Clinical, metabolic and molecular responses with sequential R-CHOP, high-dose cytarabine, and iodine-131 tositumomab-based transplant in Mantle Cell Lymphoma

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Introduction

- Intensive, cytarabine-containing therapy followed by autologous stem cell rescue (ASCR) consolidation is an efficacious treatment strategy for untreated mantle cell lymphoma (MCL)
- Interim FDG-PET/CT negativity and molecular remission (MRD negativity) are prognostic biomarkers in MCL
- A Phase II trial was executed at MSK with RCHOP-14 x 4 cycles → R-high dose cytarabine x 2 cycles → consolidation with iodine-131 tositumomab-BEAM-ASCR and preliminary results are reported here

- <u>OBJECTIVES of the current study</u>
  - Describe the preliminary efficacy of this treatment program
    - Overall response rate
    - Outcomes (event-free survival)
  - Describe interim radiographic and molecular biomarkers:
    - Interim FDG-PET/CT status
    - Interim and surveillance MRD status using a novel next-generation sequencing platform for detecting circulating tumor DNA (Sequenta LymphoSIGHT™)

Methods

- <u>TREATMENT</u>:
  - Induction chemotherapy consisted of R-CHOP-14 x 4 and 2 cycles of R-high-dose cytarabine (R-HiDAC, age <65: 3 gm/m² q12h x4 doses; age ≥ 65: 2 gm/m²). Responding patients received consolidation with iodine-131 tositumomab-BEAM-ASCR

- <u>INTERIM ASSESSEMENTS:</u>
  - Interim PET scans were performed after 4 cycles of R-CHOP therapy (Deauville 1-3: negative and Deauville 4-5: positive)
  - If FDG-PET/CT positive after RCHOP, FDG-PET/CT was repeated after 2 cycles of R-HiDAC
  - In a subset of patients (n=17), MRD was assessed by a sequencing-based method (Faham et al. Blood 2013)
    - MRD testing was performed at various time points in the peripheral blood, analyzing the acellular (plasma and serum) or cellular (peripheral blood mononuclear cell) compartments. MRD testing was also performed on cellular bone marrow aspirate samples when available. If circulating DNA was detected in any compartment at a given time point, the MRD test was considered positive.

- <u>KEY ELIGIBILITY CRITERIA</u>
  - Histologically confirmed MCL - clinical stage 2 with abdominal involvement, stage 3, and stage 4
  - Ages 18-70, KPS ≥ 70%
  - Transplant eligible with adequate organ function

Treatment Schema

RCHOP-14 x 4 → FDG-PET/CT → R-HIDAC x 2 (inpatient) → FDG-PET/CT* → Iodine ¹³¹ I – Tositumomab/BEAM/ASCR

If interim response <CR/PR →off study

* Only if FDG-PET/CT positive after RCHOP

Patient Characteristics

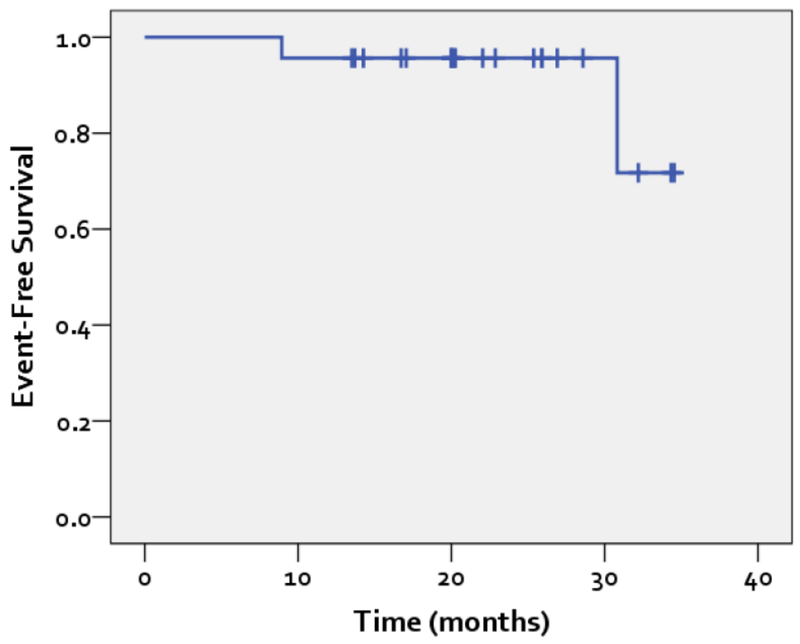
Characteristic	N = 23 (%)
Age years, median [range]	58 [46-69]
Gender	
Male	16 (70)
LDH > ULN, (N = 20)	9 (39)
Ann Arbor Stage	
Stage I/II	0 (0)
Stage III/IV	23 (100)
Bone Marrow Involvement	18 (78)
GI Tract Involvement (EGD and Colonoscopy required)	13 (57)
Ki-67	
< 10%	4 (17)
10 – 29.9%	8 (35)
≥ 30%	9 (39)
MIPI, (N = 20)	
Low	11 (48)
Intermediate	7 (30)
High	5 (22)

