The roles of Novel Agents in the landscape of Hodgkin Lymphoma in 2024

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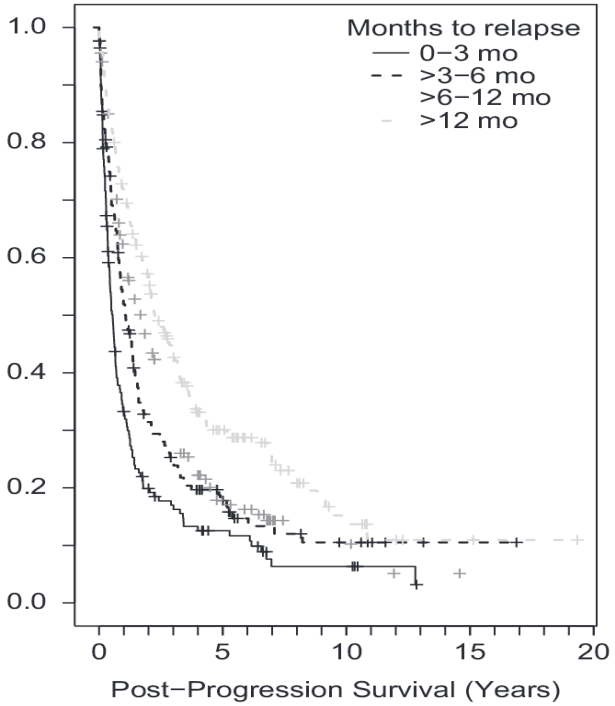
The roles of Novel Agents in the landscape of Hodgkin Lymphoma in 2024

How to treat patients after failure of two prior lines of systemic therapy?

1. Introduction on PD1-inhibition in cHL
2. Immune Checkpoint Inhibition beyond PD1
3. Other than ICI developments

The era of chemotherapy:
Intergroup analysis of *overall survival* of patients *failing HDCT*



Relapse after auto-TX OS by Time to Relapse (TTR) after TX (n=756)

post progression survival (PPS):

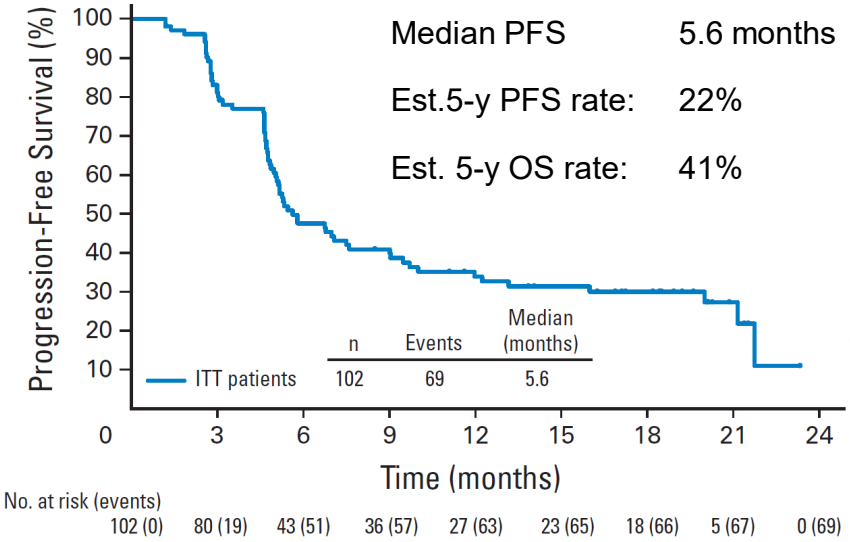
TTR > 12 months,	n=214, median PPS	2.26 years
TTR 6 – 12 months,	n=203, median PPS	1.68 years
TTR 3 – 6 months,	n=169, median	1.6 years
TTP/R < 3 months,	n=170, median PPS	0.5 years

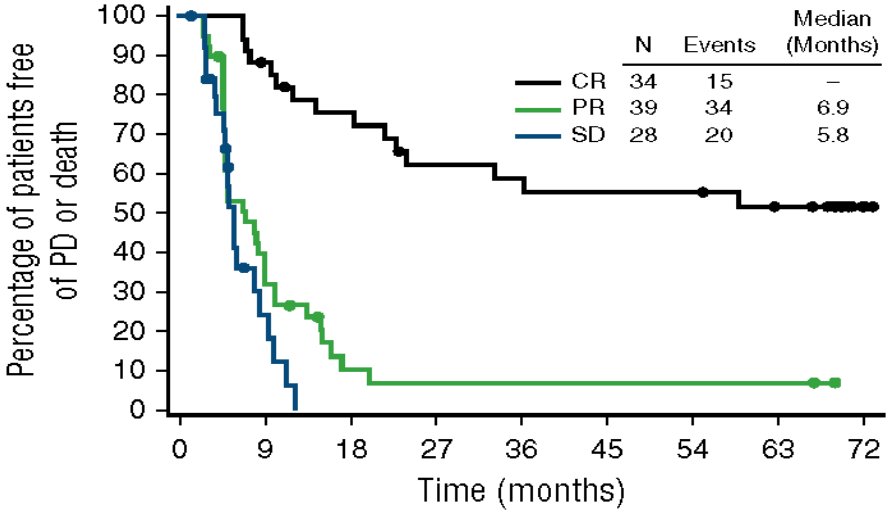
($p<0.0001$).

Overall, median OS used to be around for HDCT eligible patients	**1.5 years**

Arai Leuk Lymphoma 2013

The first drug beyond just chemo: Brentuximab vedotin



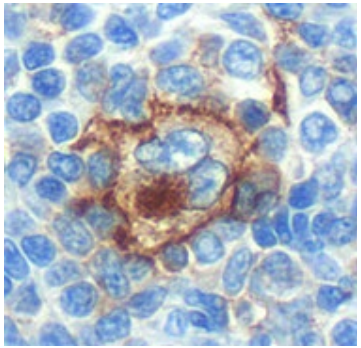


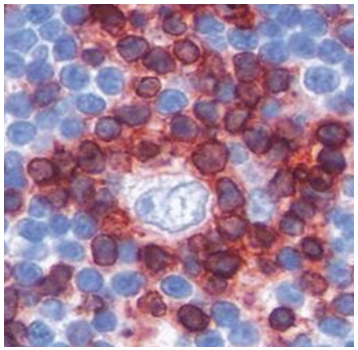
13 patients still in CR (38% of all patients with initial CR), 4/13 received allo-SCT consolidation after BV, 9/13 did not receive any other treatment after BV

- overall, 9/102 patients might have been cured with BV alone

Chen et al. Blood 2016;128(12):1562-1566

From Morbus Hodgkin to Hodgkin Lymphoma





- **H-RS cells are crippled CD30+ germinal center B cells, lacking selection for a specific antigen**
- **Multiple constitutively activated signaling pathway have been identified, including NFkB, JAK/STAT, AP-1, MEK (MAPK)/Erk**
- HRS cells are typically in close contact with and surrounded by CD4+ T cells (rosetting); this pattern is also seen in other organs such as bone marrow, and is consistently observed at relapse
- **HRS cells do not survive without these CD4+ T cells**

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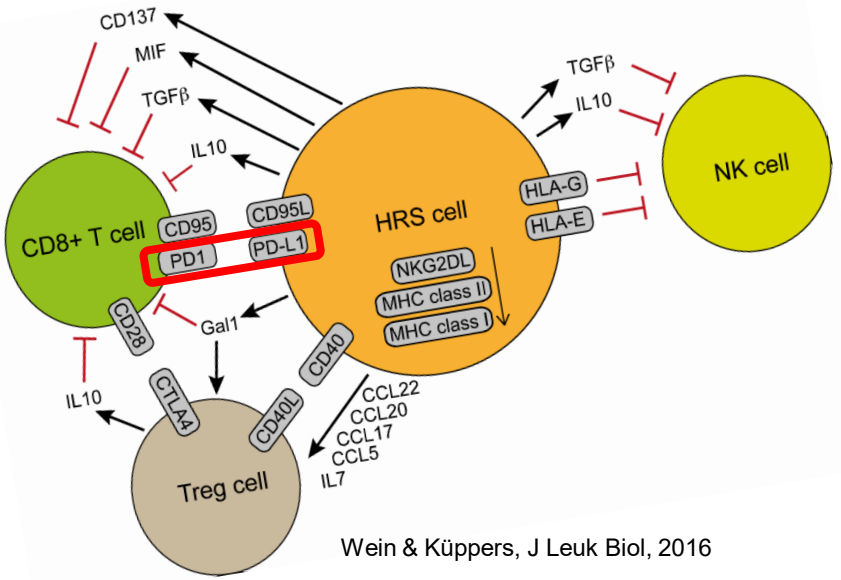
Hodgkin lymphoma is more than just the HRS cell: complex interactions orchestrate malignancy…

- **HL TME composition:**
  - 9p24.1 alterations → ↑PD-L1 expression HRS cells[1]
  - EBV infection → PD-L1 Expression HRS cells[2]
  - PD-L1+ tumor-associated macrophages & PD1+ CD4+ T cells in proximity to HRS cells[3]
  - Frequent β2M mutations → reduced MHC-I expression[4]
  - Lack of MHC-II expression in >40% of cases[5]
- **Peripheral immune landscape:**
  - PD1+ Th1 Treg & effector-memory cells enriched in the peripheral blood[6]
  - Increase of circulating PD1+ NK cells[7]
  - Exhausted lymphocyte phenotype[8]



