PDL1 inhibitors in Relapsed/ Refractory Hodgkin Lymphoma:

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Blockade of the PD-1 checkpoint with anti–PD-L1 avelumab is sufficient for clinical activity in relapsed/refractory classical Hodgkin lymphoma (cHL)

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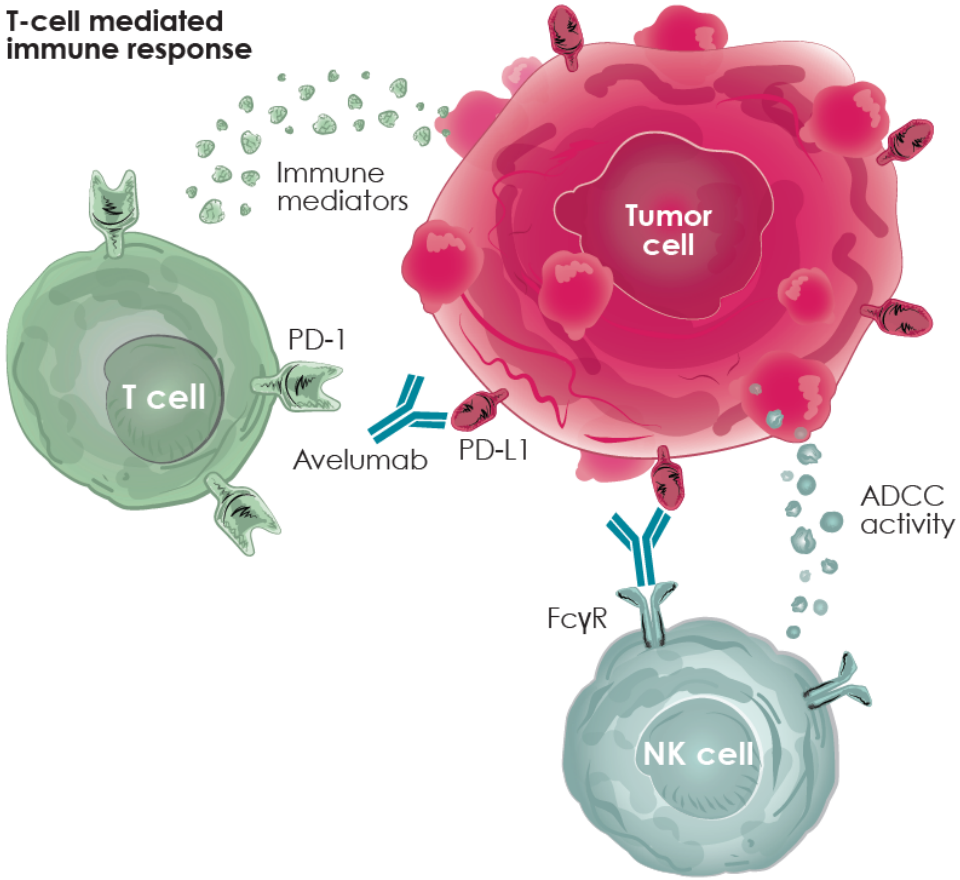
Immune checkpoint inhibitors for the treatment of classical Hodgkin lymphoma

- Amplification of chromosome 9p24.1 is frequent in classical Hodgkin lymphoma (cHL)[1,2]
  - This amplicon contains the genes encoding the PD-L1 and PD-L2 immune checkpoint proteins, resulting in their overexpression[2]
- Anti–PD-1 checkpoint inhibitors are an approved treatment option for patients with relapsed/refractory (R/R) cHL[3-6]
  - Anti–PD-1 antibodies block both the PD-1/PD-L1 and PD-1/PD-L2 interactions
  - It has not yet been established whether blockade of the PD-1/PD-L1 interaction is necessary and/or sufficient for the therapeutic effect observed in cHL

1. Joos S, et al. Cancer Res. 2000;60:549-52. **2**. Green MR, et al. Blood. 2010;116(17):3268-77. **3**. Opdivo (nivolumab) [Summary of Product Characteristics]. Uxbridge, UK: Bristol-Myers Squibb Company; 2017. **4**. Keytruda (pembrolizumab) [Summary of Product Characteristics]. Hertfordshire, UK: Merck Sharp & Dohme Limited; 2017. **5**. Opdivo (nivolumab) [package insert]. Princeton, NJ, USA: Bristol-Myers Squibb Company; 2017. **6**. Keytruda (pembrolizumab) [package insert]. Whitehouse Station, NJ, USA: Merck Sharp & Dohme; 2017.

