Post-ASCO Immunotherapy Highlights (Part 2): Biomarkers for Immunotherapy

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Objectives

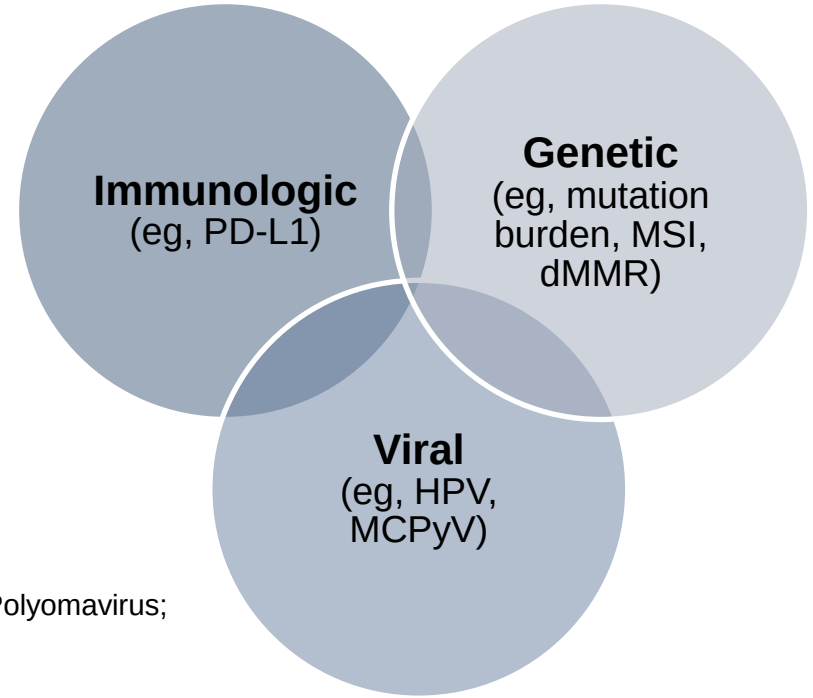
To discuss:

- PD-L1 as a biomarker for PD-1/PD-L1 inhibitors
- Tumor mutation burden as a predictor of response
- Checkpoint inhibition in colorectal cancer with high microsatellite instability or mismatch-repair deficiency
- Role of oncogenic viruses in predicting immunotherapeutic response

ASCO 2016: Biomarkers for Immunotherapy

- Checkpoint inhibitors have demonstrated unprecedented rates of durable responses; however, only a minority of patients respond
- Goal of biomarkers:
  - To predict clinical outcomes
  - To select appropriate patients for immunotherapy

Types of biomarkers for immunotherapy



dMMR: mismatch repair deficiency; MCPyV: Merkel Cell Polyomavirus; MSI: microsatellite instability.

PD-L1 as Biomarker

Complexities/Challenges of PD-L1 as Biomarker for Anti-PD-1/PD-L1 Therapies

- Multiple cell types in the tumor microenvironment can express PD-L1
  - Both tumors cells and tumor infiltrating lymphocytes (TIL)
  - IHC tests can score tumor cells and/or immune infiltrating cells
- Heterogeneity even within a single patient
  - PD-L1 expression can change over time
  - PD-L1 expression may differ at different locations
- Focal PD-L1 expression
  - Can result in sampling error

Topalian SL. Where Does the Truth Lie in Immune Biomarker Development? ASCO Annual Meeting Presentation. 2016.

PD-L1 Expression correlated with Response to Pembrolizumab in NSCLC: KEYNOTE-010

- Analysis of outcomes with PD-L1 categorized as a tumor proportion score (TPS)[1]
  - Phase III randomized study: pembrolizumab improved OS over docetaxel in previously-treated, PD-L1+ NSCLC[2]

Pembro/Doce	TPS 1%-24%	TPS 25%-49%	TPS 50%-74%	TPS ≥75%
mOS (mo)	9.7/8.5	9.8/9.9	15.8/8.2	16.6/8.2
mPFS (mo)	2.6/4.0	2.9/3.8	4.3/4.3	6.2/4.0
ORR (%)	8.6/10.9	15.8/9.1	22.6/9.6	33.7/7.0

- Increasing PD-L1 expression was associated with more favorable outcomes with pembrolizumab, but not with docetaxel
- Pembrolizumab improved OS over docetaxel even at the lowest TPS category
- PD-L1- patients were excluded in the study

Doce: docetaxel; mOS: median overall survival; mPFS: median progression-free survival; ORR: objective response rate.

1. Baas P, et al. J Clin Oncol. 2016;34 (suppl); Abstract 9015; 2. Herbst RS, et al. Lancet. 2016; 9; 387(10027):1540-50.

Nivolumab and Pembrolizumab Showed High Response in Hodgkin Lymphoma

- Reed-Sternberg cells uniformly demonstrate copy number alterations of the PD-L1 and PD-L2 loci on 9p24.1[1]
- 2 phase II studies in relapsed/refractory classical Hodgkin lymphoma: CheckMate-025 (nivolumab)[2] and KEYNOTE-087 (pembrolizumab)[3]

	Nivolumab 3mg/kg Q2W (n=80)[2]	Pembrolizumab 200 mg Q3W (n=90)[3]
mPFS	10.0 mo	-
ORR	66%	73%-83%
mDOR	7.8 mo	-
Grade 3/4 TRAE	25%	4%
Discontinuation	4%	2%