Results

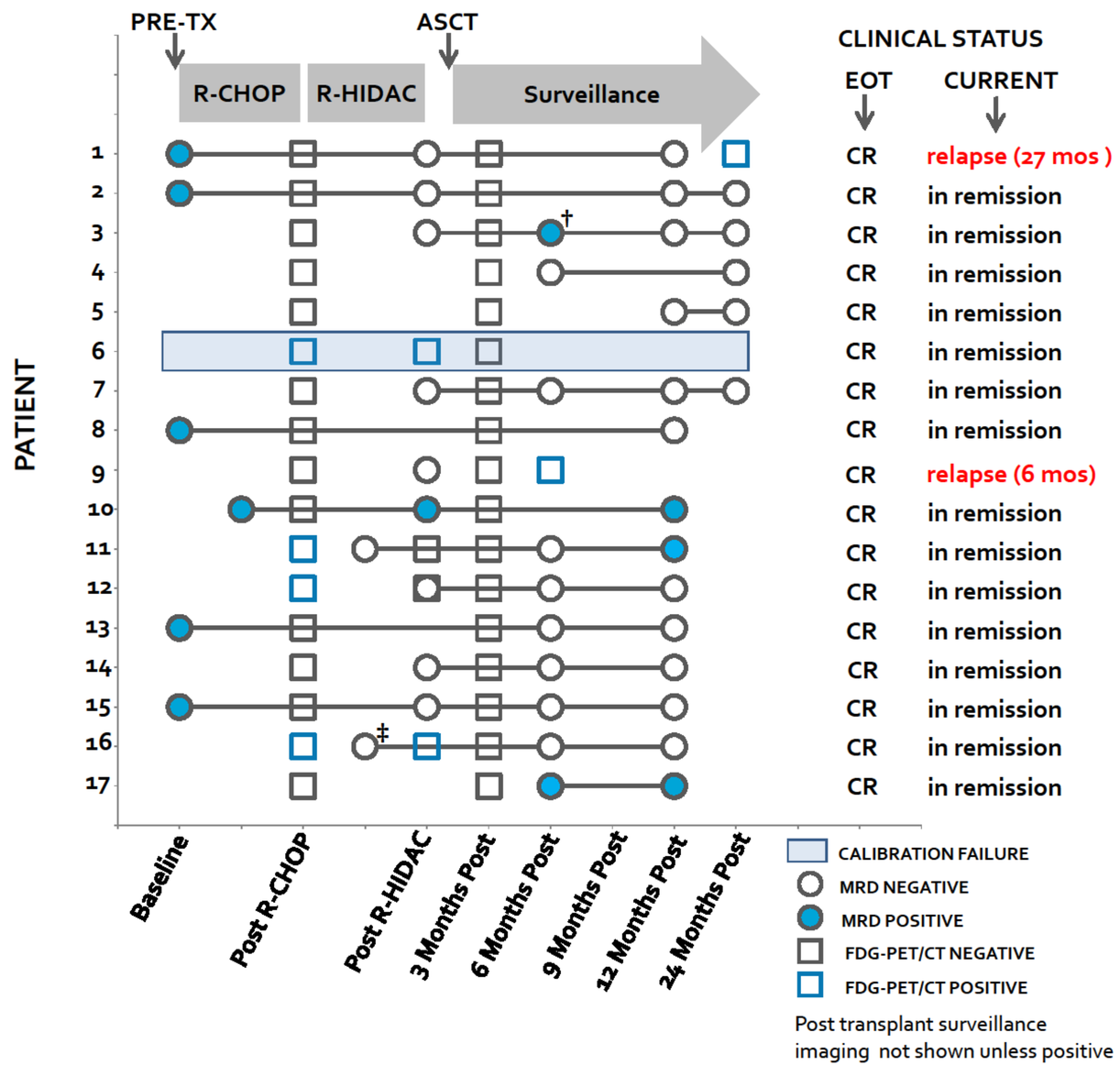
Preliminary Efficacy	N = 23 (%)
Negative FDG-PET/CT after R-CHOP-14 x 4 cycles	15 (65)
Negative FDG-PET/CT after R-HiDAC x 2 cycles	20 (87)
ORR at end-of-treatment	23 (100)
CR	22 (96)
PR	1 (4)

*One patient refused ASCR

<u>OUTCOMES</u>
- Median follow up is 22 months
- Two patients have relapsed (at 4 and 27 months post-ASCR)
- EFS at median follow-up 96%



<u>MRD RESULTS</u>



† Patient 3: MRD positive in bone marrow, but low-level positive at the detection limit (1 lymphoma molecule in sample)

‡ Patient 16: MRD negative post 1 cycle RHIDAC, but FDG-PET/CT positive (Deauville 4) post-2 cycles RHIDAC. However, this FDG-PET/CT shows dramatic reduction in disease burden (ΔSUVmax=83%). Post ASCT, pt in remission.

- A baseline clonotypic sequence was identified in 94% (16/17) of pts
- MRD status was negative in most patients at all time points, both during treatment (10/11, 91%) and at 12 months post therapy (11/14, 79%). Most pts are in continued remission (15/17, 88%), despite 3 pts with MRD positivity at 12 months post therapy.
- The 2 patients who relapsed
  - Had negative FDG-PET/CT and MRD assessments during treatment and achieved CRs at end of tx
  - Had few samples obtained during surveillance or prior to relapse, limiting our ability to assess if the MRD tool predicts relapse

Conclusion

- Sequential R-CHOP-14, R-HiDAC and RIT-BEAM followed by ASCR is a highly effective regimen with high rates of early FDG-PET/CT and MRD negativity
- Clinical remission is correlated with MRD and FDG-PET/CT negativity
- Due to the limited number of relapse events and follow up as well as sporadic MRD testing, it is difficult to describe the positive predictive value of the next-generation sequencing based MRD test

CONFLICT OF INTEREST DISCLOSURES: Katherine Kong, Malek Faham, and Tom Willis are employees of and holders of equity in Adaptive Biotechnologies. Andrew Zelenetz is on the Board of Scientific Advisors.

DOI: 10.3252/pso.eu.13icml.2015
Poster presented at: 13-ICML
Printing supported by: Takeda ONCOLOGY
PosterSessionOnline.com