HODGKIN LYMPHOMA – New Combinations

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Disclosures for Stephen Ansell, MD, PhD

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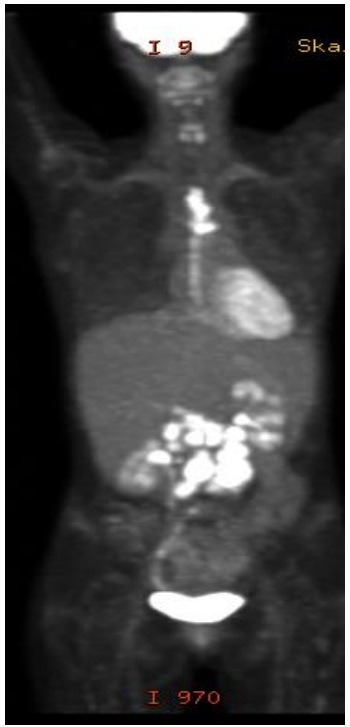
N/A = Not Applicable (no conflicts listed)

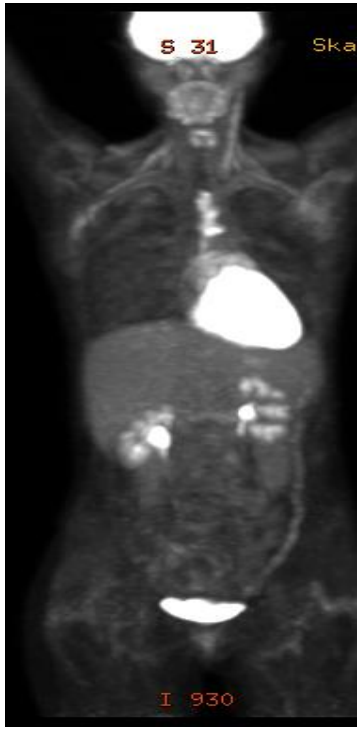
Aims -

- Why do we need combinations in Hodgkin lymphoma?
- Four combination approaches
  - With other checkpoints
  - With bispecific antibodies
  - With antibody drug conjugates
  - With chemotherapy