Avelumab

- Human anti–PD-L1 IgG1 mAb
- Inhibits PD-L1/PD-1 interactions,[1] leaving PD-L2/PD-1 pathway intact
  - Unlike anti–PD-1antibodies that target T cells, avelumab targets tumor cells
- Half-life ≈4 days; >90% target occupancy dosing Q2W at 10 mg/kg[1]
- Induces ADCC against tumor cells in vitro[2,3]
- Antitumor activity in lung, bladder, renal, and other malignancies[4-6]
- FDA-approved treatment for metastatic Merkel cell carcinoma and advanced urothelial carcinoma progressed after platinum-containing chemotherapy[7]



ADCC, antibody-dependent cell-mediated cytotoxicity; **mAb**, monoclonal antibody; **NK**, natural killer; **Q2W**, every 2 weeks.

1. Heery CR, et al. Lancet Oncol. 2017;18(5)587-98. **2**. Boyerinas B, et al. Cancer Immunol Res. 2015;3(10):1148-57. **3**. Fujii R, et al. Oncotarget. 2016;7:33498-511. **4**. Larkin J, et al. Ann Oncol. 2016;27(Suppl):Abstract 775PD. **5**. Gulley JL, et al. Lancet Oncol. 2017;18(5): 599-610. **6**. Apolo A, et al. J Clin Oncol. 2017 Apr 4. [Epub ahead of print]. **7**. Bavencio (avelumab) [package insert]. Darmstadt, Germany: Merck KGaA; 2017.

Study design: JAVELIN Hodgkin (NCT02603419)

Phase 1b, open-label, multicenter, multiple-dose, randomized, parallel-arm trial

Eligible patients

- Histologically confirmed cHL with R/R disease
- Disease progression following either auto-SCT or **allo-SCT**, or SCT-ineligible

R
1:1:1:1:1

Lead-in phase
Target enrollment:
n=6/cohort

Avelumab

Cohort	Dose (IV)	Schedule
A	70 mg	Q2W
B	350 mg	Q2W
C	500 mg	Q3W
D	500 mg	Q2W
E	10 mg/kg	Q2W

Selection criteria for dose-expansion phase

- >90% mean target occupancy after 1 treatment cycle
- ≥3 objective responses

Select endpoints

- Primary
  - Target occupancy
  - Pharmacokinetics
- Secondary
  - Safety*
  - Objective response[1]

Data cutoff date for this presentation: April 21, 2017

allo, allogeneic; **auto**, autologous; **cHL**, classical Hodgkin lymphoma; **IV**, intravenous; **NCI CTCAE**, National Cancer Institute Common Terminology Criteria for Adverse Events; **R**, randomize; **Q2W**, every 2 weeks; **Q3W**, every 3 weeks; **SCT**, stem cell transplant.
* Per NCI CTCAE v4.03.

1. Cheson BD, et al. J Clin Oncol. 2007;25(5):579-86.

Baseline patient and disease characteristics

- 31 patients were randomized in the lead-in phase

Characteristic	N=31
Age, n (%)	
<65 years	24 (77.4)
≥65 years	7 (22.6)
Median (range), years	38.0 (22.0-81.0)
Sex, n (%)	
Male	25 (80.6)
Female	6 (19.4)
Number of prior anticancer therapy regimens	
1	1 (3.2)
2	3 (9.7)
3	7 (22.6)
≥4	20 (64.5)
Prior treatment with brentuximab vedotin	31 (100.0)
SCT status, n (%)	
Post-auto	5 (16.1)
Post-allo	8 (25.8)
Ineligible	18 (58.1)

Patient disposition

- Avelumab treatment was ongoing in 9 patients (29.0%) at the time of analysis
- Median follow-up in all patients was 43.3 weeks (range 20.6-57.6)

Treatment status	N=31 n (%)
Treatment ongoing	9 (29.0)
Treatment discontinued	22 (71.0)
Reason for discontinuation	
Progressive disease	10 (32.3)
Adverse event	4 (12.9)
Withdrawal by patient	2 (6.5)
Physician decision	1 (3.2)
Randomized but did not receive treatment*	1 (3.2)
Other	4 (12.9)

* Patient no longer met eligibility criteria.