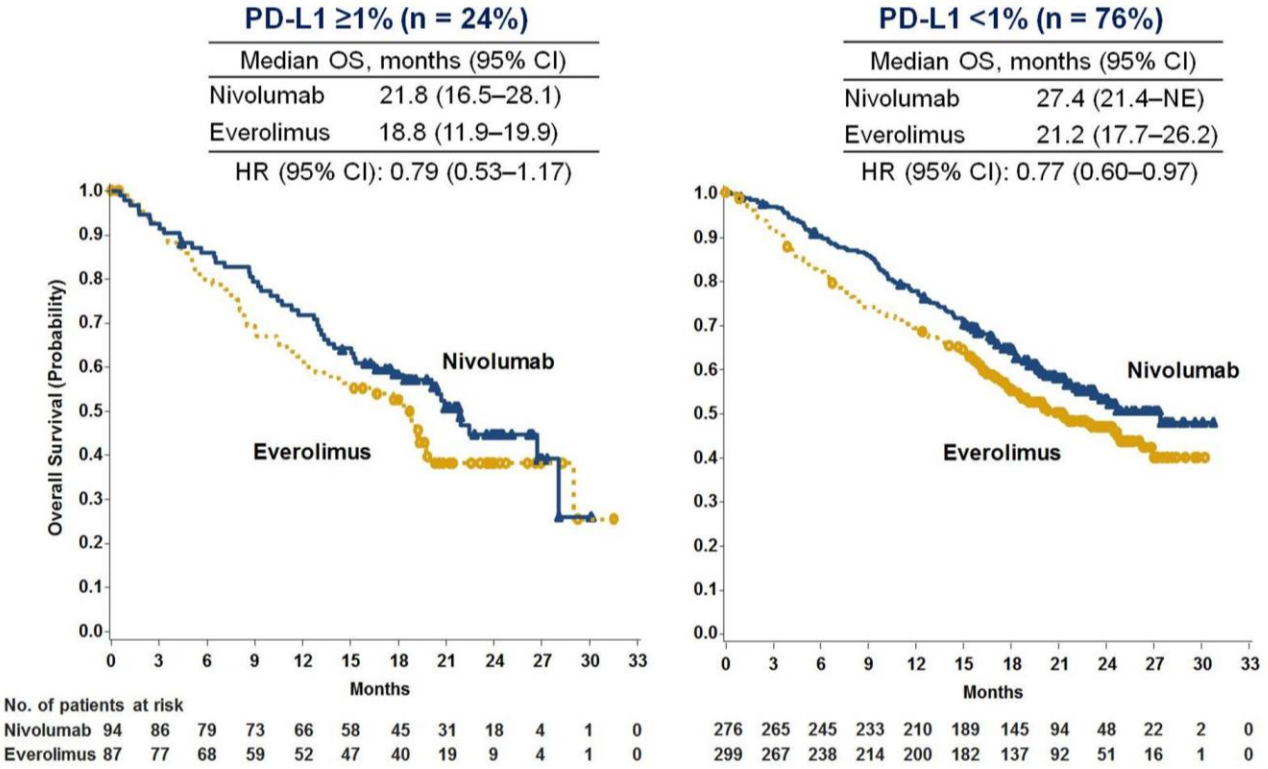
Nivolumab approved by the FDA on May 17, 2016 for cHL that has relapsed or progressed after autologous HSCT and post-transplant brentuximab vedotin

cHL: classical Hodgkin lymphoma; HSCT: hematopoietic stem cell transplantation; mDOR: median duration of response; mPFS: median progression-free survival; ORR: objective response rate; TRAE: treatment-related adverse event.

1. Ansell SM, et al. N Engl J Med. 2015 Jan 22;372(4):311-9; 2. Younes A, et al. J Clin Oncol. 2016; 34(suppl); abstract 7535; 3. Chen RW, et al. J Clin Oncol. 2016; 34(suppl); abstract 7555.

PD-L1 Expression Did Not Predict for Clinical Benefit of Nivolumab in RCC

- CheckMate-025: Phase III randomized study
  - Advanced RCC after 1-2 antiangiogenic therapy (n=821)
  - Nivolumab significantly improved ORR and OS over everolimus



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1. Sharma P. PD-1/PD-L1 as predictive biomarkers: where do we stand? ASCO Annual Meeting Presentation. 2016; 2. Motzer RJ, et al. N Engl J Med. 2015 Nov 5;373(19):1803-13.

PD-L1 Negative Patients Can Respond to Anti-PD-1/PD-L1 Therapies

- Across cancer types:
  Although PD-L1 expression is associated with higher response rates, PD-L1- patients can still respond

Data presented at ASCO 2016 on solid tumors

Tumor type	Therapy	ORR for PD-L1 <1%
HNSCC	2L Nivolumab[1]	12%
Melanoma	1L+ Pembrolizumab + ipilimumab[2]	45%
NSCLC	1L Nivolumab[3] 1L Nivolumab + ipilimumab[3]	14% 0-30%
Urothelial carcinoma	2L Atezolizumab[4] 2L Durvalumab[5]	8% 7%

Cannot exclude PD-L1- patients from anti-PD-1/PD-L1 therapies

HNSCC: head and neck squamous cell carcinoma; NSCLC: non-small cell lung cancer; ORR: objective response rate.

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1. Ferris RL, et al. J Clin Oncol. 2016;34 (suppl); Abstract 6009; 2. Long GV, et al. ASCO Annual Meeting. 2016. Abstract 9506; 3. Hellmann MD, et al. ASCO Annual Meeting. 2016. Abstract 3001; 4. Dreicer R, et al. ASCO Annual Meeting. 2016. Abstract 4515; 5. Massard C, et al. ASCO Annual Meeting. 2016. Abstract 4502.