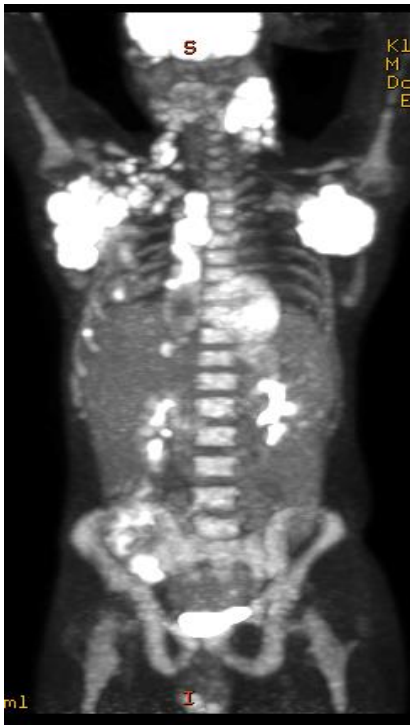
Blocking PD-1 signalling

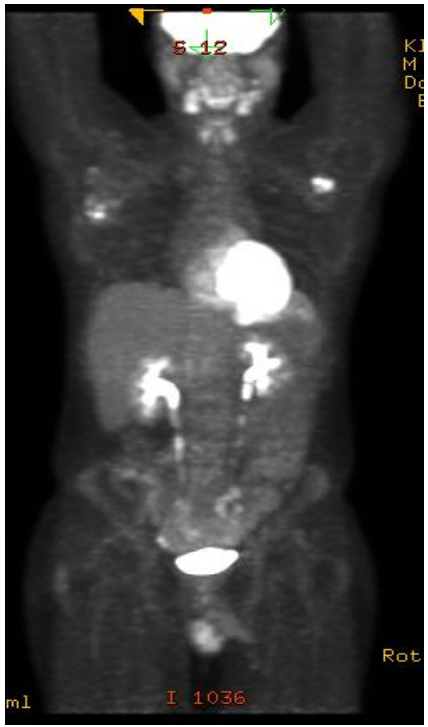
Highly effective in Hodgkin lymphoma





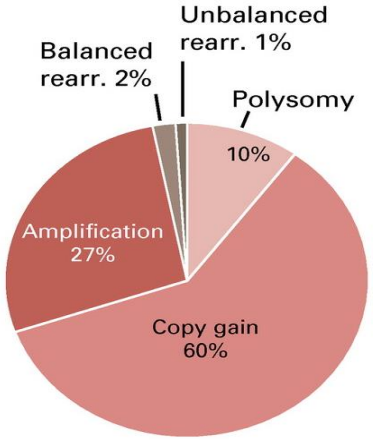
42 year old female – Hodgkin lymphoma

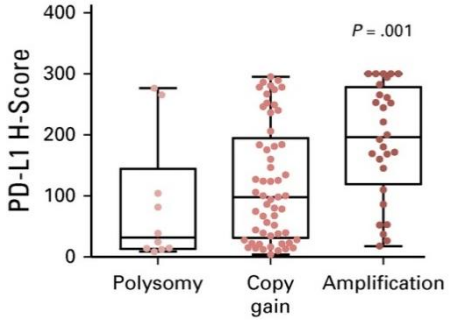


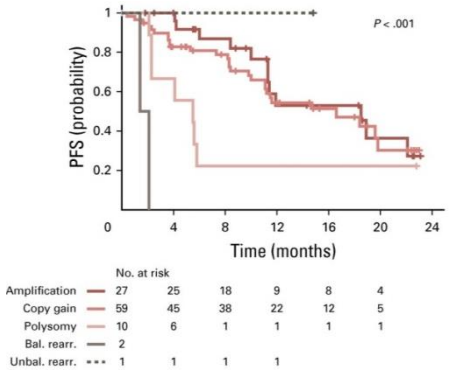


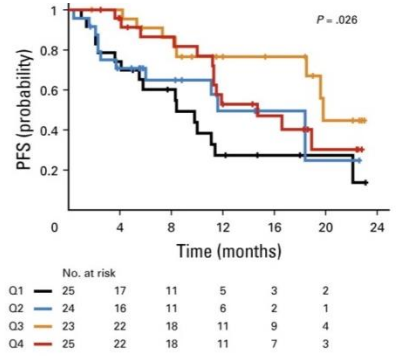
26 year old male – Hodgkin lymphoma

PD-L1 Expression Predicts Outcome After PD-1 Blockade: BUT NO ONE SEEMS TO BE CURED







