Response and Survival Results from a Phase II Trial of Pembrolizumab and Entinostat in Relapsed/Refractory Hodgkin Lymphoma

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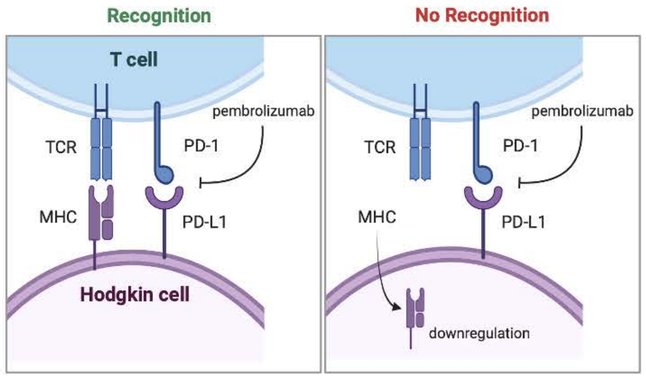
Background

- New strategies for relapsed/refractory (R/R) Hodgkin lymphoma with prior anti-PD1 exposure are needed.
- Resistance to anti-PD1 may occur via downregulation of antigen presentation machinery, including MHC I and II:



- Among other mechanisms, restoring MHC through HDAC inhibition may revive sensitivity to checkpoint blockade.
- Prior reports support anti-PD1 in combination with HDAC inhibition as a mechanism to overcome anti-PD1 resistance (Mei et al., Blood 2023; PMID: 37339586).

Methods

- We tested **pembrolizumab** in combination with the oral class I HDAC inhibitor **entinostat** (7 mg weekly).
- Pertinent eligibility included R/R HL after ≥ 2 lines of therapy. Prior anti-PD1 was allowed.
- Treatment continued until POD, unacceptable toxicity, death, or maximum of 35 cycles (2 years).
- The primary end point was 12-month PFS, with a null hypothesis of 40% versus 60%.
- Consolidation with transplant, radiation, or pembrolizumab maintenance (at completion of 35 cycles) were considered events to ensure conservative PFS estimates.
- Key secondary endpoints were safety and response per Lugano criteria.

Results and Conclusions

- 39 patients enrolled. Prior therapies included BV (82%), anti-PD1 (74%), HDAC inhibitor (10%), and/or autoHCT (67%).

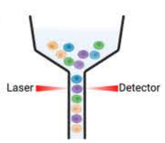
Patient Outcomes/Adverse Events

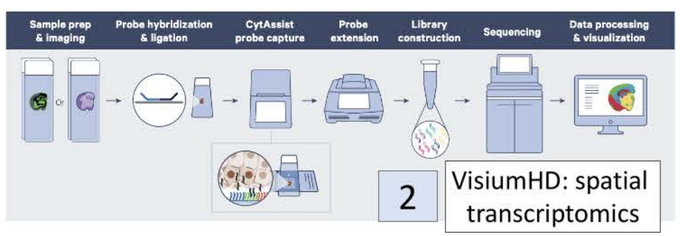
- 1 patient was unevaluable due to not completing 1 full cycle. Of 38 patients, 11 had POD, 10 withdrew due to AE, 6 completed 35 cycles, 5 had transplant/RT consolidation, and 4 remain on treatment.
- AEs of ≥ grade 3 occurred in 77% of patients, most commonly neutropenia (44%). 2 patients stopped treatment due to pericardial events (effusion, pericarditis); both recovered with medical management and tolerated single-agent pembrolizumab.

Cohort	Number	CR rate	ORR
Total	38	47%	63%
Anti-PD1 Exposure			
Prior anti-PD1	28	36%	50%
Anti-PD1 naïve	10	80%	100%
Prior anti-PD1 response[1]			
Sensitive	5	40%	40%
POD	22	36%	55%
POD as last line of tx	16	31%	44%

Ongoing Correlative Analyses

1 CITE-seq (responder vs. non-responders)

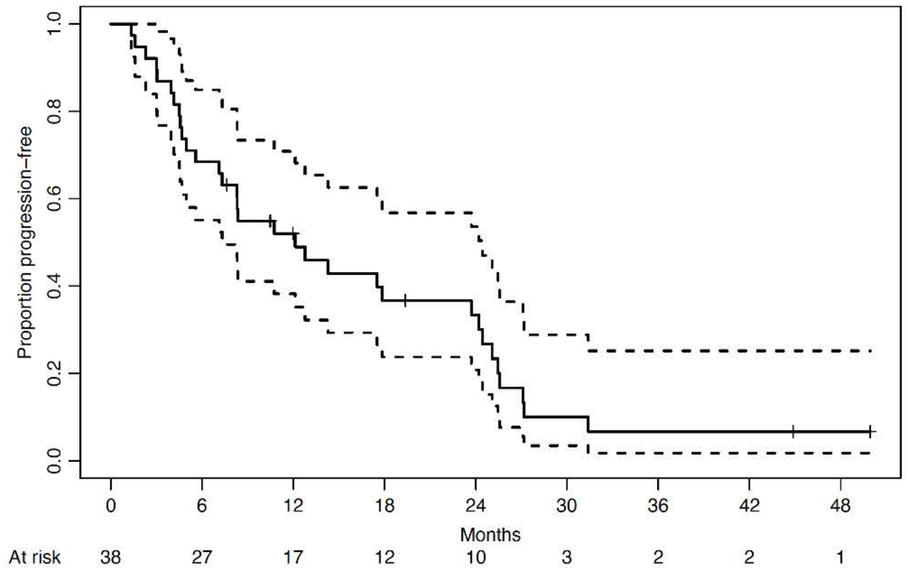




2 VisiumHD: spatial transcriptomics

Progression-Free Survival Estimates

- The 12-month PFS rate was 53% (95% CI, 38.2-70.8) and the median PFS was 12.1 months (95% CI, 7.3-24.5).



Conclusions:

- Pembrolizumab + entinostat has high response rates in R/R CHL.
- Patients with prior exposure and prior resistance to anti-PD1 therapy responded to pembrolizumab plus entinostat.
- No new, unexpected toxicities were observed. Immune-related toxicity was uncommon and low grade. Two pericardial events occurred.
- Ongoing correlative analyses will define the mechanism of response, with particular attention to antigen presentation machinery.

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