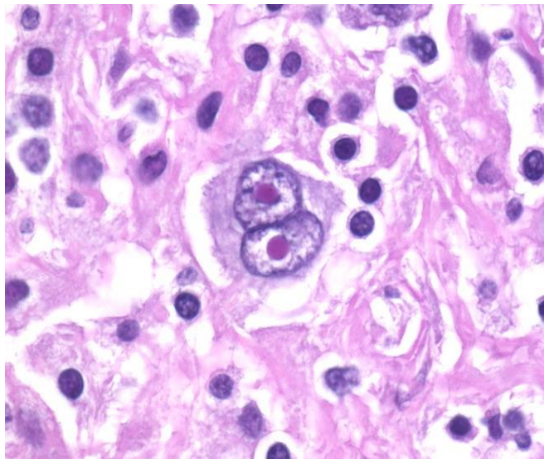
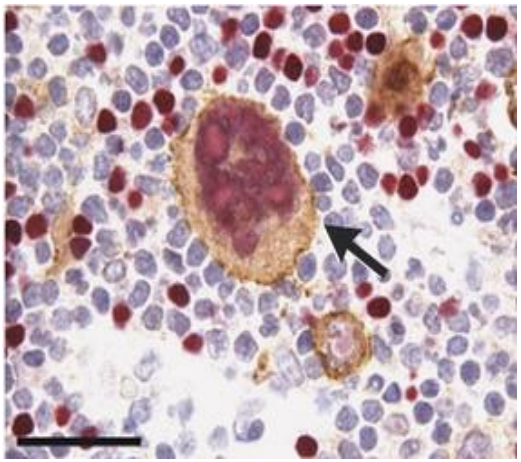
“New Drugs in Hematology” Bologna, May 9 - 11, 2016

Pembrolizumab: Hodgkin’s and Beyond





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Abramson Cancer Center

Relevant Disclosures

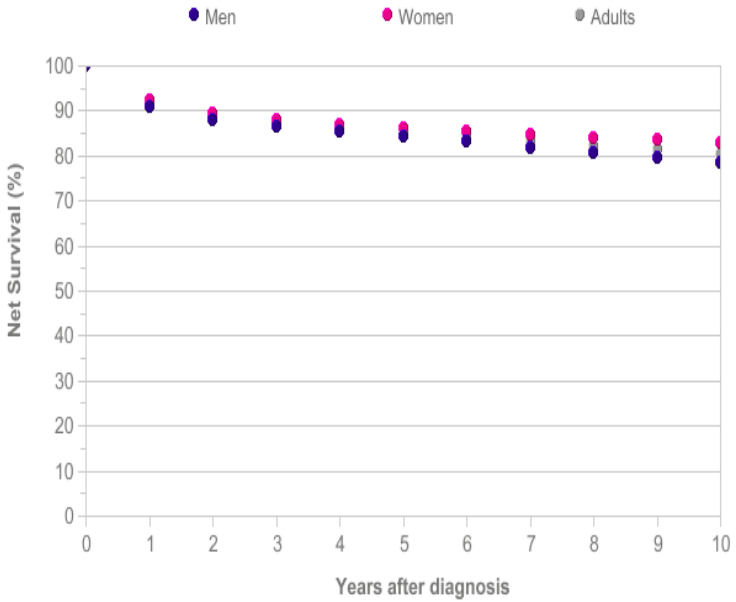
- Research support from Novartis
- Research support from Merck

Hodgkin Lymphoma: Unmet Need

Treatment outcomes for advanced cHL[2]

ABVD +/- XRT:	**73% long term remissions**
	27% relapse / fail therapy
HD chemo + ASCT:	**33% salvaged**
	82% long term remissions
unmet need	**≈ 18% of patients with HL**

Net Survival up to Ten Years after Diagnosis, Adults (Aged 15-99), England and Wales: 2010-2011[1]

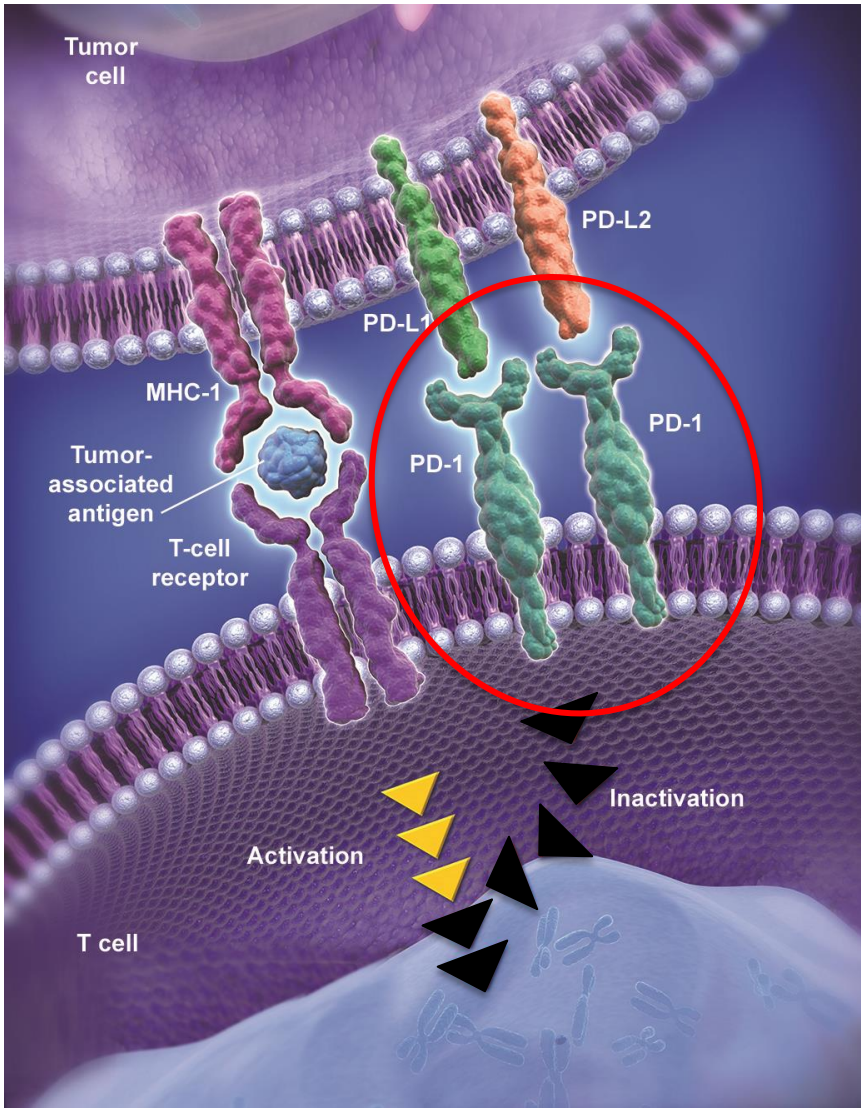


CANCER RESEARCH UK

[1]Survival estimates by the Cancer Research UK Cancer Survival; http://www.lshtm.ac.uk/eph/ncde/cancersurvival/
[2]N Engl J Med 2011;365:203-12.

