



Tumor mutational burden and other immunotherapy markers in Erdheim-Chester disease and other histiocytic neoplasms

Gaurav Goyal, Robert Vassallo, Karen L Rech, Jay H Ryu, Caroline J Davidge-Pitts, W Oliver Tobin, Matthew J Koster, Nabila N Bennani, Mithun V Shah, Minetta C Liu, and Ronald S Go on behalf of the Mayo Clinic Histiocyte Interest Group

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Goyal.Gaurav@mayo.edu

Conflicts of interest

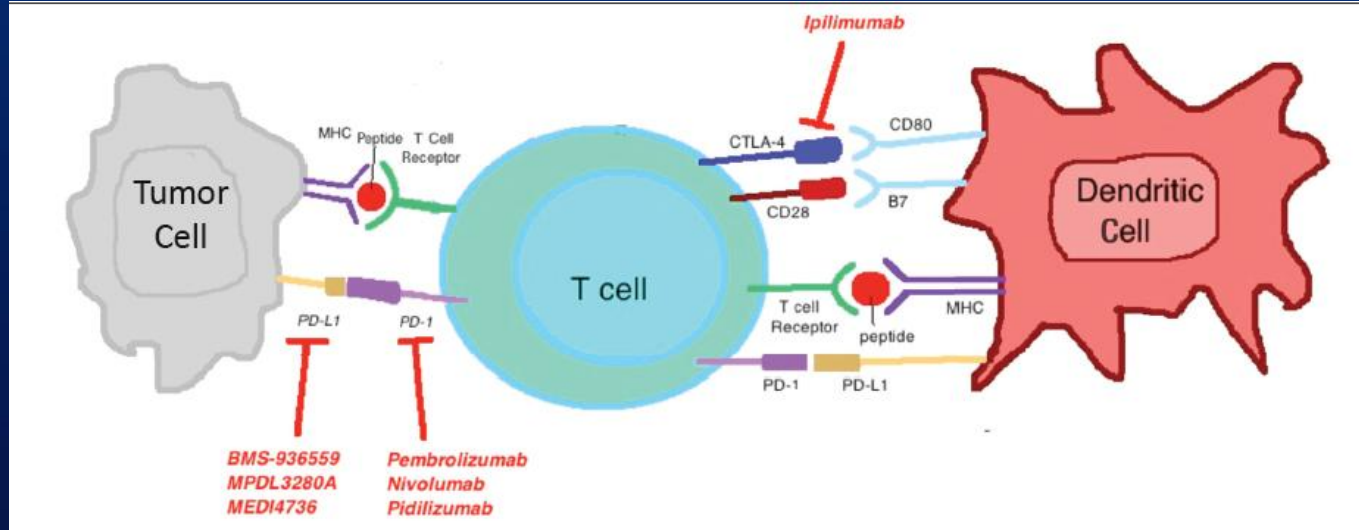
- No conflicts of interest to disclose

Background

- Recent US-FDA approval of vemurafenib in BRAF-V600-mutant Erdheim-Chester disease based on basket study
- Limited (approved) therapeutic options for non-BRAF-V600-mutant ECD and other histiocytic neoplasms

Diamond EL et al. JAMA Oncol. 2018;4(3):384-388

Immune checkpoint inhibitors: Mechanism of action



Goyal G et al. Fed Pract. 2015 May;32(suppl 4):57S-65S

Immune checkpoint inhibitor therapy

- Significant improvement in outcomes in various hematologic and solid organ malignancies
 - Progression free survival
 - Overall survival
- US-FDA approvals in Oncology
 - Solid tumors- melanoma, lung, kidney, bladder
 - Hematologic- classical Hodgkin lymphoma

Ansell SM et al. N Engl J Med. 2015;372(4):311-319
Brahmer JR et al. N Engl J Med. 2012;366(26):2455-2465
Robert C et al. N Engl J Med. 2015;372(4):320-330
Gandhi L et al. N Engl J Med. 2018;378(22):2078-2092

Immune checkpoint inhibitor therapy

- Benefits a small subset of patients
 - Variable response rates (10-50%)
- Search for biomarkers predictive of response
 - PDL-1 expression by immunohistochemistry (>1-5%)
 - Mismatch repair deficiency (MMRd)
 - Tumor mutational burden

