

New Agents Beyond Brentuximab vedotin for Hodgkin Lymphoma

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Disclosures for Stephen Ansell, MD, PhD

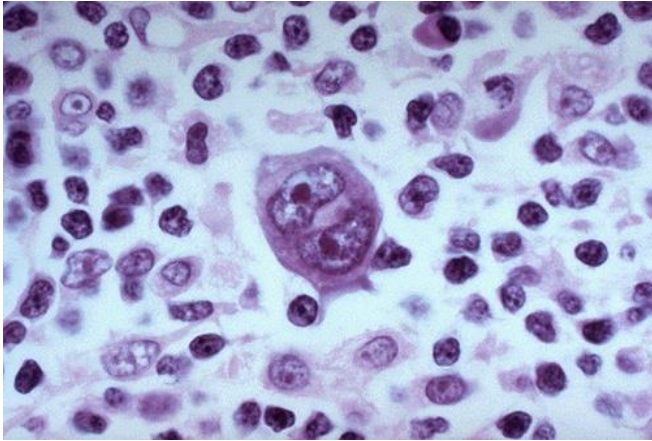
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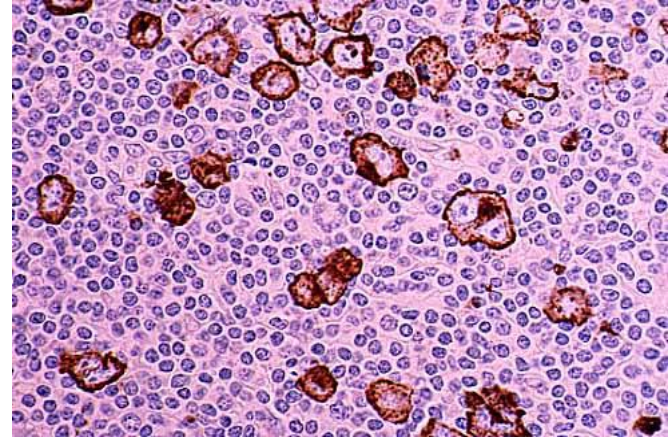
N/A = Not Applicable (no conflicts listed)

