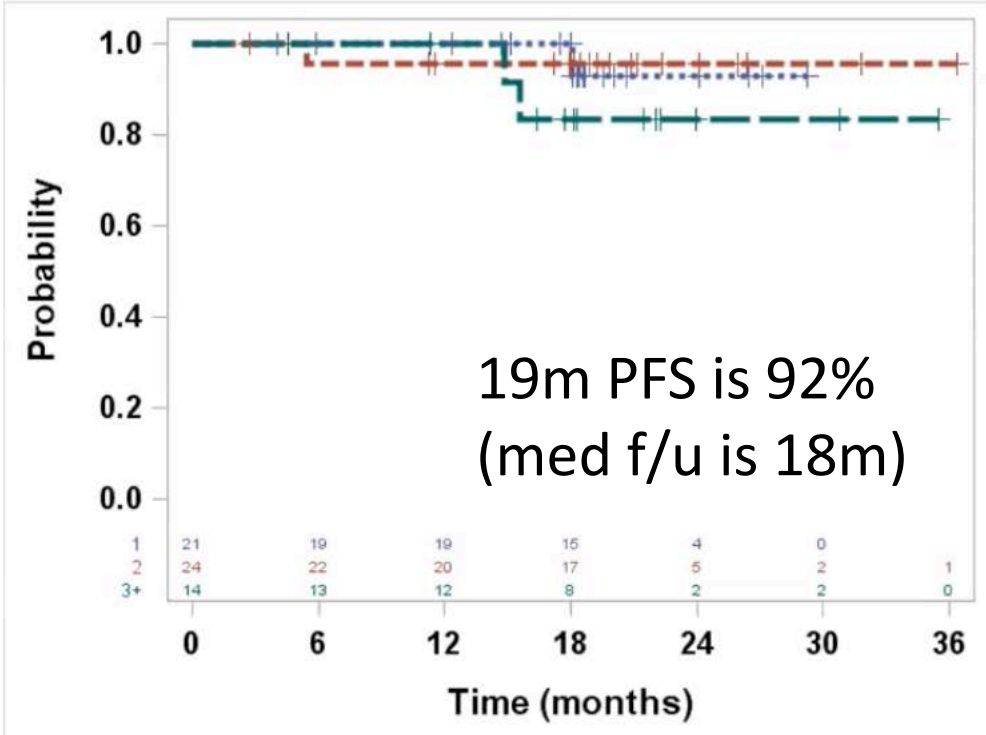
PFS according to number of risk factors

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%)