Exposure to avelumab

- Median treatment duration was 16.9 weeks

Treatment exposure	N=30
Duration of treatment, weeks*	
Mean (SD)	19.0 (13.3)
Median (range)	16.9 (2.0-52.0)
Number of cycles†	
Mean (SD)	8.6 (6.2)
Median (range)	8.0 (1.0-26.0)

* Duration of treatment was defined as (weeks) = (last dose date – first dose date + 14)/7 for Q2W schedule or (last dose date – first dose date + 21)/7 for Q3W schedule.

† 1 cycle = 14 days; includes cycles with missed doses of avelumab.

Best overall response

- ORR was 41.9%, including CR in 16.1% and PR in 25.8%
- Median time to response was 1.5 months (range 1.4-6.2)

BOR n (%)	Overall population N=31
CR	5 (16.1)
PR	8 (25.8)
SD	9 (29.0)
PD	5 (16.1)
NE*	4 (12.9)
ORR, %	41.9
DCR, %	71.0

BOR, best overall response; **CR**, complete response; **DCR**, disease control rate; **NE**, not evaluable; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease.
* Patients had no post-baseline assessments for reasons other than death.

Best overall response

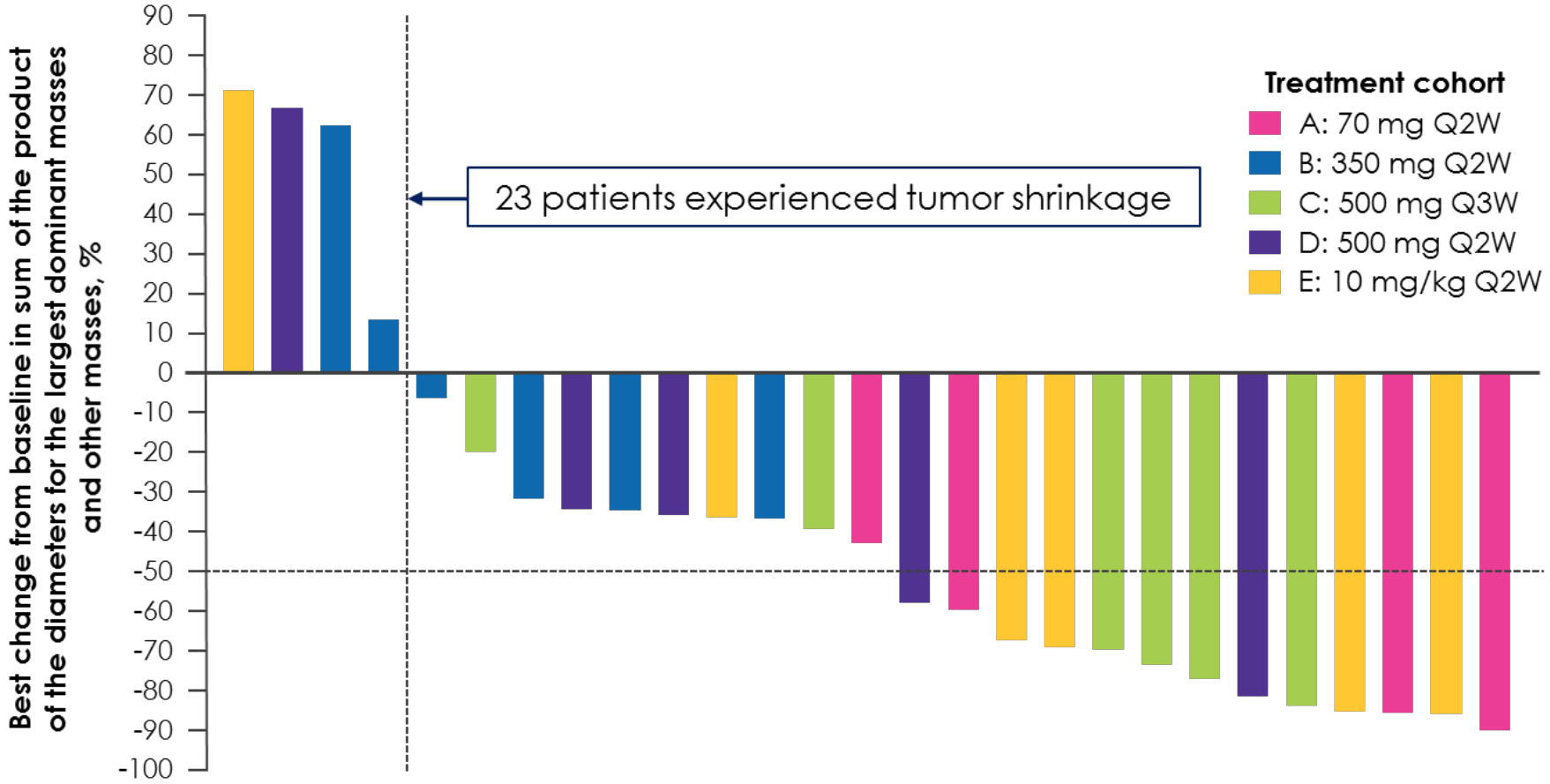
- ORRs in dose cohorts ranged from 0% to 83.3%

