BEYOND THE CONGRESS

Key Conversations from the
2021 Hematology Annual Meeting™

FRIDAY, FEBRUARY 4, 2022

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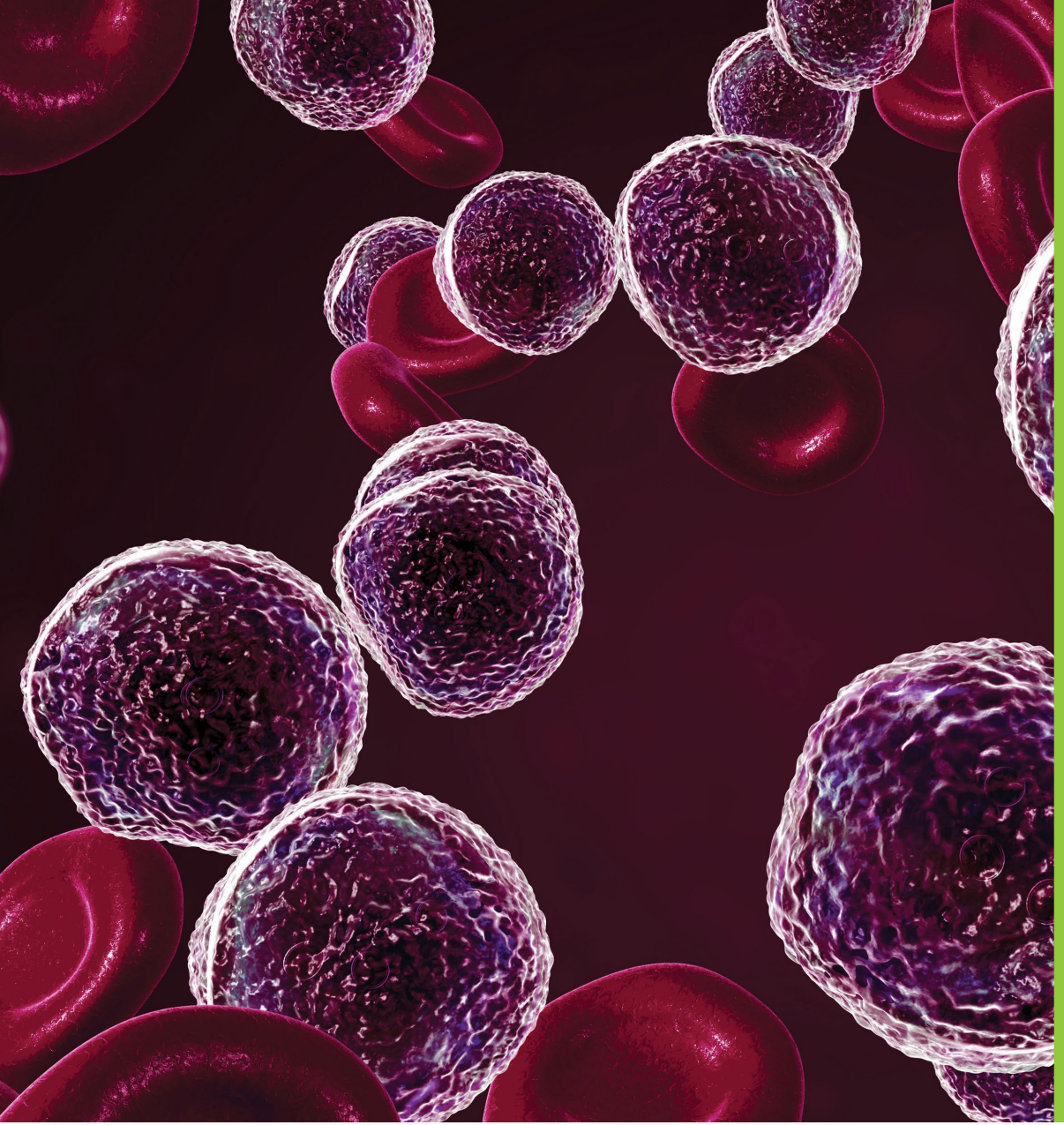

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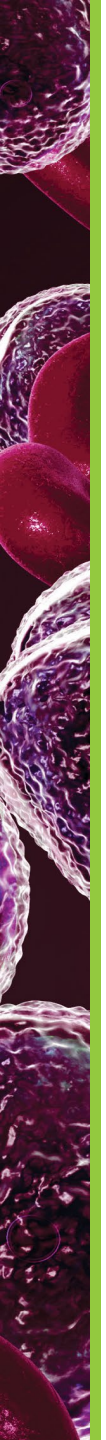

Updates in the management of Hodgkin and T-cell lymphomas

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HL and TCL: Two sides of a coin

Hodgkin Lymphoma

- Young, healthy patients
- Goal is cure
- Uniform disease
- Initial therapy cures majority of patients
- Long-term survival and late toxicity are key aspects of treatment selection

T-cell lymphomas

- Older patients, often with comorbidities
- Goal is disease control in most; cure in some
- Complex group of diseases
- Initial combination chemotherapy is insufficient for most and consolidative transplantation is common
- Long-term survival and late toxicity has not been studied and does not influence initial treatment selection

