Innovation and Current Topics in Oncology Drug Development: Industry Perspective

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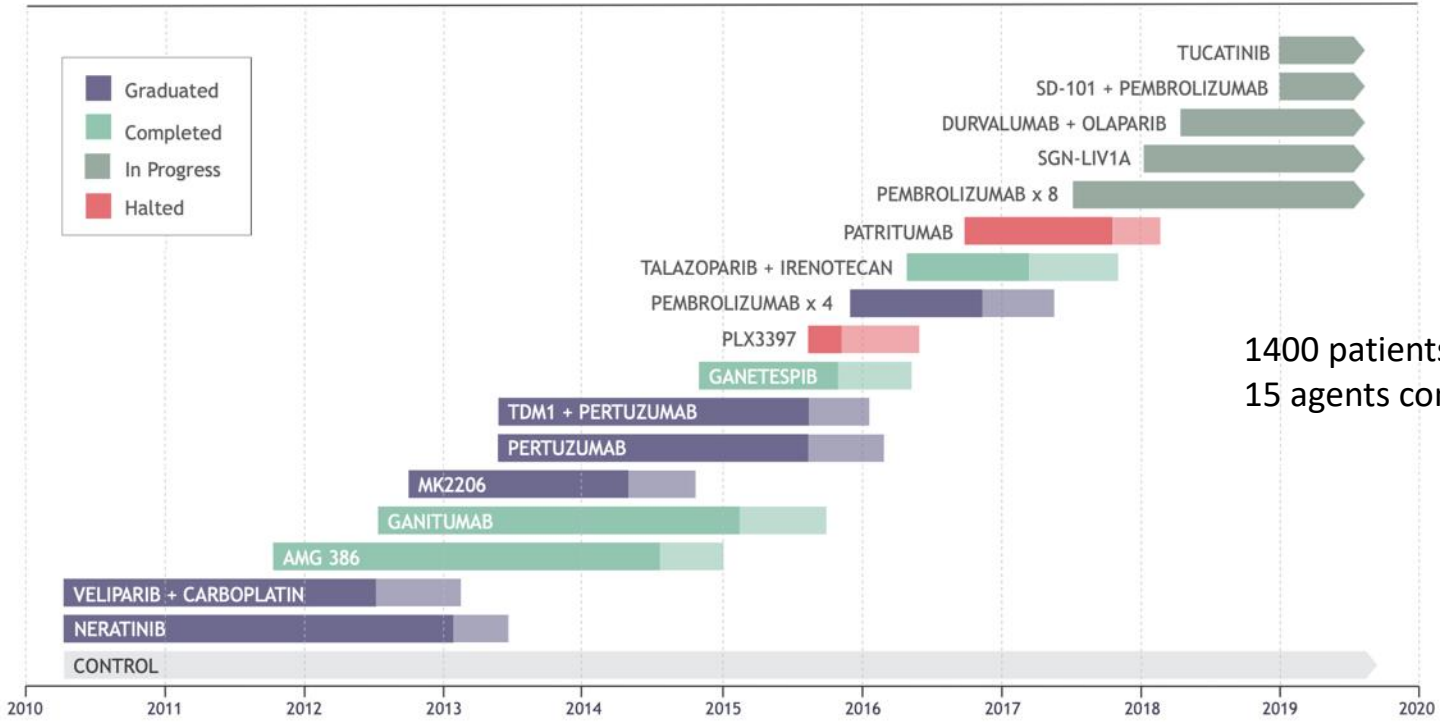
INNOVATION IN CLINICAL TRIALS - USE OF UMBRELLA/PLATFORM STUDIES TO EFFICIENTLY EVALUATE PREDICTIVE BIOMARKERS

Early and Lasting Example – ISPY 2 Platform

- Phase II, adaptively-randomized neoadjuvant breast cancer trial
  - Initiated in 2010
  - Goal is to identify drugs/combinations to take to phase III
- Simultaneous experimental arms
  - Match therapies with breast cancer subtypes
  - Comparator: standard neoadjuvant therapy (T-AC)
  - Endpoint: pathologic complete response (pCR)
  - Endpoint is assessed in 10 pre-specified "biomarker signatures": HR, HER2, and Mammaprint
- Adaptive randomization minimizes number of patients needed to determine efficacy for a particular biomarker subgroup
- "Graduation" for efficacy = reaching threshold predictive probability of success in a subsequent phase III trial of 300 patients

https://www.ispytrials.org/i-spy-platform/i-spy2

I-SPY 2 Agent Timeline



1400 patients enrolled
15 agents completed evaluation

https://www.ispytrials.org/results/past-agents

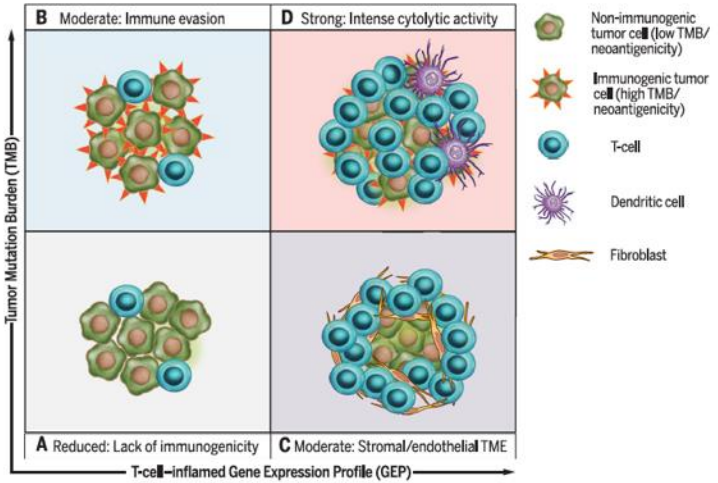
I-SPY2 Example - Pembrolizumab Combination Graduated in all HER2- signatures, both HR+ and Triple Negative