The PD-1 and PD-L1/L2 Pathway

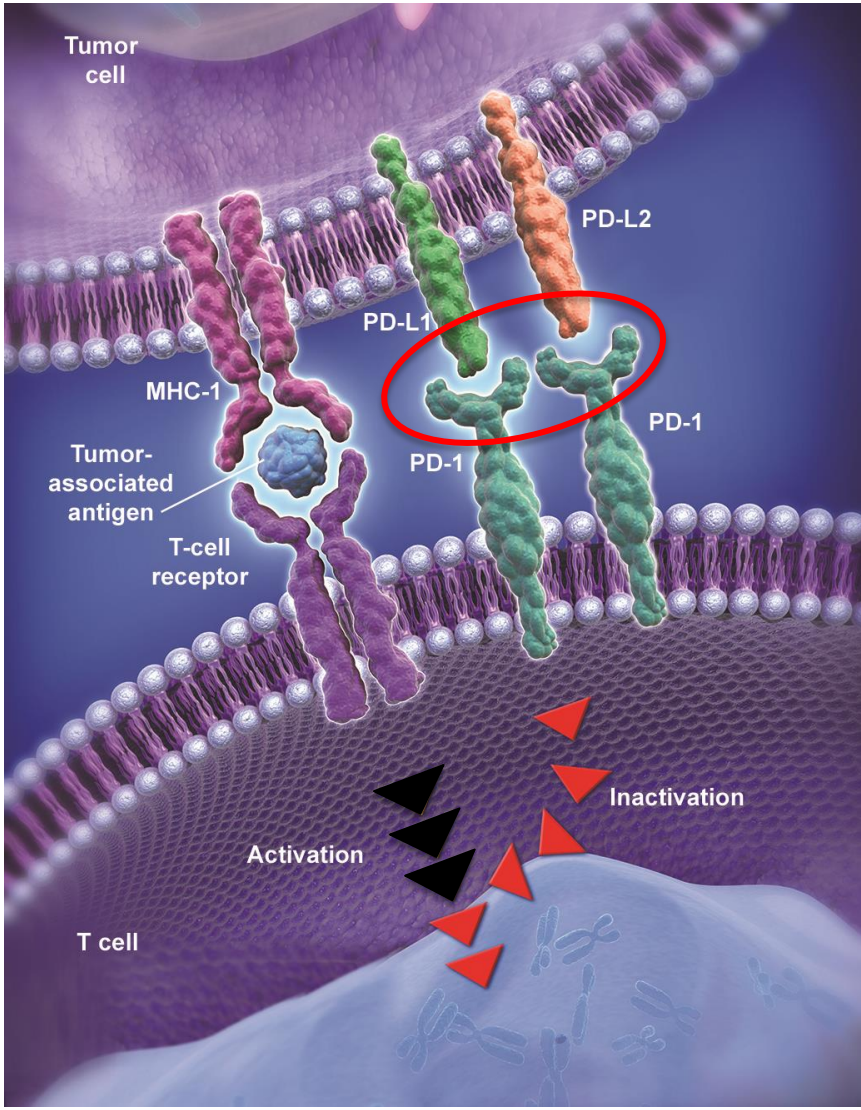
- **PD-1 is an immune checkpoint receptor**



Keir ME et al. *Annu Rev Immunol*. 2008.
Pardoll DM. *Nat Rev Cancer*. 2012.

The PD-1 and PD-L1/L2 Pathway

- PD-1 is an immune checkpoint receptor
- **Binding of PD-1 by its ligands PD-L1 or PD-L2 leads to downregulation of T-cell function**
- **This mechanism is usurped by many tumors**



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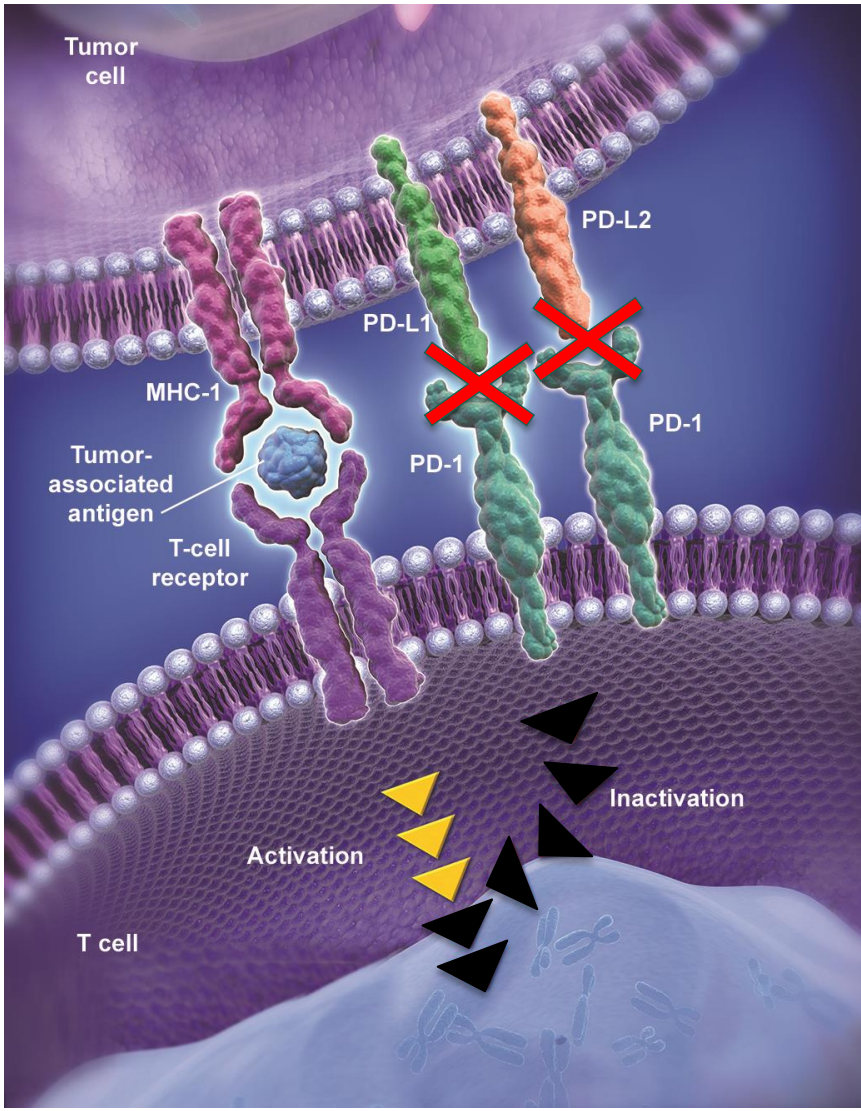
The PD-1 and PD-L1/L2 Pathway

- PD-1 is an immune checkpoint receptor
- Binding of PD-1 by its ligands PD-L1 or PD-L2 leads to downregulation of T-cell function
- This mechanism is usurped by many tumors
- **PD-1 blockade through mAb therapy can restore effective anti-tumor immunity**
- **Pembrolizumab is a humanized anti-PD1 mAb with activity in several solid tumors**



Topalian et al. *N Engl J Med*. 2012.
Garon et al. *N Engl J Med*. 2015.
Robert et al. *Lancet.* 2014.