Wein & Küppers, J Leuk Biol, 2016

➢ immune-cell rich TME with a local and systemic exhausted immune cell landscape

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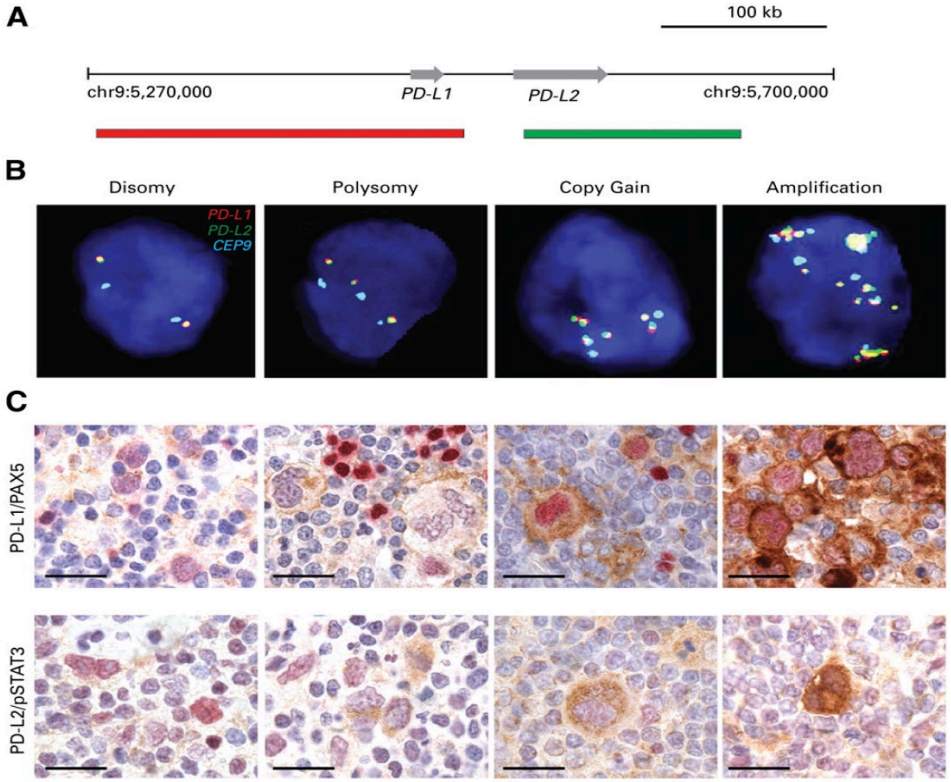
1) Roemer et al. J Clin Oncol, 2016; 34(23): 2690-2697; 2) Green et al. Clin Cancer Res, 2012; 18(6):1611-1618; 3) Carey et al. Blood, 2017; 130(22):2420-2430; 4) Reichel et al. Blood, 2015; 125(7):1061-1072; 5) Diepstra et al. J Clin Oncol, 2007; 25(21):3101-3108; 6) Cader et al. Blood, 2018; 132(8):825-836; 7) Vari et al. Blood, 2018; 131(16):1809-1819; 8) Garcia-Marquez et al. Leukemia, 2021; 36(3):760-771.

PD-L1/2 overexpression is a hallmark of cHL.[1]



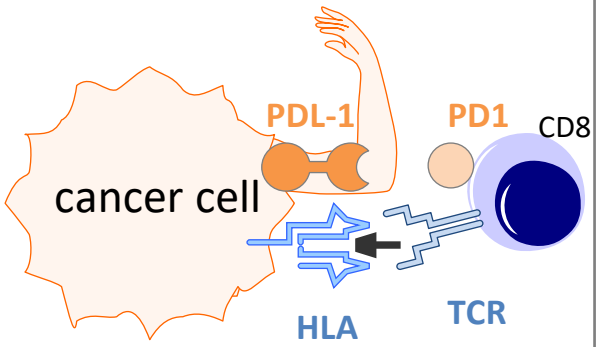
cHL, classical Hodgkin lymphoma; PD-1, programmed death receptor 1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2.

If PD-L1 overexpression is a hallmark of HRS cells,

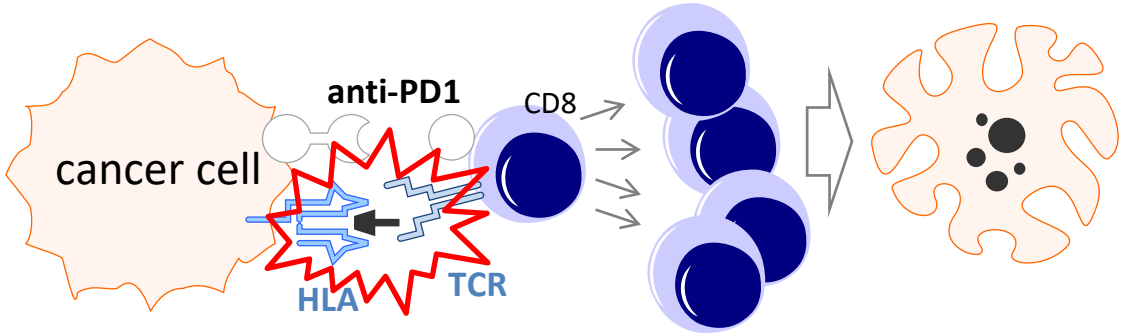
can we then assume that PD1 blockade should activate CD8 positive cytotoxic T-cells, which should then attack the HRS cells?

1) Roemer et al. J Clin Oncol, 2016; 34(23): 2690-2697;

Checkpoints, blockade, and HRS-cells: a complicated story



Inhibitory signaling (e.g. by PDL-1) prevents activation of CD8 T-cells by TCR recognicing neo-epitopes on cancer cells.



Inhibition of check-point enables activation of CD8+ cells by TCR, clonal expansion of epitope specific cells and tumor regression.

HL: Nivolumab for r/r HL (Ansell et al. NEJM 2015), **NSCLC (from left to right):** Nivolumab in previously treated nsNSCLC (Borghaei et al. NEJM 2015), Nivolumab in previously treated sNSCLC (Brahmer et al. NEJM 2015), Pembrolizumab in untreated NSCLC (Garon et al. NEJM 2015), **Melanoma (from left to right):** Pembrolizumab in previously treated melanoma (Robert et al. NEJM 2015), Nivolumab in untreated melanoma (Postow et al. NEJM 2015), Nivolumab for previously treated melanoma (Weber et al. Lancet Oncology 2015), **RCC:** Nivolumab for previously treated mRCC (Motzer et al. NEJM 2015)

HRS cells: 60% no HLA I, loss of beta2M 80%, 40% no HLA II, HRS cells thus are „invisible“ for T-cells

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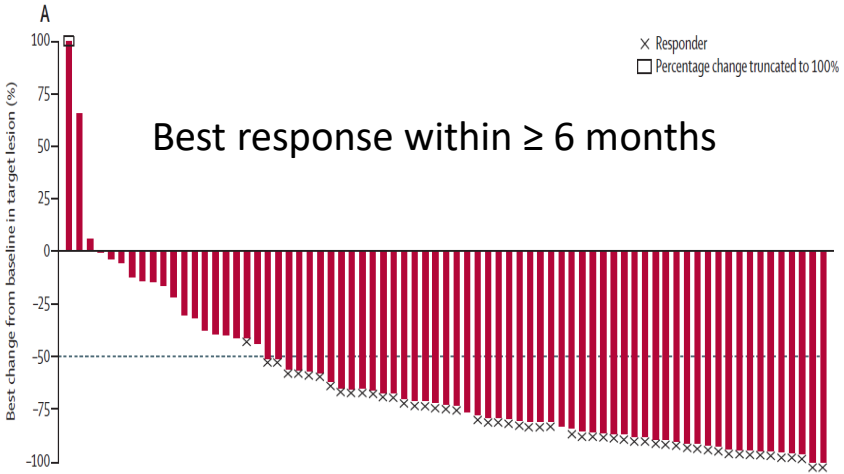
Nijland et al. Oncolimmunology 2017

PD1 inhibiton in cHL: Nivolumab phase II pivotal trial (Checkmate 205)

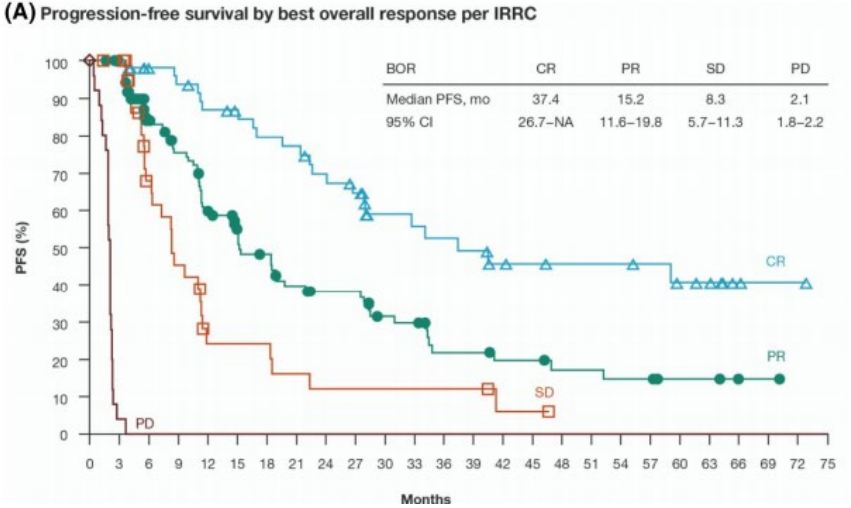


- 80 Pat., relapse after HDCT and BV
- 66,3 % ORR, **CR 9 %,** PR 58 %
- Median PFS 10 months
- AEs: fatigue (25 %), IRR (20 %), rash (16 %)
- AEs Gr. 3–4: neutropenia (5 %), lipase increased (5 %)
- FDA & EMA approval in 2016