Brahmer JR et al. N Engl J Med. 2012;366(26):2455-2465

Robert C et al. N Engl J Med. 2015;372(4):320-330

Le DT et al. N Engl J Med 2015;372:2509-2520

Patel SP et al. Mol Cancer Ther. 2015;14(4):847-856

Yarchoan M et al. N Engl J Med. 2017;377(25):2500-2501

PDL-1 expression in histiocytic disorders

- Increased expression of PD-L1 ($\geq 2+$ / $\geq 5\%$) was seen in
 - 3/4 ECD,
 - 7/8 LCH,
 - 1/1 HS
- Another study PD-L1 positivity ($\geq 5\%$)
 - 3/15 cases of LCH (20%)
 - 2/11 cases of RDD (18%)

Gatalica Z et al. Oncotarget. 2015 Aug 14;6(23):19819-25
Xu J et al. Am J Surg Pathol. 2016 Apr;40(4):443-53

Tumor mutational burden

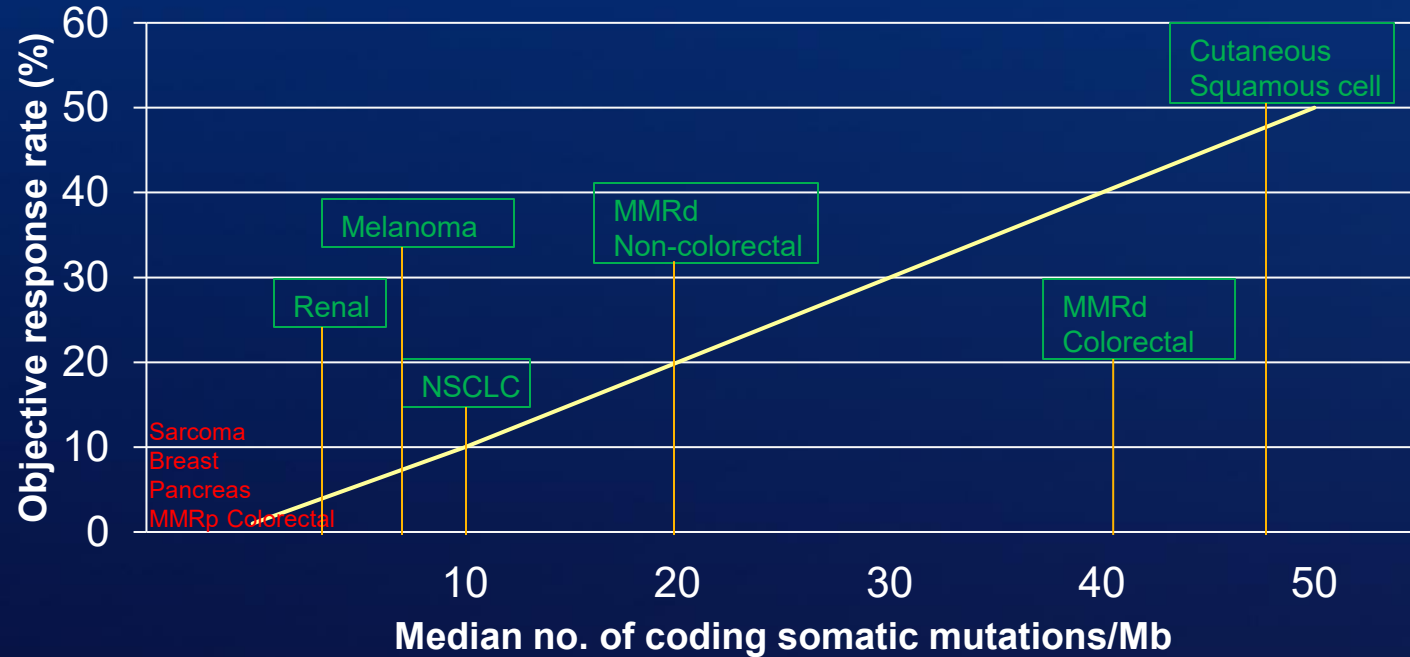
- Number of mutations per coding region within a tumor genome
- Reported as mutations per megabase (mut/Mb)
- Positive correlation with
 - Tumor response to checkpoint inhibitors
 - Mismatch repair deficiency status
 - Germline mutations in mismatch repair genes (MSH2, MSH6, PMS2 and MLH1)

Yarchoan M et al. N Engl J Med. 2017;377(25):2500-2501

Le DT et al. Science. 2017;357(6349):409-413.