PD-1 and Hodgkin Lymphoma

- Classical HL (cHL) is characterized pathologically by a failed immune response
- HL frequently harbors amplification at 9p24.1 leading to overexpression of PD-L1 and PD-L2
- HL may have a genetically driven vulnerability to PD-1 blockade

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- cHL independent expansion cohort in KEYNOTE-013, a phase 1 study of pembrolizumab in hematologic malignancies

Green MR et al. *Blood*. 2010.
Green MR et al. *Clin Cancer Res*. 2012.

PD-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure: Safety, Efficacy, and Biomarker Assessment

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Hackensack University Medical Center, Hackensack, NJ, USA

Merck & Co, Inc, Kenilworth, NJ, USA

Memorial Sloan Kettering Cancer Center, New York, NY, USA

KEYNOTE-013 Study

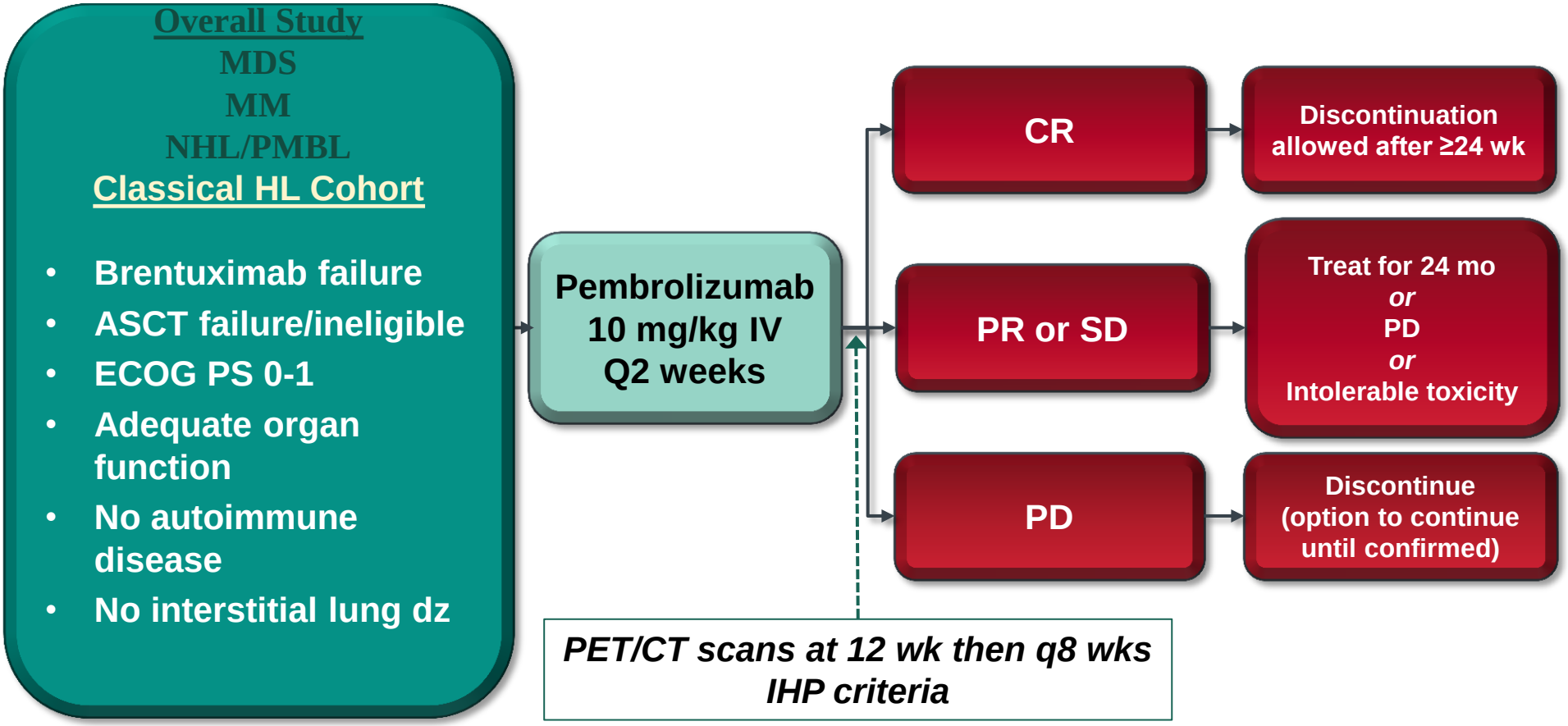
Overall Study
MDS
MM
NHL/PMBL
Classical HL Cohort

Data cutoff date: October 27, 2015

Armand *et al* December 7, 2015

KEYNOTE-013 Study

Armand *et al* December 7, 2015



Primary endpoints: Safety, CR rate

Secondary endpoints: OR, DOR, PFS, OS, biomarkers

Patient Characteristics

Overall Study
MDS
MM
NHL/PMBL
Classical HL Cohort

31 patients

Characteristic (N = 31)	n (%)
Age, median (range)	32 (20-67)
Nodular sclerosis Mixed cellularity	30 (97) 1 (3)
Prior radiation therapy	10 (32)
Prior systemic therapy	
2-4	14 (45)
≥5	17 (55)
Prior brentuximab failure	31 (100)
Prior ASCT failure Transplant ineligible/refused	22 (71) 9 (29)

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Safety

Treatment-Related AEs Any Grade in ≥ 3 Patients	n (%)
Any Related AE	**21 (68)**
Gastrointestinal	**11 (36)**
Diarrhea	5 (16)
Nausea	4 (13)
General	**9 (29)**
Endocrine	**6 (19)**
Hypothyroidism	5 (16)
Investigations	**6 (19)**
Metabolism and nutrition	**5 (16)**
Respiratory	**5 (16)**
Pneumonitis	3 (10)
Skin	**5 (16)**
Musculoskeletal	**3 (10)**

Armand *et al* December 7, 2015

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Pneumonitis	3 (10)
Skin	**5 (16)**
Musculoskeletal	**3 (10)**

Treatment-Related AEs Grade 3-5	n (%)
Any Grade 3 Related AE	**5 (16)**
ALT and AST increased	1 (3)
Colitis	1 (3)
Nephrotic syndrome Back pain	1 (3) 1 (3)
Joint swelling	1 (3)
Axillary pain	1 (3)

No grade 4 related AE
No fatal related AE

AEs leading to discontinuation
Grade 2 pneumonitis
Grade 3 nephrotic syndrome

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Efficacy

	Brentuximab Failure		
	Transplant Failure N = 22	**Transplant Ineligible/ Refused N = 9**	**Total N = 31**
Overall Response Rate	**16 (73%)**	**4 (44%)**	**20 (65%)**
Complete Remission	3 (14%)	2 (22%)	5 (16%)
Partial Remission	13 (59%)	2 (22%)	15 (48%)
Stable Disease	4 (18%)	3 (33%)	7 (23%)
Progressive Disease	2 (9%)	2 (22%)	4 (13%)