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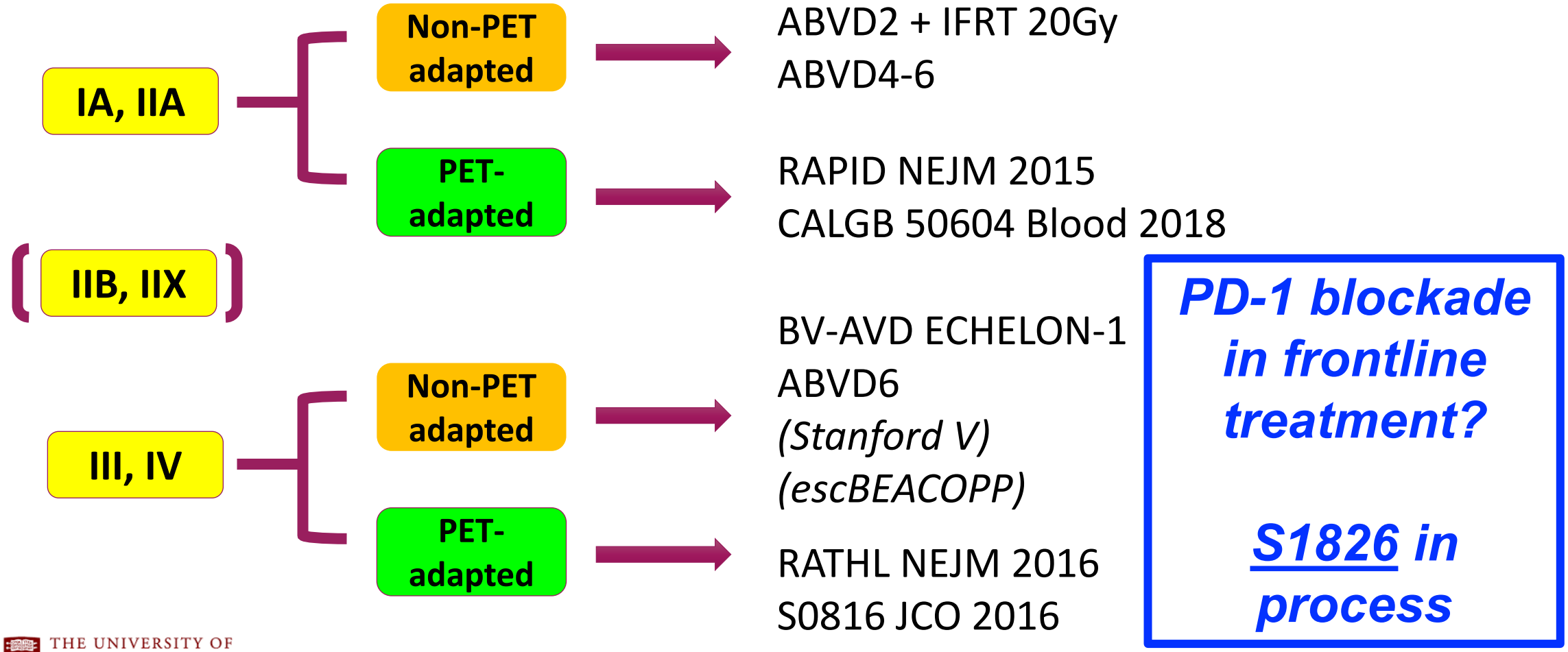
Snapshot of frontline standard treatment approach in cHL



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Sequential **pembro-AVD in frontline cHL**

Pembro x 3 cycles → AVD x 4-6 cycles

N=30

Med f/u 33.1m

Response to single agent PEM:

- Partial metabolic response 36.7%
- Near-complete metabolic response 26.7%
- Complete metabolic response 36.7%

Response to AVD:

- 100% complete metabolic response
- PFS and OS 100% at 33m

**No update on toxicity

Allen ASH 2021 abstract 231

Concurrent pembro-AVD in frontline cHL

APVD x 2 cycles → PET2 → APVD x 4-6 cycles

N=30

Med f/u 10.1m

Pt Characteristics:

- Med age 32y
- 60% st III/IV
- 17% bulky disease

Results

- 68% PET2 neg (5PS 1-3)
- 78% EOT PET neg

Toxicity

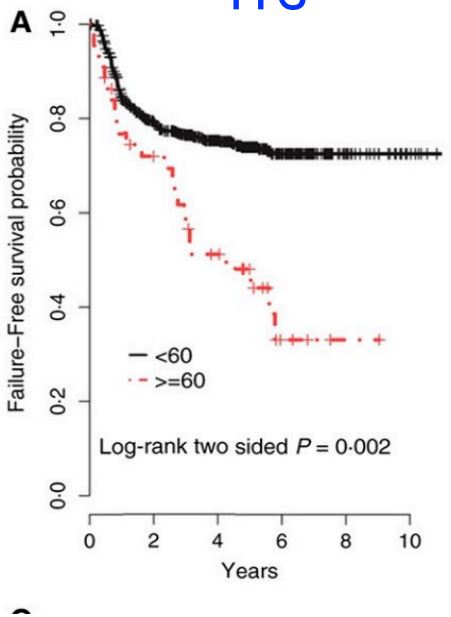
- 83% ≥ gr 2 transaminitis (transient)
- No pneumonitis
- No ≥ gr 3 IRAE's