Younes et al., Lancet Oncol. 2016 Sep 17; (9): 1283–94

Duration of remission with nivolumab in r/r cHL Checkmate 205 Phase II – 5 year follow-up

- 243 patients
- **ORR 71 %, CRR 21 %**
- median duration of therapy 14 months
- **median PFS 15 months**
- 12 pat. stopped nivolumab after ≥ 1 year CR, 6 patients in ongoing CR



- Stopping Nivolumab in sustained CR for ≥1 year: 50% of patients remained in CR (6/12)
- overall, 11/243 patients without PFS event at 60 months FU might have been cured

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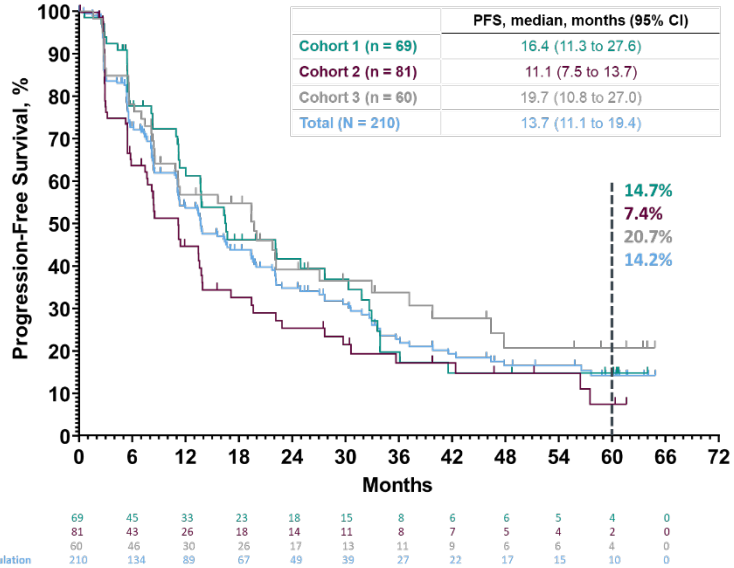
Ansell et al., ICML 2021 and Blood Adv. 2023 Aug 2:bloodadvances.2023010334.

Pembrolizumab in KN-087: Progression-free Survival and Overall Survival

B



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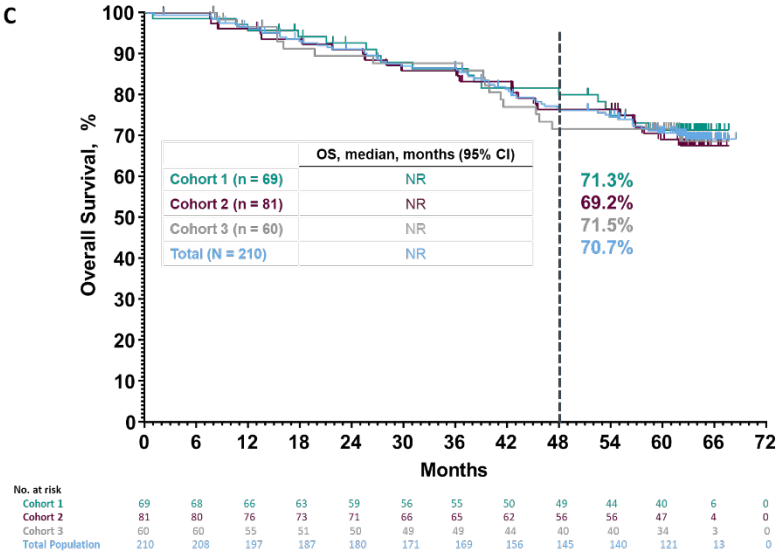
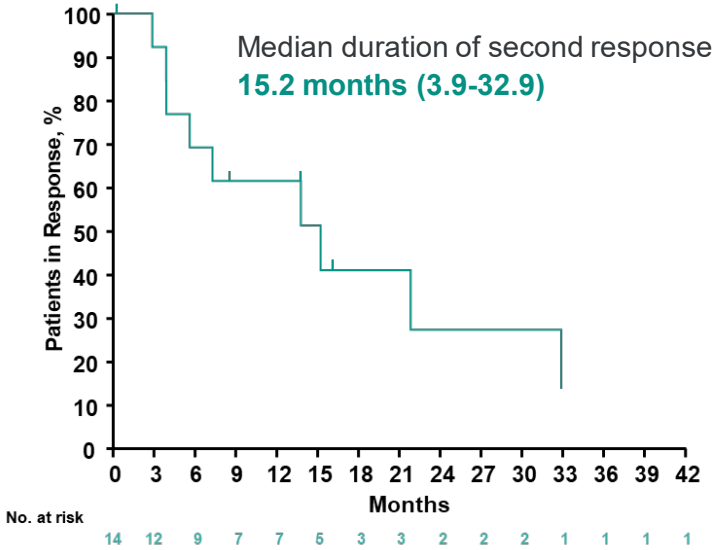


DOR, duration of response; NR, not reached; PFS, progression-free survival.

Armand P et al. Presented at: Annual Meeting of the American Society of Hematology; Dec 11-14, 2021; virtual and in-person/Atlanta, GA. Abstract 1366.

Second course pembrolizumab: response in Keynote 087 Phase II – 5 year follow-up

	Total[a] N = 19
ORR,[b] %	73.7
95% CI	48.8-90.9
BOR, n (%)	
CR	7 (36.8)
PR	7 (36.8)
SD	3 (15.8)
PD	2 (10.5)



- anti-PD1-retreatment is possible
- However, is PD1 inhibition in multiple r/r cHL superior to BV?

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Armand et al., ASH 2021

The management of multiple relapsed Hodgkin Lymphoma

PD1-antibodies or Brentuximab vedotin or both?

MK-3475-204/KEYNOTE-204
NCT02684292

Brentuximab vedotin — R — Pembrolizumab

CheckMate 812
NCT03138499

Brentuximab vedotin — R — Brentuximab + Nivolumab

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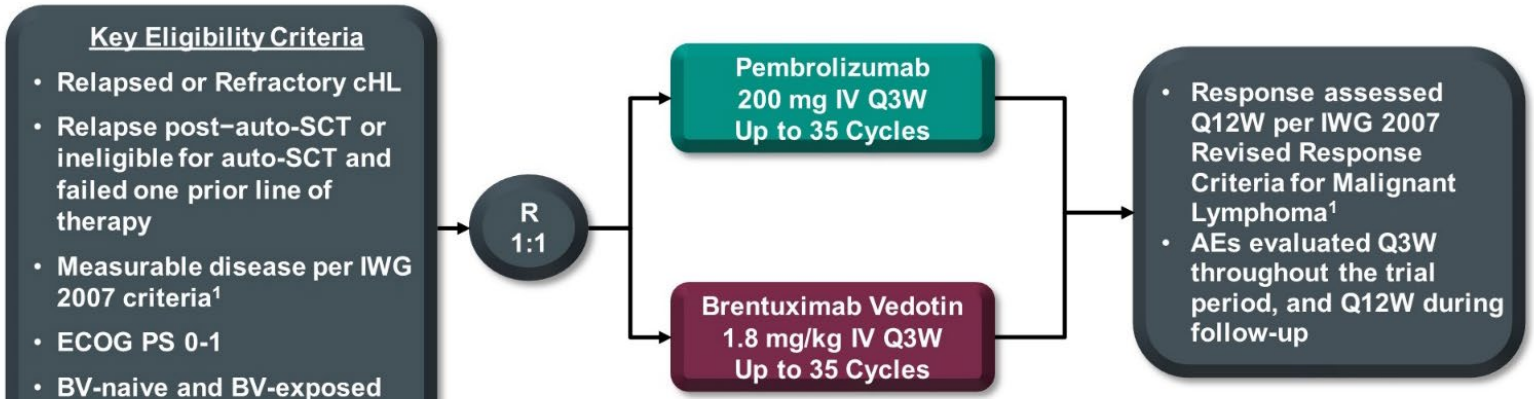
KN-204 Study Phase III Brentuximab vedotin versus pembrolizumab in r/r cHL



Primary End Point: PFS per blinded independent central review (BICR) by IWG 2007 criteria including clinical and imaging data following auto-SCT or allogeneic stem cell transplant (allo-SCT); OS

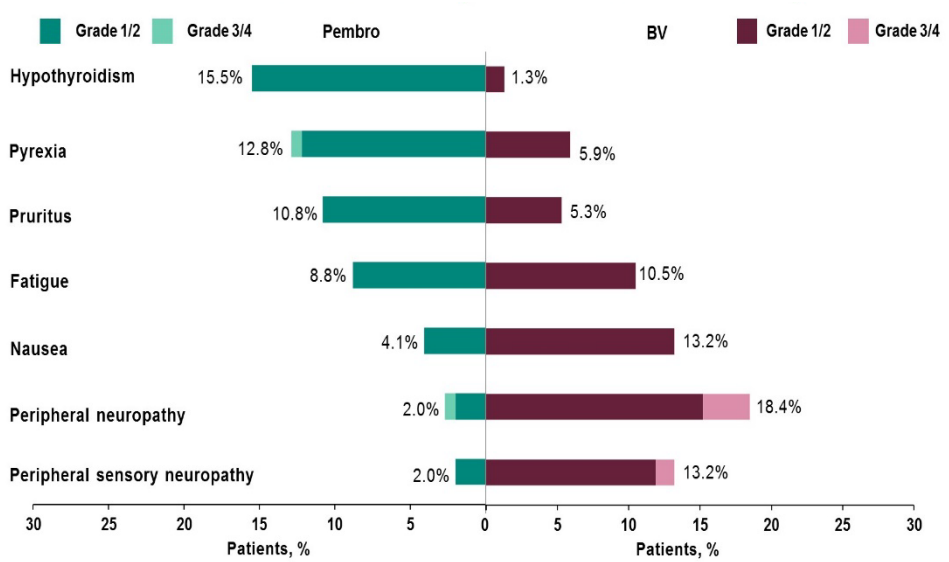
Secondary End Points: PFS per BICR by IWG 2007 criteria excluding clinical and imaging data following auto-SCT or allo-SCT; ORR by BICR per IWG 2007; PFS per investigator review; DOR; safety