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Efficacy

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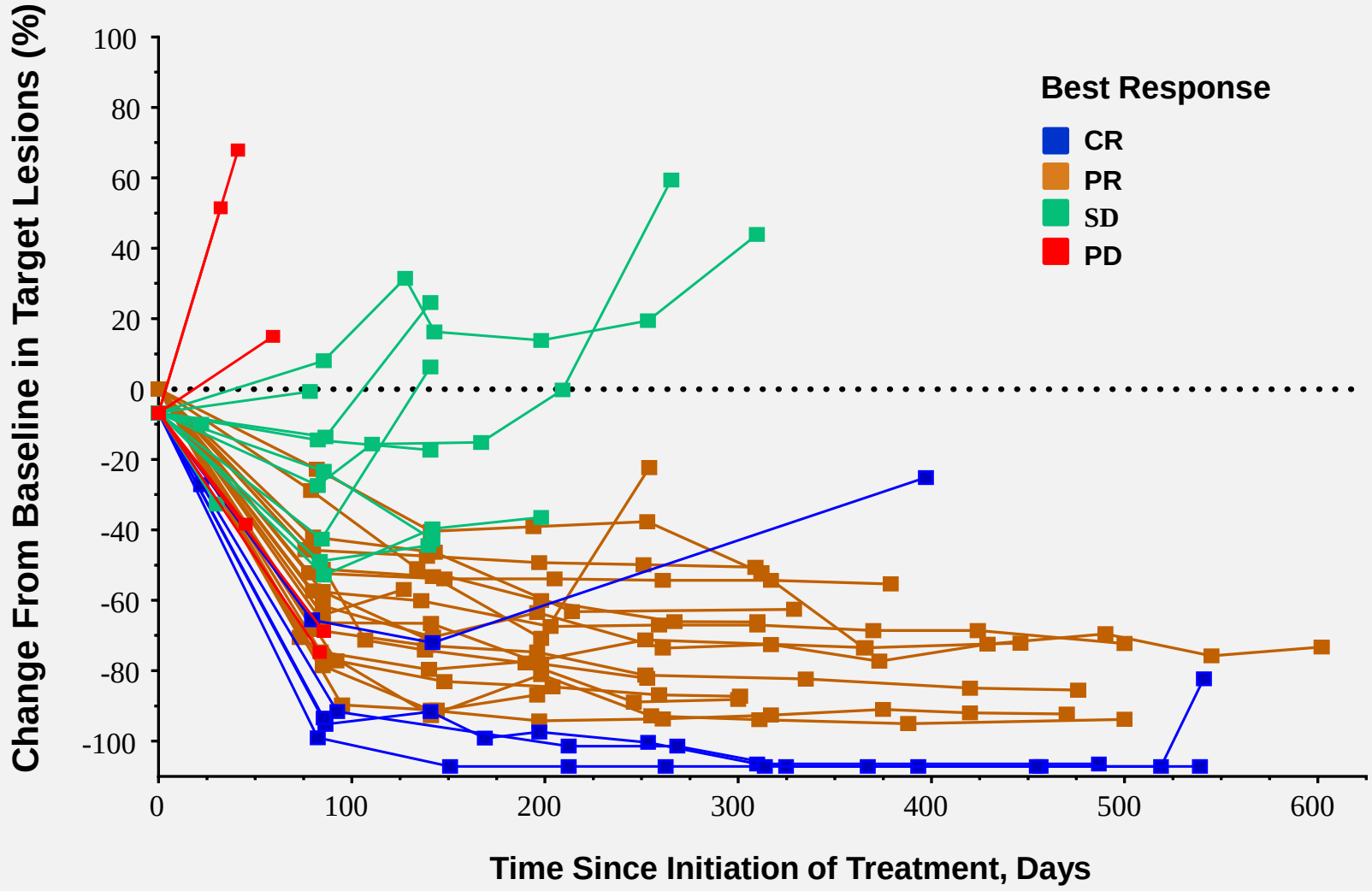
Change From Baseline in Target Lesions



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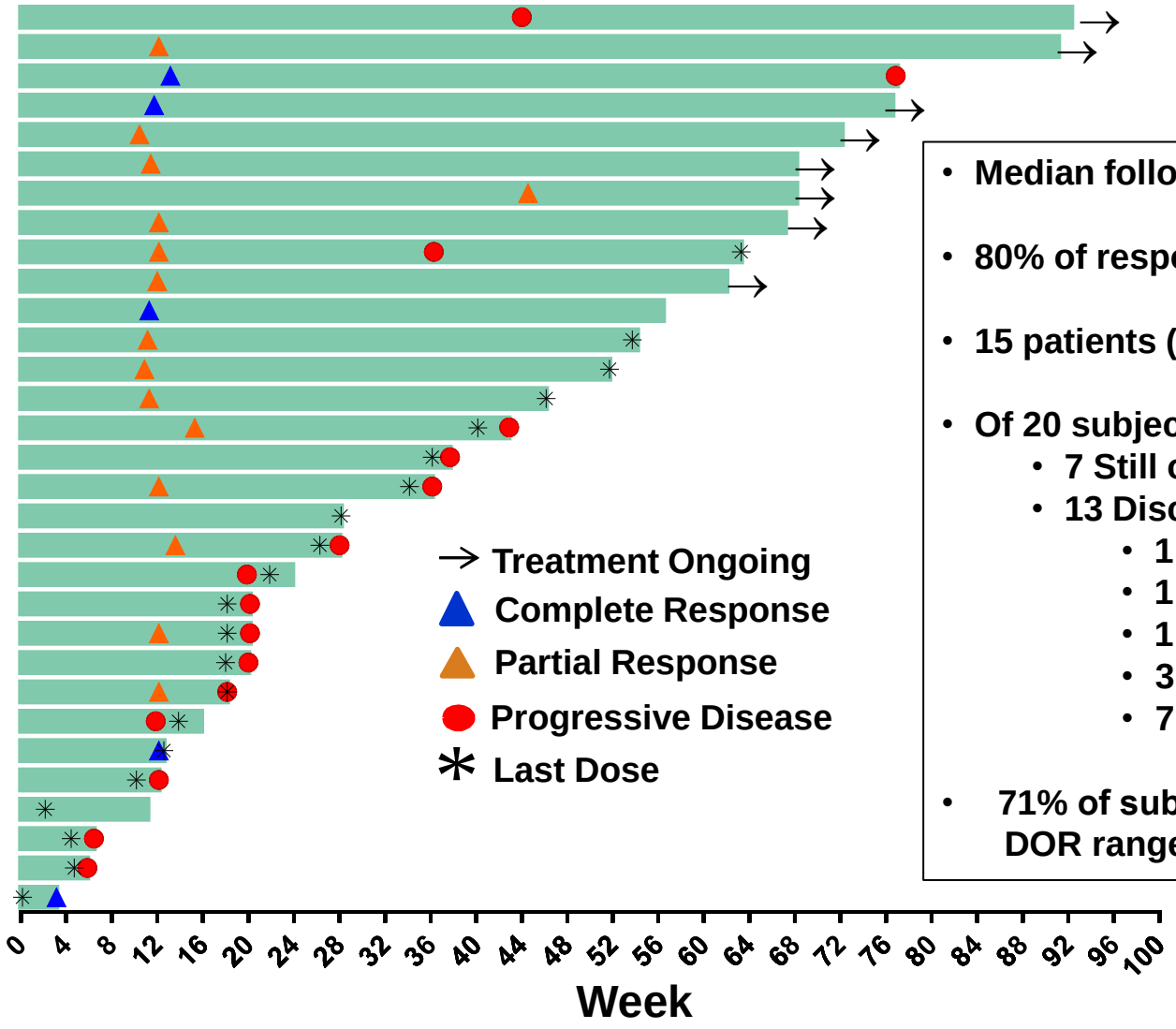
Time Since Initiation of Treatment