Only 49% completed both agents

Most common AEs were neuropathy, neutropenia

27% had immune-related AE's requiring steroids

Herrera AF et al. ASH 2020; Abstract 472

Courtesty of Sonali M Smith, MD

Post-transplant BV + nivo

Impact on Patient Care and Treatment Algorithm

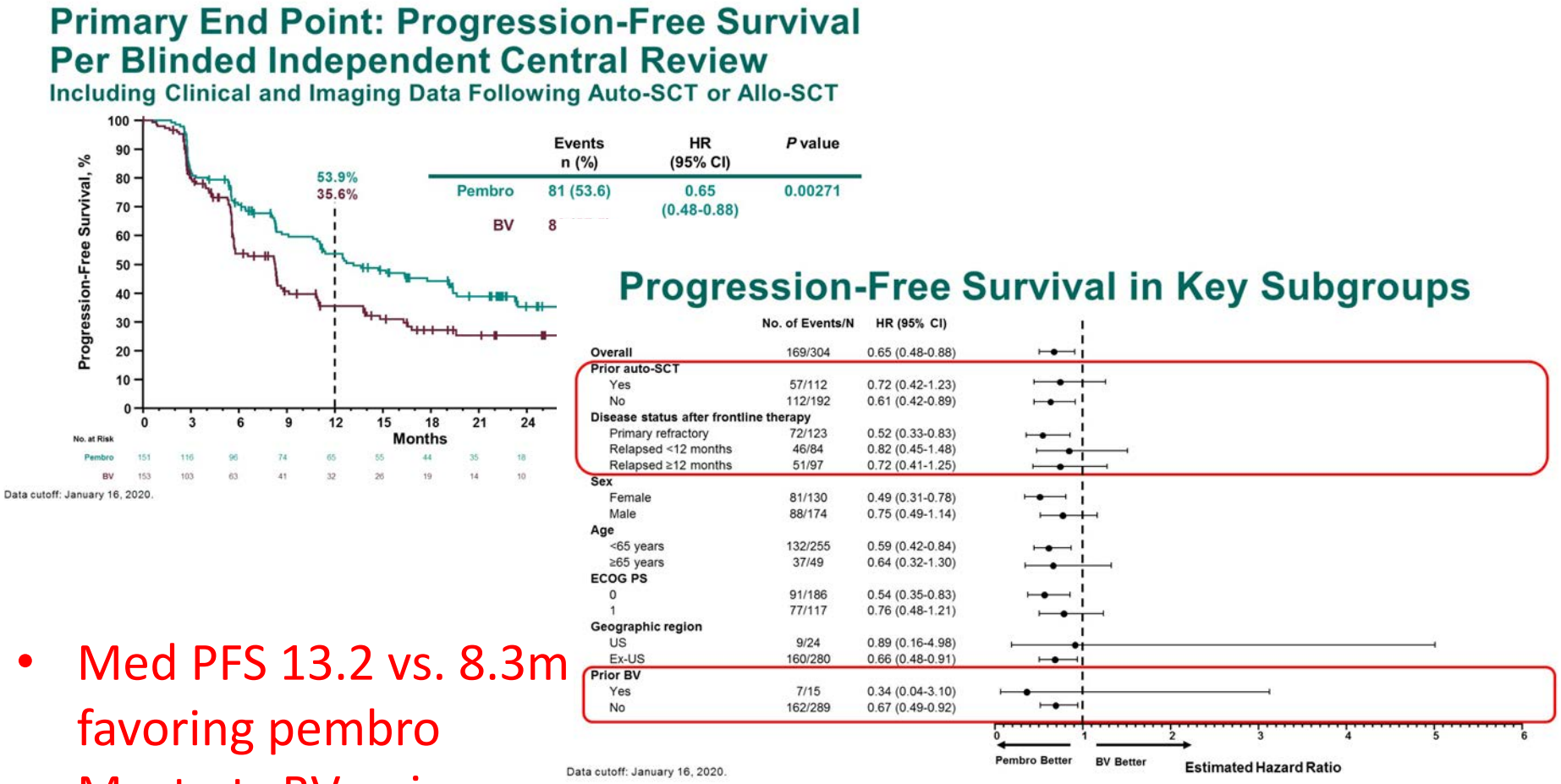
- Shorter consolidation is appealing
- Intolerance rate seems high