1. Cheson BD et al. *J Clin Oncol*. 2007;25:579-586.

Kuruvilla J et al., Lancet 2021

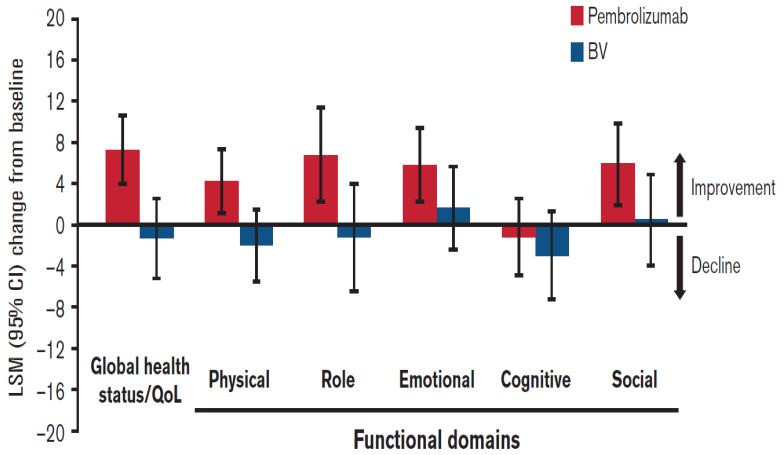
Gibt es relevante Unterschiede in der Verträglichkeit? Die KN-204 Studie.

Treatment-Related AEs (≥10%)



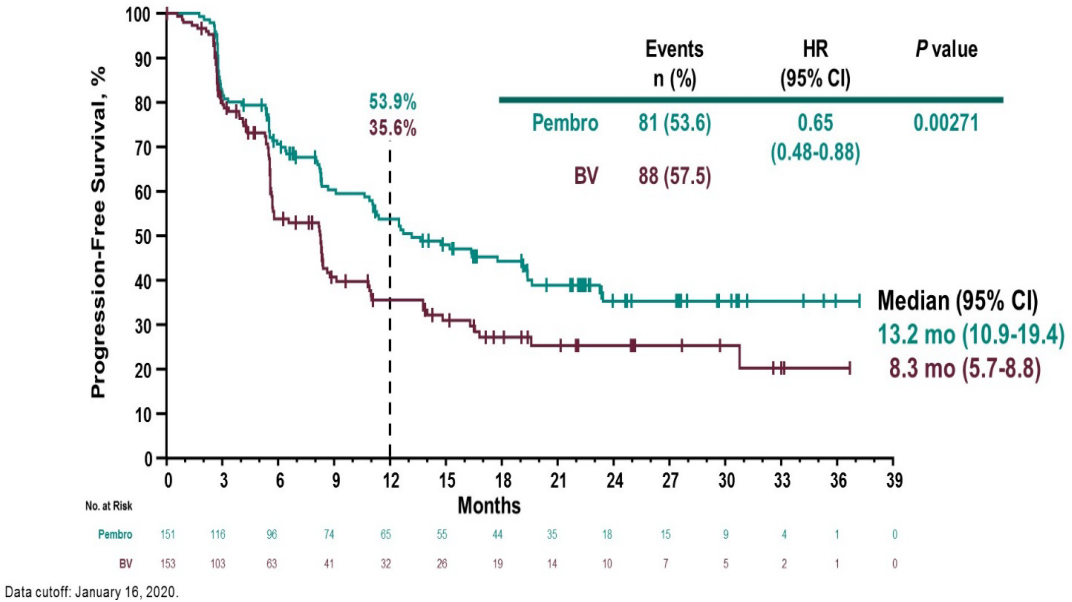
Data cutoff: January 16, 2020.

Quality of Life



Kuruvilla J et al., Lancet 2021

KN204 Primary End Point Progression-Free Survival*



Data cutoff: January 16, 2020.

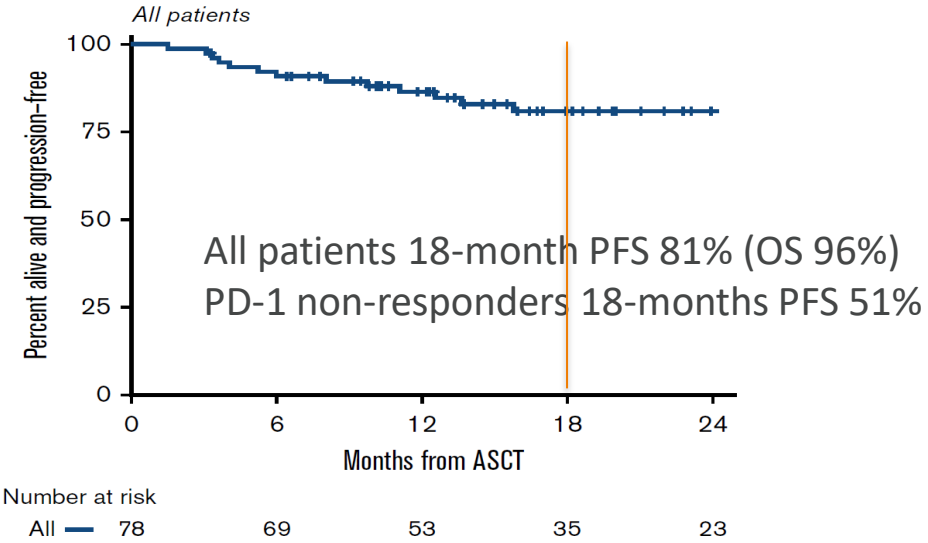
- **~45% (133/304) of patients in KN-204 were high-dose ineligible due to chemo-refractory disease.**
- **Should we offer high-dose chemotherapy in high-dose naïve PD1-responders?**

* Per Blinded Independent Central Review Including Clinical and Imaging Data Following Auto-SCT or Allo-SCT

Kuruvilla J et al., Lancet 2021

Consolidation high dose chemotherapy in ≥2 line anti-PD1 responders? Retrospective analysis

- 78 pts. underwent high-dose chemotherapy after anti-PD-1 mAb (alone or in combination) as 3rd-line or later therapy
- 42 pts. (54%) refractory to ≥2 consecutive systemic therapies immediately before anti-PD-1 treatment
- 58 (74%) pts. received immediate high-dose after anti-PD1, 20 (26%) pts. received interjacent therapy
- Median 4 systemic therapies before high-dose (3-7); 41% PET+ before high dose



➢ **Consolidative HDCT is effective for anti-PD1 responders and an option for all patients**

Merryman Blood Adv 2021

Allo-Tx treated patients after nivolumab in r/r cHL Checkmate 205 Phase II – 2 years follow-up

Supplemental Table 1. Disease status after subsequent allo-HCT	Cohort A (BV-naive) (n = 13)	Cohort B (BV after auto-HCT) (n = 14)	Cohort C (BV before and/or after auto-HCT) (n = 30)	Overall (N = 57)
CR, n (%)[a]				
At allo-HCT	6 (46.2)	7 (50.0)	13 (43.3)	26 (45.6)
100 days	8 (61.5)	11 (78.6)	14 (46.7)	33 (57.9)
6 months	7 (53.8)	11 (78.6)	16 (53.3)	34 (59.6)
1 year	8 (61.5)	12 (85.7)	14 (46.7)	34 (59.6)
2 years	7 (53.8)	9 (64.3)	13 (43.3)	29 (50.9)

- **Patients in CR before allo-Tx maintain their remission at 2 FU, however,**
- **Very few (3/57) improve their response towards a durable CR**

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Ansell et al., Blood Adv. 2023 Aug: bloodadvances.2023010334.

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How to treat patients after failure of two prior lines of systemic therapy?