Ryan ASH 2021 abstract 233

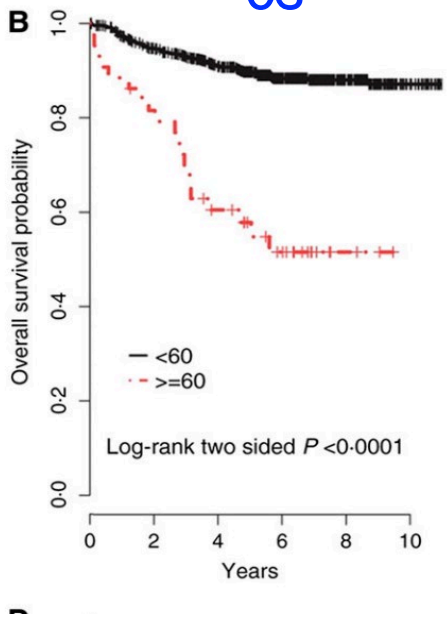
How should older patients with cHL be treated?

Older patients with cHL have inferior FFS and OS

FFS



OS



NCCN Guidelines 1.2022

Stage I–II Favorable Disease

- A(B)VD[a] (2 cycles) ± AVD (2 cycles) + ISRT[b] (preferred)[7,8,9]
- CHOP (4 cycles) + ISRT[b,10]

Stage I–II Unfavorable or Stage III–IV Disease

- A(B)VD[a] (2 cycles) followed by AVD (4 cycles),[c] if PET scan is negative after 2 cycles of ABVD.[11]
  - Patients with a positive PET scan after 2 cycles of ABVD need individualized treatment.
- Brentuximab vedotin followed by AVD, conditionally followed by brentuximab vedotin in responding patients with CR or PR[12]
- Brentuximab vedotin + DTIC (dacarbazine)[13,14]
- CHOP (6 cycles) ± ISRT[b,10]

PD-1 blockade in frontline treatment?

Evens Hematology Am Soc Hematol Educ Program. 2019 Dec 6; 2019(1): 233–242;
NCCN Guidelines www.nccn.org (accessed January 2022)

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Nivolumab monotherapy for TN cHL in older patients

TN cHL
- > 60 y
- CIRS-G ≥ 6

Induction:
Nivolumab 240mg q14d x 6

CMR →

Consolidation:
Nivolumab plus vinblastine x 18

Primary endpoint EOT CMR

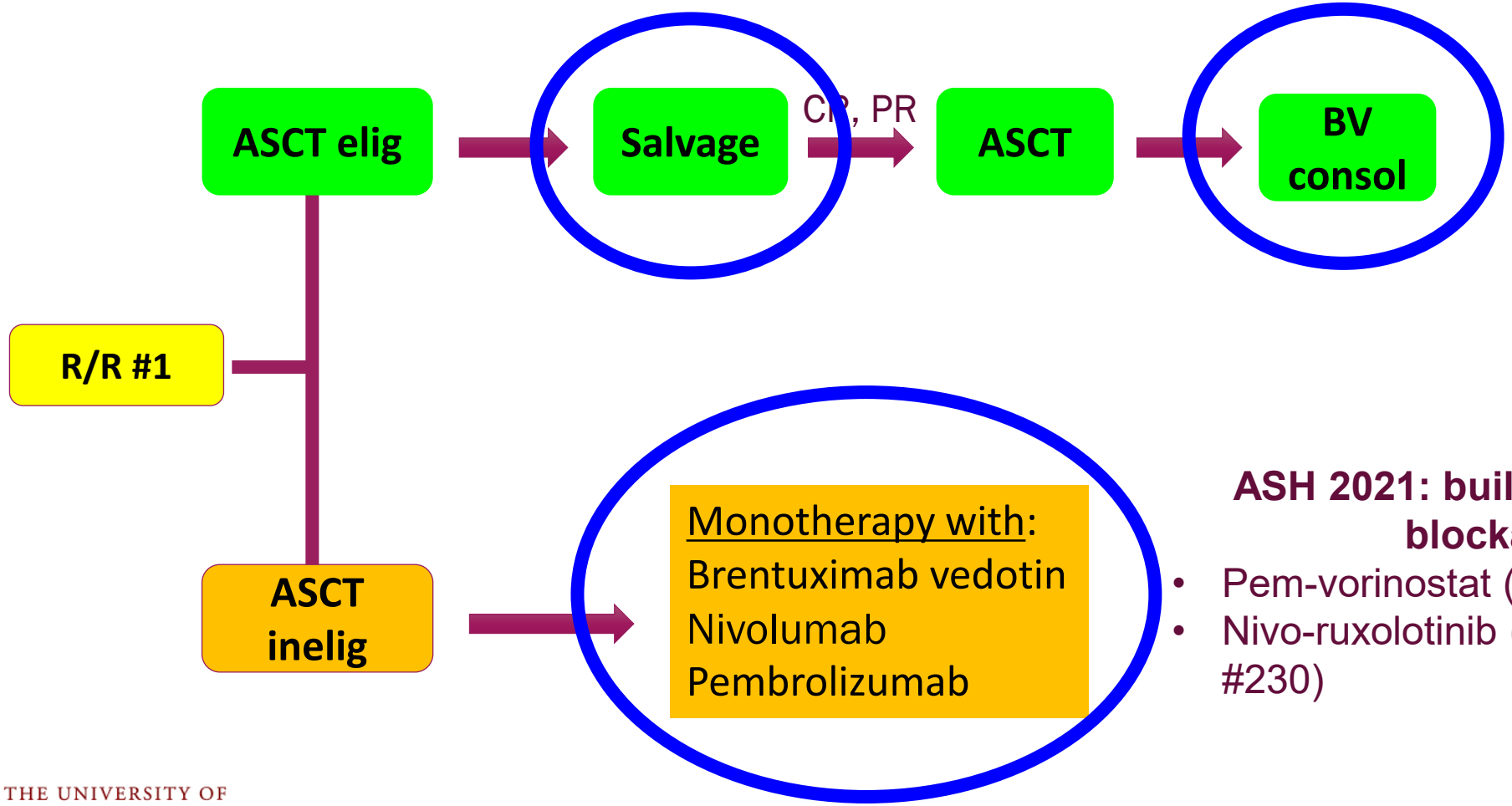
Pt Characteristics:
- Med age 75y (62-91)
- Med CIRS-G 10
- 73% st III/IV
- 43% B symptoms