BOR n (%)	Avelumab				
	A 70 mg Q2W n=6	B 350 mg Q2W n=7	C 500 mg Q3W n=6	D 500 mg Q2W n=6	E 10 mg/kg Q2W n=6
CR	3 (50.0)	0	2 (33.3)	0	0
PR	0	0	3 (50.0)	2 (33.3)	3 (50.0)
SD	0	5 (71.4)	1 (16.7)	2 (33.3)	1 (16.7)
PD	1 (16.7)	1 (14.3)	0	1 (16.7)	2 (33.3)
NE*	2 (33.3)	1 (14.3)	0	1 (16.7)	0
ORR, %	50.0	0	83.3	33.3	50.0
DCR, %	50.0	71.4	100	66.7	66.7

* Patients had no post-baseline assessments for reasons other than death.

Best percent change in tumor burden from baseline (n=27*)

- 13 patients experienced tumor shrinkage of ≥50%
- 3 patients experienced tumor growth of ≥50%



* Only patients with baseline and ≥1 post-baseline largest dominant mass or other mass based on investigator assessment per Response Criteria for Malignant Lymphoma are included.

Best overall response in patients whose disease progressed following SCT

- ORR in patients with cHL progressed following either auto-SCT or allo-SCT was 20.0% and 62.5%, respectively

BOR n (%)	Post-auto SCT n=5	Post-allo SCT n=8
CR	0	2 (25.0)
PR	1 (20.0)	3 (37.5)
SD	2 (40.0)	2 (25.0)
PD	0	0
NE*	2 (40.0)	1 (12.5)
ORR, %	20.0	62.5
DCR, %	60.0	87.5

* Patients had no post-baseline assessments for reasons other than death.

Treatment-related adverse events

- Grade 3/4 TRAEs occurred in 36.7% of patients; there were no treatment-related deaths
  - 2 patients with prior allo-SCT and prior GVHD developed grade 3 liver acute GVHD, which resolved completely following immunosuppressive therapy and discontinuation of avelumab
  - Incidence of TRAEs across the 5 dose cohorts was similar

TRAEs in >10% of patients and any grade 4 events N=30	n (%)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Patients with events	24 (80.0)	4 (13.3)	9 (30.0)	6 (20.0)	5 (16.7)
Infusion-related reaction*	9 (30.0)	1 (3.3)	6 (20.0)	2 (6.7)	0
Nausea	6 (20.0)	5 (16.7)	0	1 (3.3)	0
Rash	5 (16.7)	4 (13.3)	1 (3.3)	0	0
ALT increased	4 (13.3)	2 (6.7)	0	2 (6.7)	0
Fatigue	4 (13.3)	4 (13.3)	0	0	0
Lipase increased	3 (10.0)	0	1 (3.3)	0	2 (6.7)
GGT increased	2 (6.7)	1(3.3)	0	0	1 (3.3)
Immune thrombocytopenic purpura	1 (3.3)	0	0	0	1 (3.3)
Thrombocytopenia	1 (3.3)	0	0	0	1 (3.3)