- Median follow-up for survivors: ~18 months
- 80% of responses occurred by 12 weeks
- 15 patients (48%) progressed
- Of 20 subjects who achieved CR or PR:
  - 7 Still on treatment
  - 13 Discontinued treatment:
    - 1 CR no longer on treatment
    - 1 PR switched treatments
    - 1 adverse event
    - 3 allogeneic transplant
    - 7 (35%) progressive disease
- 71% of subjects have a DOR ≥ 24 weeks
  DOR range 0.14+ to 74+ weeks

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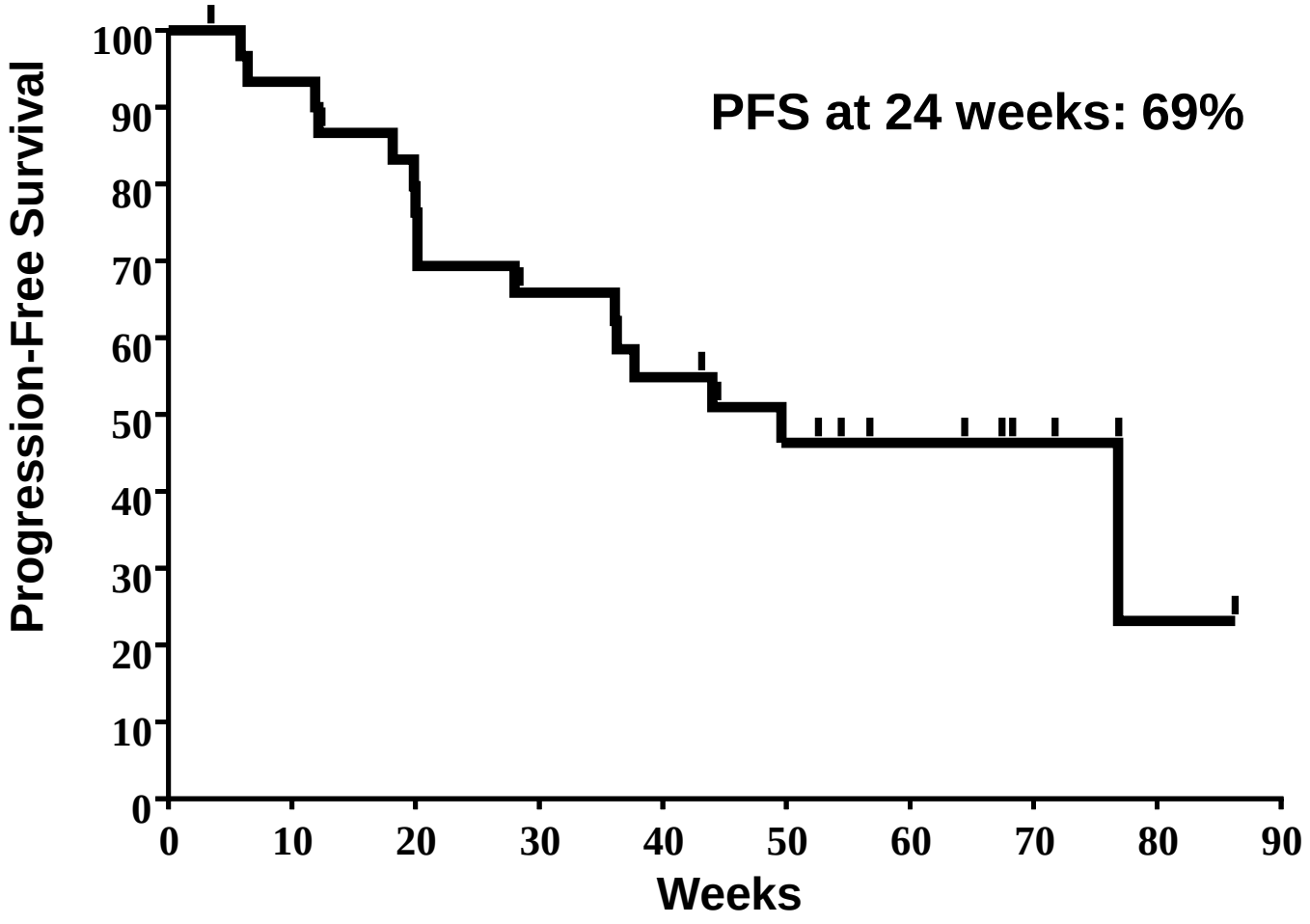
Progression-Free Survival



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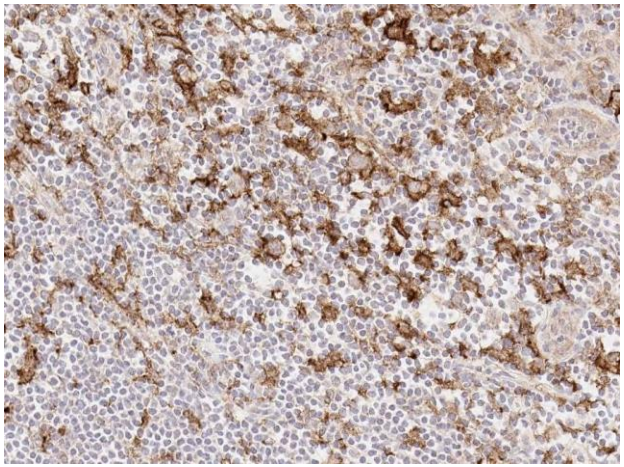
Immunohistochemistry

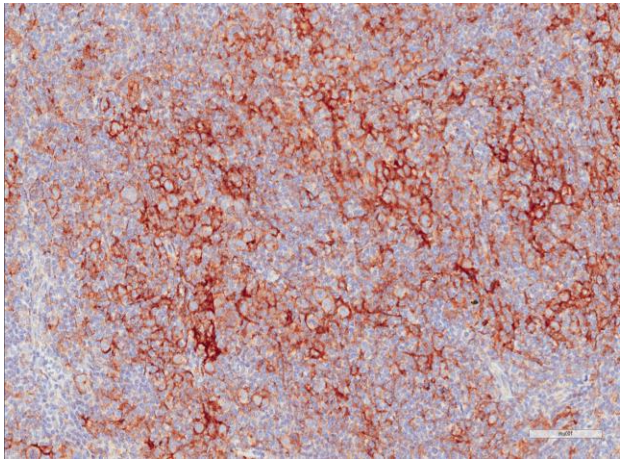
- **16 samples were evaluable at screening for PD-L1**
  - **15 (94%) were PD-L1 positive in tumor cells**