Tumor Mutation Burden as Biomarker

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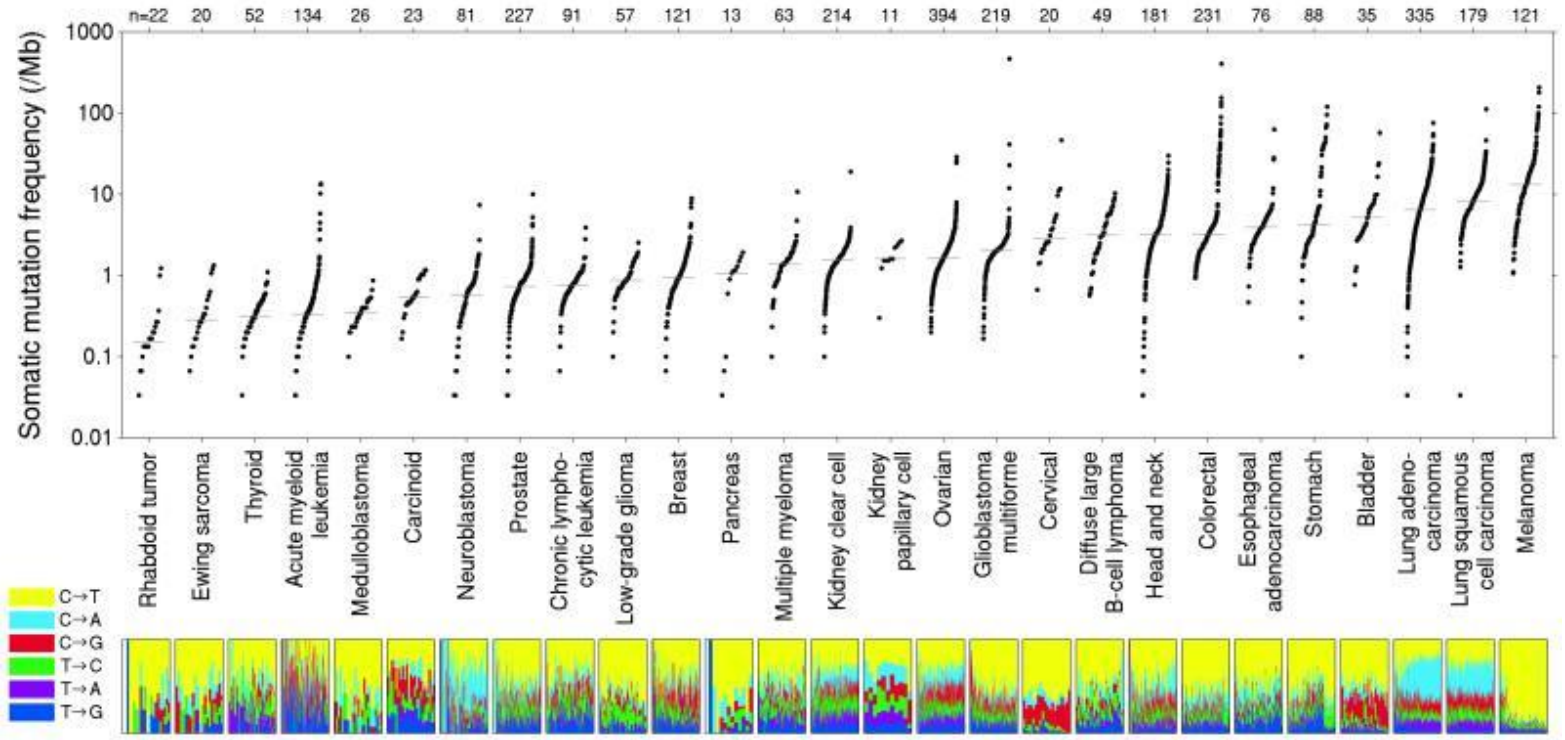
Tumor Mutation Burden (TMB) in Different Cancer Types

Somatic mutation frequencies observed in exomes from 3,083 tumor-normal pairs



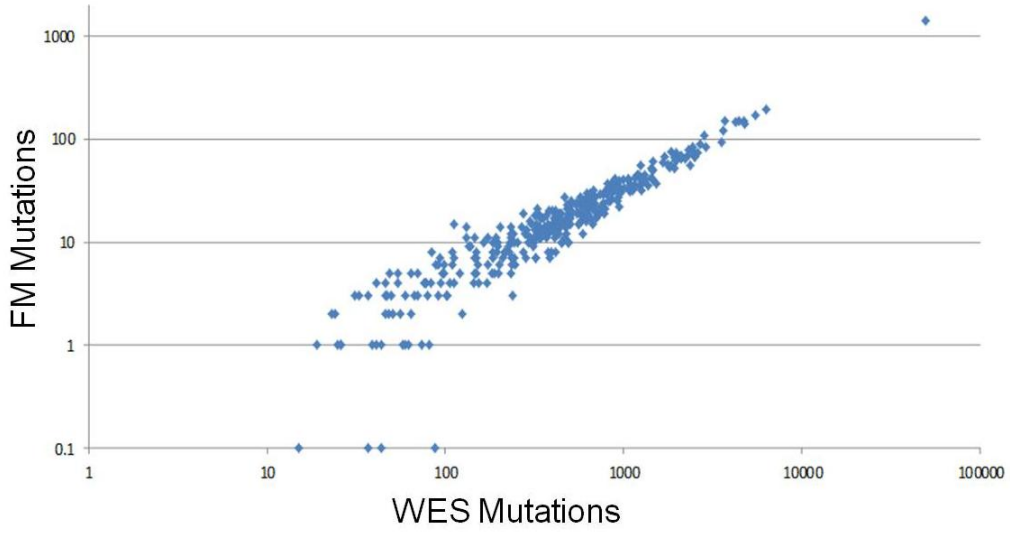
Each dot corresponds to a tumor-normal pair, with vertical position indicating the total frequency of somatic mutations in the exome.