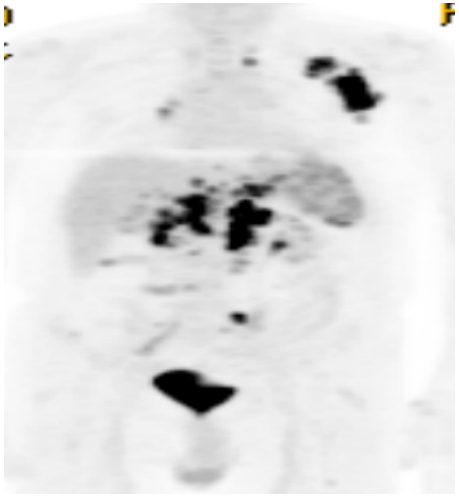
ALT, alanine aminotransferase; **GGT**, gamma-glutamyltransferase; **GVHD**, graft vs host disease; **TRAE**, treatment-related adverse event.
* Infusion-related reaction is a composite preferred term that includes infusion-related reaction, back pain, chills, and pyrexia.

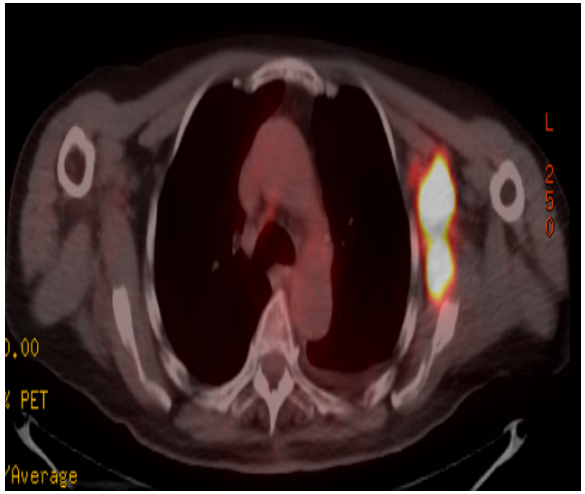
Patient Case 1

- 81 yo male initially presented with stage IV HL
- BV only clinical trial → CR → PD
- AVD x 4 → CR 2014, PD in 2016
- Enrolled onto avelumab clinical trial