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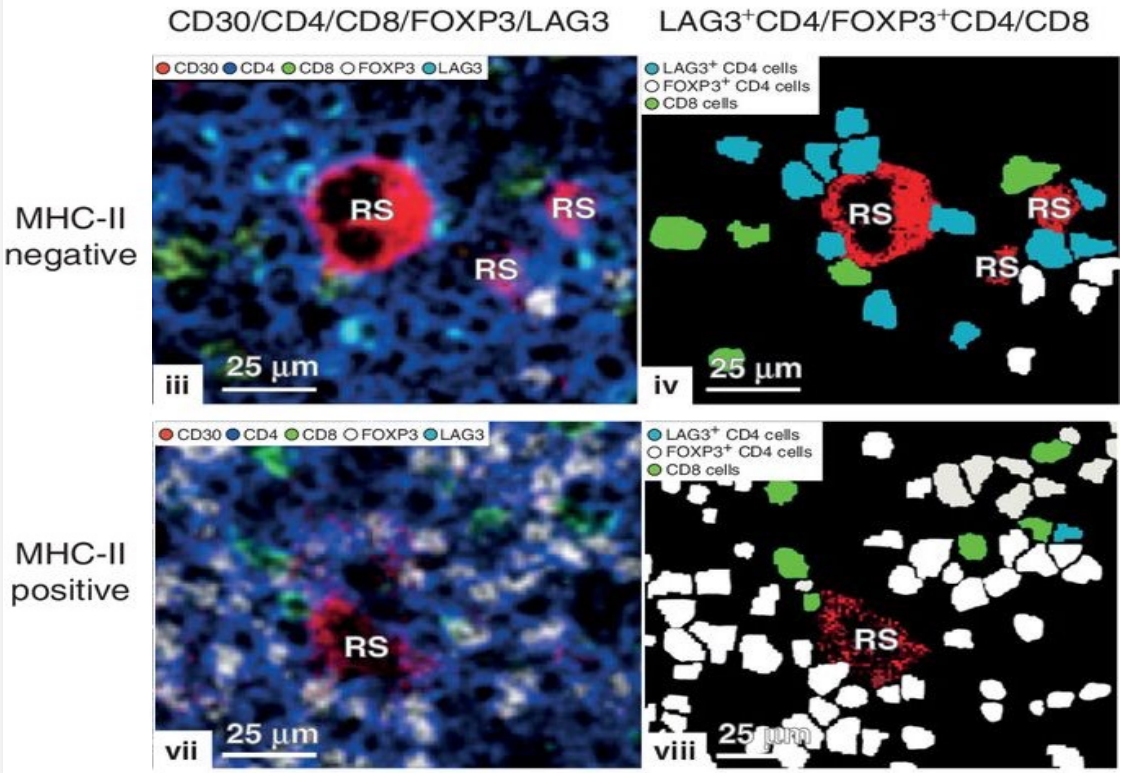
3. Other than ICI developments

Enhancing aPD1 with aLAG3?



LAG3+CD4+ T cells rosetting MHC-II negative HRS cells

- target LAG3?

Aoki *Cancer Discovery* 2021

MK-4280-003 Study Design
NCT03598608

Combination cohorts

- Anti–PD-1-naive R/R cHL (cohort 1)
- Anti–PD-1-refractory R/R cHL (cohort 2)
  - Age ≥18 years
  - R/R cHL after ASCT or no response to salvage chemotherapy or ineligible for ASCT
  - PD after anti–PD-1 therapy
  - ECOG PS of 0 or 1
- R/R DLBCL (cohort 3)
- R/R iNHL (cohort 4)

Safety lead-in phase (part 1)
N = 21

Pembrolizumab 200 mg IV Q3W

+

Favezelimab 200 mg or 800 mg IV Q3W

- Dose escalation per mTPI study design
- DLTs monitored for 21 days from first study dose

RP2D

Dose expansion phase (part 2)
N = 34

Pembrolizumab 200 mg IV Q3W

+

Favezelimab 200 mg or 800 mg IV Q3W

≤35 cycles

(~2 years)

- CT (Q12W) and PET (weeks 12 and 24) response assessments per IWG 2007 criteria by investigator
- Safety analysis

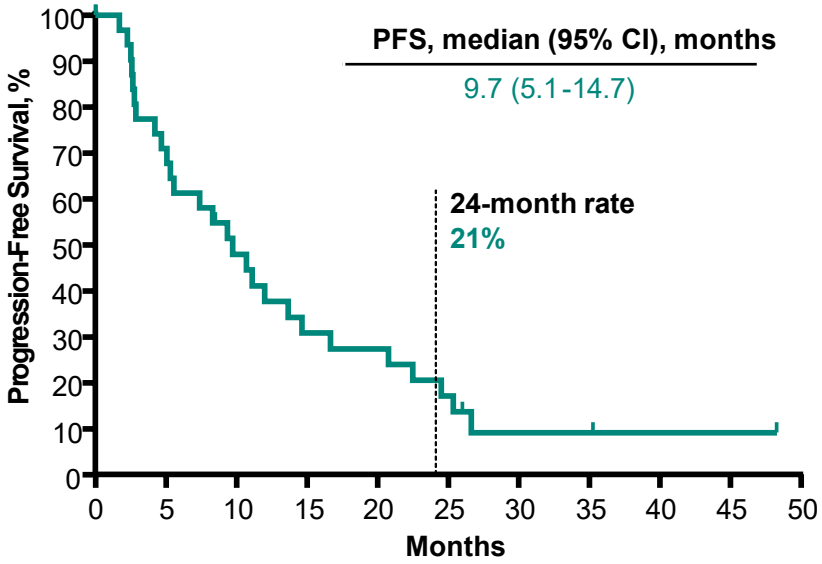
Survival follow-up

- **Primary end point:** Safety
- **Secondary end point:** ORR per IWG 2007 criteria
- **Exploratory end points:** DOR per IWG 2007 criteria, PFS per IWG 2007 criteria, and OS

Timmermann et al., ASH 2023

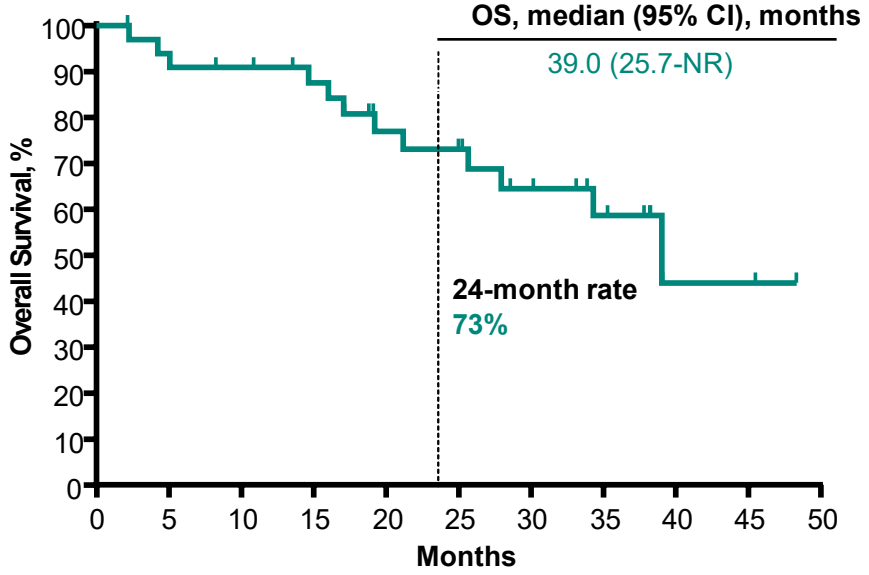
Database cutoff: August 15, 2023.

Kaplan-Meier Estimates of PFSa and OS



No. at risk

34 22 14 9 8 5 2 2 1 1 0

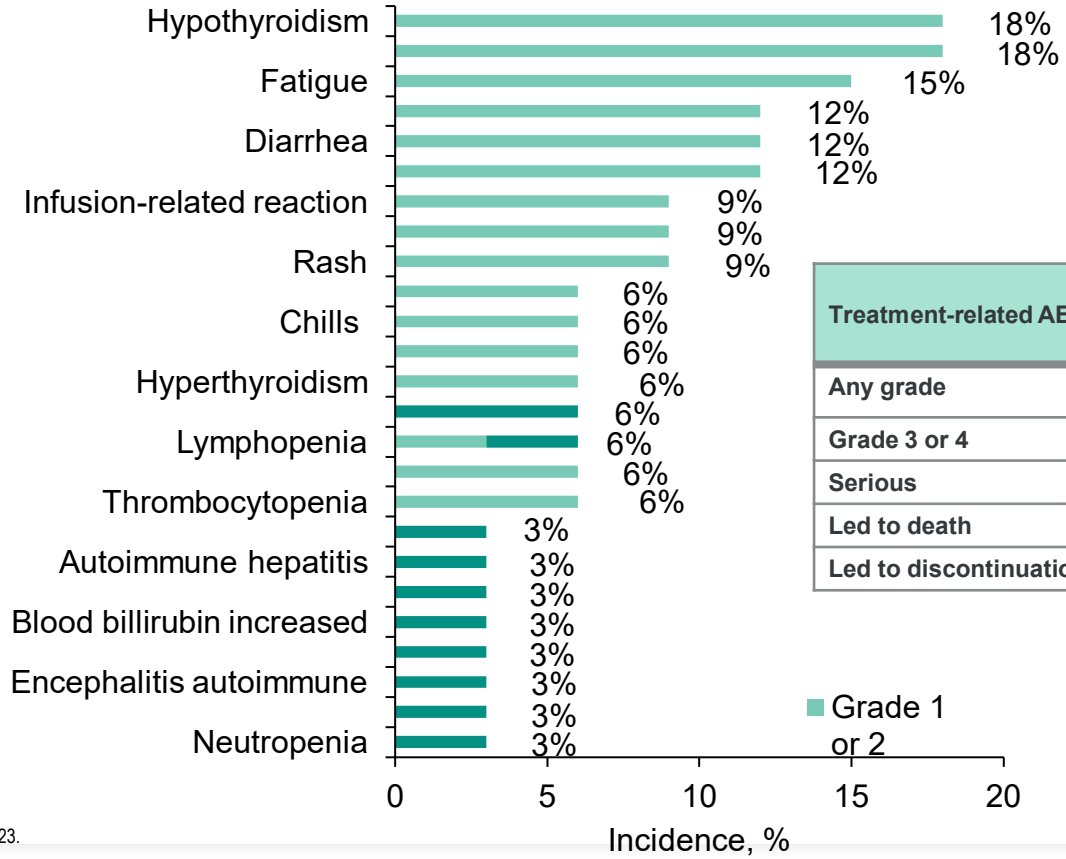


No. at risk

34 31 29 26 20 18 14 8 2 2 0

[a]per IWG 2007 by investigator assessment
Database cutoff: August 15, 2023.