Results
- EOI: 52% ORR
- EOT:
  - 29% CMR
  - 18% PMR
- Med PFS 9.8m

Toxicity
- 15/64 (23.4%) deaths during treatment (6 from HL, 2 toxicity)
- Approximately 50% had gr 3-4 AE's
- One-third of pts stopped treatment due to nivo-related toxicity

Lazarovici ASH 2021 abstract 232

Treatment approach for relapsed cHL



ASH 2021: building on PD-1 blockade:

- Pem-vorinostat (Herrera #234)
- Nivo-ruxolotinib (Bachanova #230)

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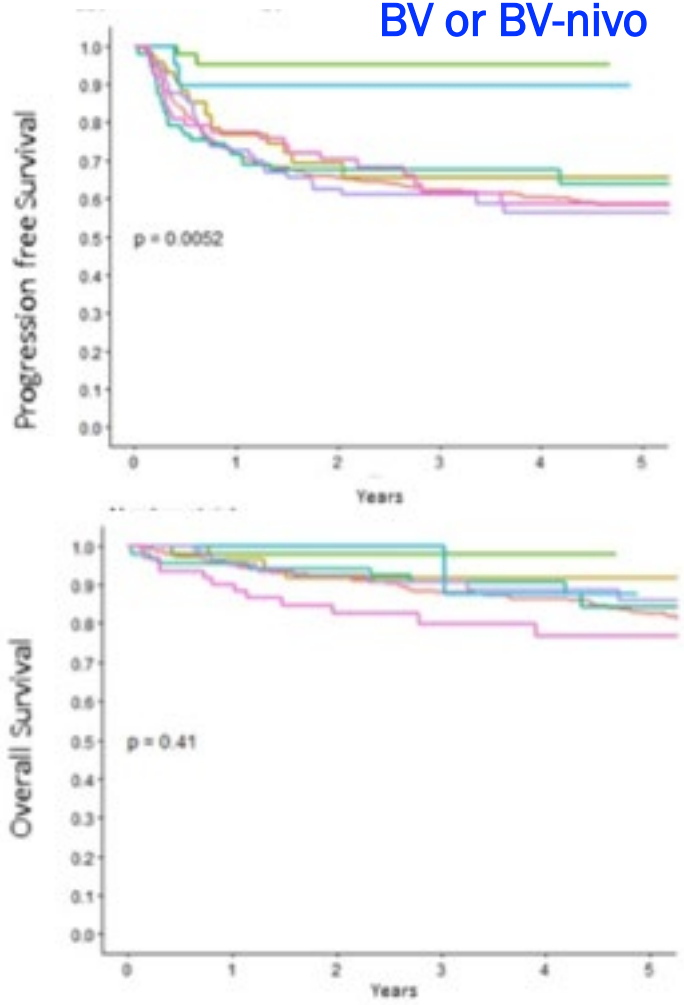
Evolving field: what is the best 1st line salvage for patients with cHL?

- Approximately 20-30% of patients with advanced stage disease will have relapsed or refractory disease to initial treatment
- Pre-transplant chemosensitivity is critical predictor of outcome
- Current SOC for 1st line salvage: ICE, gemcitabine-based regimens, BV-based regimens
- ***Locke ASH 2021 abstract #229***:
  - Phase 2 Trial: PEM-ICE x 2 → stem cell mobilization/collection → optional PEM-ICE x 1 → autoHCT
  - N= 37 evaluable pts (Med age 34y, 16 pts with primary refractory disease)
  - **RESULTS**:
    - CMR via PET/CT after PEM-ICE x 2 86.5% (95% CI, 71.2–95%) meeting primary endpoint of improvement over historical outcomes of 70%
    - ORR 97% and 35/37 pts proceeded to autoHCT
    - No impact on stem cell mobilization
    - No unexpected toxicities

Evolving field: what is the best 1st line salvage for patients with cHL?