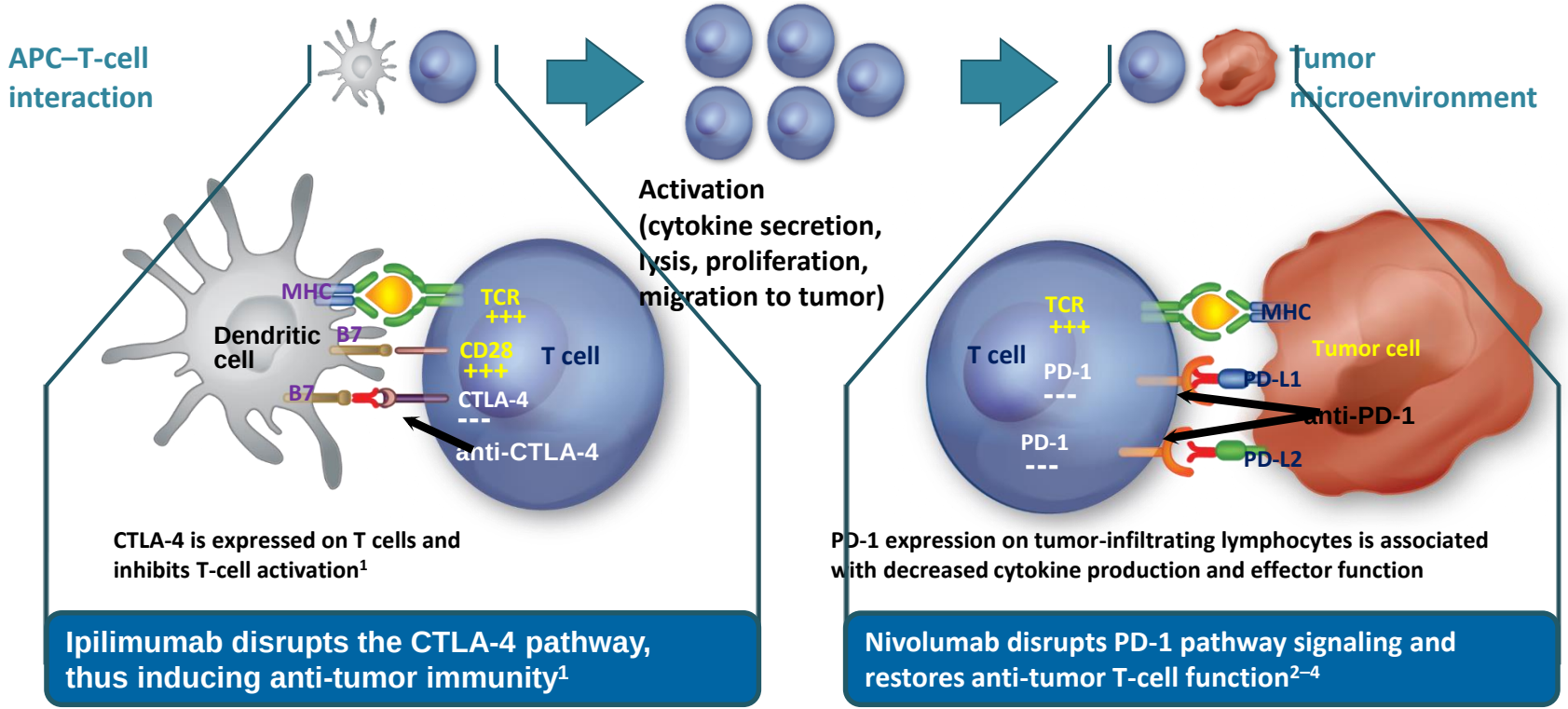


Roemer et al. J Clin Oncol. 2018 Apr 1;36(10):942-950.

1. Combination Approaches – Nivolumab and Ipilimumab in cHL

CTLA-4 blockade (ipilimumab)

PD-1 blockade (nivolumab)



CTLA-4 is expressed on T cells and inhibits T-cell activation[1]

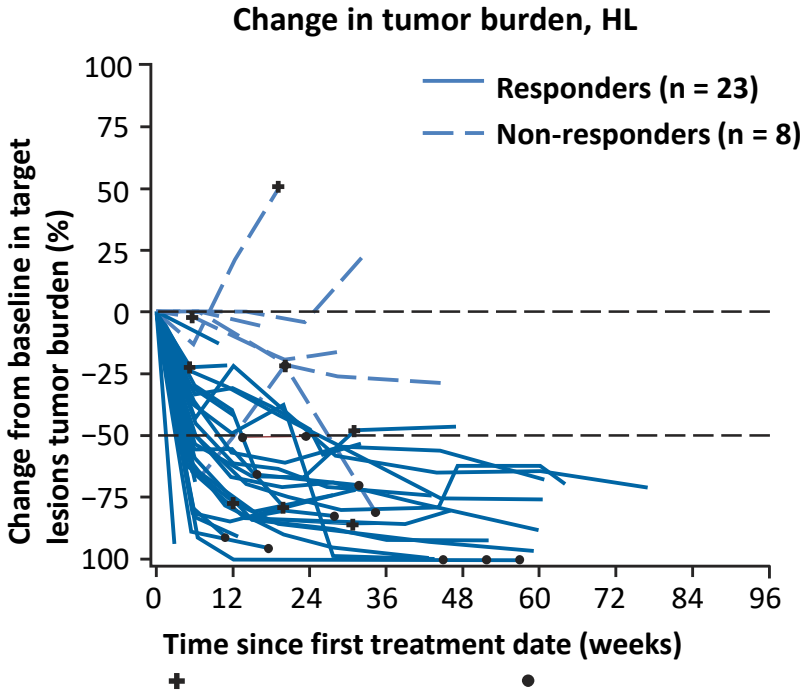
PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function