Relapsed Hodgkin lymphoma – Targets for Novel agents

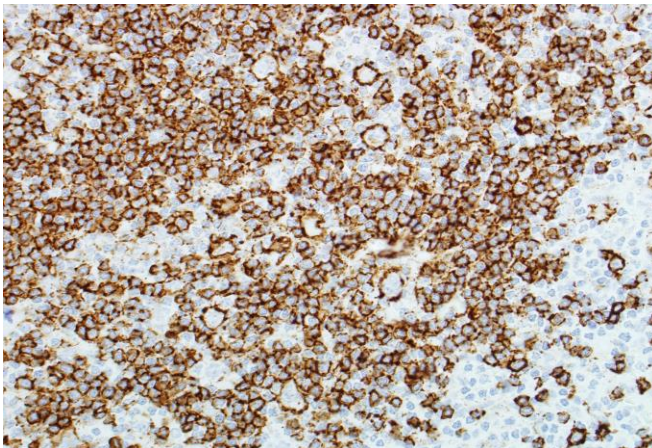
Signaling Pathways



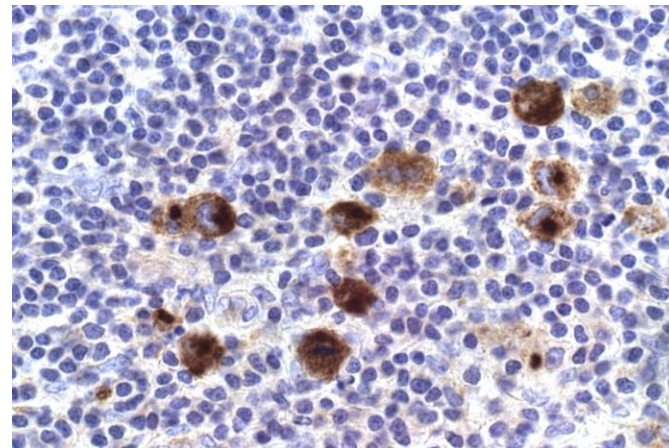
Surface Receptors



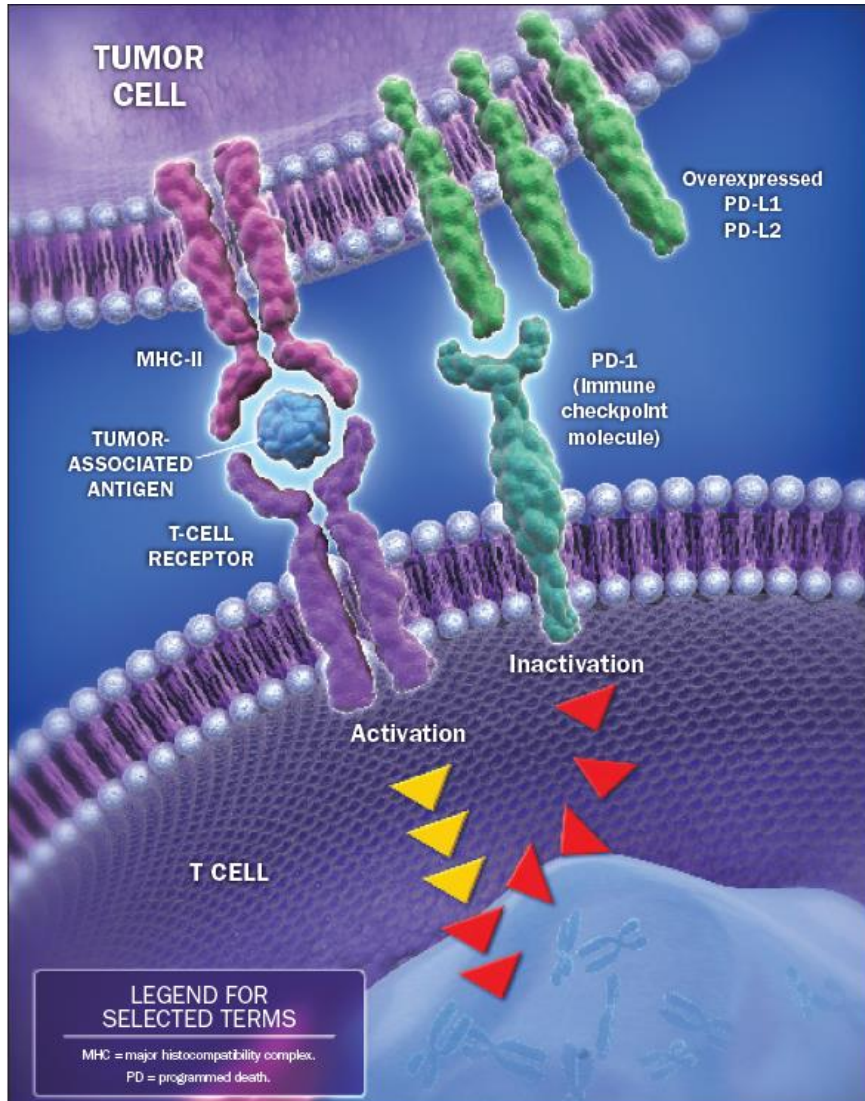
Non-malignant cells



Intratumoral Cytokines

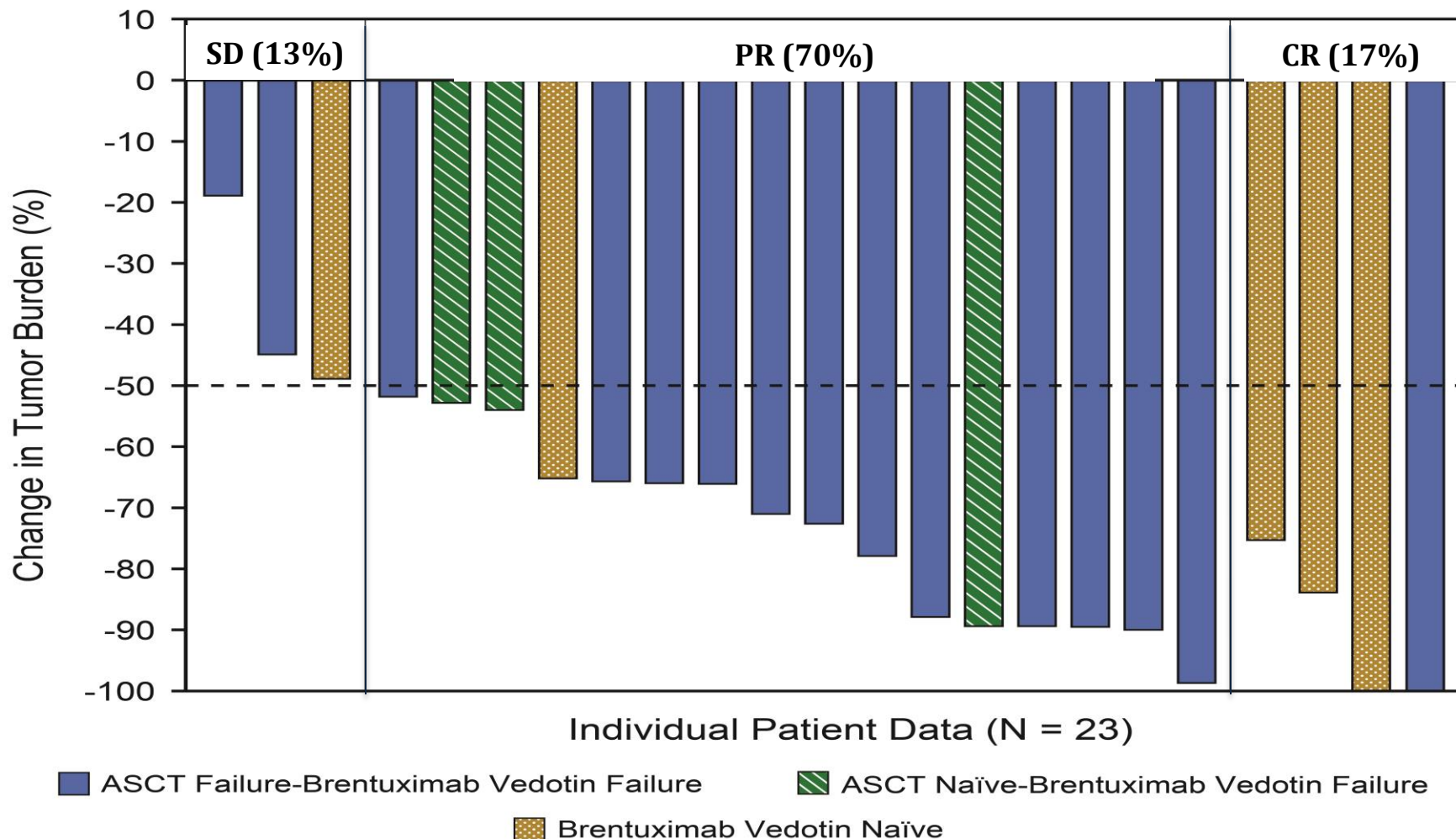


PD-1 Pathway and Immune Surveillance



- PD-1 is expressed on the surface of activated T cells
- Its ligands, PD-L1 and PD-L2, are overexpressed in certain tumor cells
- Binding of PD-1 to its ligands inhibits T-cell activation, allowing tumors to evade the immune response

Best Response to Nivolumab (n=23)

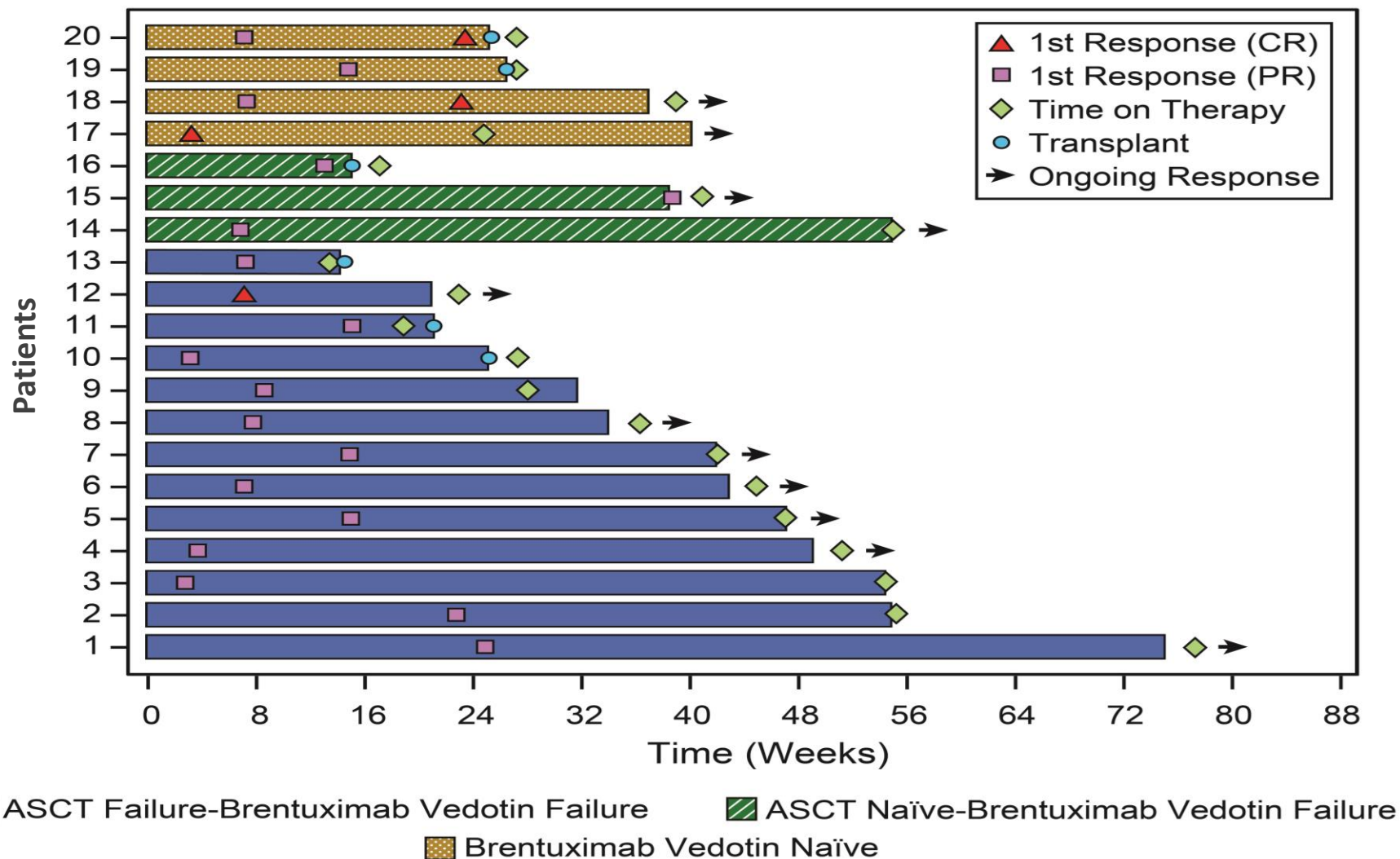


Safety of Nivolumab

	Any AE	Related AE	Grade 3 Related AE	Grade 4 Related AE	Discontinued for Related AE
Patients, n (%)	22 (96)	18 (78)	5 (22)	0 (0)	2 (9)

- No drug-related grade 4 AEs or drug-related deaths
- AEs leading to discontinuation:
 - MDS with grade 3 thrombocytopenia (*6 prior treatments including ASCT*)
 - Grade 3 pancreatitis
- Other grade 3 related AEs:
 - Lymphopenia
 - Increased lipase
 - GI inflammation
 - Pneumonitis, colitis and stomatitis (post autologous stem cell transplant)
- Safety profile similar to that in solid tumors

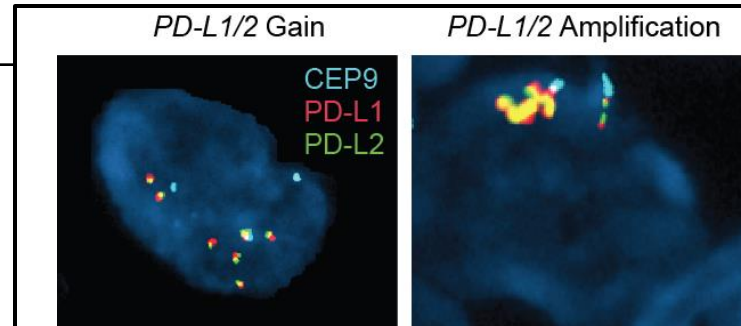
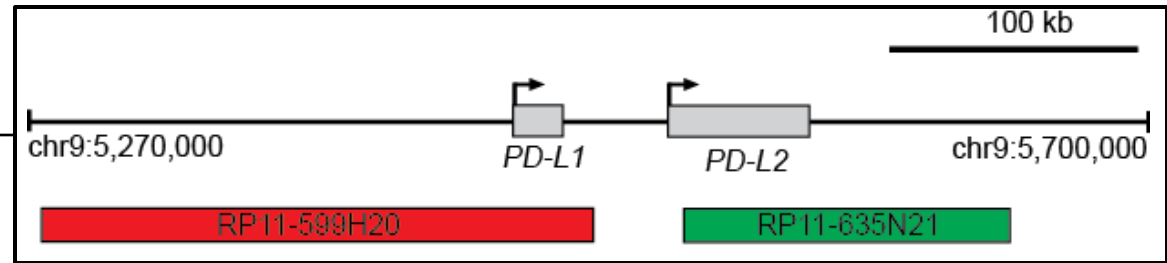
Response Duration - Nivolumab