BV or BV-nivo



Pre-ASCT ST (N)	2 Year PFS % (CI_{95})	2 Year OS % (CI_{95})	2 Year PFS pts with CR, % (CI_{95})	2 Year OS in pts with CR % (CI_{95})
PBC (451)	65.4 (61.9-68.9)	91.8 (90.3-93.3)	73.2 (69.5-76.9)	94.2 (92.7-95.7)
BBV (76)	69.3 (60.2-78.4)	91.8 (87.5-96.1)	75 (66-84)	94.9 (91.2-98.6)
BV/Nivo (48)	**95.2 (91.7-98.7)**	**97.7 (95.3-100)**	**100 (-)**	**100 (-)**
BV (87)	67.6 (60-75.2)	94.4 (91.7-97.1)	75.2 (67.3-83.1)	96.3 (93.7-98.9)
CPI (24)	**89.7 (82.1-97.3)**	**100 (-)**	**87.5 (86.2-88.8)**	**100 (-)**
Gem (90)	62.6 (54-71.2)	92.4 (89.2-95.6)	67.2 (56.3-78.1)	97.8 (95.6-100)
Others (64)	70.3 (62-78.6)	82.5 (76.4-88.6)	79.3 (70.5-88.1)	88.0 (81.6-94.4)

Table 1 Survival probability by type of ST

N=853 pts; all time to event analyses are from autoHCT

Desai ASH 2021 abstract 878

Update in T-cell lymphomas: key themes

- **Optimize initial treatment**
  - CHOP as a backbone
  - CHOEP as a backbone
  - *Chemo-free approaches*
- **New agents/regimens for RR PTCL**
  - Duvelisib-romidepsin
  - BV-benda
  - Cerdulatinib
- **New approaches for RR PTCL**
  - *Bispecific antibodies*
  - *CAR-T*

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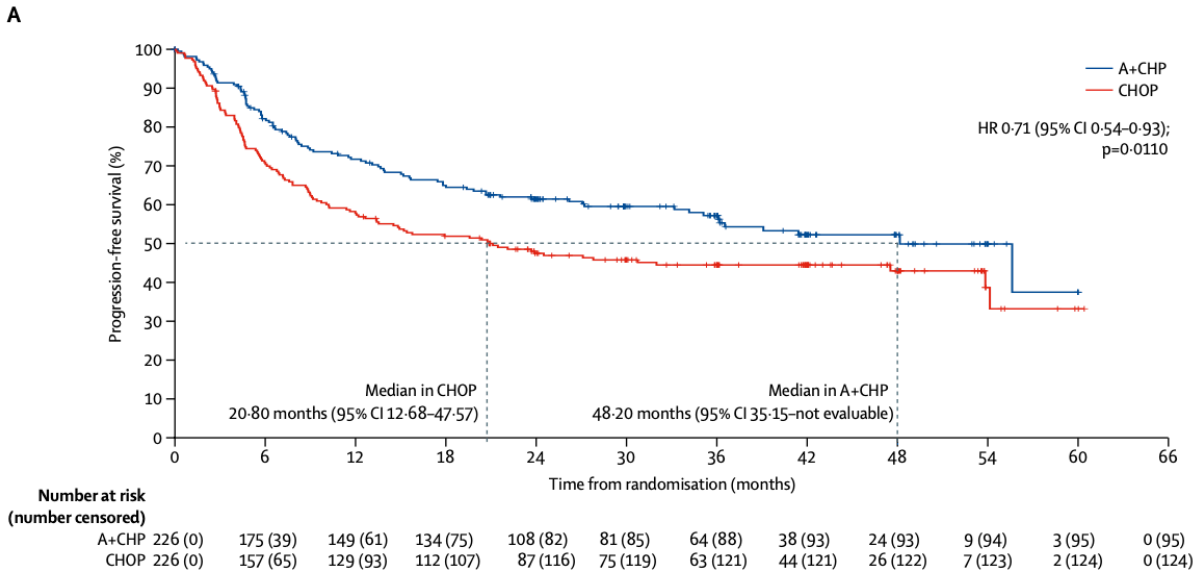
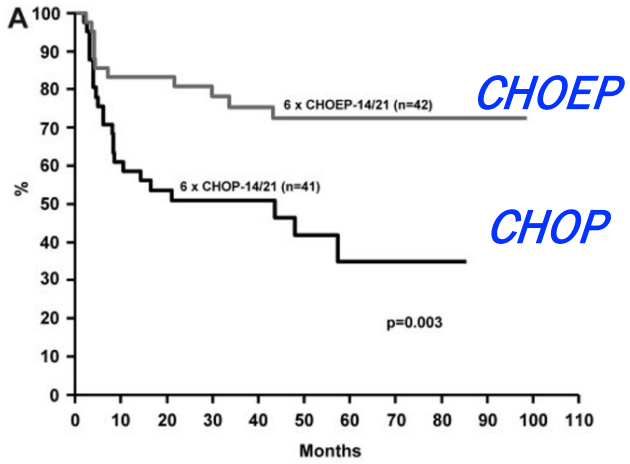
ECHELON-2: BV-CHP vs. CHOP in PTCL (but mostly ALCL)



- *Two-thirds of pts had ALCL*
- CD30 positivity defined as ≥ 10%
- CHOP has med PFS 20.8m
- BV-CHP has med PFS 48.2m

Is CHOP the "right" or "best" backbone?

