High rates of undetectable MRD by PhasED-Seq on interim and end of treatment timepoints in untreated advanced stage CHL treated with pembrolizumab + AVD

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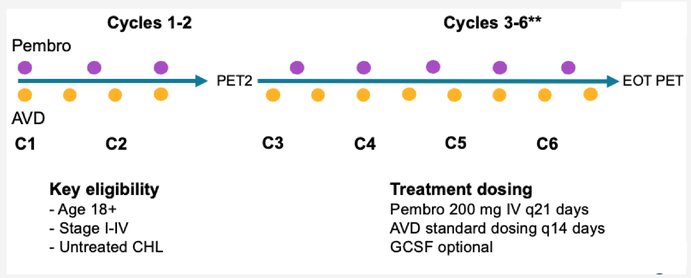
Background

- Concurrent pembrolizumab with AVD chemotherapy is highly effective in the treatment of classic Hodgkin lymphoma (CHL) (Lynch et al. ASH 2023)
- We present updated clinical data for our full 50-patient study including interim and end of treatment (EOT) MRD testing by PhasED-Seq

Methods



- **First 30 patients received 2-6 cycles based on stage, final 20 patients all received 6 cycles for Stage III or IV
- Primary endpoint of larger cohort: Efficacy, Secondary and exploratory endpoints: safety, ctDNA analysis
- Single Center IIT, N = 50 patients, NCT03331341
- Samples were analyzed for ctDNA at baseline, post cycle 1 (if available), post cycle 2, and end of treatment. ctDNA levels were quantified as haploid genome equivalents/mL plasma using PhasED-Seq (Kurtz et al. Nat Biotech 2021).

Results

Demographics

Description	n = 50
Male sex, n (%)	12 (40%)
Age, median (range)	32 (18-69)
Stage	
I	1 (2%)
II	11 (22%)
III	13 (26%)
IV	25 (50%)

Number of cycles administered	N = 50
2 cycles	5 (10%)
4 cycles	3 (6%)
6 cycles	42 (84%)

Description	n = 50
B symptoms, n (%)	21 (42%)
Bulk (> 10 cm), n (%)	9 (18%)
Elevated ESR (> 50)	15 (30%)
Extranodal involvement, n (%)	24 (48%)
Spleen involvement, n (%)	14 (28%)
Early stage favorable, n (%)	6 (50%)
Early stage unfavorable, n (%)	6 (50%)
IPS (advanced stage, n=38)	
0-1	5 (13%)
2-3	23 (61%)
4-7	10 (26%)

Grade 3-4 non-Heme AEs

CTCAE Category	Grade 3-4
Febrile neutropenia	5 (10%)
Hyponatremia	4 (8%)
Syncope	4 (8%)
Sepsis	3 (6%)
Vomiting	1 (2%)
Rash	1 (2%)
Upper respiratory infection	1 (2%)
Conjunctivitis	1 (2%)
Colonic obstruction	1 (2%)
Colon abscess	1 (2%)
Hypophosphatemia	1 (2%)

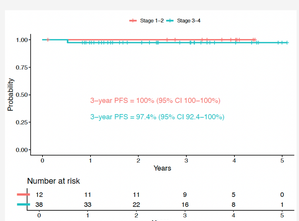
Key Safety Data
- 8 SAEs (5 febrile neutropenia)
- 8 patients missed ≥ 1 dose of pembrolizumab
  - 5/8 due to grade 2+ transaminitis, all reversible

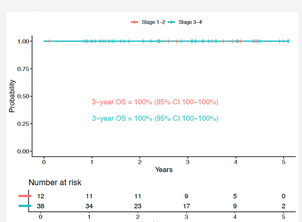
Efficacy Data
- PET2 CR: (n=49)
  - All patients: 61%
  - Early stage: 73%
  - Advanced stage: 58%
- EOT CR: (n=48)
  - All patients: 77%
  - Early Stage: 91%
  - Advanced stage: 73%

Immune-related adverse effects

Adverse event	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Elevated ALT	29 (58%)	23 (46%)	3 (6%)	2 (4%)	1 (2%)
Elevated AST	18 (36%)	16 (32%)	1 (2%)	-	1 (2%)
Rash	16 (32%)	13 (26%)	2 (4%)	1 (2%)	-
Hypothyroidism	5 (10%)	1 (2%)	4 (8%)	-	-
Hyperthyroidism	3 (6%)	1 (2%)	2 (4%)	-	-
Total Bili Elevation	3 (6%)	1 (2%)	2 (4%)	-	-
Arthritis	1 (2%)	-	1 (2%)	-	-
Colitis	1 (2%)	-	1 (2%)	-	-
Guillain-Barre Syndrome	1 (2%)	-	-	1 (2%)	-

Long-term efficacy: Median Follow-up 3.1 years





PhasED-Seq Analysis

uMRD by Timepoint

	C2D1 uMRD	C3D1 uMRD	EOT uMRD
All patients	29/37 (78%)	36/43 (84%)	39/42 (93%)
Advanced stage	22/29 (76%)	29/35 (83%)	31/34 (91%)

- Baseline ctDNA was detectable in 11/12 (92%) of early-stage patients, and 36/37 (97%) of advanced stage patients.
- Only patient in the study to relapse had a negative interim PET but did not clear ctDNA at any timepoint.
- Two additional patients had minute amounts of ctDNA detectable at the end of treatment after levels dropped >20,000 fold when compared to baseline.
  - Both patients have not relapsed 3 years and 14 months after completion of treatment, respectively.
- Some timepoints did not have plasma samples available, and no samples were drawn for sequencing during follow-up

- Non-invasive genotyping using ctDNA available in 25 patients
- 6 patients with H2 genotype (24%), only advanced stage
- Remaining patients, including all early-stage patients, were classified as H1 (76%)
  - No relapses among H1 patients

Conclusion

- Pembrolizumab + AVD continues to demonstrate durable efficacy in previously untreated CHL.
- No patient who has cleared ctDNA as measured by PhasED-Seq has relapsed to date despite high rates of interim-PET and EOT PET positivity.
- The role of PhasED-Seq will be further examined in the upcoming Phase 2 MRD-adapted PRECISE-HL study in untreated advanced stage CHL.

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