9p24.1/*PD-L1*/*PD-L2* Locus Integrity and Protein Expression

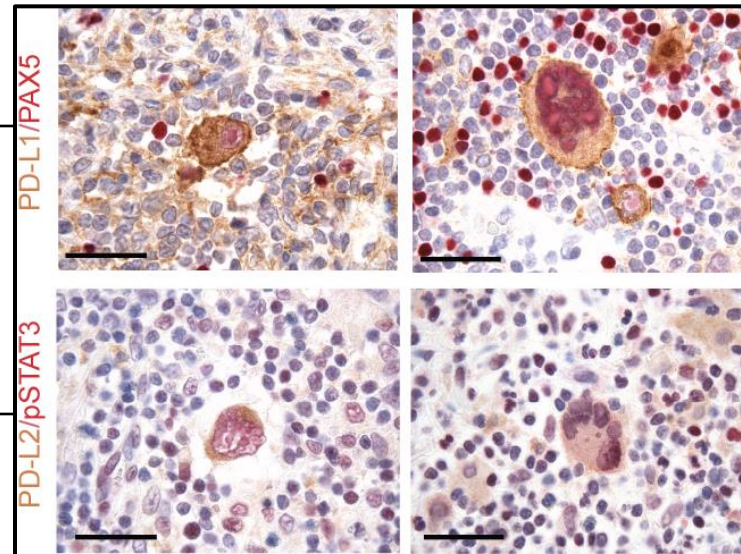
PD-L1/2 locus integrity

- Red=PD-L1
- Green=PD-L2
- Yellow= Red + Green
- Cyan=Centromere

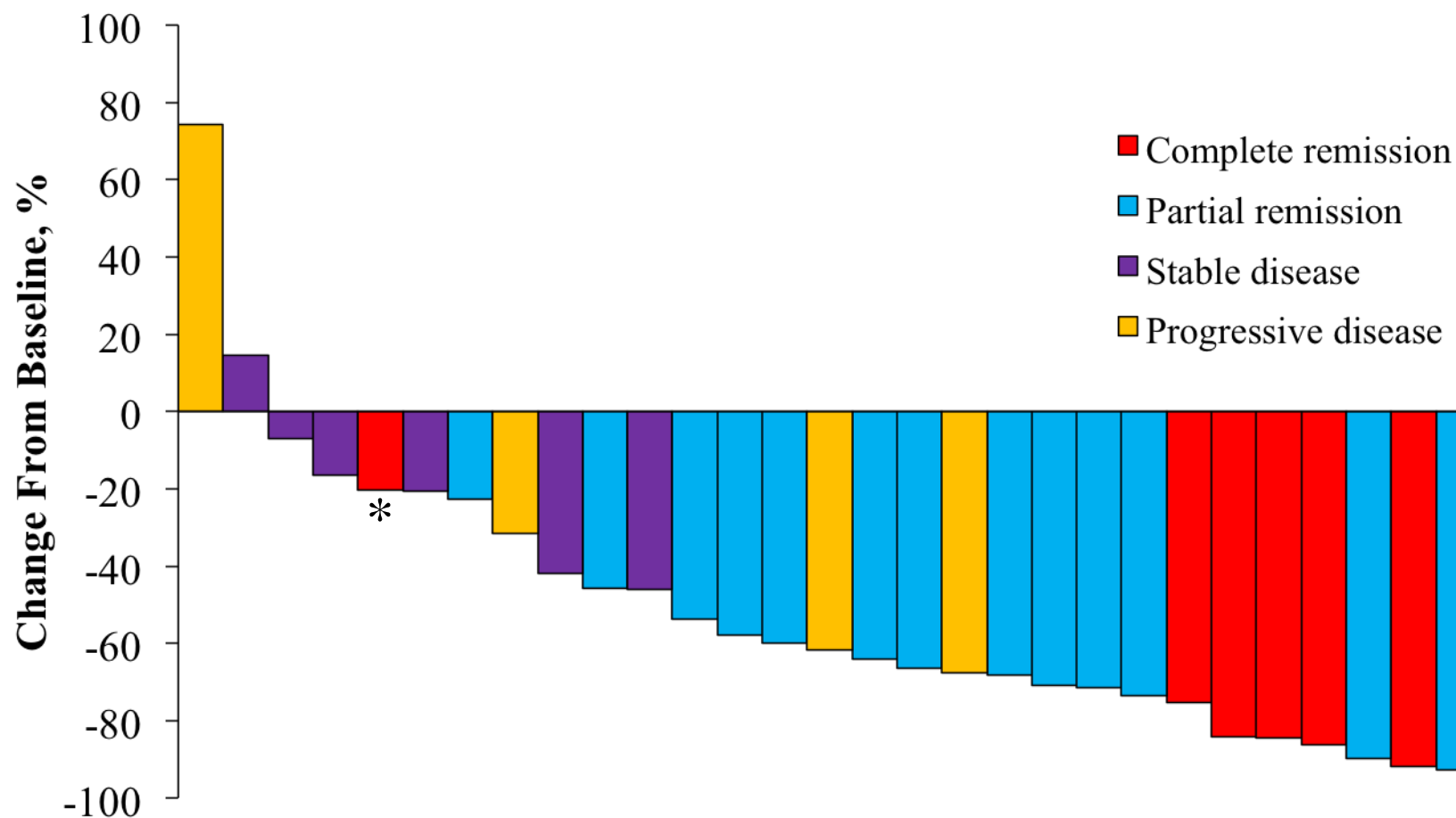


Immunohistochemistry

- PD-L1 (brown)
PAX-5 (red)
- PD-L2 (brown)
pSTAT3 (red)



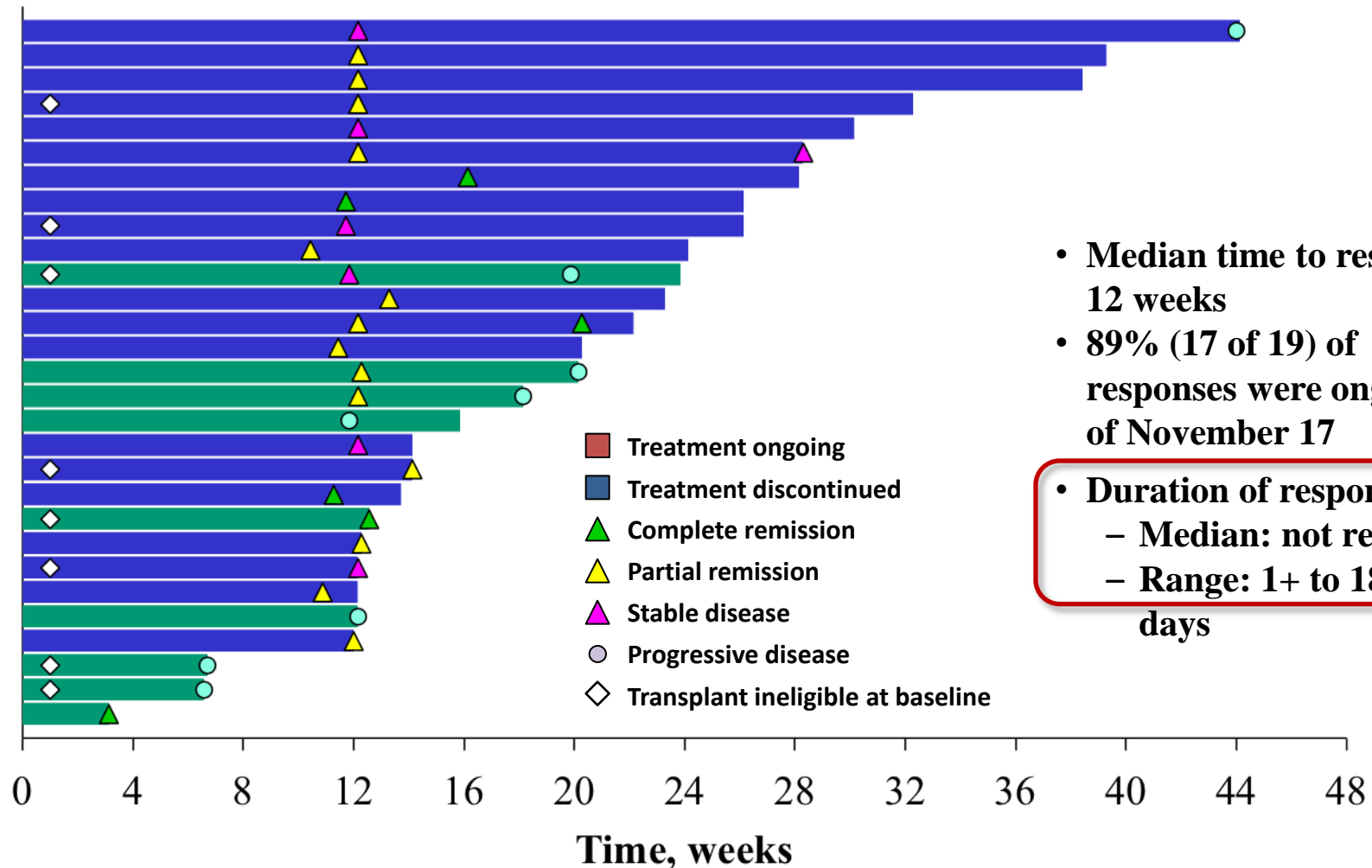
Response to Pembrolizumab (n=29)



*Patient became PET negative and was therefore declared to be in complete remission.
Analysis cut-off date: November 17, 2014.