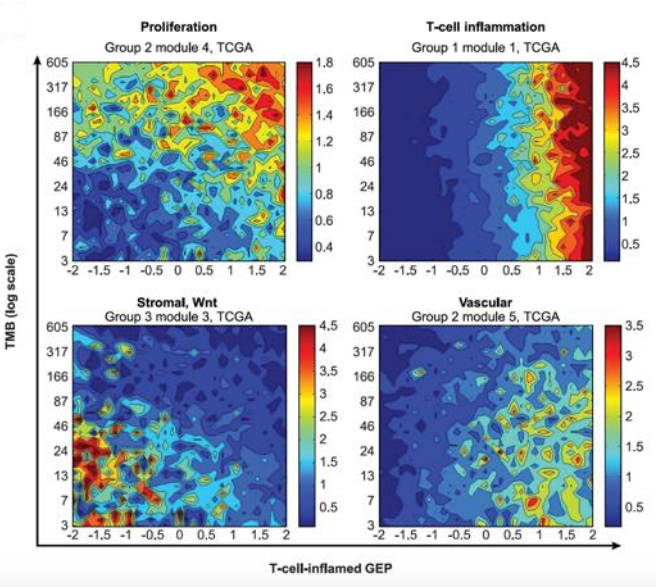
Signature	Estimated pCR Rate (95% Probability Interval)		Probability Pembro Superior to Control	Predictive Probability of Success in Phase 3
	Pembro	Control		
HER2-	**0.44** (0.33 – 0.55)	**0.17** (0.11 – 0.23)	>0.999	0.985
HR-HER2-	**0.60** (0.44 – 0.75)	**0.22** (0.13 – 0.30)	>0.999	0.996
HR+HER2-	**0.30** (0.17 – 0.43)	**0.13** (0.07 – 0.19)	0.996	0.834

Nanda R, Liu MC, Yau C, et al. Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BC): Results from I-SPY 2 . 2017 American Society of Clinical Oncology Annual Meeting

UMBRELLA STUDY EXAMPLE 2 - USING A CLINICAL-GENOMICS DATABASE TO SELECT COMBINATION TARGETS FOR PEMBROLIZUMAB

Tumor Mutational Burden and an Inflamed Gene Expression Profile Used to Identify Targets for Specific Tumor Subgroups