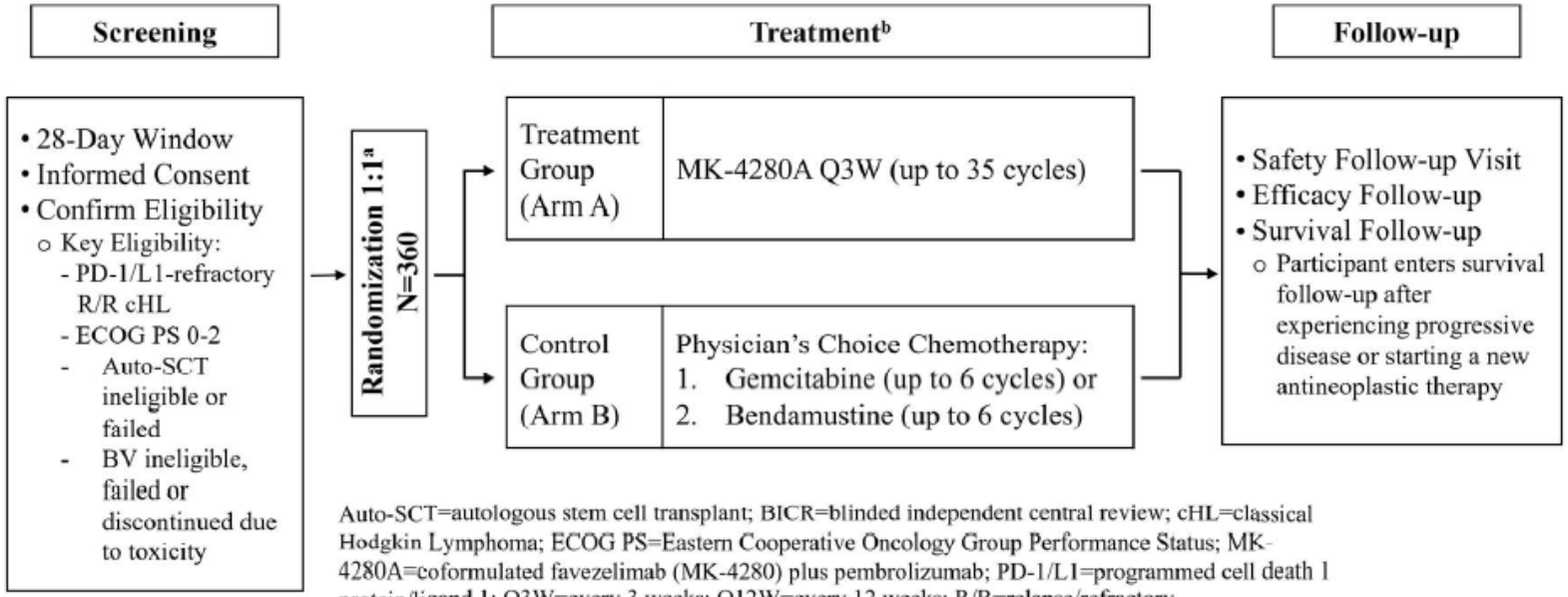
Treatment-Related AEs With Incidence ≥5%/all Grade 3 or 4 Events



Treatment-related AEs	Cohort 2 N = 34 n (%)
Any grade	28 (82)
Grade 3 or 4	6 (18)
Serious	6 (18)
Led to death	0 (0)
Led to discontinuation	6 (18)

Database cutoff: August 15, 2023.

aPD1/LAG3i MK4280A-003 Phase III



Auto-SCT=autologous stem cell transplant; BICR=blinded independent central review; cHL=classical Hodgkin Lymphoma; ECOG PS=Eastern Cooperative Oncology Group Performance Status; MK-4280A=coformulated favezelimab (MK-4280) plus pembrolizumab; PD-1/L1=programmed cell death 1 protein/ligand 1; Q3W=every 3 weeks; Q12W=every 12 weeks; R/R=relapse/refractory

a. **Stratification Factor:**
1. Prior Stem Cell Transplant (yes versus no)
2. ECOG Performance Status (0/1 versus 2)

b. Scans Q12W for 2 years from C1D1. Responses will be assessed by BICR

ClinicalTrials.gov Identifier: NCT05508867

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How to treat patients after failure of two prior lines of systemic therapy?

1. Introduction on PD1-inhibition in cHL
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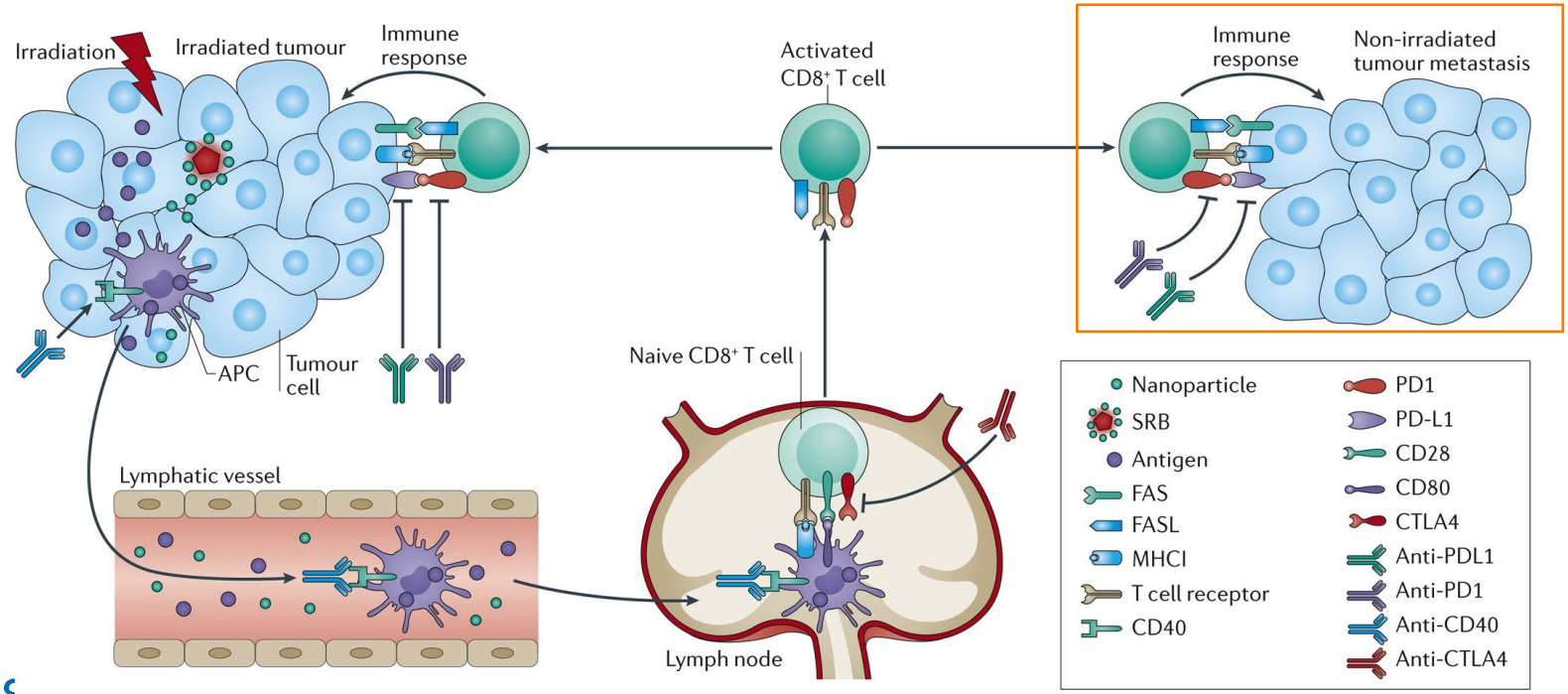
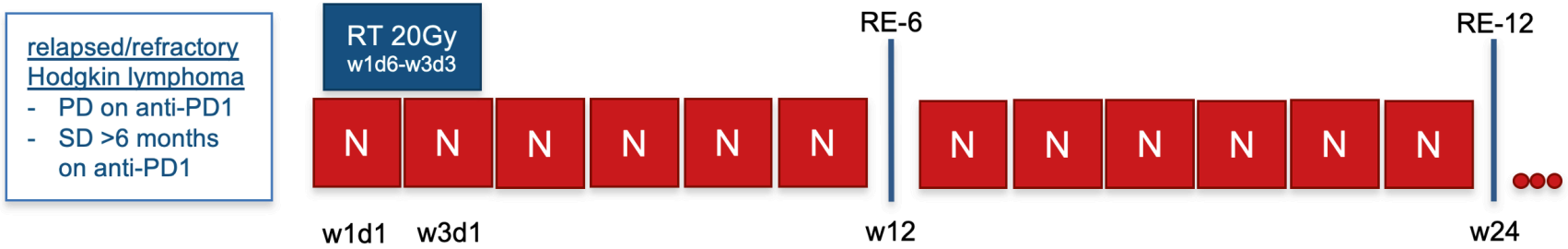
Patients failing PD1 therapy: options?