Ipilimumab disrupts the CTLA-4 pathway, thus inducing anti-tumor immunity[1]

Nivolumab disrupts PD-1 pathway signaling and restores anti-tumor T-cell function[2–4]

1. Combination Approaches – Nivolumab and Ipilimumab in cHL

	HL (N = 31)
ORR, n (%)[a]	23 (74)
Complete response	6 (19)
Partial response	17 (55)
Stable disease	3 (10)
Relapsed or progressive disease	3 (10)
Median duration of OR, months (range)	NR (0.0+, 13.4+)
	Transplant naïve[b] (n = 18)
ORR, n (%)	12 (67)

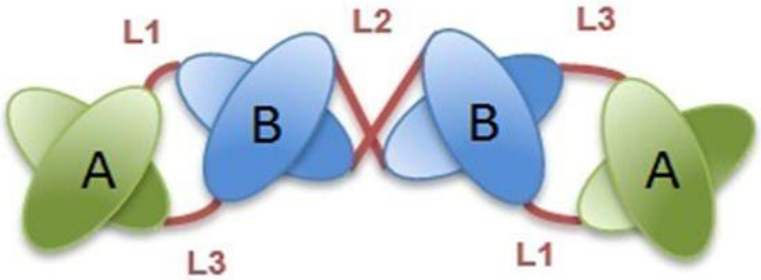


[a]Response was not reported for 2 (6%) patients with HL
bTransplant-naïve patients are a subset of the total number of patients with HL; a total of 13 transplant-naïve patients were chemoresistant and 3 were ineligible for the procedure
NR = not reached; + = censored value