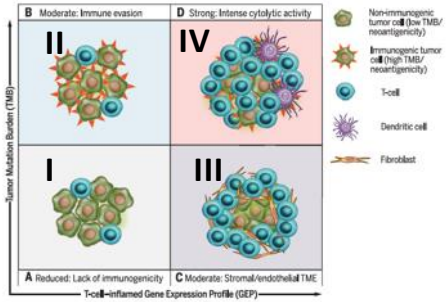


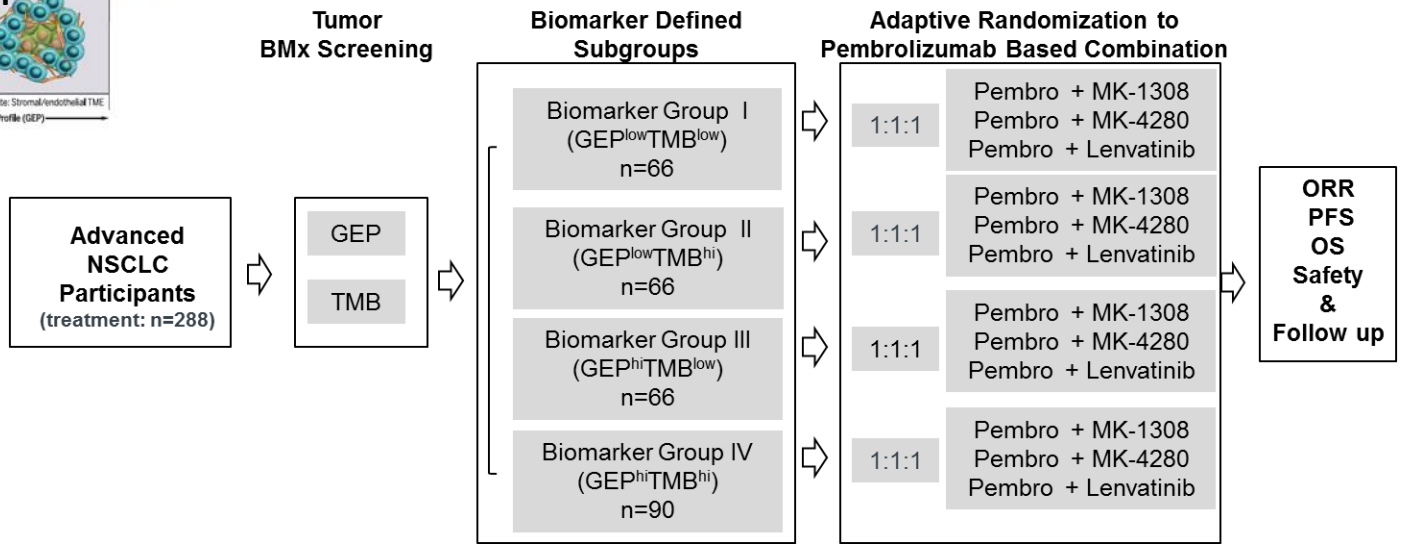


- Evaluated pre-treatment biopsies taken from >300 patients treated with pembrolizumab, including 22 cancer types
- Using training and validation approach, evaluated ~40 modules of pathway gene signatures, each consisting of ~100-200 genes
- 4 pathway gene signatures had distinct patterns in relation to T-cell inflamed GEP and TMB status
- These upregulated pathways represent potential resistance mechanisms and thus combination approaches
- Different combinations may benefit different patients according to GEP/PD-L1 and TMB status

Cristescu R , Mogg R , Ayers M , *et al* . Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy. Science 2018;**362**:eaar3593

Evaluation of Optimal Pembrolizumab Combinations for Individual NSCLC Patients - KeyImPaCT (Keynote-495)





ClinicalTrials.gov Identifier: NCT03516981

INNOVATION IN CLINICAL TRIALS - APPROACHES TO ENABLE RAPID DEVELOPMENT IN ADVANCED CANCER POPULATIONS

1. Approach to defining a patient population refractory to immunotherapy
2. Use of external data to support single arm submissions

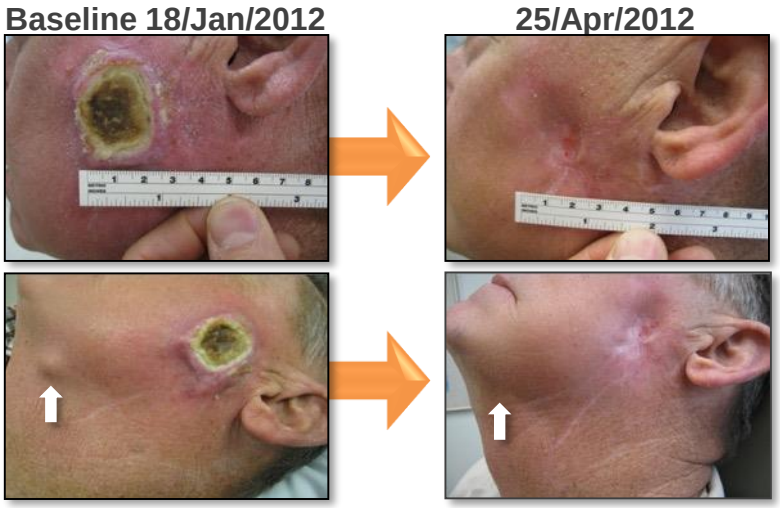
How to Define an Anti-PD-1 Refractory Population?

- “Pseudoprogression” can confound characterization of a refractory population
- Friends of Cancer Research Annual Meeting 2019: “Immuno-Oncology Drug Development for Patients with Disease Progression After Initial anti-PD-(L)1 Therapy”
- Among 6 sponsors, 3 used a harmonized definition of refractory disease within the company
- Important considerations:
  - dose or length of anti-PD-(L)1 therapy that was used before disease progression
  - confirming progression of disease, including the type of scan, and the timing at which this scan would be done
  - timing of progression in relation to last dose of anti-PD-(L1)1 therapy and most recent treatment

https://www.focr.org/sites/default/files/pdf/Panel-2_Combo_IO_Tx_2019AM.pdf

Example: First in Human Study for Pembrolizumab Keynote-001

- Initiated in 2011 - 3+3 dose escalation with expansion cohort in melanoma, estimated sample size 32
- Striking responses observed in initial melanoma patients enrolled in dose escalation cohort
  - Led to increase in expansion cohort sample size to 60, including patients who progressed on ipilimumab