PD-L1



- **10 samples were evaluable at screening for PD-L2**
  - **9 (90%) were PD-L2 positive**

PD-L2



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Summary and Conclusions

- **Pembrolizumab is associated with an acceptable safety profile in cHL**
- **Pembrolizumab has high anti-tumor activity with durable responses in heavily pre-treated patients with brentuximab failure**
  - **ORR for entire HL cohort = 65%**
    - **ORR for transplant failure = 73%**
    - **ORR for transplant ineligible = 44%**
  - **71% of subjects have a DOR ≥ 24 weeks**
- **Exploratory analyses (flow cytometry and NanoString) suggest that pembrolizumab induces increases in T and NK cell numbers and upregulates T-cell / IFN-γ signaling pathways (data not shown)**
- **High prevalence of PD-L1/L2 positivity in HL supports notion of genetic vulnerability to PD-1 blockade**

- **Supports further development of pembrolizumab in cHL**

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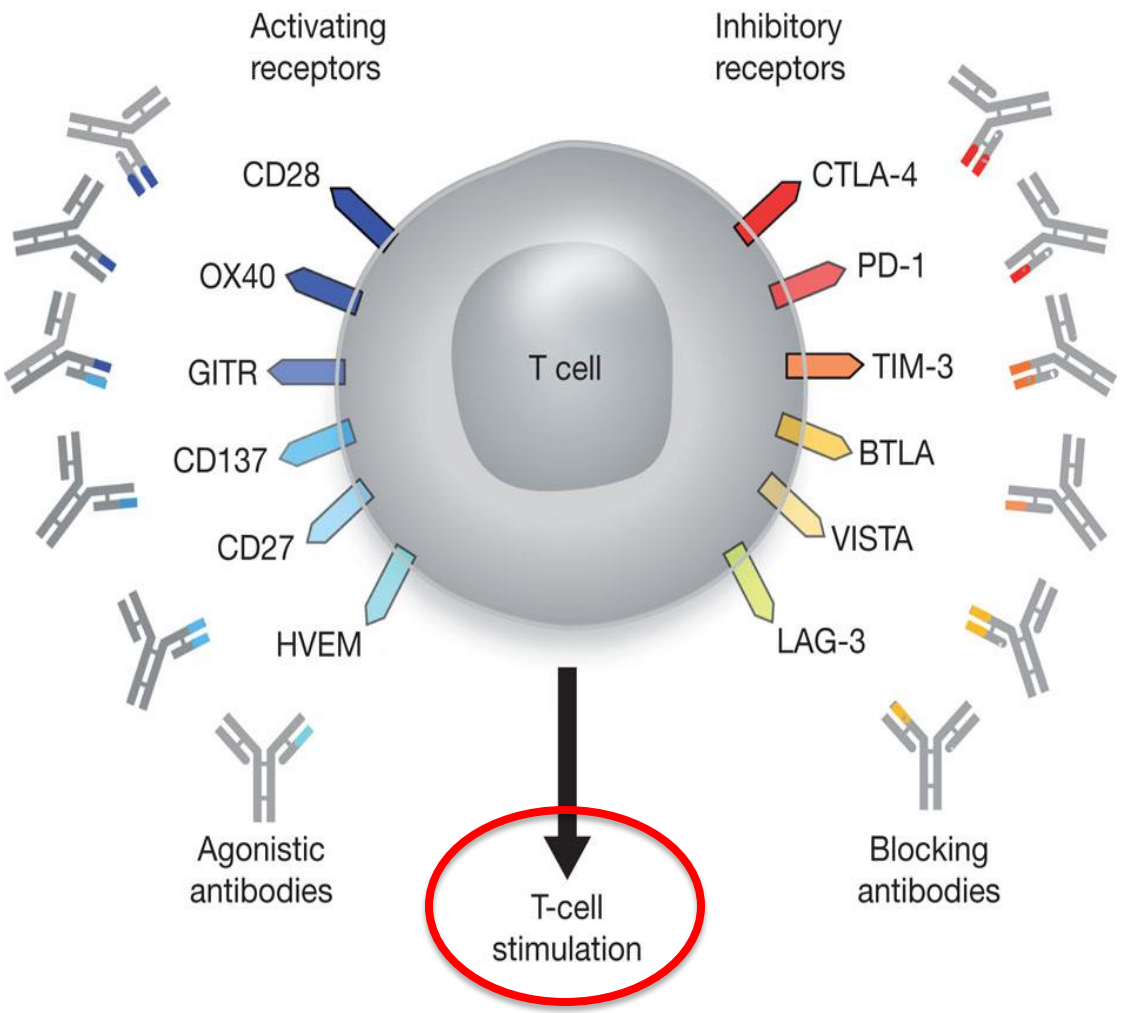
PD-1 Blockade + CAR T Cells ?



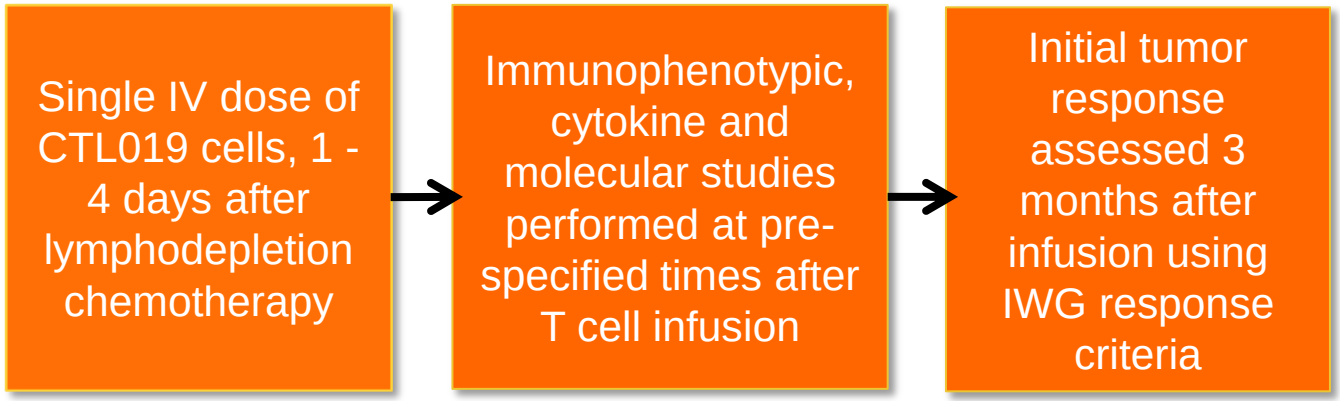
[1] Mellman *et al. Nature* 480, 480-489 (2011) doi:10.1038/nature10673