Lawrence MS, et al. Nature. 2013 Jul 11;499(7457):214-218.

Determining TMB by Limited Gene Sets vs. Whole Exome Sequencing (WES)

- Profiling a smaller fraction of the genome could serve as an accurate surrogate for TMB
- HC NGS of the coding sequence of 236-315 genes compared with WES

Mutations in limited gene set vs. WES



TMB as determined by HC NGS in 236-315 genes strongly correlated with WES mutation load

HC NGS: hybrid capture-based next-generation sequencing; TMB: tumor/total mutation burden.

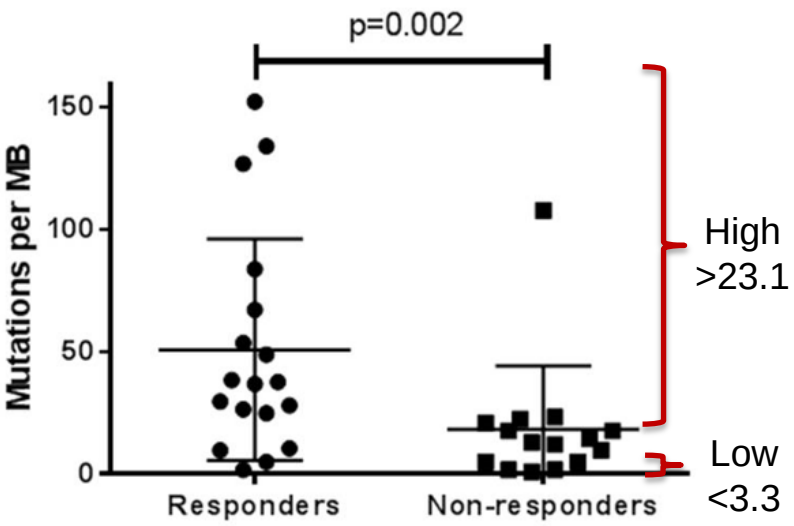
Johnson DB, et al. J Clin Oncol. 2016; 34(suppl); abstr 105.

TMB Correlated with Immunotherapy Response in Melanoma

- 65 melanoma patients treated with anti-PD-1/PD-L1 (nivolumab, pembrolizumab, atezolizumab)
- Initial cohort and validation cohort

TMB (mut/MB)	Response	No response
High: >23.1	85%	15%
Intermediate: 3.3-23.1	29%	71%
Low: <3.3	14%	86%

Validation cohort

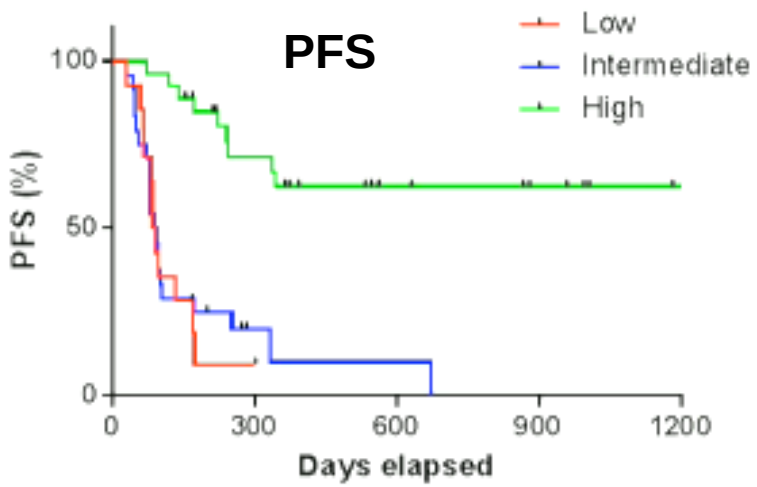


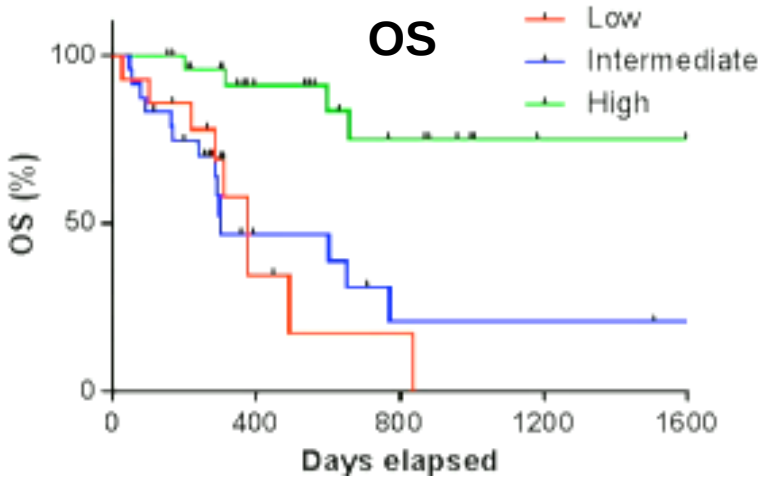
Responders to anti-PD-1/PD-L1 had higher mutation burden than non-responders

HC NGS: hybrid capture-based next-generation sequencing; TMB: tumor/total mutation burden.

Johnson DB, et al. J Clin Oncol. 2016; 34(suppl); abstr 105.