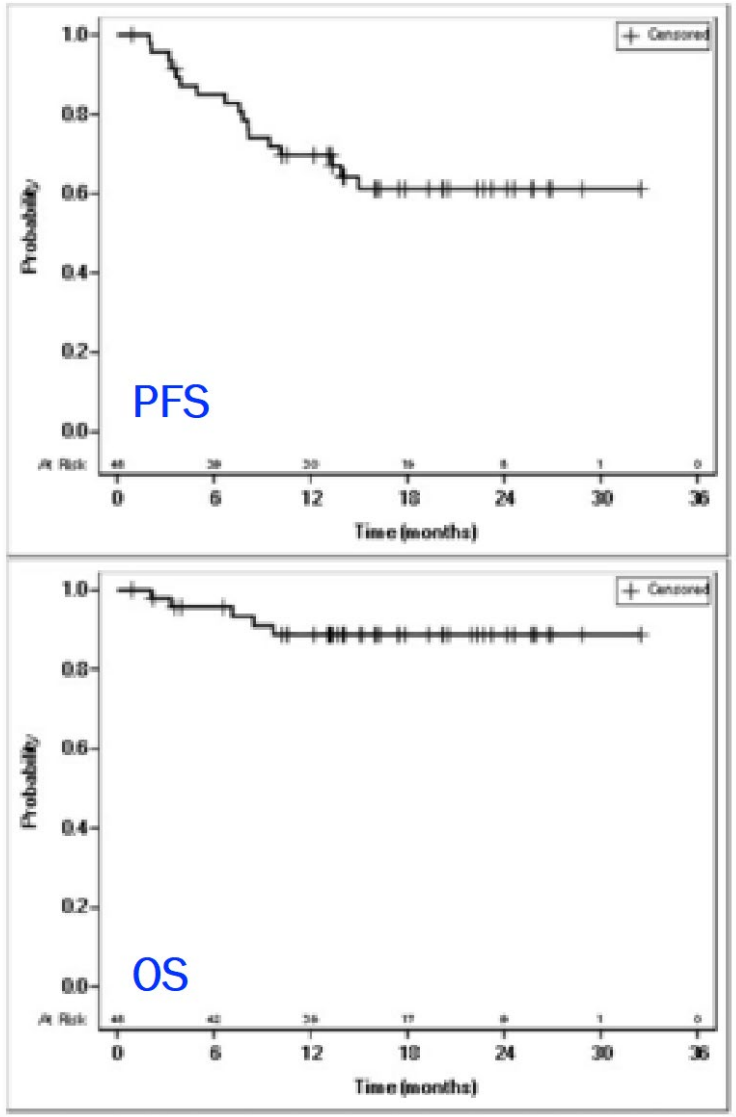


- *CHOEP vs. CHOP has superior PFS in patients ≤60 years (HR, 0.49; P 5 .008) (Swedish registry)*
- *CHOEP vs. CHOP has superior 5-yr PFS and OS (59.0% vs. 32.9%; p.001 and 65.6% vs. 47.6%; p.008, respectively)*

Horwitz Lancet 2019 Jan 19;393(10168):229-240; Janikova Ann Hematol. 2019 Aug;98(8):1961-1972; Ellin Blood 2014 Sep 4;124(10):1570-7

Phase 2 multicenter trial of BV-CHEP

Baseline Characteristics	N (%)
Total	48 (100)
PTCL Subtype	
AITL	18 (37.5)
ALCL	16 (33)
ALK+	13 (27)
ALK-	3 (6)
PTCL NOS	11 (23)
TFH PTCL	2 (4)
ATLL	1 (2)
Male gender	30 (62.5)
Age, median in years	56 (24–79)
CD30 expression	
1-9%	16 (33)
10% or greater	32 (67)



The most common G3+ AEs were neutropenia (37.5%), febrile neutropenia (23%), lymphopenia (21%), anemia (19%), thrombocytopenia (19%).

Herrera Blood (2021) 138 (Supplement 1): 133.

Other agents added to CHOP/CHOEP in PTCL

- **Phase I/II PTCL13 trial of romidepsin plus CHOEP (n=86) → autoHCT**
  - RP2D is romidepsin 14mg/m2 plus CHOEP21 x 6
  - No improvement in 18m PFS (primary endpoint) which was 48%
  - No further development of this regimen
    - *Chiappella ASH 2021 abstract 134*

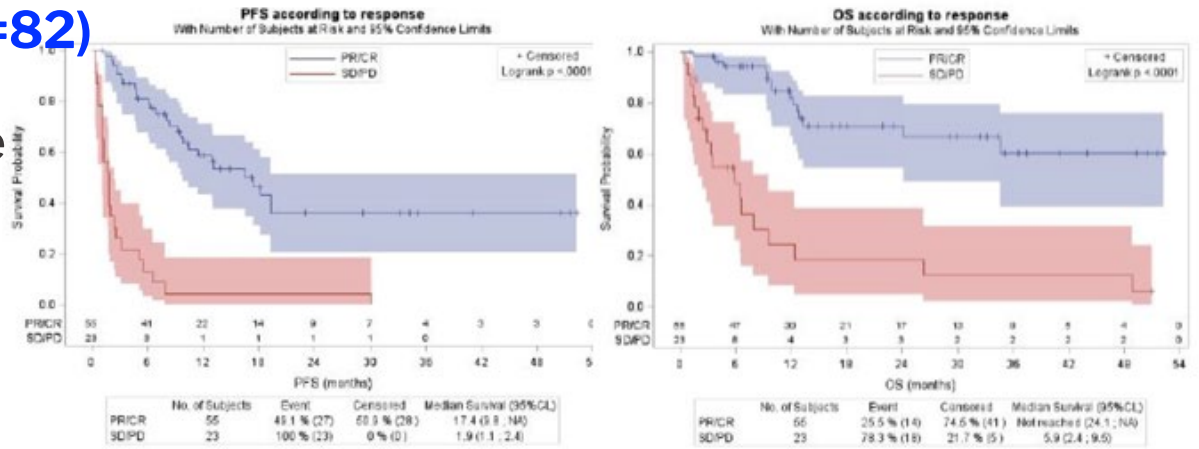
- **Phase II multicenter trial of oral azacytidine plus CHOP in PTCL-TFH (n=20)**
  - Oral aza priming → CHOP21 x 6; Primary endpoint was CR
  - Results: CR 75% and med PFS 36m
  - *TET2* mutations associated with CR and *DNMT3A* associated with adverse PFS
  - **NEXT STEPS**: ALLIANCE/ US Intergroup randomized study A051902, comparing oral azacitidine-CHO(E)P vs duvelisib-CHO(E)P against CHO(E)P in CD30 negative PTCL
    - *Ruan ASH 2021 abstract 138*