Moskowitz et al. ASH 2014, abstract 290

Treatment Exposure and Response Duration



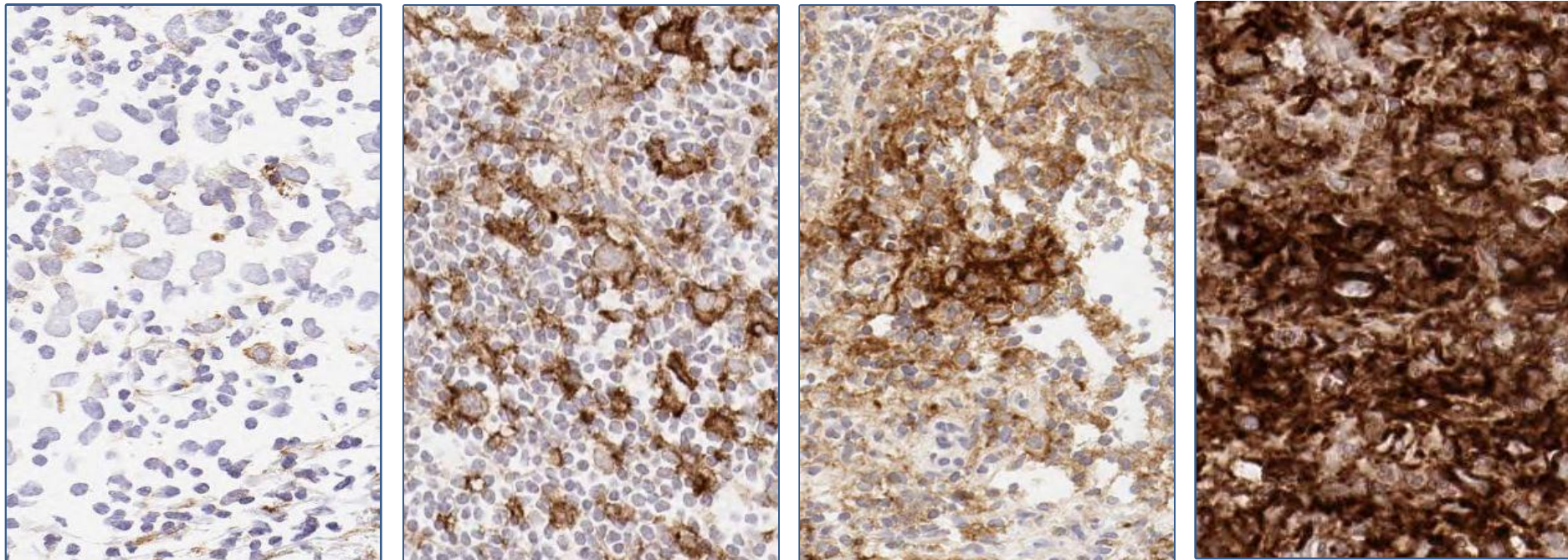
- **Median time to response:**
12 weeks
- **89% (17 of 19) of responses were ongoing as of November 17**
- **Duration of response**
 - **Median: not reached**
 - **Range: 1+ to 185+ days**

Treatment-Related Adverse Events of Any Grade Observed in ≥ 2 Patients

Adverse Event, n (%)	N = 29
Hypothyroidism	3 (10)
Pneumonitis	3 (10)
Constipation	2 (7)
Diarrhea	2 (7)
Nausea	2 (7)
Hypercholesterolemia	2 (7)
Hypertriglyceridemia	2 (7)
Hematuria	2 (7)

- 16 (55%) patients experienced ≥ 1 treatment-related AE of any grade

PD-L1 Expression



PD-L1 Negative

PD-L1 Positive

- Among the 10 enrolled patients who provided samples evaluable for PD-L1 expression, 100% were PD-L1 positive
- Best overall response in these 10 patients was CR in 1 patient, PR in 2 patients, SD in 4 patients, and PD in 3 patients

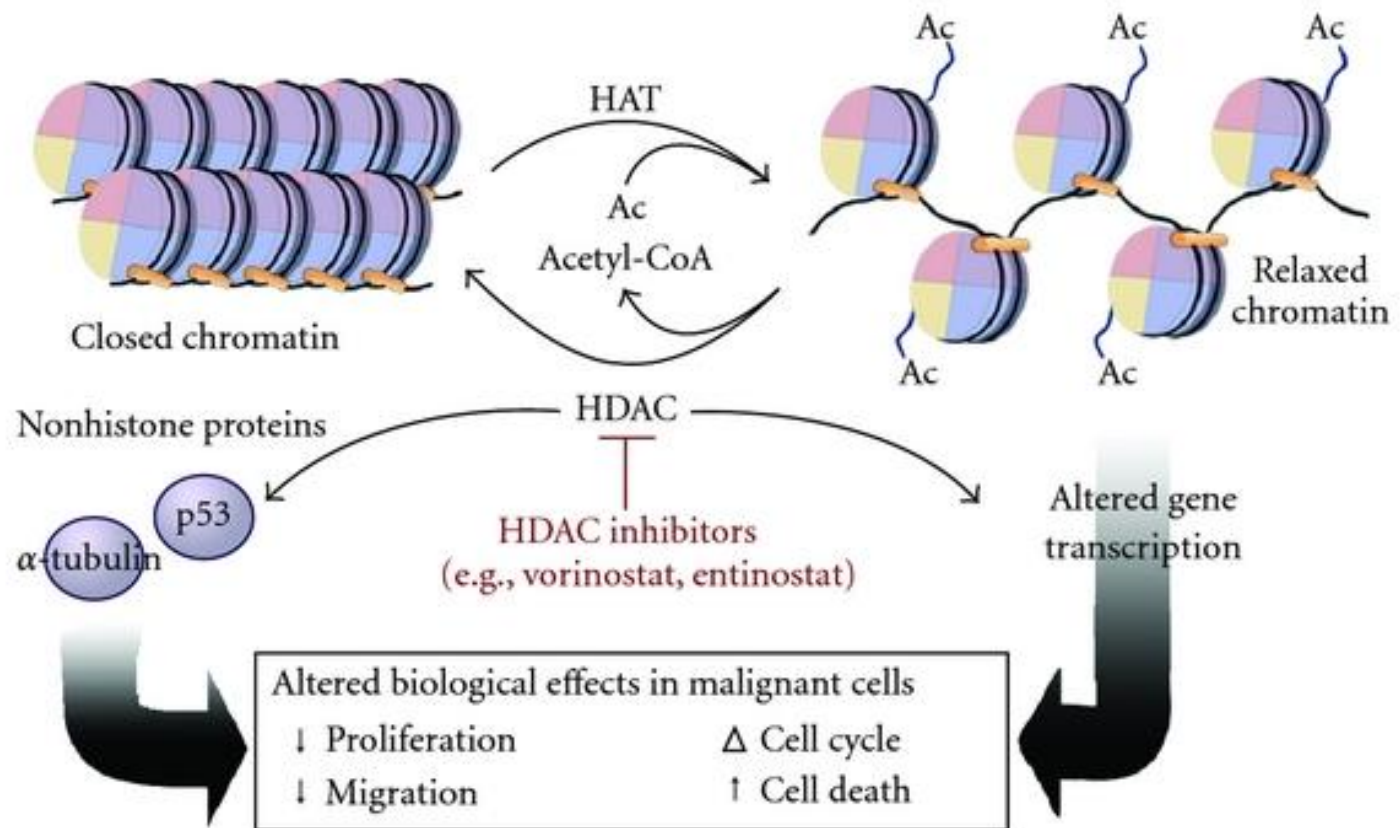
PD-L1 expression was assessed using a prototype immunohistochemistry assay and the 22C3 antibody. PD-L1 positivity was defined as Reed-Sternberg cell membrane staining with 2+ or greater intensity.