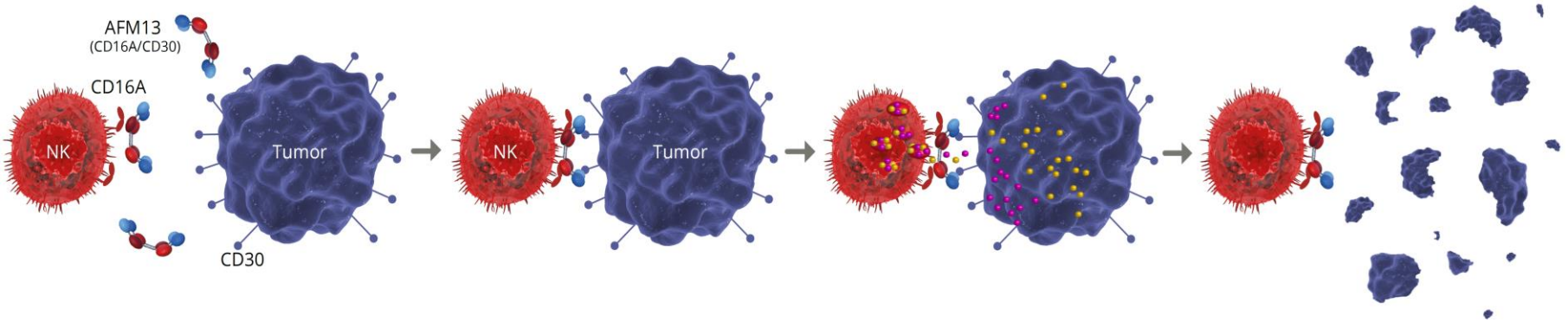
Ansell et al. ASH 2016 abstract #183

2. Combination Approaches - Bispecific antibodies

AFM13: a first-in-class tetravalent bispecific anti-CD30/CD16A antibody



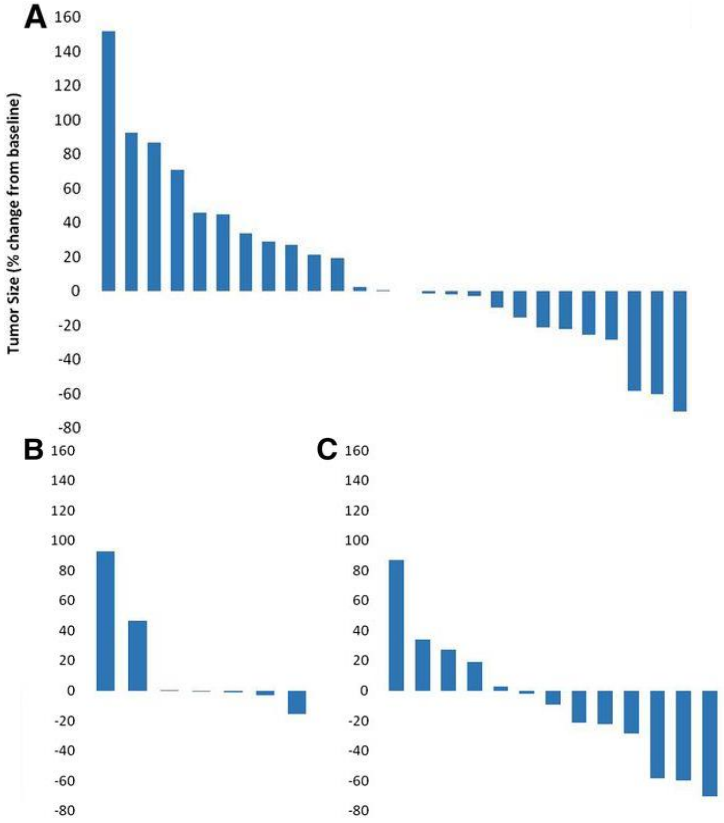
Tetravalent functional homodimer (~110 kDa)



Engager Therapy | Immunological Synapse | Release of Perforins and Granzymes | Tumor Cell Lysis

Wu et al. J Hematol Oncol. 2015 Aug 1;8:96.

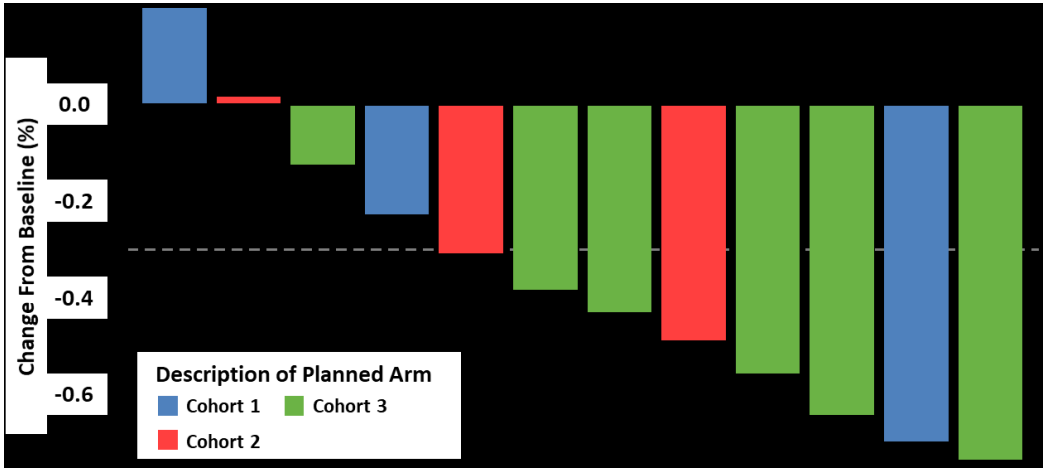
2. Targeting CD30 with AFM13 - a bispecific anti-CD30/CD16A antibody construct



- 28 cHL patients in a phase I study.
- Overall, 12% and 50% of patients achieved a PR and SD, respectively.
- Considering only patients that received higher doses, the PR and SD rate improved to 23 and 54%, respectively

Rothe et al. Blood 2015;125:4024-4031

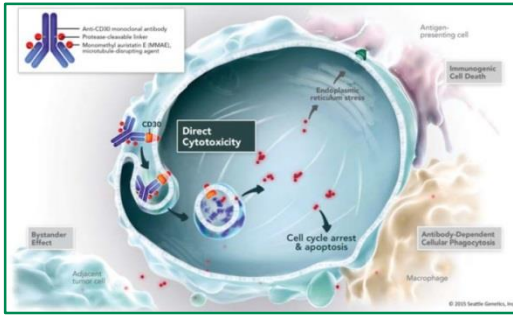
2. A Phase 1 Study of AFM13 and Pembrolizumab in Hodgkin Lymphoma after Brentuximab Vedotin Failure



- 12 patients enrolled into the dose escalation phase were evaluable for efficacy at 3 months.
- In Cohort 1, there were 2 PRs and 1 progression. In Cohort 2 , 1 CR, 1 PR and 1 Progression. In Cohort 3, 5 PRs and 1 progression.
- The ORR for the dose selected for the extension cohort was 83% (5/6).