Courtesy of
A. Ribas, MD,
B. Chimielowski, MD
P. Tumeh, MD

54-yr-old male with desmoplastic melanoma, progressed on ipilimumab

Hamid et al NEJM, 2013

Approach to Defining an Ipilimumab-Refractory Cohort

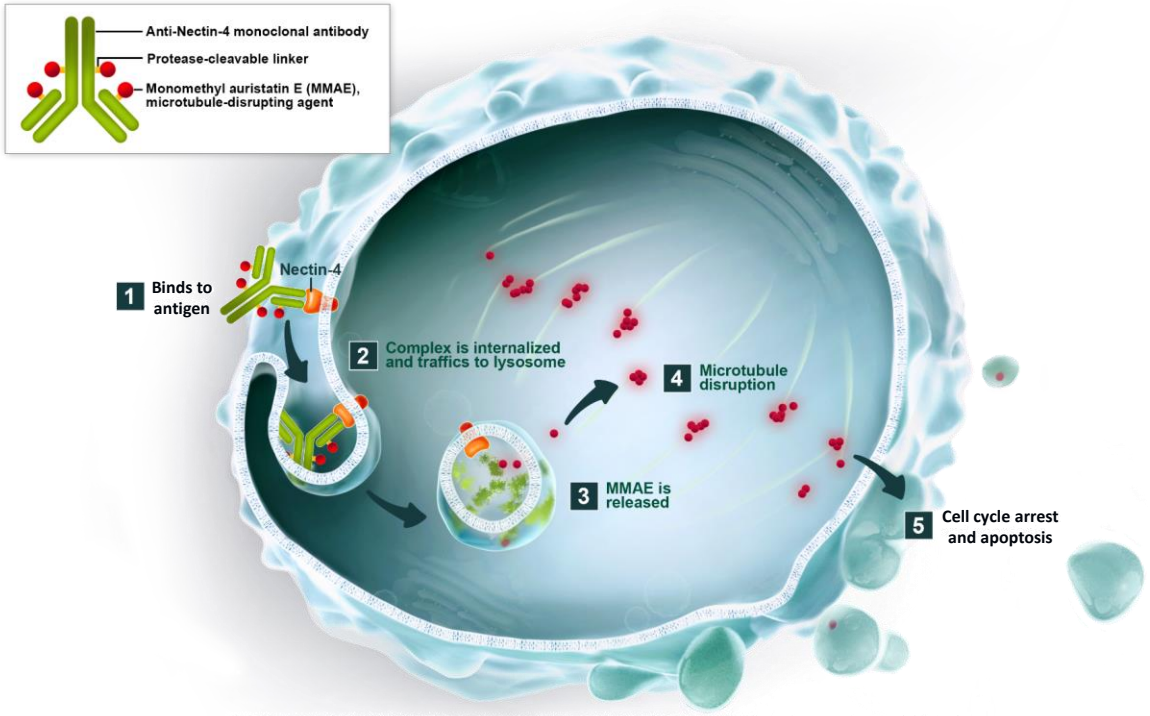
- Given preliminary evidence of activity in patients who progressed on ipi, added ipi-refractory cohort B2 to evaluate efficacy in a strictly defined population with high unmet need
  - Discussed cohort design with FDA to allow for potential accelerated approval
  - To address concern over pseudoprogression, required previous treatment with at least two doses of ipilimumab 3 mg/kg or higher administered every 3 weeks
  - Confirmed disease progression using immune-related response criteria within 24 weeks of the last dose of ipilimumab (confirmatory CT scan required)
- Randomized cohorts to confirm recommended dose of 2 mg/kg (vs 10 mg/kg) Q3W
- 80 ipilimumab-refractory patients at each dose
  - 85% power to detect a 15% difference in ORR between the two doses at 10% type 1 error (one-sided) when the ORR in the inferior group was 10%
- ORR 26% for both doses, median duration of response not reached at time of analysis (median follow-up 8 months)

Robert et al., Lancet 2014

First Approval of Pembrolizumab in an Ipilimumab-Refractory Population

- On September 4, 2014, pembrolizumab (Keytruda) was granted accelerated approval for the treatment of patients with unresectable or metastatic melanoma with disease progression following treatment with ipilimumab (Yervoy) and, in *BRAF* V600 mutation–positive patients after treatment with a BRAF inhibitor.

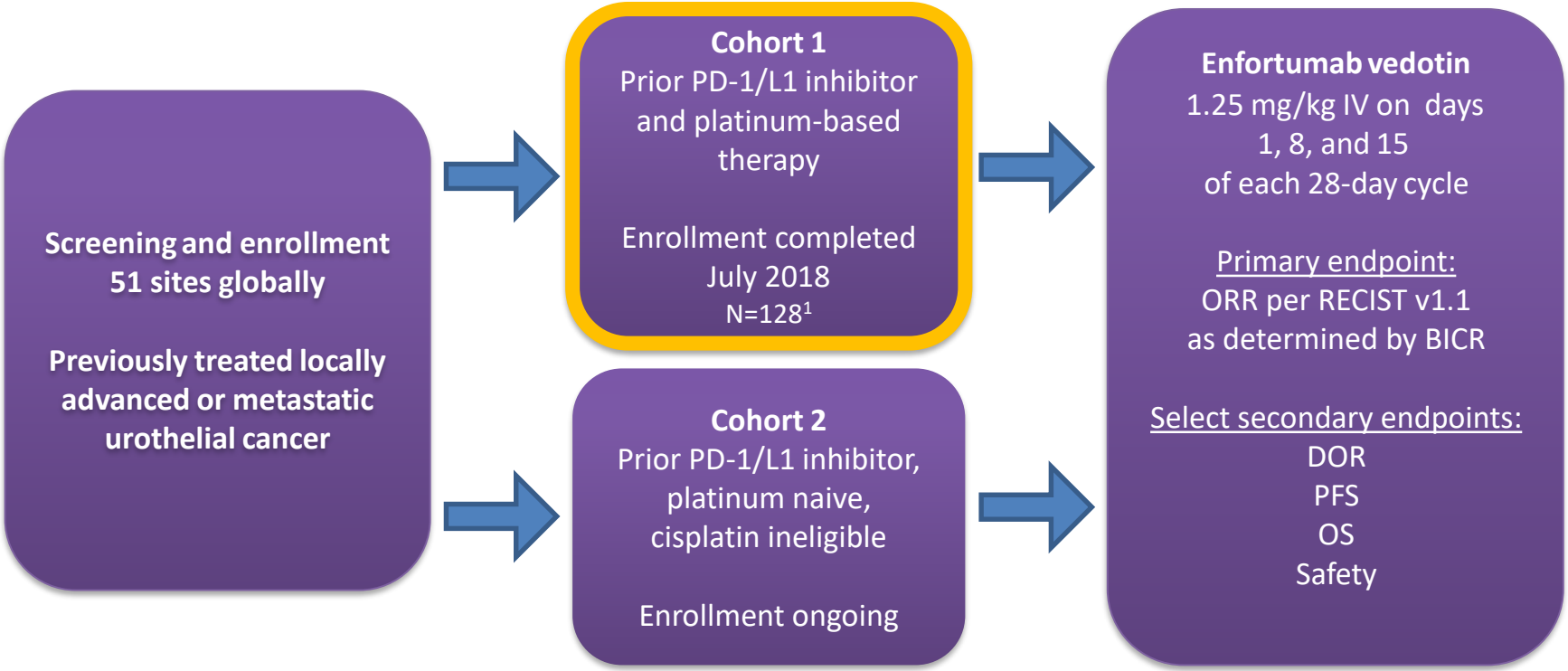
Enfortumab Vedotin: Nectin-4 Targeted Therapy