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Relapsed Hodgkin lymphoma – Novel agents

Panobinostat (LBH 589) – pan-DAC inhibitor



Relapsed Hodgkin lymphoma – Novel agents

Panobinostat (LBH 589) – pan-DAC inhibitor

129 pts with Hodgkin lymphoma

Median age 32 (range, 18-75)

All patients had a prior SCT

ORR = 27% (35/129) – 5 CR, 30 PRs

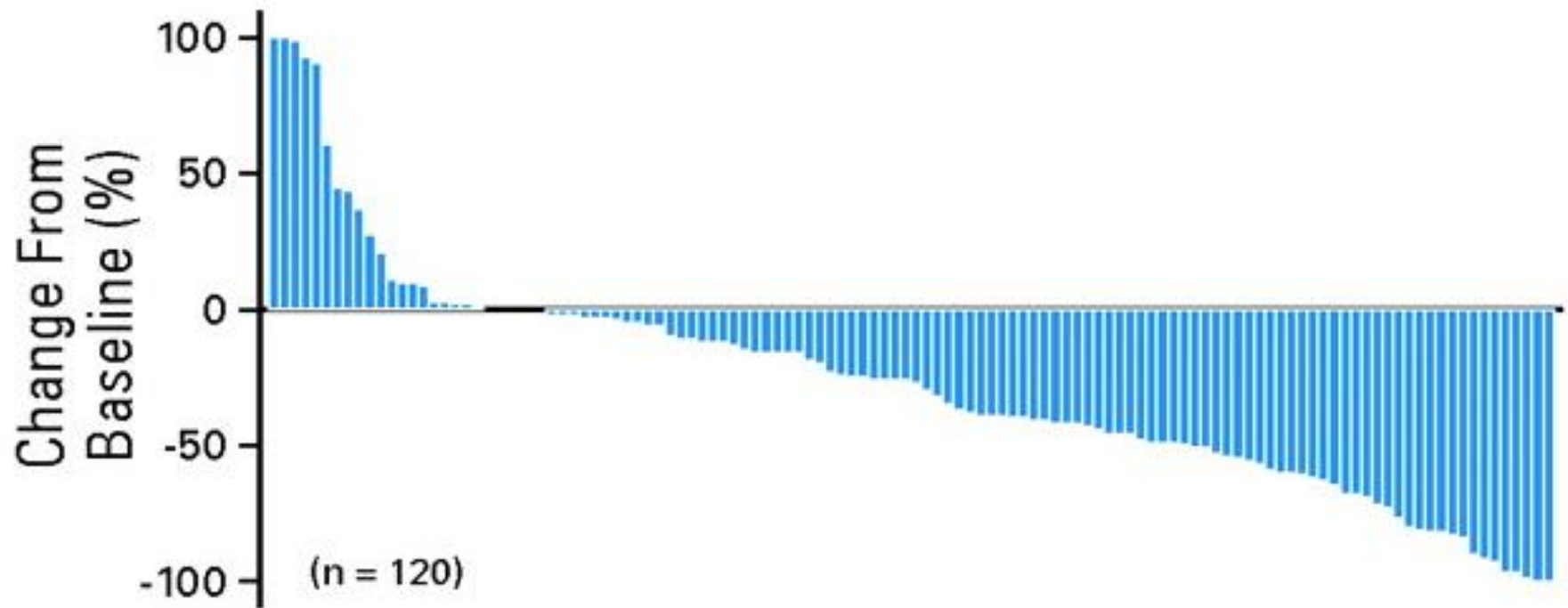
Median duration of response – 6.9 months

Median PFS – 6.1 months

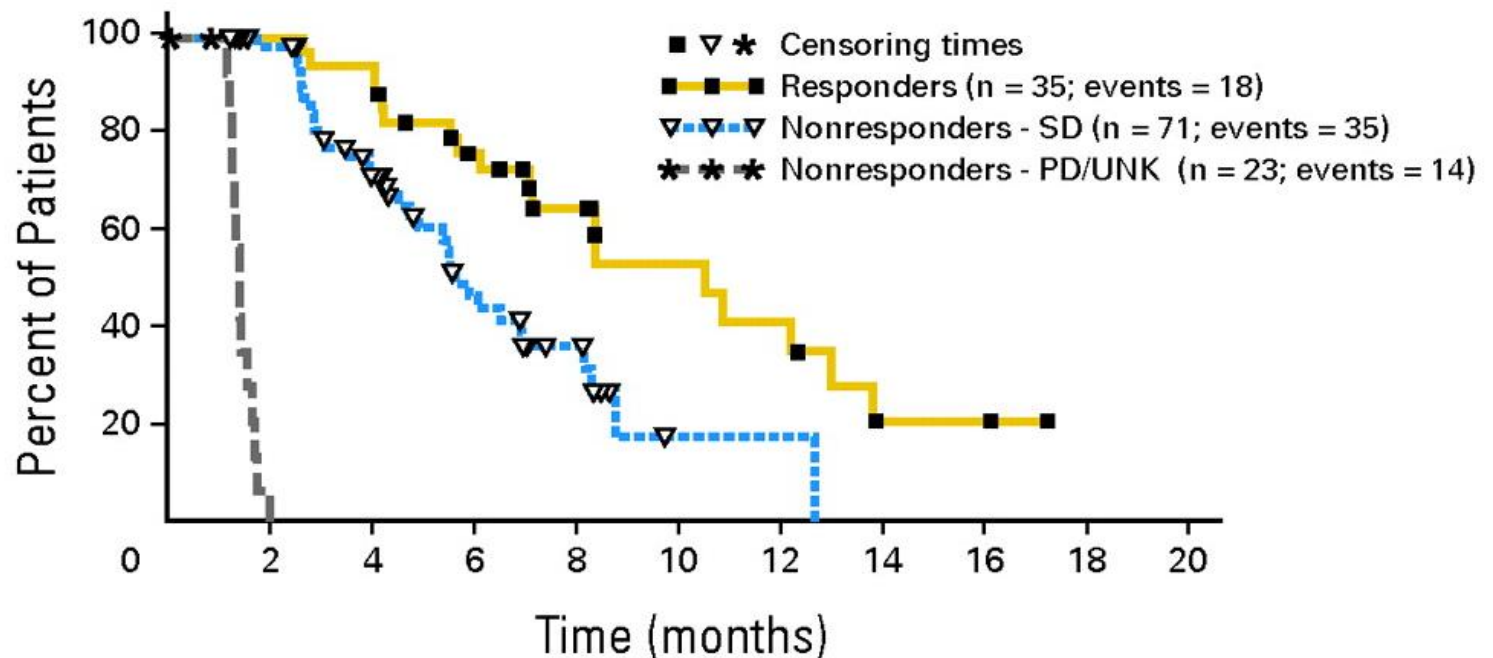
AEs - diarrhea, nausea, vomiting, cytopenias and fatigue

Early reductions in TARC chemokine were observed in patients achieving complete or partial response.

Tumor reduction for lymphoma patients treated with Panobinostat.



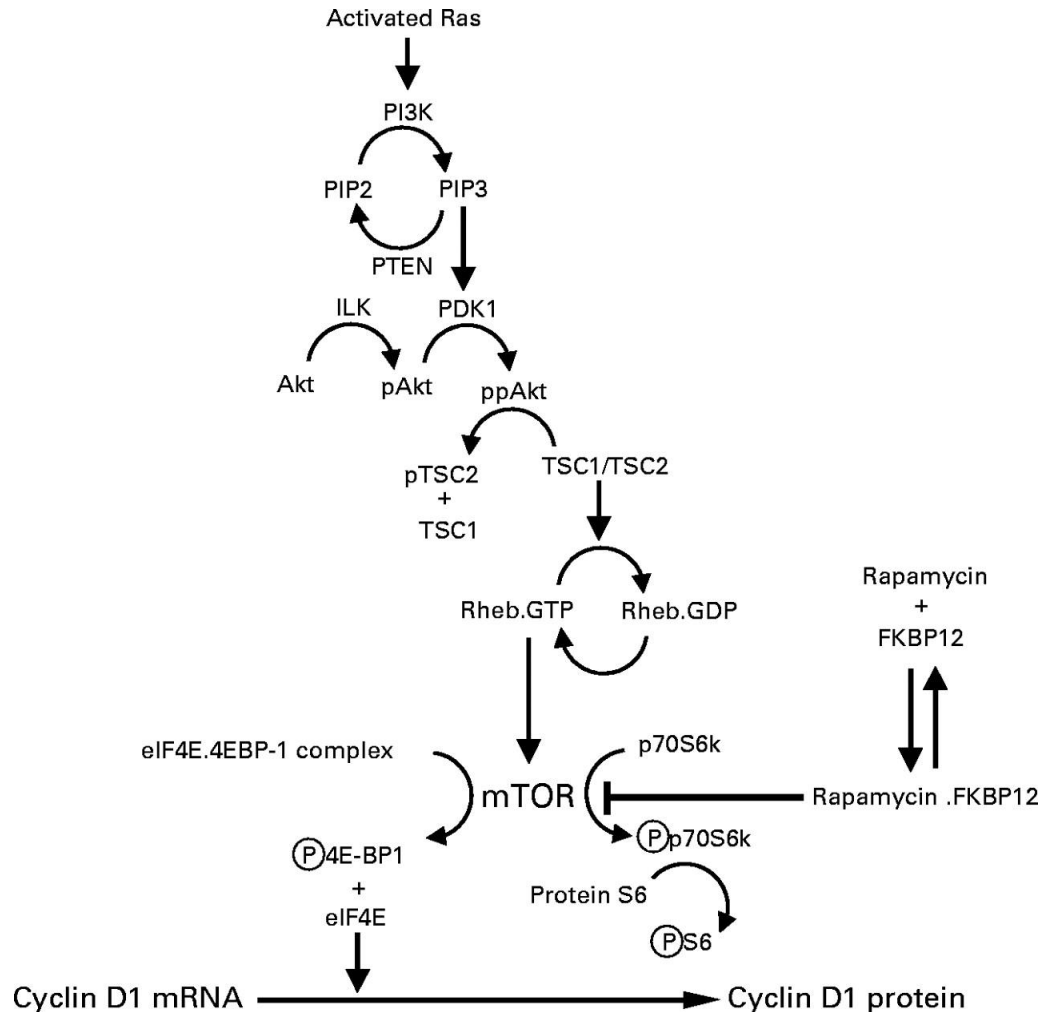
Progression-free survival for responders to panobinostat (complete response and partial response).