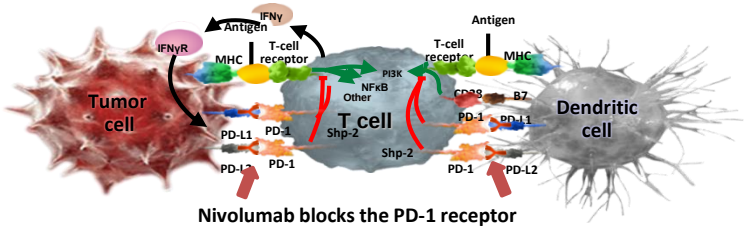
Ansell et al. Blood 2017 130:1522

3. Combination Approaches - Brentuximab vedotin (BV) plus nivolumab as Salvage Therapy



Brentuximab vedotin disrupts the microtubule network and triggers an immune response through the induction of endoplasmic reticulum stress[a]

Nivolumab targets the programmed death-1 (PD-1) immune checkpoint pathway and restores antitumor immune responses

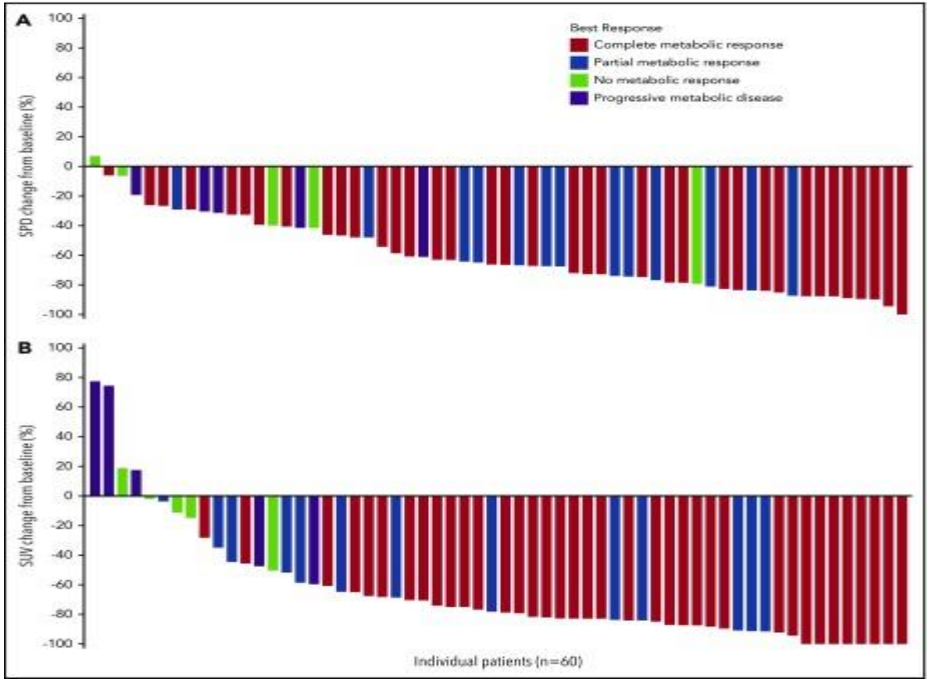


Nivolumab blocks the PD-1 receptor

- **Both agents are well tolerated with high single-agent response rates in patients with R/R HL (BV=72% ORR, 33% CR; Nivo=73% ORR, 28% CR)**
- **Together, they could yield improved CR rates and improved durability of responses, and potentially lead to better long-term outcomes**

Herrera et al. ASH 2016 abstract #1105

3. Brentuximab vedotin plus nivolumab in patients with relapsed Hodgkin lymphoma



- 62 patients received up to 4 cycles of brentuximab vedotin (BV) and nivolumab (Nivo). Patients could then proceed to ASCT.
- The CR rate (n = 61) was 61%, with an objective response rate of 82%.
- The combination of BV plus Nivo was an active and well-tolerated first salvage regimen, potentially providing patients with R/R HL an alternative to traditional chemotherapy.