CTL019 T Cells in Relapsed or Refractory CD19+ NHL: Study Design

Enrollment started Feb 2014

Key eligibility criteria

- Adult histologically proven CD19+ relapsed or refractory DLBCL and FL
- r/r DLBCL after ASCT or ineligible for ASCT; transformation from CLL/SLL or FL allowed
- r/r FL with ≥2 prior CIT regimens and PD <2 years after prior therapy
- Measurable disease
- ECOG PS 0 or 1



Primary Objectives: ORR at 3 months; determine response rate by lymphoma histology

Secondary endpoints: Determine CTL019 cell manufacturing feasibility; safety; best response; PFS; in vivo expansion of CTL019 cells; effects on B cells and CD19 expression in vivo

Schuster et al. ASH 2015. Abstract 183.
- NCT02030834

Response Rates: Diffuse Large B Cell Lymphoma

DLBCL: ORR at 3 months 47% (N = 15)	DLBCL: Best Response Rate 47% (N = 15)
- CR: 3 - PR: 4 - PD: 8	- CR: 6 - PR: 1 - PD: 8

- 3 patients with PRs by CT criteria at 3 months converted to CRs by 6 months
- 1 patient with PR at 3 months had PD at 6 months
- Response duration is 86% at median follow-up 17 months (n = 7)

Response Rates: Follicular Lymphoma

FL: ORR at 3 Months 77% (N = 13)	FL: Best Response Rate 77% (N = 13)
- CR: 6 - PR: 4 - PD: 3	- CR: 9 - PR: 1 - PD: 3

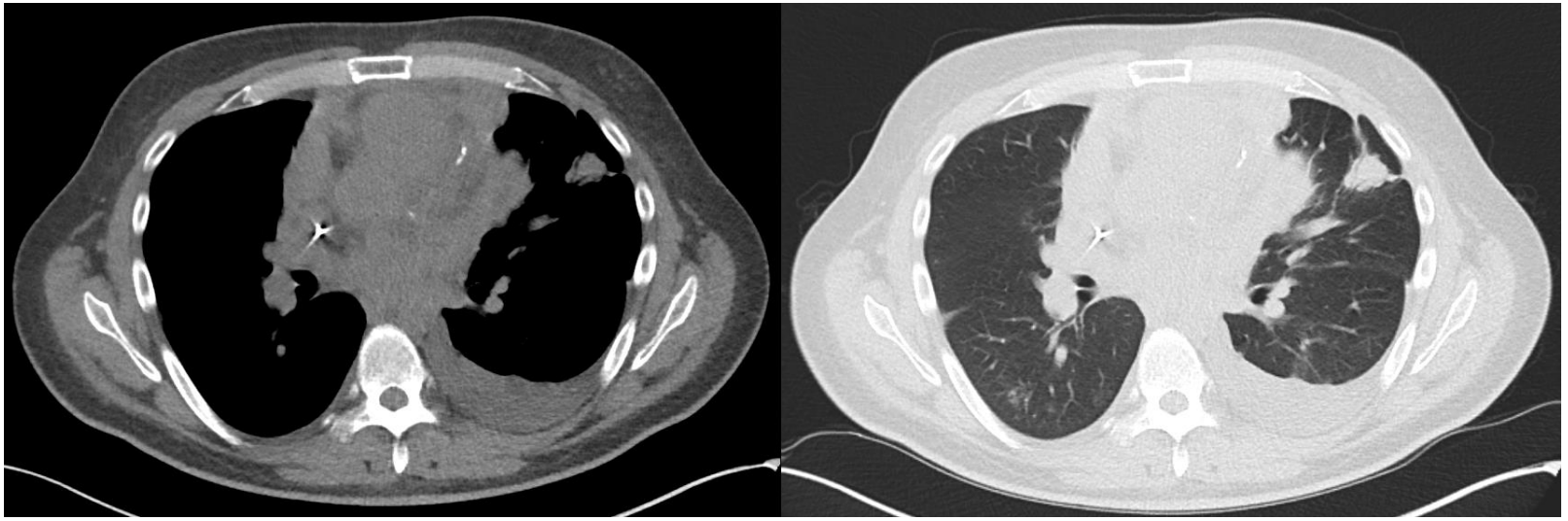
- 3 patients with PRs by CT/MR criteria at 3 months converted to CRs by 6 months
- 1 patient with PR at 3 months who remained in PR at 6 and 9 months had PD at approximately 12 months
- Response duration is 83% at median follow-up 17 months (n = 10)

13413-39: DLBCL

- 35 year old man with primary refractory DLBCL
  - pulmonary nodules, bulky mediastinal mass, pericardial and mesenteric involvement
- Past therapies included:
  - DA-REPOCH (PR)
  - R-ICE x2 (PR) + BCV-ASCT followed by consolidative mediastinal radiation therapy
  - brentuximab vedotin + bendamustine
- Lymphodepleting chemotherapy: 10/7/15 - 10/10/15
  - cyclophosphamide 300 mg/m2 IV q 12 hrs x 6 doses
- CTL019 infusion: 10/16/15