No. at risk											
Responders	35	35	33	23	15	9	7	2	2	0	0
Nonresponders - SD	71	59	38	19	10	1	1	0	0	0	0
Nonresponders - PD/UNK	23	1	0	0	0	0	0	0	0	0	0

Relapsed Hodgkin lymphoma – Novel agents

Everolimus (mTOR inhibitor)



Relapsed Hodgkin lymphoma – Novel agents

Everolimus (RAD001)

10mg PO daily

19 patients with relapsed Hodgkin lymphoma

Median age 37 (range, 27-68)

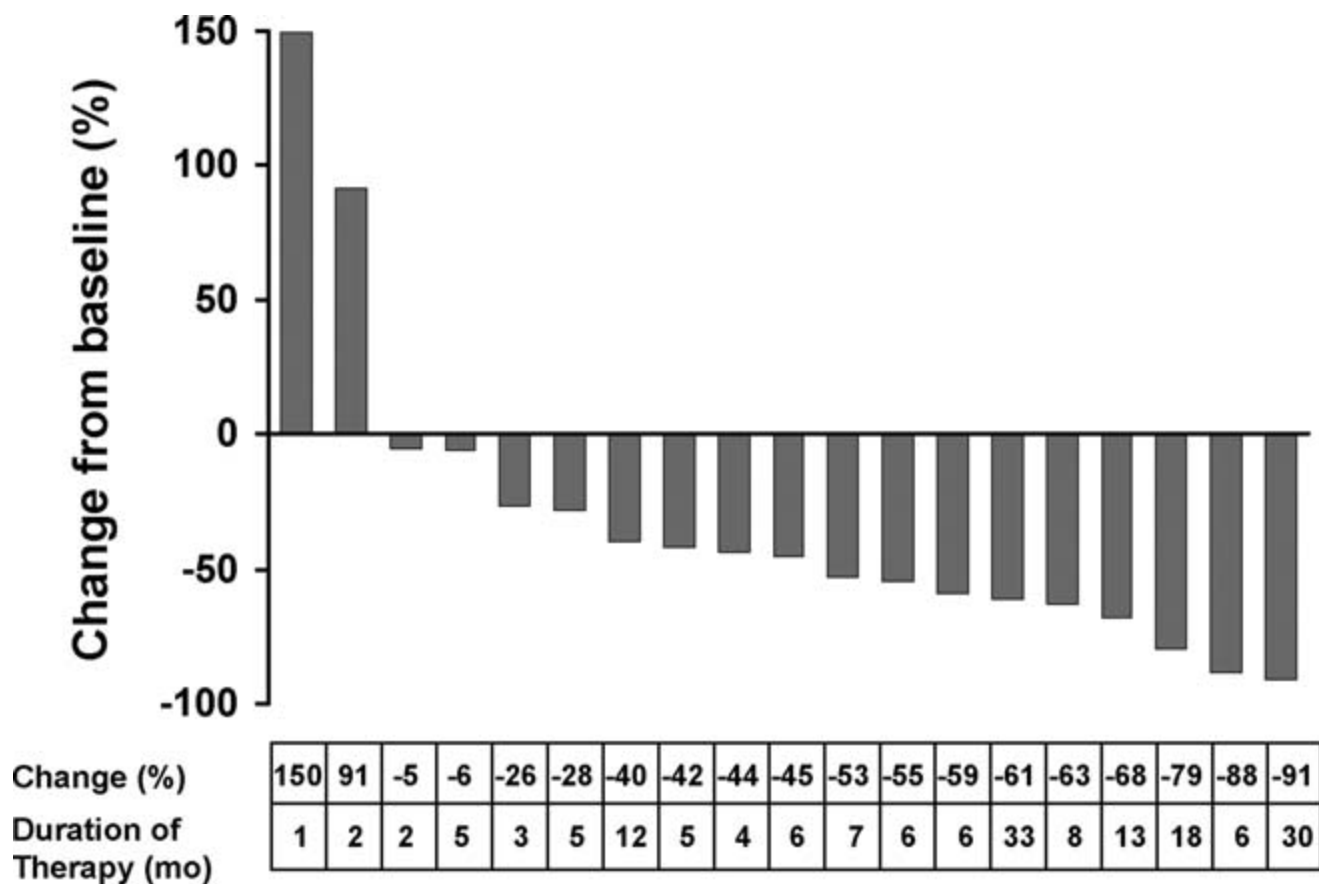
Median of 6 (range, 4-14) prior therapies

84% had a prior SCT

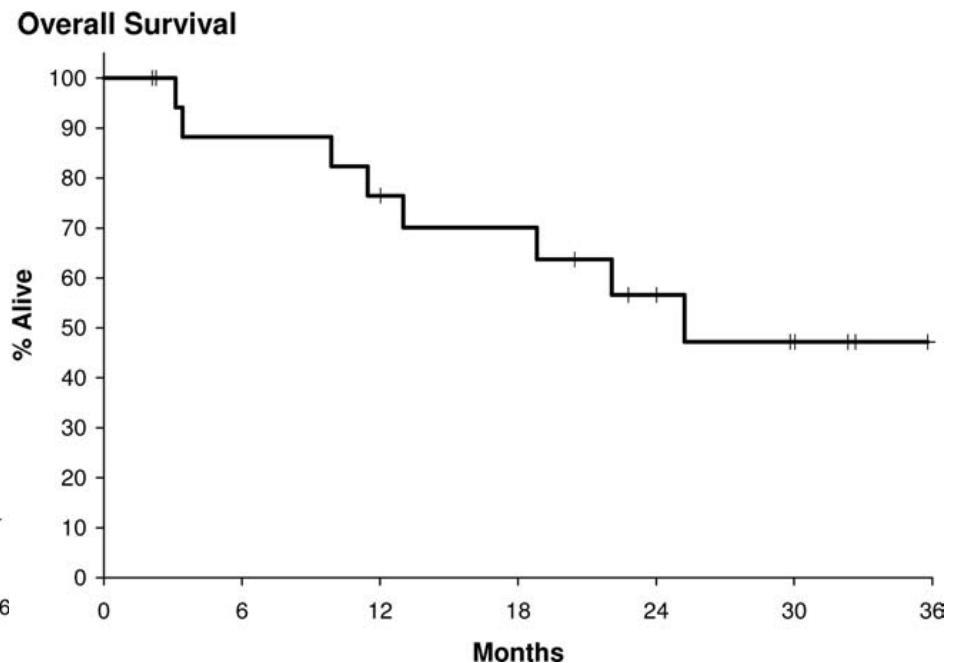
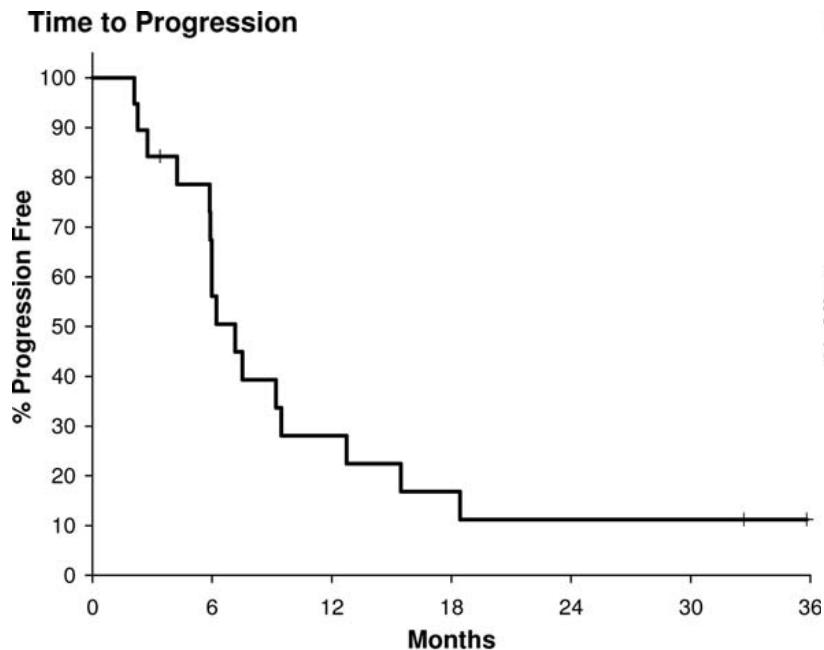
ORR = 47% (1 CR, 8 PRs)

Median Time to Progression – 7.2 months

Response of measurable lesions from baseline in Hodgkin patients treated with single-agent everolimus.