Herrera et al. Blood. 2018 Mar 15;131(11):1183-1194.

3. BV+Nivolumab for Relapsed Patients

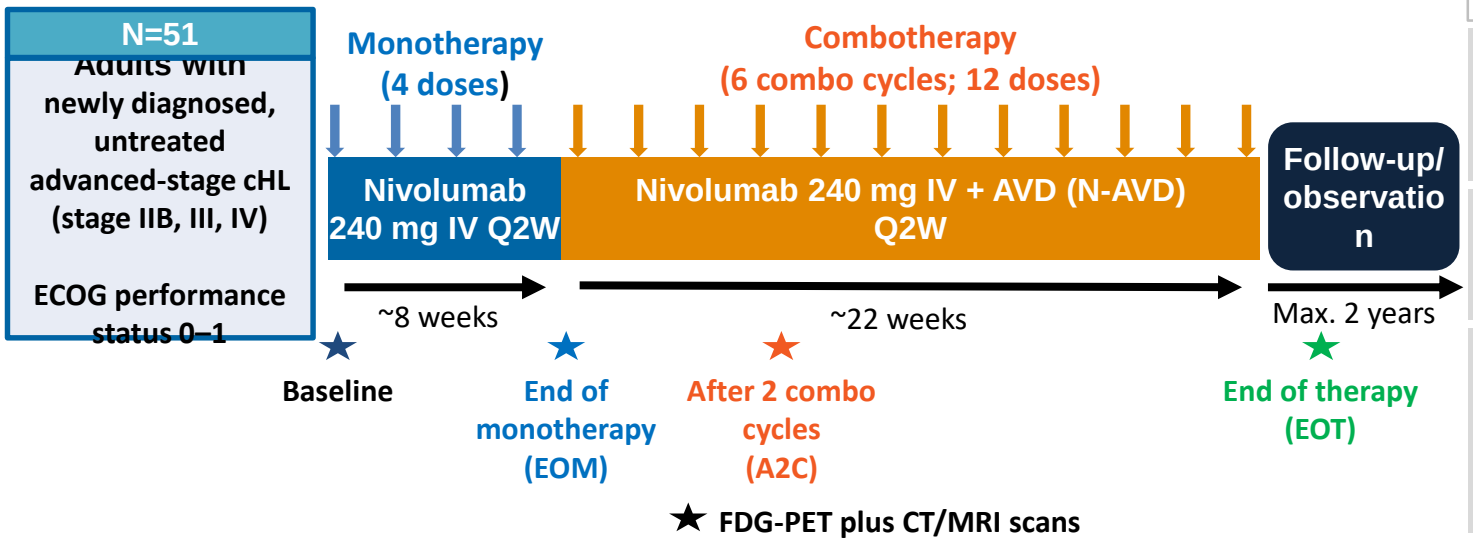
E4412 Schema: (Arms D-F)

Evaluable Patients (n = 12)	ORR
ORR	12/12 (100%)
CR	8/12 (66%)
PR	4/12 (34%)

2 of 2 patients with prior BV evaluable= CR

Diefenbach et al. ASH 2016 abstract #1106

4. Combination Approaches – PD-1 Blockade with Chemotherapy



Endpoints included:

Primary

Safety and tolerability (G3–5 treatment-related AEs)