Implications for Future Research

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

Courtesty of Sonali M Smith, MD

KEYNOTE-204: Pembro vs. BV in R/R cHL

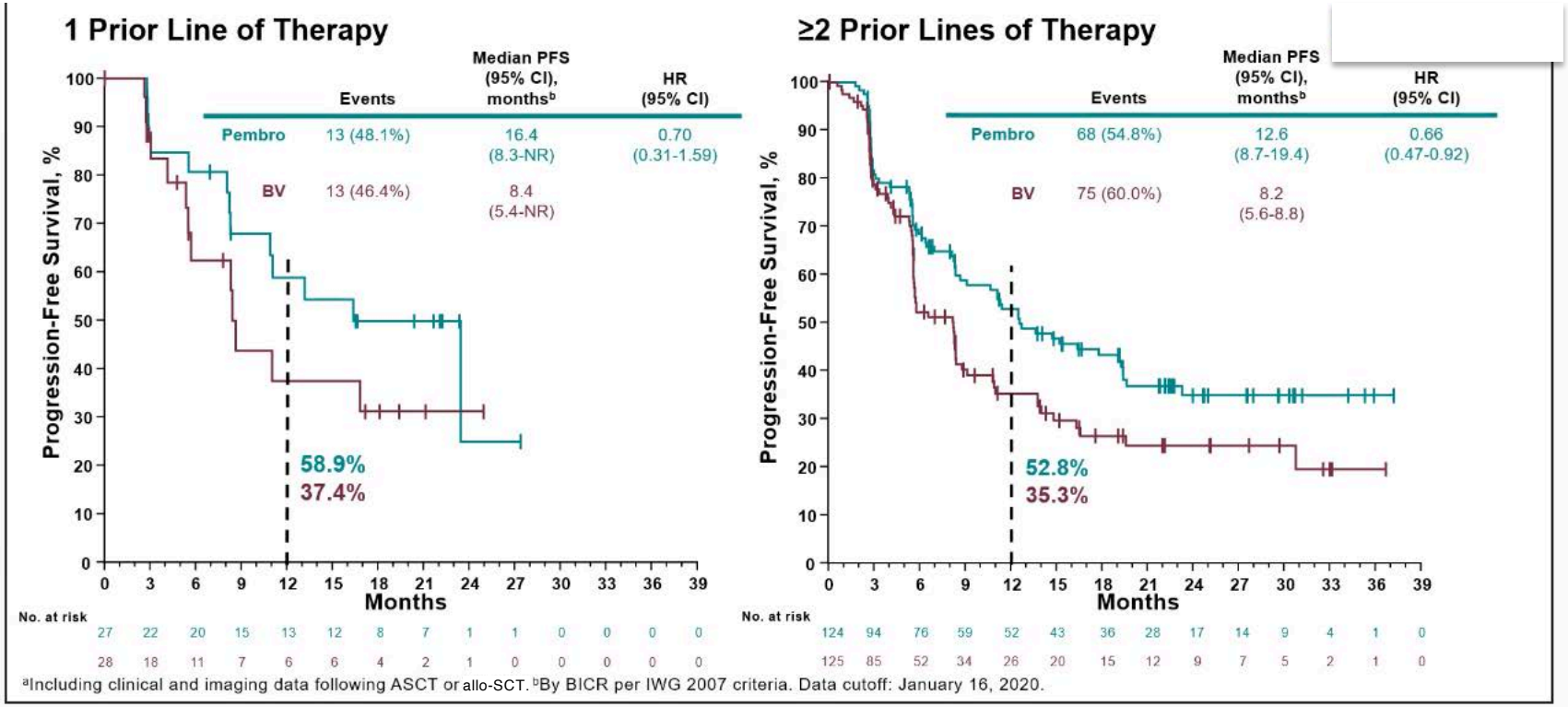


- Med PFS 13.2 vs. 8.3m favoring pembro
- Most pts BV-naive

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

Courtesty of Sonali M Smith, MD

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%

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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

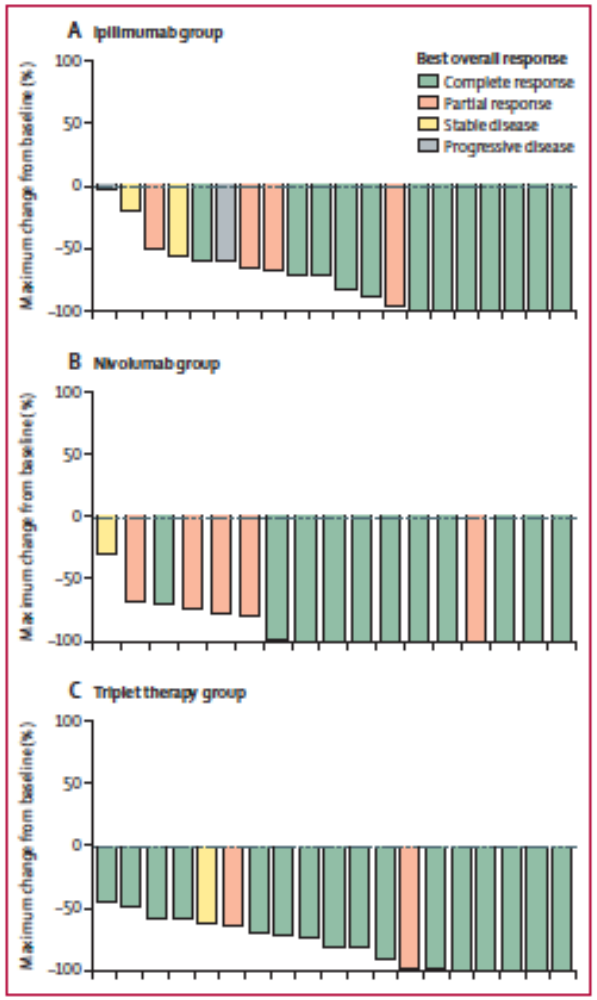
Combination targeted therapy in R/R cHL

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)



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Diefenbach CS et al. Lancet Haematol. 2020 Sep;7(9):e660-e670.

Courtesy of Sonali M Smith, MD

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

Courtesty 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

Courtesty of Sonali M Smith, MD

Thank you

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