Enfortumab vedotin (ASG-22ME) is an investigational agent, and its safety and efficacy have not been established.
Enfortumab vedotin is being developed in collaboration with Astellas Pharma Inc.

Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

EV-201: Single-Arm, Pivotal Phase 2 Trial



[1] 3 patients did not receive enfortumab vedotin treatment: one each due to clinical deterioration, patient decision, and low hemoglobin after enrollment

BICR=blinded independent central review; DOR=duration of response; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

SeattleGenetics | astellas

EV-201: Cohort 1 Objective Response Rate with Enfortumab Vedotin

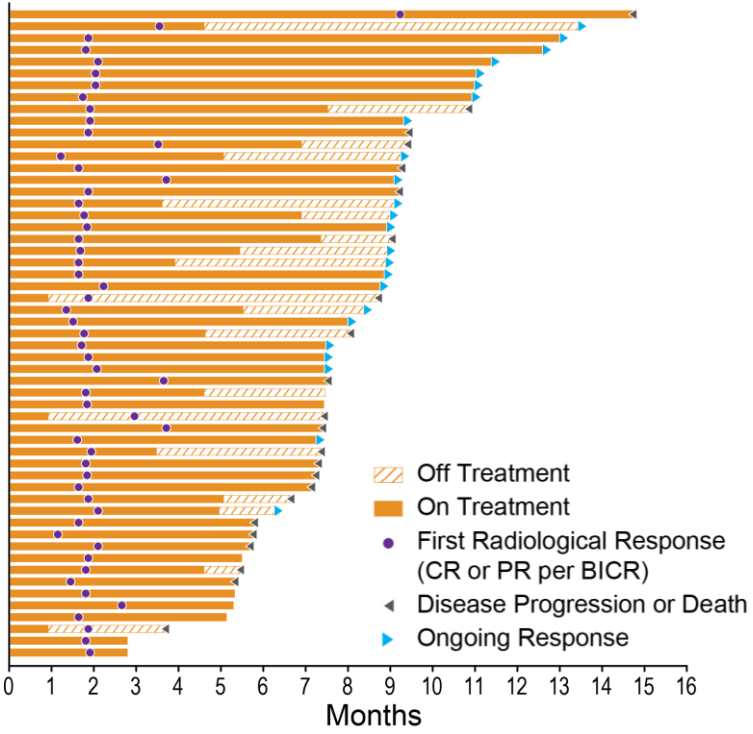
ORR per RECIST v 1.1 assessed by BICR	Patients (N=125) n (%)
Confirmed objective response rate	**55 (44)**
95% confidence interval[1]	(35.1, 53.2)
Best overall response per RECIST (v. 1.1)	
Complete response	15 (12)
Partial response	40 (32)
Stable disease	35 (28)
Progressive disease	23 (18)
Not evaluable[2]	12 (10)

[1] Computed using the Clopper-Pearson method

[2] Includes 10 patients who discontinued study prior to post-baseline response assessment, 1 patient who had uninterpretable post-baseline assessment, and 1 patient whose post-baseline assessment did not meet the minimum interval requirement for stable disease

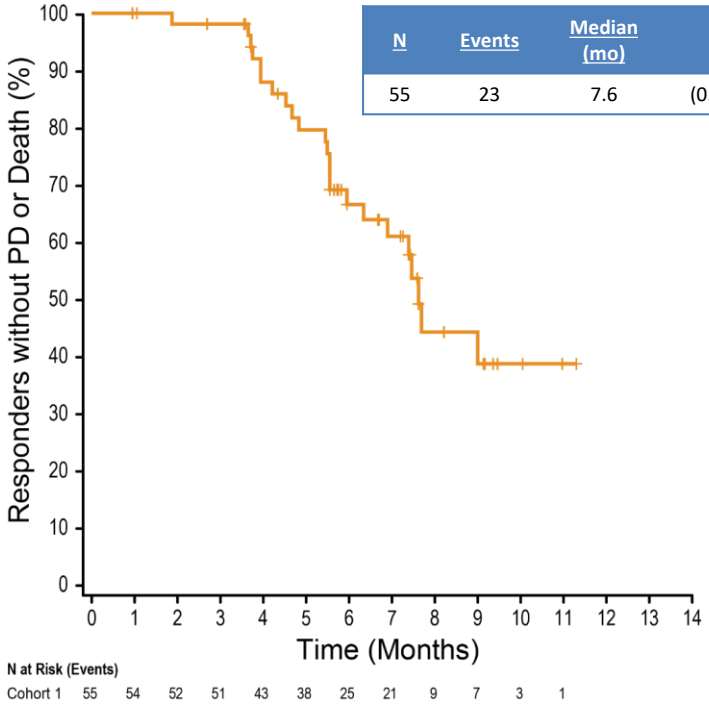
Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