TMB Correlated with Immunotherapy Outcome in Melanoma (continued)





High TMB	Intermediate	Low	*P* value
Not reached	89 days	86 days	<0.001

High TMB	Intermediate	Low	*P* value
Not reached	300 days	375 days	<0.001

Patients with high TMB had higher PFS and OS compared with patients with intermediate and low TMB

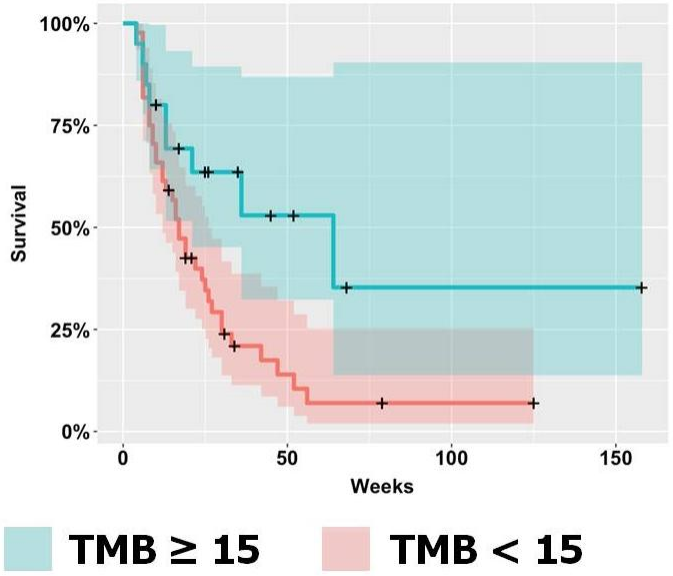
OS: overall survival; PFS: progression-free survival; TMB: tumor/total mutation burden.

Johnson DB, et al. J Clin Oncol. 2016; 34(suppl); abstr 105.

TMB Correlated with Time on Immunotherapy in NSCLC

- Comprehensive genomic profiling (CGP) to assess TMB and MSI status
- Analysis of 64 NSCLC patients

TMB (mut/MB)	Median time on anti-PD-1/PD-L1	
≥15	64 weeks	(HR, 0.396; 95% CI, 0.190-0.825; *P*=0.010)
<15	17 weeks	
≥12.1	27 weeks	(HR, 0.619; 95% CI, 0.339-1.127; *P*=0.117)
<12.1	17 weeks	



- High TMB correlated with longer duration of anti-PD-1/PD-L1 therapy (nivolumab/pembrolizumab/avelumab)
- MSI-H status strongly correlated with high TMB

MSI-H: microsatellite instability high; mut: mutations; NSCLC: non-small cell lung cancer; TMB: tumor/total mutation burden.

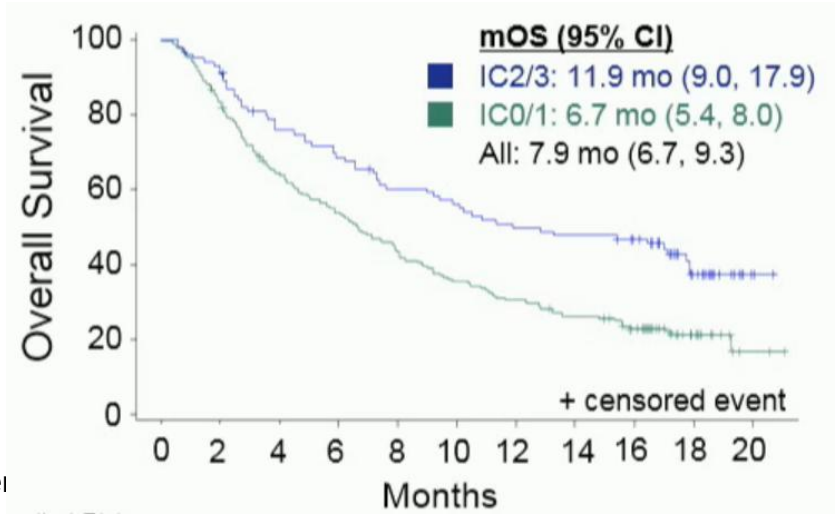
Spigel DR, et al. J Clin Oncol. 2016; 34(suppl); abstr 9017.

Biomarkers of Outcome to Atezolizumab in Urothelial Cancer

- Exploratory analysis of biomarkers of response to atezolizumab
  - IMvigor210 study: metastatic urothelial cancer (n=310)
  - Focus on PD-L1, Cancer Genome Atlas (TCGA) subtype, TMB