Relapsed/refractory PTCL: new combinations

- **Phase II Trial of duvelisib plus romidepsin**
  - Duvelisib monotherapy is associated with high rates of transaminase elevation
  - Combined duvelisib plus romidepsin was more tolerable (?) and more active
    - 58% ORR, 42% CR rate
    - Successful bridge to transplant
    - *TET2* mutations predict response while *TP53* mutations were associated with non-response
    - Toxicity: (≥Gr 3 in ≥10% of patients)
      - neutropenia (36%), diarrhea (15%), increased ALT/AST (14%), thrombocytopenia (10%), and infection (10%). Five patients (9%) had ≥Gr 3 rash
      - Toxicity was less if DR started together versus duvelisib lead-in

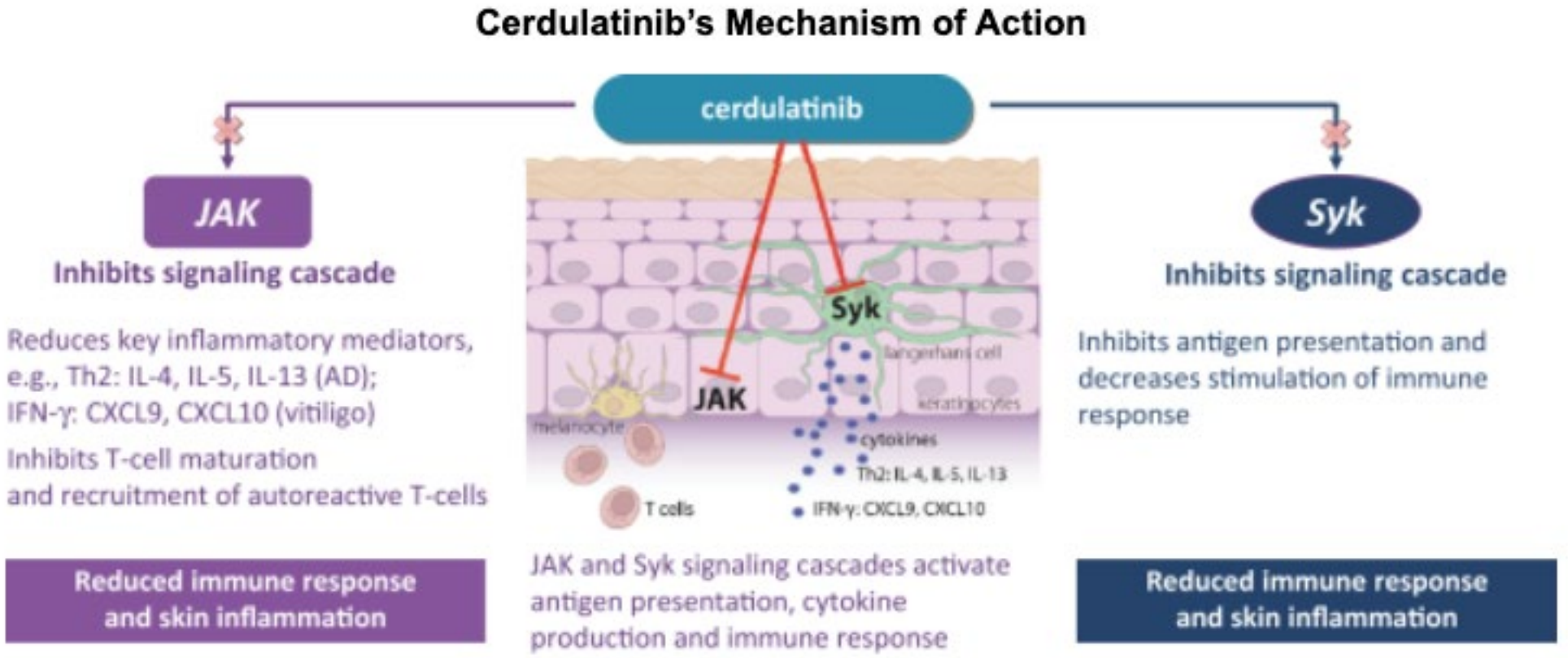
Horwitz ASH 2021 abstract 619

- **Phase II Trial of BV plus bendamustine (n=82)**
  - 71% ORR, 51% CR rate
  - Relapsed patients with better outcome compared to refractory pts
  - Successful bridge to transplant