EV-201: Cohort 1 Duration of Response with Enfortumab Vedotin



Median time to response: 1.8 mo (range: 1.2–9.2)
Most responses identified at first assessment

Duration of Response



N	Events	Median (mo)	Range
55	23	7.6	(0.95-11.30+)

Median duration of response: 7.6 mo (range: 0.95–11.30+)
44% of responders still being followed

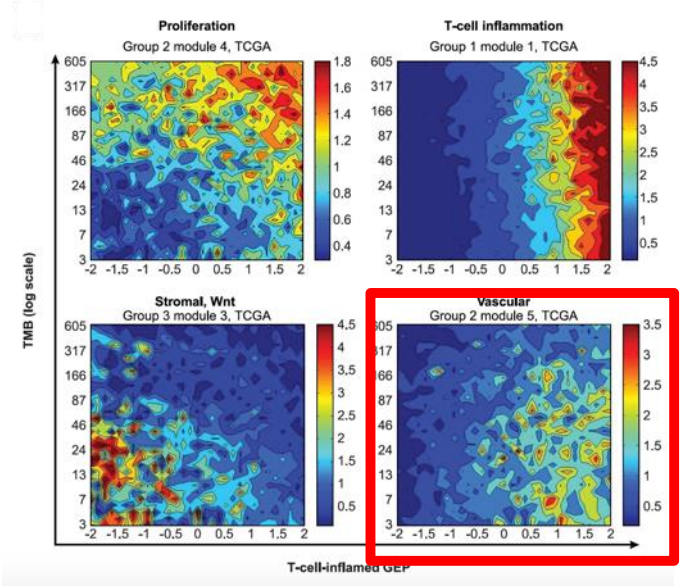
Petrylak DP, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4505)

First Approval of Enfortumab Vedotin in a PD-(L)1-Exposed Population

- On December 18, 2019, the Food and Drug Administration granted accelerated approval to enfortumab vedotin-ejfv (PADCEV) for adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

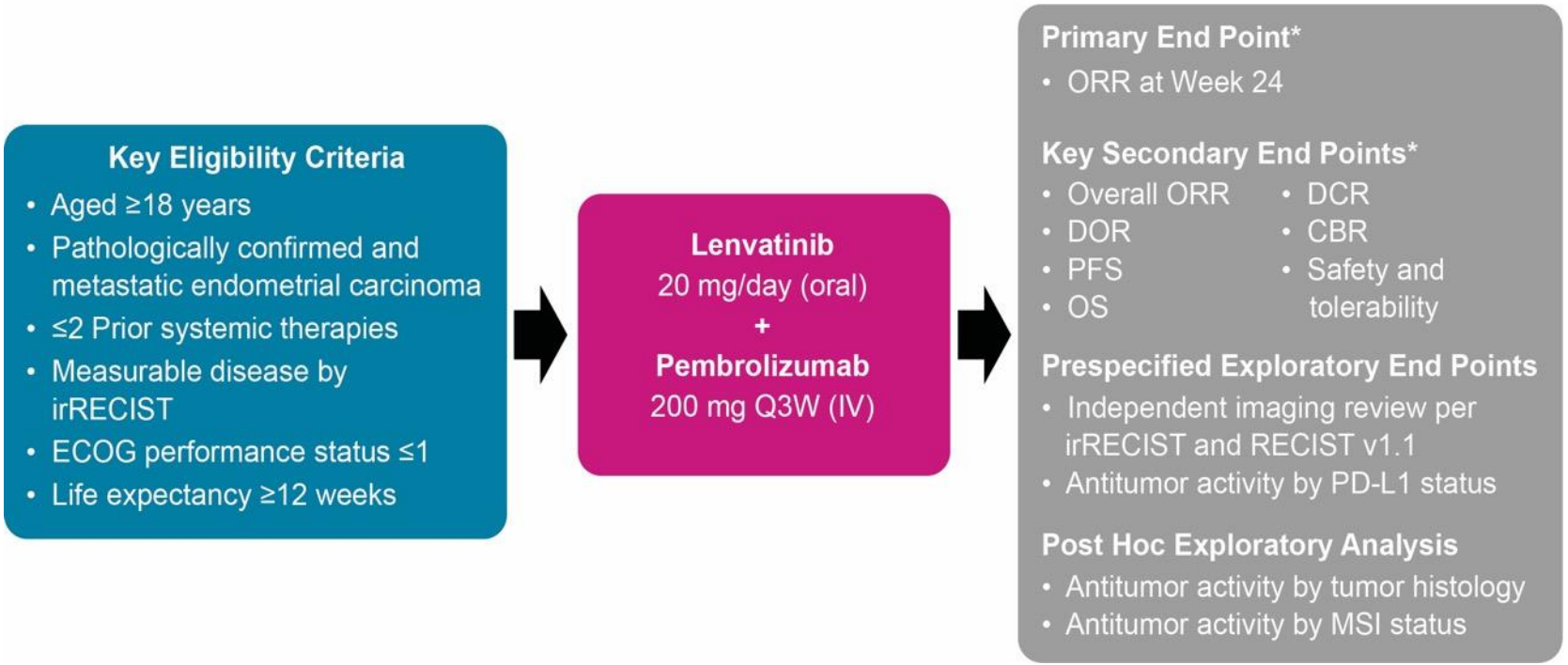
Use of External Data to Support Single Arm Submissions
Pembrolizumab + Lenvatinib Example