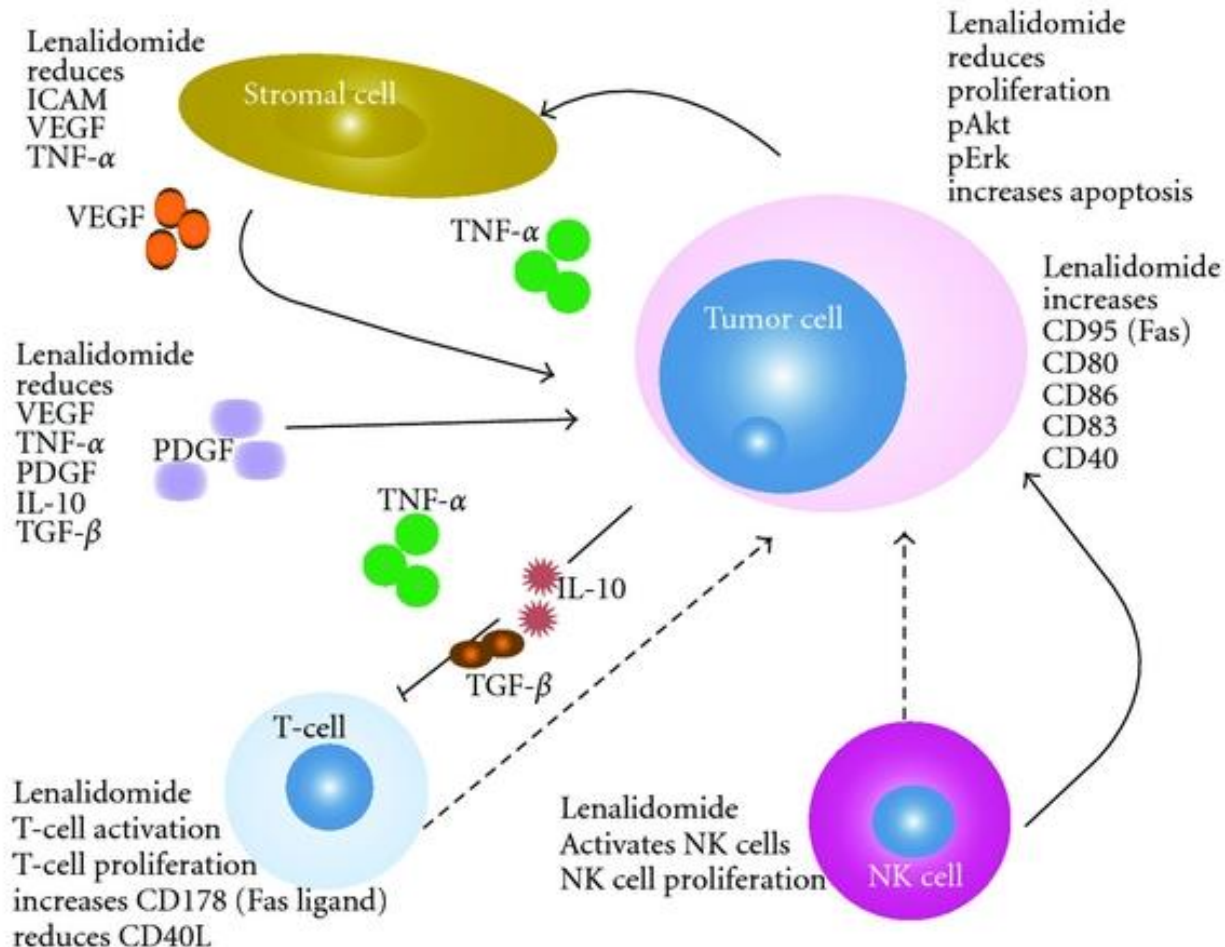


Time to progression and overall survival in Hodgkin lymphoma patients treated with single-agent everolimus.



Relapsed Hodgkin lymphoma – Novel agents

Lenalidomide (IMiD)



Relapsed Hodgkin lymphoma – Novel agents

Lenalidomide

25mg PO days 1-21 of a 28 day cycle

38 patients with relapsed Hodgkin lymphoma

Median of 4 (range, 2-9) prior therapies

87% had a prior SCT

55% had not responded to the prior therapy

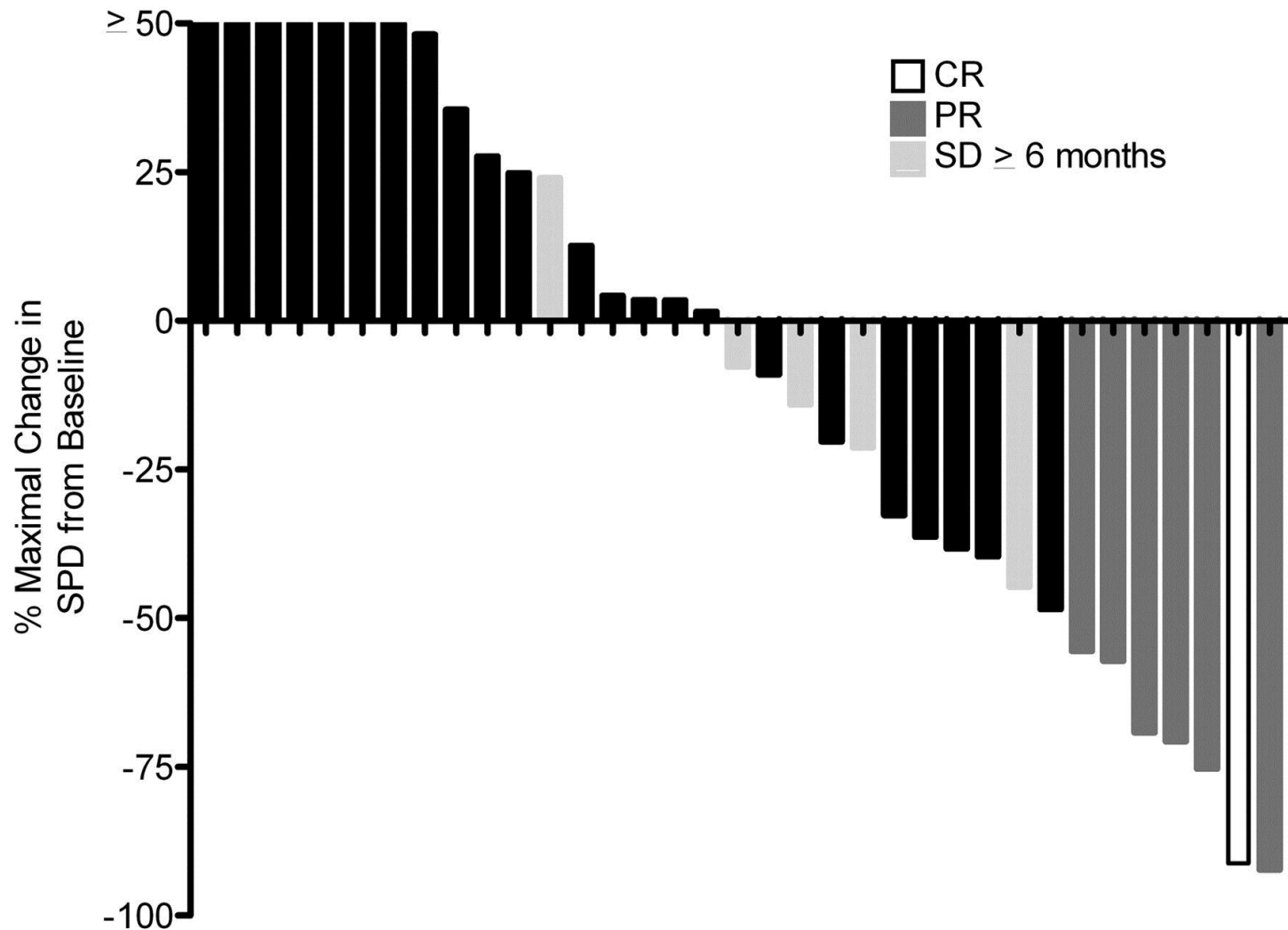
ORR = 19% (1 CR, 6 PRs)