- Local radiotherapy may induce systemic antitumor immunity
- This proposed *abscopal effect* may be augmented by aPD1[1]



[1] Ngwa et al. *Nat Rev Cancer* 2018. aPD1: anti-PD1 blockade

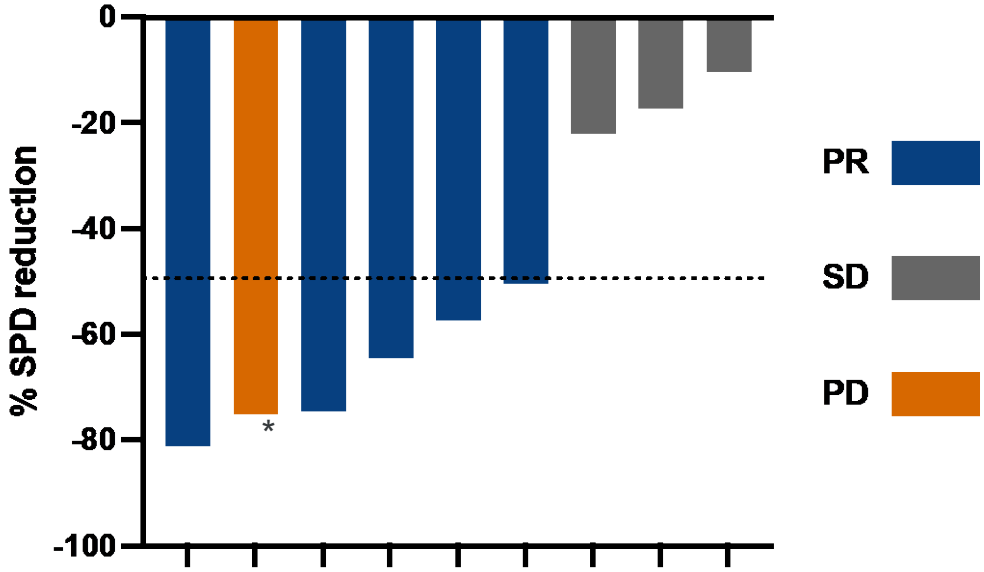
AERN: Trial Treatment



- RT: 20Gy RT in 2Gy fractions to a single lesion starting within the first week after first dose of nivolumab on trial
- Systemic treatment: continued aPD1 with nivolumab 240mg Q2W for up to 1.5 years, relevant PD or unacceptable toxicity

N: Nivolumab 240mg, aPD1: anti-PD1 blockade, RT: radiotherapy, Q2W: every 2 weeks, PD: progressive disease

Stage 1: Response at 1st Interim Restaging



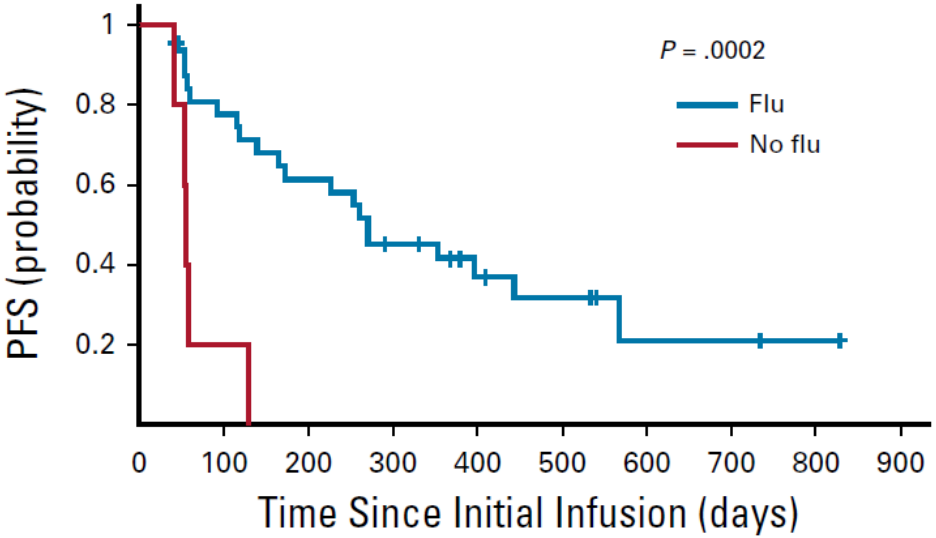
Median SPD reduction of -57.44% from baseline

Abscopal Response Rate:
56% (5/9 patients)
95%CI: 16.9% - 74.9%

→ Criteria for stage 2 continuation were met

* PD due to new lesion despite reduction of SPD >50%. PR: partial remission, SD: stable disease, PD: progressive disease, SPD: sum of the product of diameters

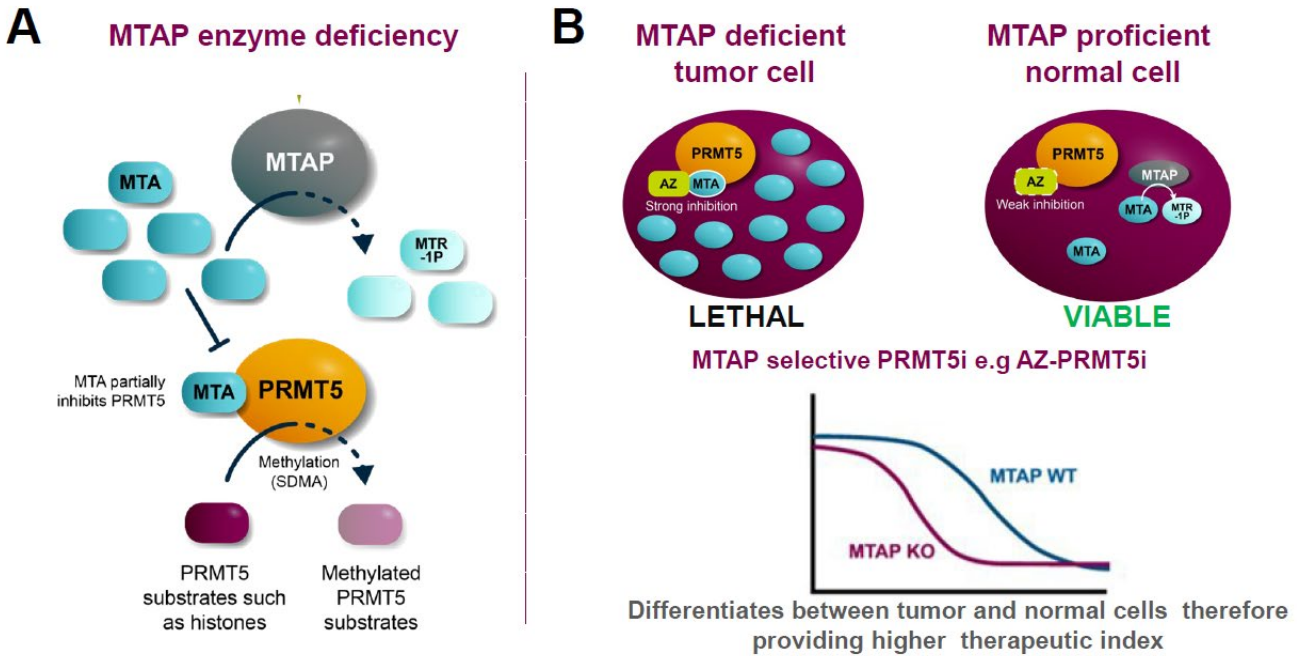
Anti-CD30 CAR-T in r/r cHL?



- 41 patients received CD30.CAR-Ts
- Median 7 prior lines
- 10 patiens with grade 1 CRS, no ICANs
- ORR with fludarabine-LD-chemo 72%; 59% CR
- All patients: 1-year PFS 36%, 1-year OS 94%

Ramos et al., J Clin Oncol 2020

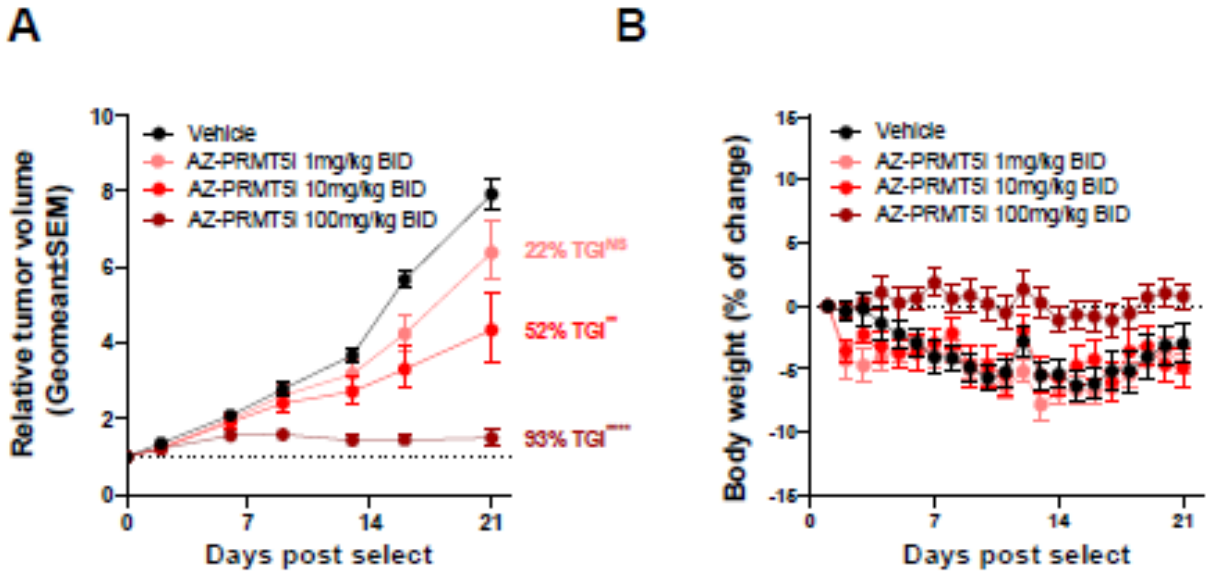
2nd Generation PRMT5 Inhibition in cHL



MTA:
methylthioadenosine

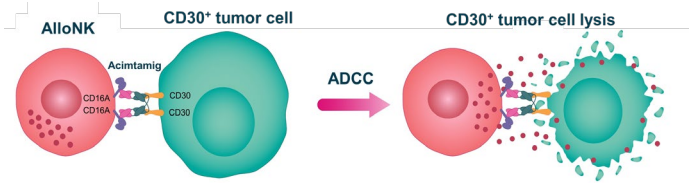
- ASH 2023: Urosevic J. *et al.,* 4185: Epigenetic Silencing of MTAP in Hodgkin's Lymphoma Renders It Sensitive to a 2nd Generation PRMT5 Inhibitor.