- Translational data support combination studies of pembrolizumab with anti-angiogenesis agents such as lenvatinib
- KEYNOTE-146/Study 111 - basket study of pembrolizumab + lenvatinib combination
  - endometrial
  - renal
  - NSCLC
  - urothelial
  - SCCHN
  - melanoma



KEYNOTE-146 Study Design

Phase 2, Open-label, Single-arm Study (NCT02501096)



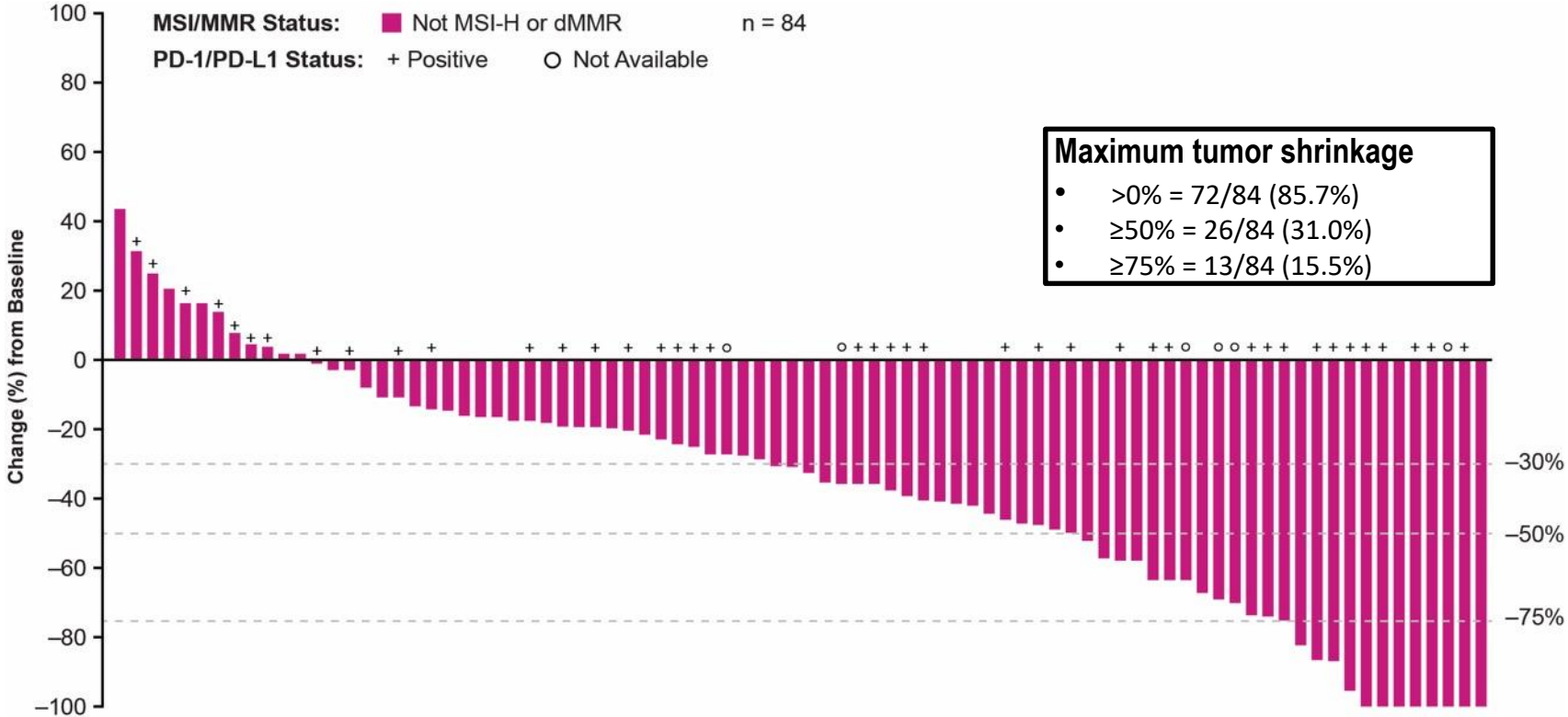
*Tumor responses for primary and secondary end points were assessed by the investigator per irRECIST.

Response in Endometrial Cancer (Independent Imaging Review; RECIST version 1.1)

Response Category	Total (n = 108)[a]	Not MSI-H or dMMR (n = 94)	MSI-H/dMMR (n = 11)
Best overall response, n (%)			
Complete response	11 (10.2)	10 (10.6)	1 (9.1)
Partial response	33 (30.6)	26 (27.7)	6 (54.5)
Stable disease	42 (38.9)	38 (40.4)	3 (27.3)
Progressive disease	14 (13.0)	12 (12.8)	1 (9.1)
Not evaluable	8 (7.4)	8 (8.5)	0
Objective response rate (complete response + partial response), n (%)	44 (40.7)	36 (38.3)[b]	7 (63.6)
95% CI[c]	31.4, 50.6	28.5, 48.9	30.8, 89.1
Duration of response (months), median (range)[d]	14.8 (1.2+, 35.6+)	NE (1.2+, 33.1+)	NE (2.1+, 35.6+)