Goodman AM et al. Mol Cancer Ther. 2017;16(11):2598-2608

Tumor mutational burden and anti-PD1/PD-L1 therapy



MMRd: mismatch repair-deficient, MMRp: mismatch repair-proficient, NSCLC: non-small-cell lung cancer

Tumor mutational burden and anti-PD1/PD-L1 therapy

All tumor types including melanoma and NSCLC (n = 151)			
Best response	Number of patients	Median TMB (mutations/mb) (Range)	P-value
SD/PD	106	5 (1-115)	<0.0001
CR/PR	45	19 (1-347)	
All tumor types excluding melanoma and NSCLC (n = 63)			
Best response	Number of patients	Median TMB (mutations/mb) (Range)	P-value
SD/PD	51	6 (1-115)	0.0001
CR/PR	12	32 (1-347)	
Patients with melanoma and NSCLC (n = 88)			
Best response	Number of patients	Median TMB (mutations/mb) (Range)	P-value
SD/PD	55	5 (1-92)	0.0003
CR/PR	33	16 (1-133)	

Tumor mutational burden and anti-PD1/PD-L1 therapy

- No response to checkpoint inhibitors with a TMB of <5 mutations/megabase (mut/Mb)
- TMB for malignancies responsive to checkpoint therapy:
 - Melanoma 15 mut/Mb
 - Mismatch repair deficient colorectal cancer 45 mut/Mb

Yarchoan M et al. N Engl J Med. 2017;377(25):2500-2501
Goodman AM et al. Mol Cancer Ther. 2017;16(11):2598-2608

Objective

- To report the TMB and other immunotherapy markers in histiocytic neoplasms

Methods

- Patients with histiocytic neoplasms:
 - Erdheim-Chester disease
 - Rosai-Dorfman disease
 - Langerhans cell histiocytosis
 - Histiocytic sarcoma
- Consented to institutional protocol (IRB #17-006627)
- Tissue genotyping by next generation sequencing (NGS) and correlation with clinical outcomes