PD-L1 status and outcome

PD-L1 status	ORR
IC2/3	28%
IC0/1	10%
All	16%



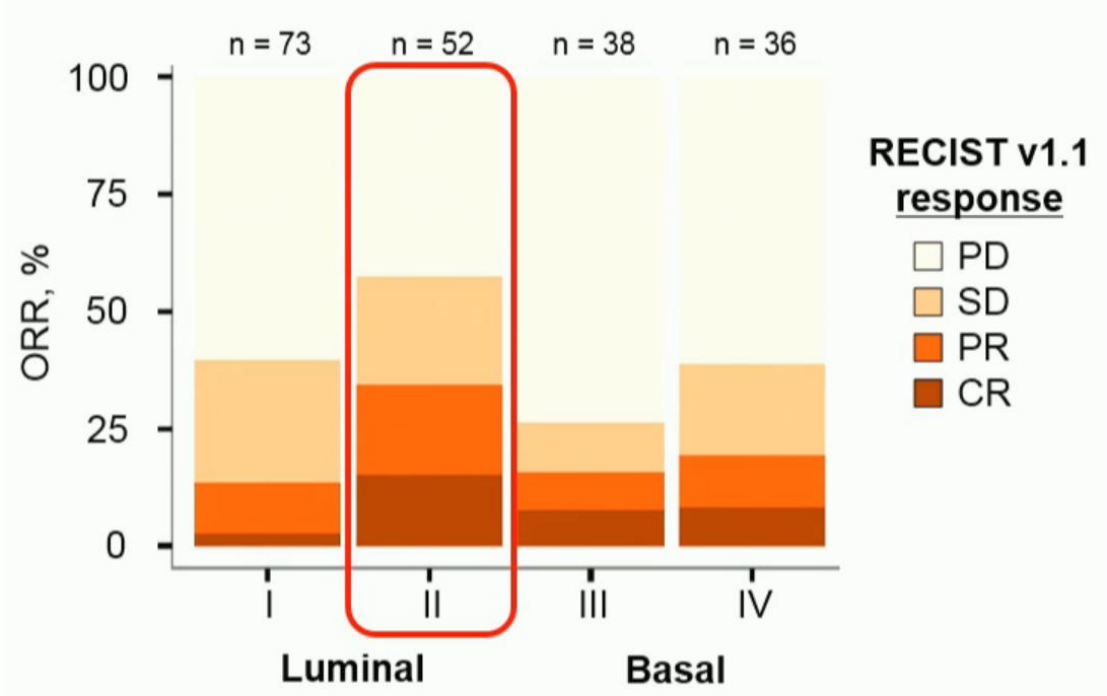
IC: immune cells; TMB: tumor/total mutation burde

Rosenberg JE, et al. J Clin Oncol. 2016; 34(suppl); abstr 104.

Biomarkers of Outcome to Atezolizumab in Urothelial Cancer (continued)

- ORR significantly higher in luminal II vs. other subtypes (*P*=0.0072)

TCGA subtype and outcome

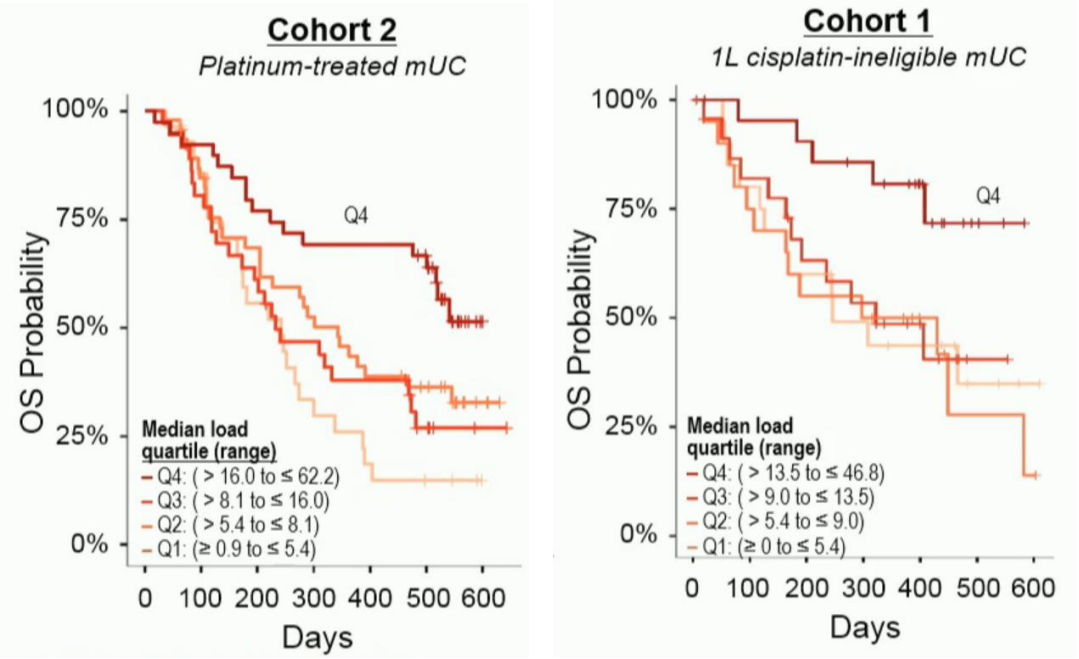


Rosenberg JE, et al. J Clin Oncol. 2016; 34(suppl); abstr 104.

Biomarkers of Outcome to Atezolizumab in Urothelial Cancer (continued)

- Highest TMB quartile was associated with improved OS with atezolizumab
- Both in pretreated (cohort 2) and previously untreated patients (cohort 1)

TMB and outcome



PD-L1, TCGA subtype, and TMB are significant independent predictors of response to atezolizumab

Rosenberg JE, et al. J Clin Oncol. 2016; 34(suppl); abstr 104.

Microsatellite Instability and Mismatch Repair Deficiency as Biomarkers

Microsatellite Instability (MSI) and Mismatch Repair Deficiency (dMMR)

MSI: hypermutable phenotype with changes in microsatellites (short, tandem repeat sequences of DNA)[1]

- Categories: MSI-high, MSI-low, MSS (microsatellite stable)

MSI caused by DNA mismatch repair (MMR) deficiency (dMMR)[2]

- dMMR due to inactivating mutations of MMR genes:
  MLH1, MLH3, MSH2, MSH3, MSH6, PMS1, PMS2
- MSI-H mainly due to inactivation of *MLH1*

MSI-H represents 15% of colorectal cancer (CRC)[3]

- MSI-H associated with improved OS in CRC

1. Lech G, et al. World J Gastroenterol. 2016 Feb 7;22(5):1745-55; 2. Peltomaki P. Hum Mol Genet. 2001 Apr;10(7):735-40.; 3. Boland CR, et al. Cancer Res. 1998 Nov 15;58(22):5248-57.