Median PFS - 4 months

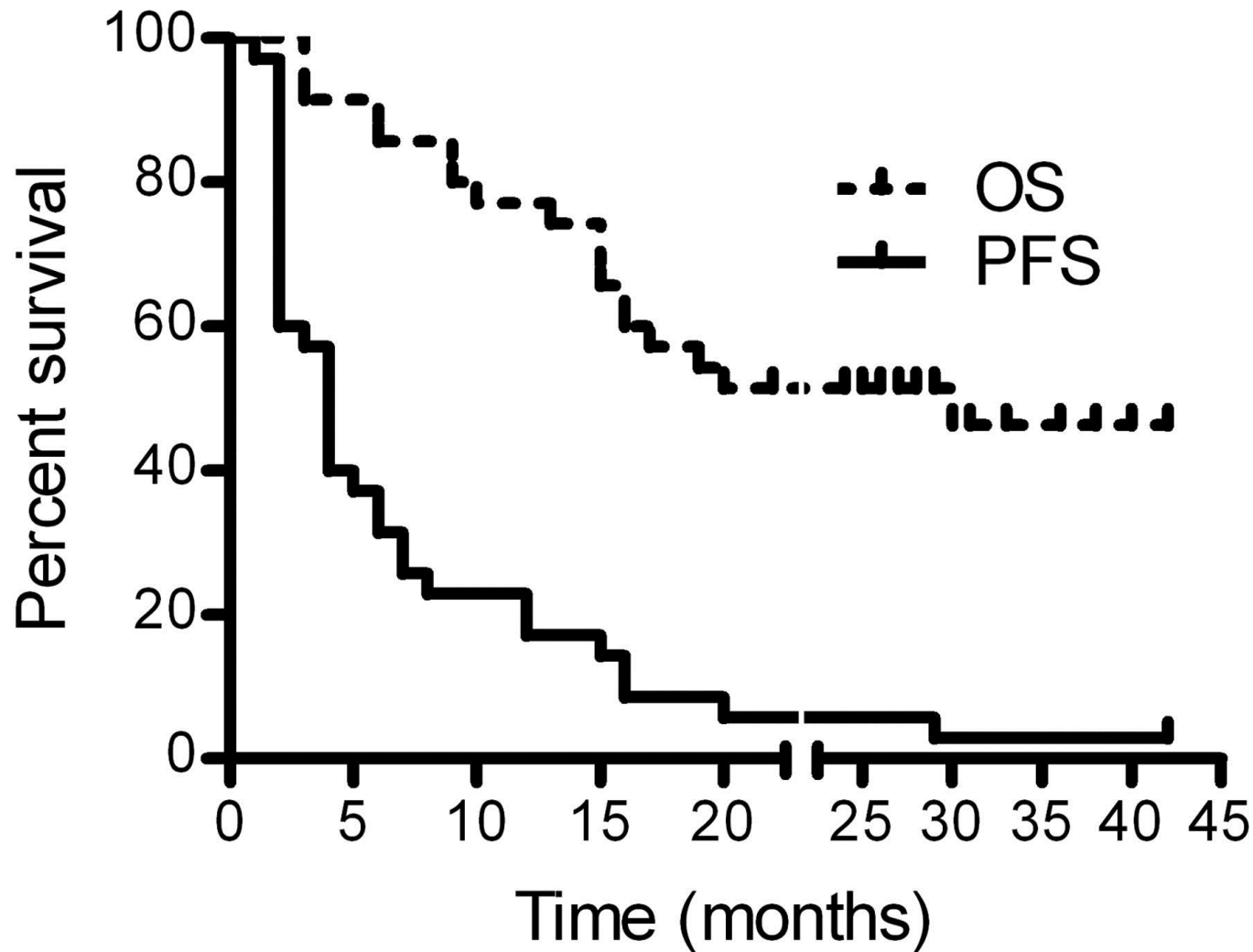
Median OS - 20 months.

AEs - neutropenia (47%), anemia (29%), and thrombocytopenia (18%)

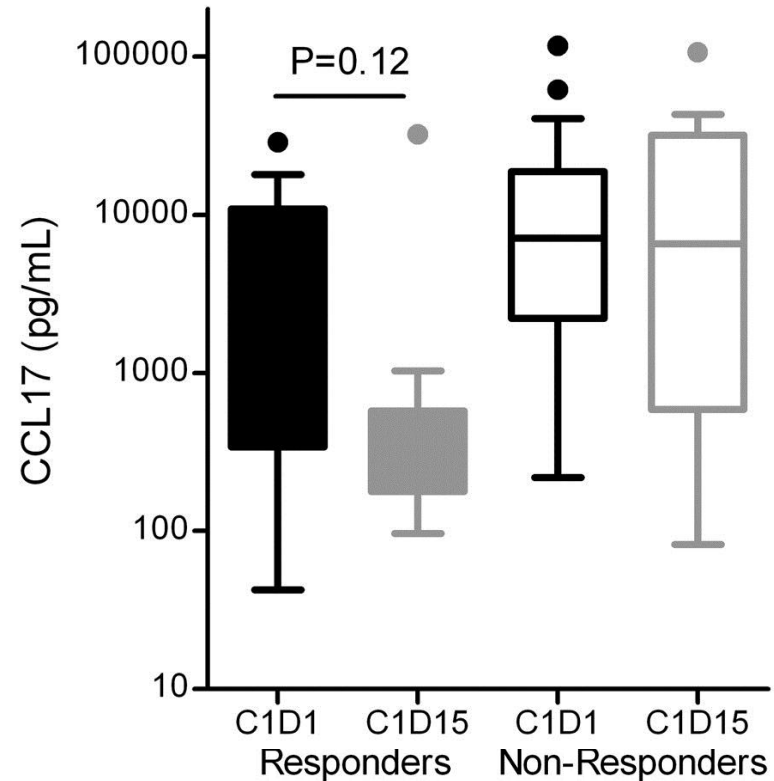
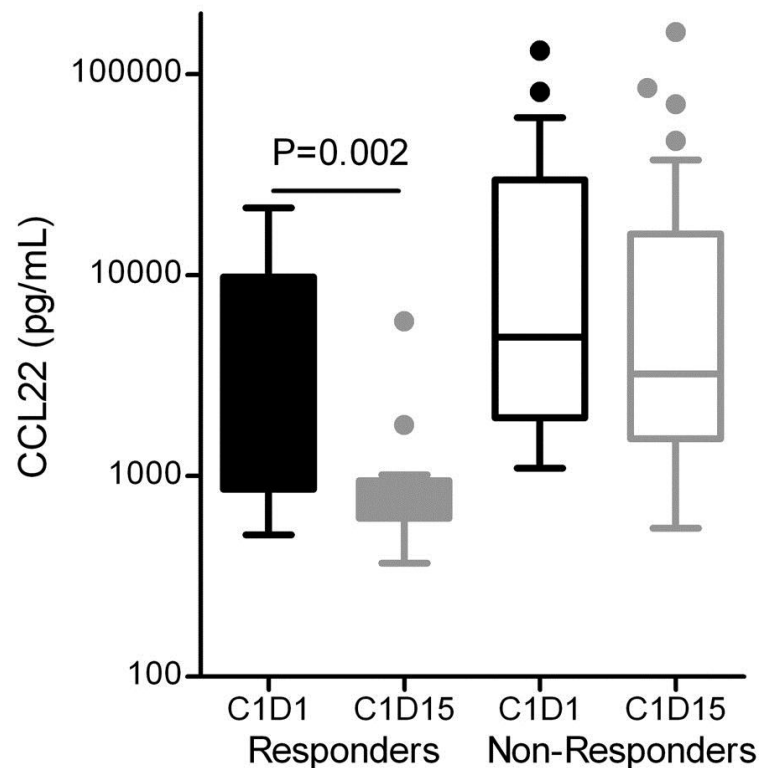
Maximal response for 35 cHL patients treated with ≥ 2 cycles of lenalidomide.



PFS and OS for Hodgkin lymphoma patients treated with lenalidomide.



Changes in CCL17/TARC and CCL22/MDC after treatment with lenalidomide.



Conclusions

Multiple new approaches have promising activity in Hodgkin lymphoma patients

Although promising as single agents, the future is to combine new agents with each other and with standard chemotherapy