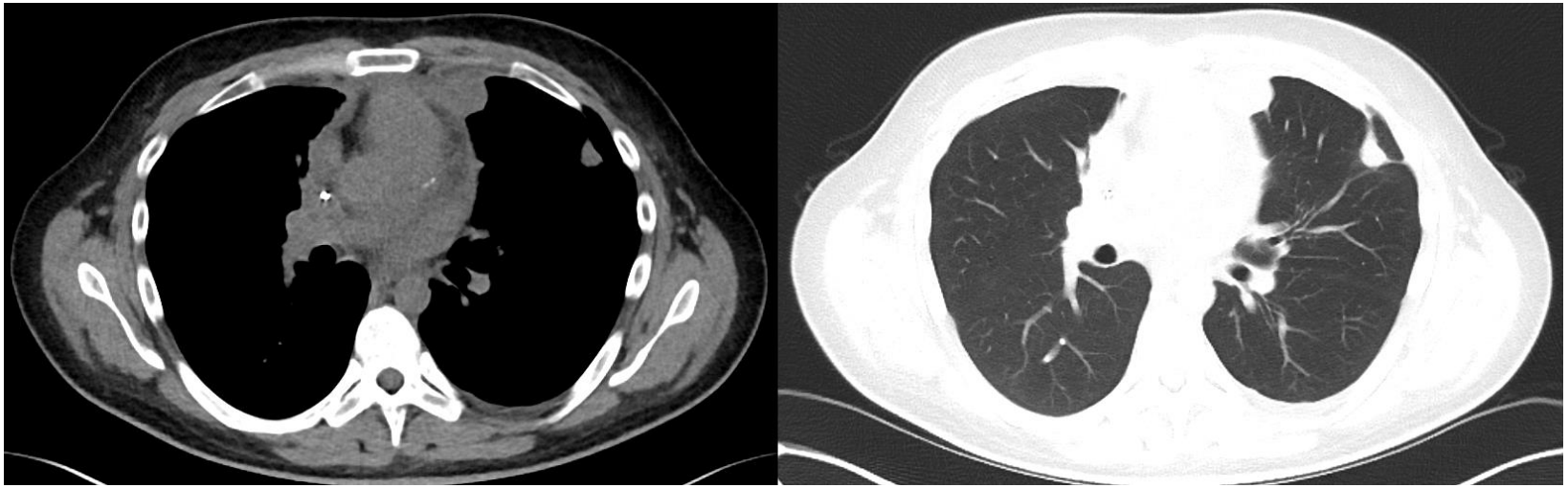
13413-39: DLBCL

November 11, 2015: Day +25 CTL019



→ **Nov.11: Pembrolizumab**

November 30, 2015

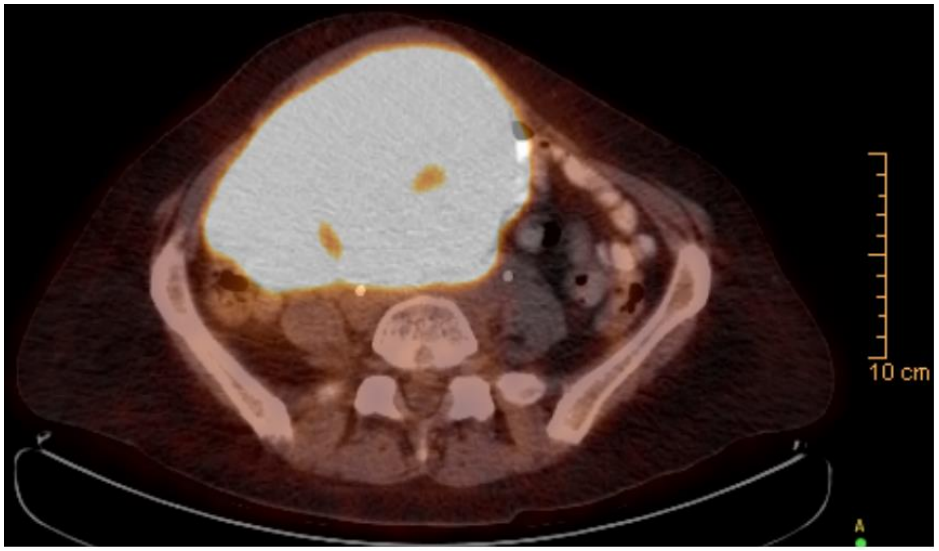


13413-34: FL

- 34 year old woman with FL, grade 2
- Past therapies included:
  - rituximab - CVP + maintenance rituximab
  - rituximab - chlorambucil - prednisone
  - Zevalin
  - R-CHOP
  - cyclophosphamide - etoposide
  - R-EPOCH
  - allogeneic bone marrow transplant
  - lenalidomide - rituximab
  - Ibrutinib
  - carboplatin - gemcitabine
- Lymphodepleting chemotherapy: 7/20/15
  - carboplatin - gemcitabine
- CTL019 infusion: 7/29/15

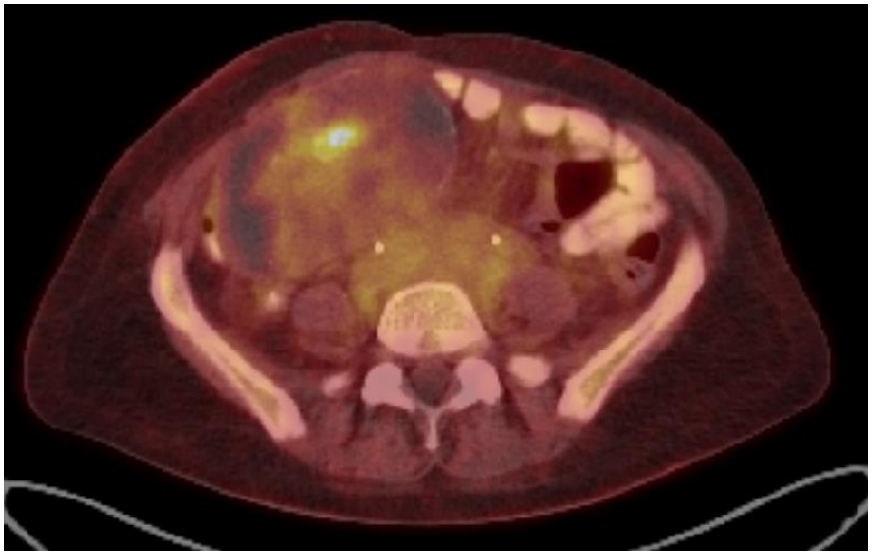
13413-34: FL Transformed to “Double Hit” DLBCL

October 15, 2015: Day +78 CTL019

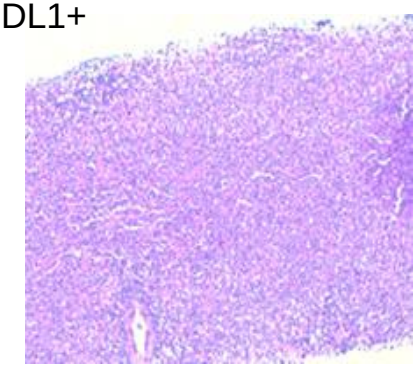


→ Nov. 2 & 3: radiation therapy (1400 cGy)
→ Nov. 19 & Dec. 9: nivolumab

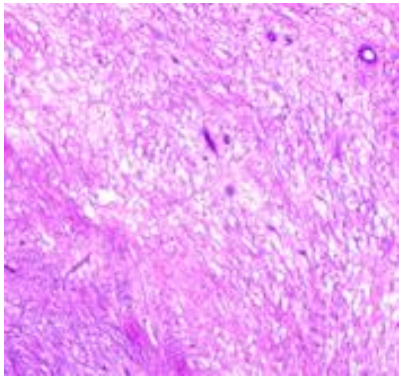
December 30, 2015



Biopsy: October 23, 2015
- Flow: kappa LC, CD10+, CD19+
- IHC: large PAX5+ B cells; PDL1+
- FISH: c-MYC and BCL-2 rearranged



Biopsy: March 6, 2016
- Extensive necrosis
- No tumor seen



CAR T Cells and PD-1 Blockade: Studies in Progress

- Phase I/II study of pembrolizumab in patients failing to respond to or relapsing after anti-CD19 chimeric antigen receptor modified T cell therapy for relapsed or refractory CD19+ lymphomas
  - NCT02650999
- Test combination PDR001, a humanized antibody directed against PD-1 that blocks the binding of PD-L1 and PD-L2, with CTL019 in 7 DLBCL patients
  - NCT02030834 (*PDR001 cohort pending*)
- Correlative studies planned:
  - Study modulation of tumor immunophenotype and microenvironment and their effects on CAR T cells in patients failing CTL019, as well as effects of PD-1 blockade on CAR T cells, tumor and microenvironment
  - Determine CD19 expression by tumors in patients failing CTL019

Questions