In vivo efficacy of PRMT5 Inhibition in cHL models



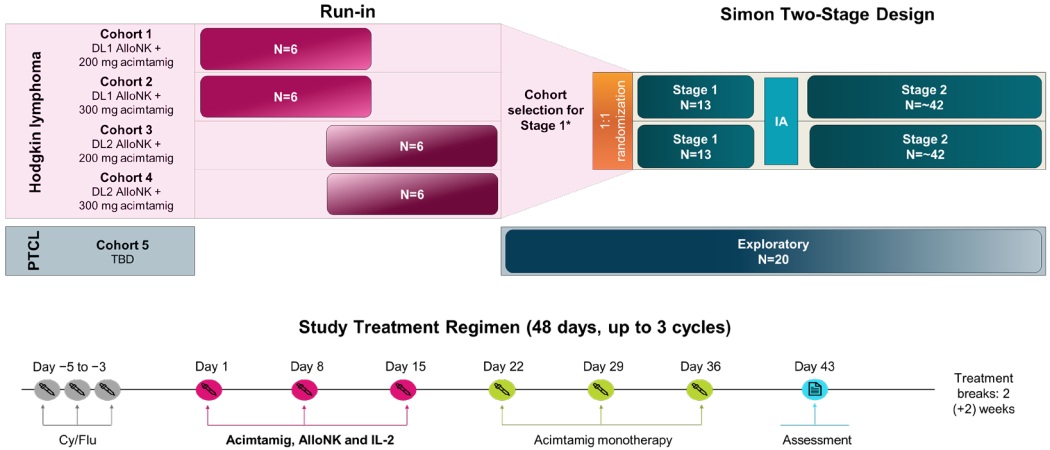
ASH 2023: Urosevic J. *et al.,* 4185: Epigenetic Silencing of MTAP in Hogdkin's Lymphoma Renders It Sensitive to a 2nd Generation PRMT5 Inhibitor.

AFM13 in Combination with Allogeneic Natural Killer Cells (AB-101) in Relapsed or Refractory Hodgkin Lymphoma and CD30+ Peripheral T-Cell Lymphoma: A Phase 2 Study (LuminICE-203)



Acimtamig (AFM13) is a tetravalent, bispecific Innate Cell Engager (ICE) that binds CD16A on natural killer (NK) cells and CD30-positive (CD30+) on HL and a subset of PTCL, enhancing NK cell-mediated antibody-dependent cellular cytotoxicity

Figure 2: Phase 2 design for acimtamig in combination with AlloNK (LuminICE-203; NCT05883449)



DL1: 2 ×10^9 AlloNK on Day 1, Day 8, and Day 15; DL2, 4 ×10^9 AlloNK at Day 1, 2 ×10^9 AlloNK at Day 8 and Day 15.
*Following the run-in observation period and after cycle 1 has completed for each subject enrolled in the four HL cohorts, two cohorts will be selected and further evaluated in the Simon two-stage design part of the study. Cohorts 3 and 4 will only start if no more than one Grade 3 or 4 treatment-related adverse event is observed in the first six patients enrolled.
Cy/Flu, cyclophosphamide and fludarabine; DL, dose level; HL, Hodgkin lymphoma; IA, interim analysis; IL-2, interleukin-2; IV, intravenously; PTCL, peripheral T-cell lymphoma; TBD, to be determined.

GHSG

ASH 2023Allison et al., AFM13 in Combination with Allogeneic Natural Killer Cells (AB-101) in Relapsed or Refractory Hodgkin Lymphoma and CD30+ Peripheral T-Cell Lymphoma: A Phase 2 Study (LuminICE-203)

AFM13 in Combination with Allogeneic Natural Killer Cells (AB-101) in Relapsed or Refractory Hodgkin Lymphoma and CD30^{+} Peripheral T-Cell Lymphoma: A Phase 2 Study (LuminICE-203)

Baseline patient characteristics	N=42
Age, median (range)	43 (20–75)
Gender (male/female)	27 / 15
Diagnosis (HL / NHL)	37 / 5
No. prior lines therapy, median(range)	7 (1–14)
Prior brentuximab vedotin	42
Prior anti-PD-1	39
Prior SCT (autologous / allogeneic)	32 (22 / 10)
Prior CD30.CAR-T	4

There was 1 grade 2 infusion-related reaction (IRR) in 115 infusions of AFM13-NK (0.8%) and 27 IRR infusion related reactions in 350 infusions of AFM13 (7.7%) (1 G3, 26 G2).

DL3 (10^{8} NK/Kg) was established as the RP2D.

The ORR and CR were 92.8% and 66.7%, respectively (94.4% and 72.2%, respectively, in 36 pts treated at the RP2D).

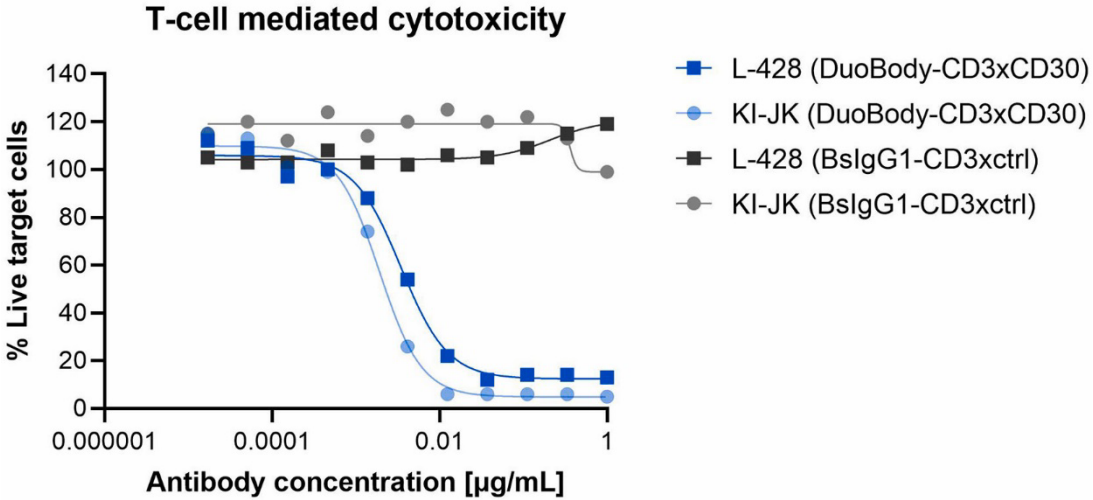
At median follow-up of 14 (6-34) months, the EFS/OS rates are 31%/76%; median EFS/OS are 8 months/not reached. No relapses were associated with antigen loss.

In the subset of pts planned for 4 cycles at RP2D, 15 of 23 pts remained event free at 6 mo (4 pts with and 11 without SCT consolidation), for 6-month EFS/OS rates of 65%/83%.

GHSG

ASH 2023 Nieto et al., 774 Innate Cell Engager (ICE®) AFM13 Combined with Preactivated and Expanded (P+E) Cord Blood (CB)-Derived Natural Killer (NK) Cells for Patients with Refractory CD30-Positive Lymphomas: Final Results

A First-in-human Trial of GEN3017 in Hodgkin Lymphoma and Non-Hodgkin Lymphoma (ClinicalTrials.gov ID NCT06018129)



A First-in-human Trial of GEN3017 in Hodgkin Lymphoma and Non-Hodgkin Lymphoma ClinicalTrials.gov ID NCT06018129

GHSG

Simone C et al.: Duobody-CD3xCD30 Demonstrates Potent Anti-Tumor Activity in Preclinical Models of CD30⁺ Hematologic Malignancies, Blood, 2022

The roles of Novel Agents in the landscape of Hodgkin Lymphoma in 2024

1. PD1 antibodies show very high overall response rates, manageable CR rates (around 20-25%), some of which may be durable, median PFS is just over 1 year
2. PD1 AK re-therapy makes sense
3. HDCTx and APBSCT after achieving remission with PD1 AK is safe and appears to achieve good survival outcomes
4. Combination of dual ICI with aPD1 and aLAG3 antibodies is under investigation
5. New developments im immunotherapy include CAR-T-cells, bispecific antibodies, off-the-shelf allo-NK cells in combination with a CD30xCD16A innarte cell engager
6. A PRMT5 inhibitor is also under development.

➢ Many more options for chemotherapy refractory patients become available.