Bouabdallah ASH 2021 abstract 620

Cerdulatinib MOA



https://www.sec.gov/Archives/edgar/data/1753483/000119312519157086/d625659ds1.htm

Phase II multicenter trial of oral cerdulatinib in RR PTCL

Table 1. Tumor response to cerdulatinib monotherapy in patients with PTCL (efficacy-evaluable population[a])	AITL/TFH (N=27)	PTCL NOS (N=9)	Other[b] (N=22)	Total PTCL (N=58)
ORR, n (%)	14 (51.9)	0	7 (31.8)	21 (36.2)
CR, n (%)	10 (37.0)	0	2 (9.1)	12 (20.7)
PR, n (%)	4 (14.8)	0	5 (22.7)	9 (15.5)
SD, n (%)	3 (11.1)	2 (22.2)	9 (40.9)	14 (24.1)
PD, n (%)	10 (37.0)	7 (77.8)	6 (27.3)	23 (39.7)
TTR, months, median (range)[c]	1.9 (1.5–16.5)	NR	1.9 (1.7–4.4)	1.9 (1.5–16.5)
DoR, months, median (range)[c]	12.9 (0–35.5)	NR	5.3 (1.0–26.2)	8.3 (0–35.5)

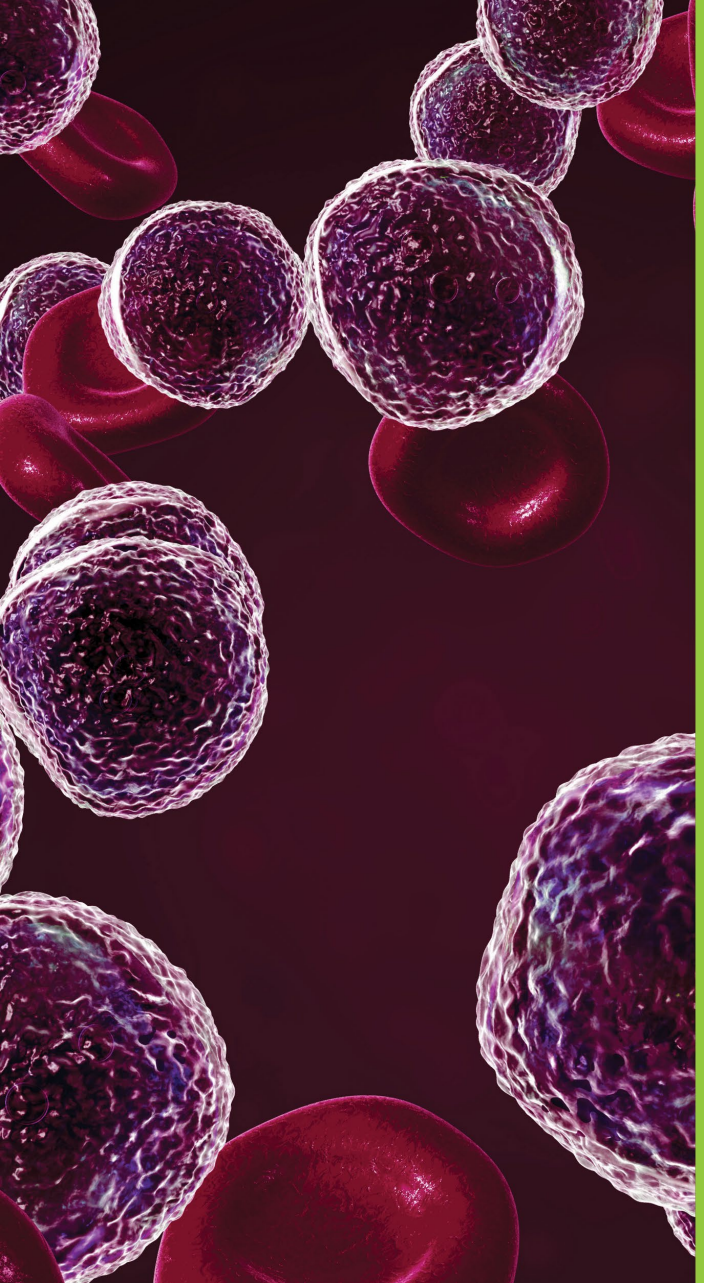
[a]Efficacy evaluable patients had baseline and ≥1 follow-up disease assessment. [b]Other disease types include anaplastic large-cell lymphoma, adult T-cell leukemia/lymphoma, hepatosplenic T-cell lymphoma, large granular lymphocytic leukemia, CD8-positive epidermotropic cytotoxic T-cell lymphoma, cutaneous gamma-delta T-cell lymphoma, and natural killer T-cell lymphoma. [c]Determined for patients with objective response.

**Proof of concept and a promising efficacy/safety profile for a first-in-class, dual SYK/JAK inhibitor in relapsed/refractory PTCL

Toxicity profile: overall well-tolerated

- increased amylase (23.1%) and lipase (18.5%)→transient, reversible, asymptomatic
- neutropenia (12.3%)
- sepsis (9.2%)
- diarrhea (7.7%)

Horwitz ASH 2021 abstract 622



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