Nivolumab ± Ipilimumab Showed Activity in mCRC with MSI-H: CheckMate-142

- In CRC, MSI-H is associated with increase in immune infiltration and expression of checkpoint regulators
- Interim analysis of CheckMate-142: phase 2 study
  - MSI-H cohort and MSS cohort treated by nivolumab ± ipilimumab

	MSI-H cohort (n=100)		MSS cohort (n=20)	
	Nivo 3	**Nivo 3 + ipi 1**	**Nivo 1 + ipi 3**	**Nivo 3 + ipi 1**
ORR	25%	33%	10%	0
mPFS	5.3 mo	Not reached	2.3 mo	1.3 mo
mOS	17.1 mo	Not reached	11.5 mo	3.7 mo
Discontinuation	5.7%	13.3%	50%	20%

Nivolumab and ipilimumab demonstrated durable responses in MSI-H mCRC

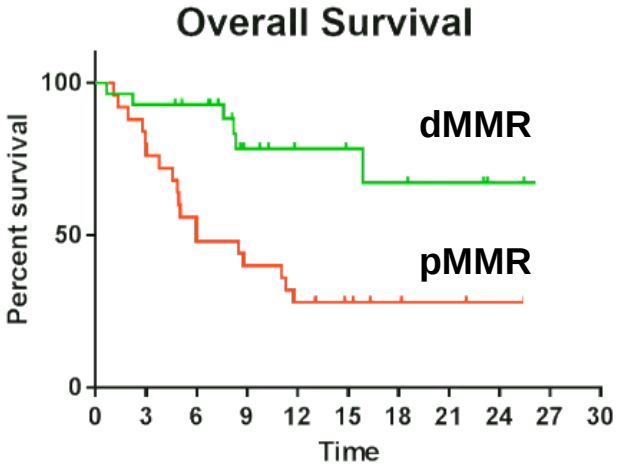
Ipi: ipilimumab; mCRC: metastatic colorectal cancer; MSI-H: microsatellite instability high; MSS: microsatellite stable; nivo: nivolumab.

Overman MJ, et al. J Clin Oncol. 2016; 34(suppl); abstr 3501.

Pembrolizumab Showed Activity in MMR-Deficient CRC

- Genetic and epigenetic defects in MMR lead to MSI-H
  - MMR deficiency associated with Lynch Syndrome
- Phase II study: pembrolizumab in refractory MMR deficient (dMMR) and MMR proficient (pMMR) CRC

	CRC cohort (n=53)	
	dMMR	**pMMR**
ORR	57%	0%
mPFS	Not reached	2.3 mo
mOS	Not reached	6.0 mo
Grade 3/4 AE	<5%	



Complete and durable responses seen in more than 50% of patients

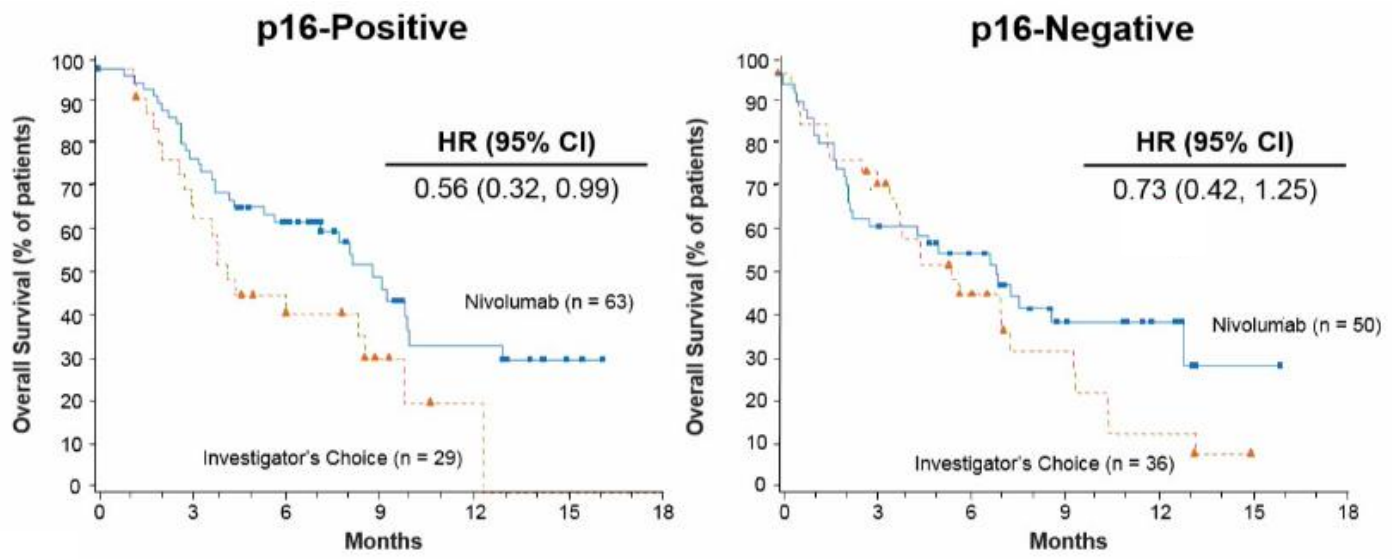
AE: adverse events; CRC: colorectal cancer; MMR: mismatch repair; MSI-H: microsatellite instability high.

Le DT, et al. J Clin Oncol. 2016; 34(suppl); abstr 103.

Oncogenic Viruses as Biomarkers

Trend Towards Higher Benefit of Nivolumab for HPV-Positive HNSCC

- CheckMate 141: phase III randomized study of nivolumab vs. investigator's choice
  - Recurrent or metastatic HNSCC (n=361)
- Documentation p16 for HPV status (oropharyngreal)



HNSCC: head and neck squamous cell carcinoma.