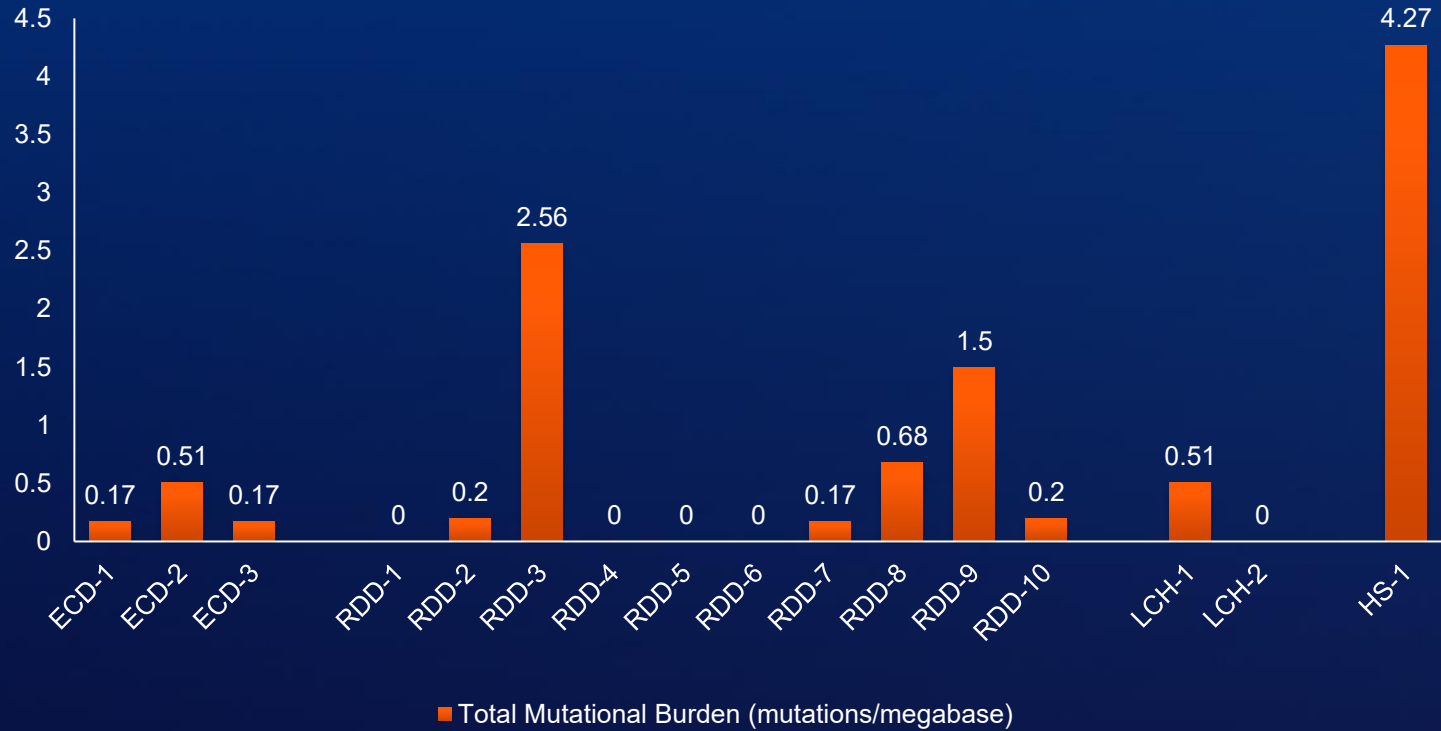
Methods

- NGS method: Tempus xO Assay (Tempus Labs; Chicago)
 - 1,711 gene targeted somatic and germline DNA sequencing panel
 - RNA-sequencing
- Alterations identified:
 - Single nucleotide polymorphisms,
 - Insertions/deletions (indels),
 - Copy number alterations, and
 - Gene rearrangements

Methods

- TMB calculated and reported as somatic mutations in tumor tissue per million base-pairs or mut/Mb
- RNA sequencing to assess for PD-L1 and PD-1 gene expressions as compared to matched tumor and normal reference sets (percentiles)
- DNA mismatch repair status
 - Alterations in mismatch repair genes in somatic and germline DNA (MSH2, MSH6, MLH1, PMS2, and EPCAM)
 - If no alterations, reported as microsatellite stable (MSS)

Results



Results: ECD cohort

- Median TMB 0.19 mut/Mb

Patient ID	Organ involvement	BRAF-status	PD-L-1 expression (percentile)	PD-1 expression (percentile)	DNA mismatch repair status (predicted)
ECD-1	Pituitary, bone, skin	BRAF-WT	NA	NA	NA
ECD-2	Subcutaneous, bone	<i>BRAF-V600E</i>	90	90	MSS
ECD-3	CNS, orbital	<i>BRAF-V600E</i>	60	90	NA

NA: Not available (due to test failure or insufficient sample); MSS: Microsatellite stable; CNS: Central nervous system; WT: wild-type

Results: Other histiocytic neoplasms

Patient ID	Organ involvement	PD-L1 expression (percentile)	PD-1 expression (percentile)	DNA mismatch repair status (predicted)
RDD-1	Lymph nodes	NA	NA	NA
RDD-2	Bone, lymph nodes, skin	30	100	NA
RDD-3	Orbit, bone, skin	100	100	NA
RDD-4	Lymph nodes	NA	NA	MSS
RDD-5	Subcutaneous, bone, lymph node	<10	20	MSS
RDD-6	Subcutaneous	NA	NA	NA
RDD-7	Subcutaneous, soft tissue	NA	NA	NA
RDD-8	Testicular	<10	20	MSS
RDD-9	Testicular	<10	<10	NA
RDD-10	Subcutaneous	NA	NA	NA
LCH-1	Bone	<10	<10	NA
LCH-2	lymph nodes	NA	NA	NA
HS-1	Nasal cavity	NA	NA	NA

NA: Not available (due to test failure or insufficient sample); MSS: Microsatellite stable;
 CNS: Central nervous system

Limitations

- Small sample size
- PD-L1 expression not confirmed with IHC methods
- RNA expression not available for 50% of patients due to lack of enough tissue specimen
- PD-1, PD-L1 and MSI status exploratory and need verification in larger studies

Summary

- ECD, RDD and LCH have low TMB
- Predicts a lack of response to checkpoint inhibitors
- HS has higher TMB than others
 - Rationale for anti-PD1 therapy
 - Case of radiographic response to nivolumab
- *BRAF-V600E* ECD has high PDL-1 expression
- RDD has low PDL-1 expression

Conclusions and future directions

- TMB alone may not predict for a response to checkpoint inhibitor therapy in ECD, RDD and LCH
- Concern for worsening of ECD and LCH with immune checkpoint inhibitors
 - M1 polarization induction
- Further exploration of immunotherapy (and other) markers in larger cohort of patients with histiocytic neoplasms

Stoppacciaro A et al. *Arthritis Rheum.* 2006 Dec;54(12):4018-22

Fleming MD et al. *Blood.* 2003 Apr 1;101(7):2473-5.

Mediavilla-Varela M et al. *Journal of Clinical Oncology* 35, no. 15_suppl.e23090



Thank you

Goyal.Gaurav@mayo.edu



[GauravGoyalMD](#)