Secondary

- Discontinuation rate
- CR by IRC at EOT

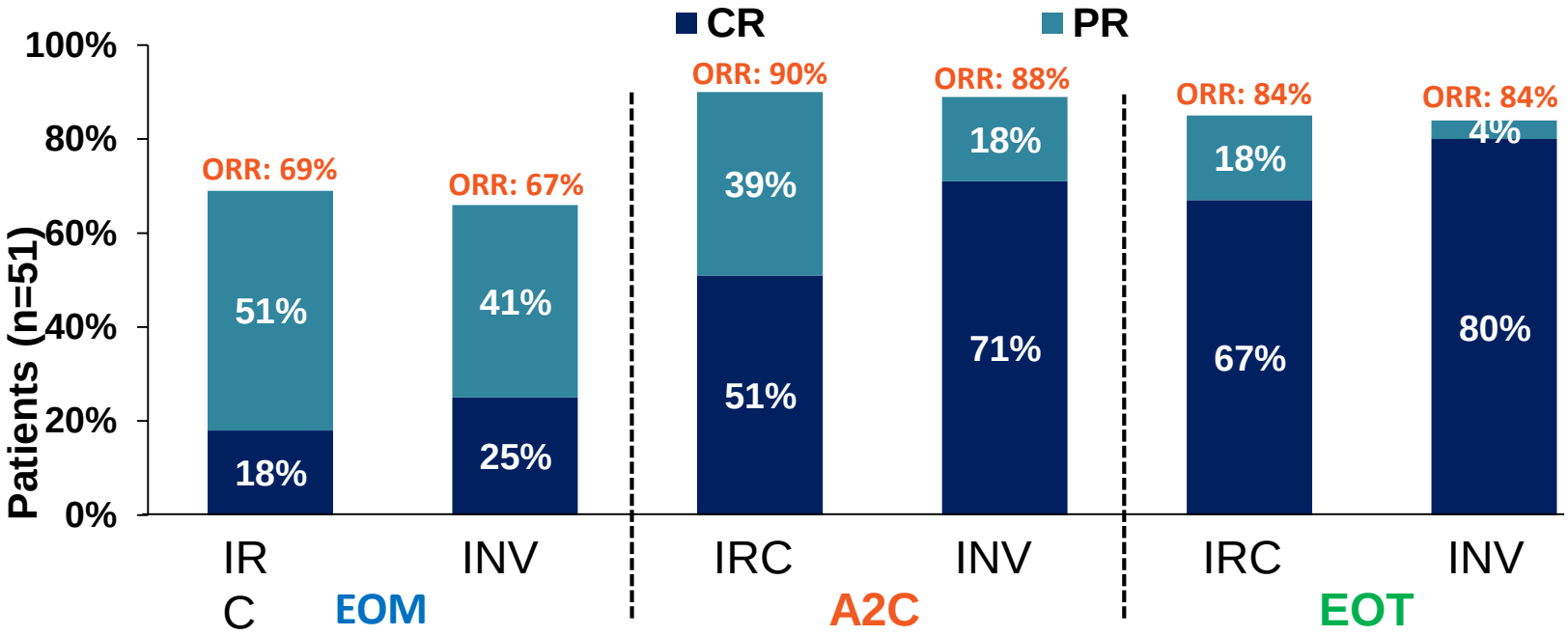
Exploratory

- CR and ORR by IRC and investigator at EOM, A2C and EOT
- mPFS

- **Responses were assessed using the IWG 2007 criteria**
- Median duration of follow-up was 11.1 months (database lock: 12 October 2017)
- Bleomycin was excluded due to potential overlapping pulmonary toxicity

AE, adverse event; AVD, doxorubicin (25 mg/m^2)/vinblastine (6 mg/m^2)/dacarbazine (375 mg/m^2); CR, complete remission; ECOG, Eastern Cooperative Oncology Group; FDG-PET, fluorodeoxyglucose–positron emission tomography; G, grade; IRC, Independent Radiology Review Committee; IWG, International Working Group; mPFS, modified progression-free survival; OS, overall survival; Q2W, every 2 weeks

4. Response Per IRC and Investigator – ITT Population



- At EOT, ORR per investigator in the ITT population was 84%, with 80% of patients achieving CR

Response assessed using IWG 2007 criteria. Five patients were non-evaluable at end of therapy. Biopsies were not required for patients to be considered to have progressive disease. Values may not total ORR due to rounding. INV, investigator; PR, partial remission

What does this teach us?

- Efficacy of PD-1 blockade in Hodgkin lymphoma is high but may not be durable
- Combination approaches are safe but it is not clear whether additional benefit is seen with other immune therapies
- New combinations with chemotherapy may be the most promising