Ferris RL, et al. J Clin Oncol. 2016;34 (suppl); Abstract 6009.

Trend Towards Higher Response to Pembrolizumab for HPV-Positive HNSCC

- KEYNOTE-055: single-arm phase II
  - Pembrolizumab for recurrent or metastatic HNSCC after progression on platinum and cetuximab (n=172)

	HPV + (n=18)	HPV – (n=74)
ORR	4 (22%)	12 (16%)
PR	4 (22%)	12 (16%)
SD	3 (17%)	14 (19%)
PD	9 (50%)	42 (57%)

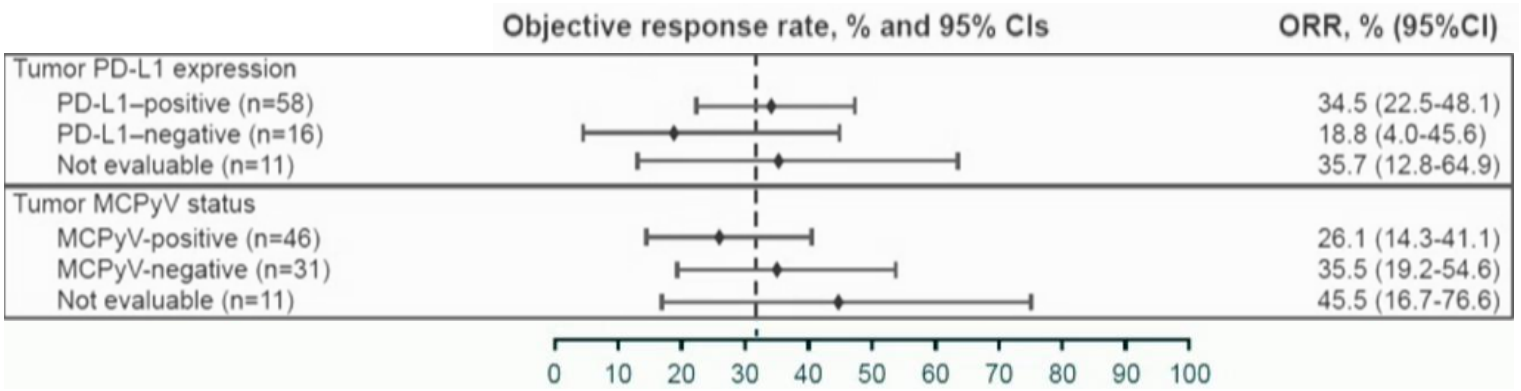
- Preliminary data show trend towards higher response or benefit of anti-PD-1 therapy in HPV positive patients
- More data is warranted

HNSCC: head and neck squamous cell carcinoma; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease.

Bauml J, et al. J Clin Oncol. 2016;34 (suppl); Abstract 6011.

MCPyV Status and PD-L1 Expression Did Not Impact Response to Avelumab in MCC

- Merkel Cell Polyomavirus (MCPyV) negative tumors have higher mutation burden
- JAVELIN Merkel 200: phase 2 study of avelumab (anti-PD-L1) in MCC (n=88)



Avelumab showed activity in MCC regardless of MCPyV or PD-L1 status

MCC: Merkel cell carcinoma.

Kaufman H, et al. J Clin Oncol. 2016;34 (suppl); Abstract 9508.

2016 ASCO Annual Meeting: Summary

- PD-L1 expression correlated with response to pembrolizumab in NSCLC
- Nivolumab and pembrolizumab showed high response in Hodgkin Lymphoma
- PD-L1 expression did not predict for clinical benefit of nivolumab in RCC
- PD-L1 negative patients can respond to anti-PD-1/PD-L1 therapies

2016 ASCO Annual Meeting: Summary (Continued)

- TMB correlated with immunotherapy outcome in melanoma and with time on immunotherapy in NSCLC
- PD-L1, TCGA subtype, and TMB are significant independent predictors of response to atezolizumab
- Nivolumab and ipilimumab demonstrated durable responses in MSI-H mCRC
- Pembrolizumab showed activity in MMR-deficient CRC
- Preliminary data show trend towards higher response or benefit of anti-PD-1 therapy in HPV positive patients
- Avelumab showed activity in MCC regardless of MCPyV or PD-L1 status

Questions?

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3. Herbst RS, et al. Lancet. 2016; 9; 387(10027):1540-50.
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12. Dreicer R, et al. J Clin Oncol. 2016; 34(suppl); Abstract 4515.
13. Massard C, et al. J Clin Oncol. 2016; 34(suppl); Abstract 4502.
14. Lawrence MS, et al. Nature. 2013 Jul 11;499(7457):214-218.
15. Johnson DB, et al. J Clin Oncol. 2016; 34(suppl); Abstract 105.
16. Spigel DR, et al. J Clin Oncol. 2016; 34(suppl); Abstract 9017.
17. Rosenberg JE, et al. J Clin Oncol. 2016; 34(suppl); Abstract 104.
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21. Overman MJ, et al. J Clin Oncol. 2016; 34(suppl); Abstract 3501.
22. Le DT, et al. J Clin Oncol. 2016; 34(suppl); Abstract 103.
23. Ferris RL, et al. J Clin Oncol. 2016;34 (suppl); Abstract 6009.
24. Bauml J, et al. J Clin Oncol. 2016;34 (suppl); Abstract 6011.
25. Kaufman H, et al. J Clin Oncol. 2016;34 (suppl); Abstract 9508.