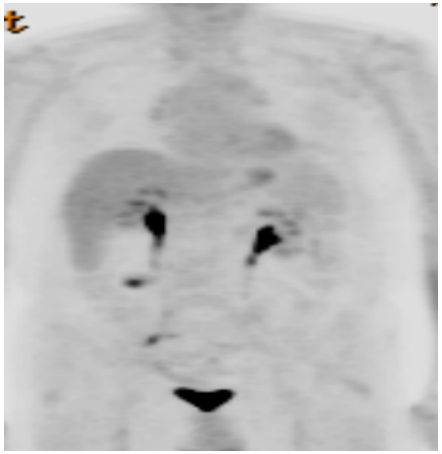
CT/PET Response

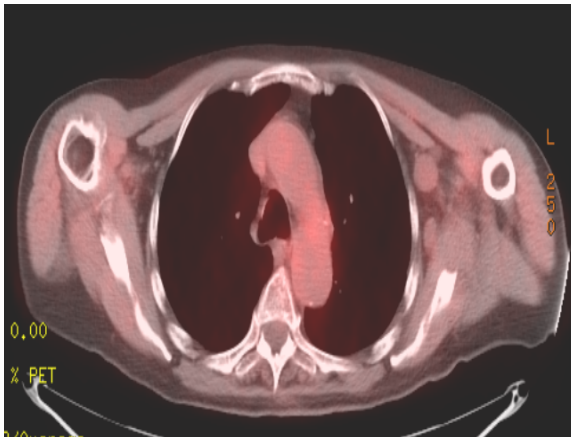
- Baseline





- Post 4 cycles

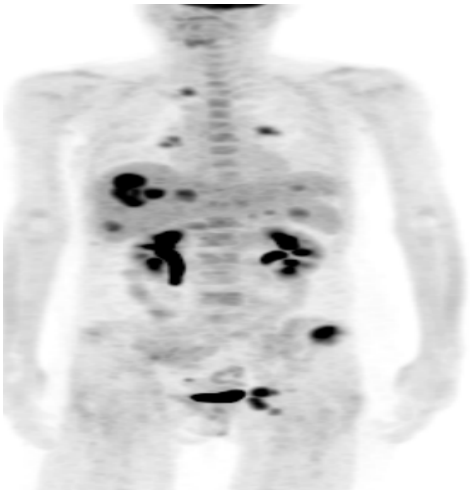


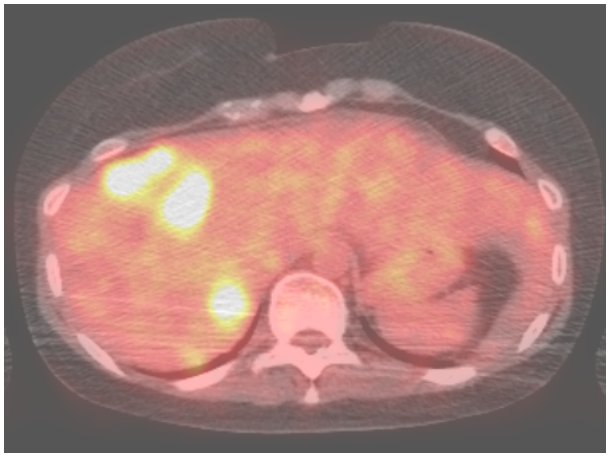


Patient Case 2

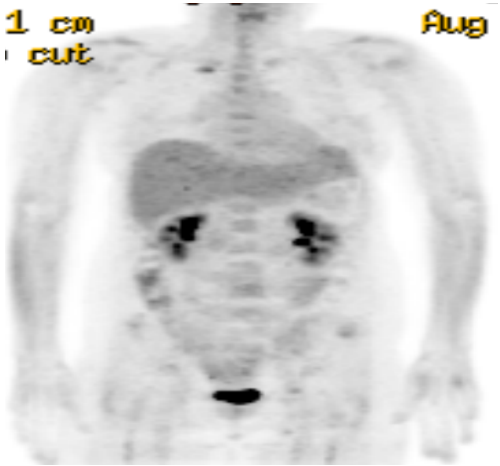
- 33 yo female initially presented with stage IIIB disease
- ABVD → CR → PD
- ICE plus ASCT → CR → PD
- BV → PR → AlloHCT → CR → PD
- BV → PR → PD
- BV + Bendamustine → PR → DLI → PR → PD
- Enrolled on avelumab clinical trial

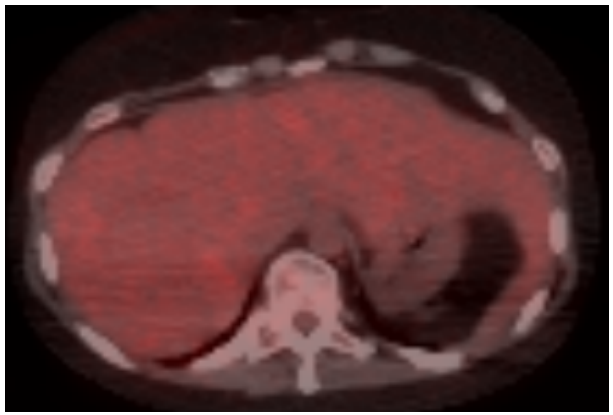
- Baseline





- Post 4 Cycles





Conclusions

- Avelumab (anti–PD-L1) has clinical activity with an acceptable safety and tolerability profile in patients with heavily pretreated cHL
  - PD-L1 blockade is sufficient to produce clinical responses in cHL
- With a sample size of 31 patients, the ORR with avelumab was 41.9%, with CR in 16.1%
  - PD-L2 blockade may not be necessary for the therapeutic effect observed with PD-1 inhibitors in some patients
- The ORR observed in the post-allo SCT setting (62.5%) suggests that PD-L1 blockade may potentiate the graft vs. lymphoma response
  - Grade 3 liver acute GVHD was observed in 2 post-allo SCT patients with prior GVHD, but immunosuppressive therapy resulted in complete resolution
- Based on the observed efficacy and safety profiles and unmet need, the study has recently been amended to focus the expansion on patients who progressed post-allo SCT

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