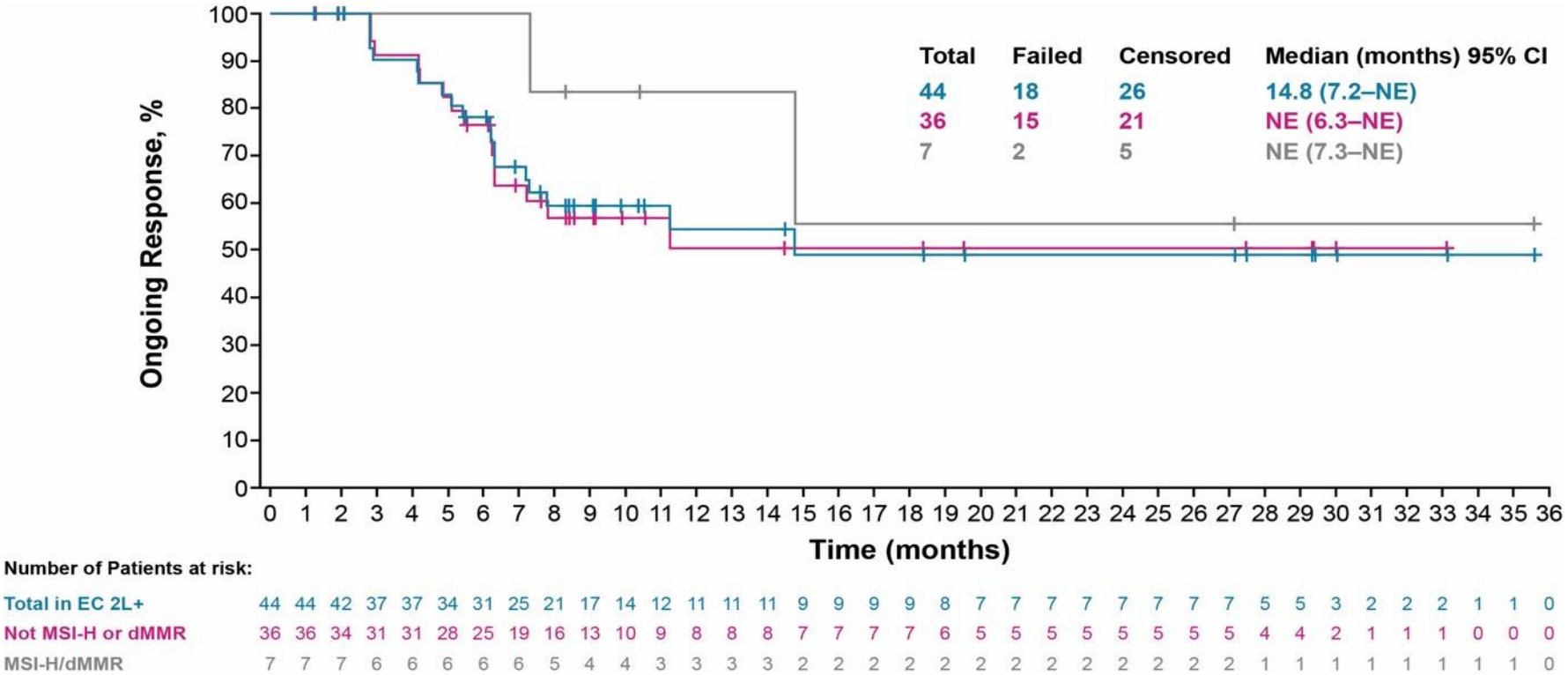
[a]The MSI or MMR status was not available for 3 patients; [b]As found in the United States Prescribing Information; [c]95% CIs were calculated with the Clopper-Pearson method; [d]Duration of response was estimated with the Kaplan-Meier method.

Percentage Change in Sum of Diameters of Target Lesions at Postbaseline Nadir (Independent Imaging Review; RECIST version 1.1)



n = the number of previously treated not MSI-H or dMMR patients with both baseline and at least 1 postbaseline target lesion assessment.

Kaplan-Meier Plot (Independent Imaging Review; RECIST version 1.1): Duration of Response



Duration of response was estimated with the Kaplan-Meier method, and 95% CIs were calculated with a generalized Brookmeyer and Crowley method.

Comparison to External Monotherapy Endometrial Cancer Cohorts

Study	Population (n)	ORR; 95% CI
KN146 lenva+pembro	Non-MSI-H (n=94)	36% ; (28.5, 48.9); 10 CR
KN146 lenva+pembro	MSI-H (n=11)	63.6%
Lenvatinib monotherapy (Study 204, NCT01111461)	MSI-H status not determined; (n=133)	14.3%; (8.8, 21.4); 1 CR
Pembrolizumab monotherapy KEYNOTE-158- Cohort D (NCT02628067)	Non-MSI-H (n=90)	7.8% ; (3.2, 15.4); 0 CR
Pembrolizumab monotherapy KEYNOTE-158	MSI-H (n=49)	57.1%; (42.2, 71.2); 8 CR

Approval of Lenvatinib + Pembrolizumab Combination

- Several innovative aspects to the study and regulatory interactions
- FDA, Australian Therapeutic Goods Administration, and Health Canada granted simultaneous review decisions in all 3 countries on Sept 17, 2019
- Lenvatinib plus pembrolizumab was granted accelerated approval for the treatment of advanced endometrial carcinoma that is not MSI-H or dMMR
- Patients must have had disease progression following prior systemic therapy and must not be candidates for curative surgery or radiation

SIMPLIFICATION AND HARMONIZATION OF COMPANION DIAGNOSTICS DEVELOPMENT

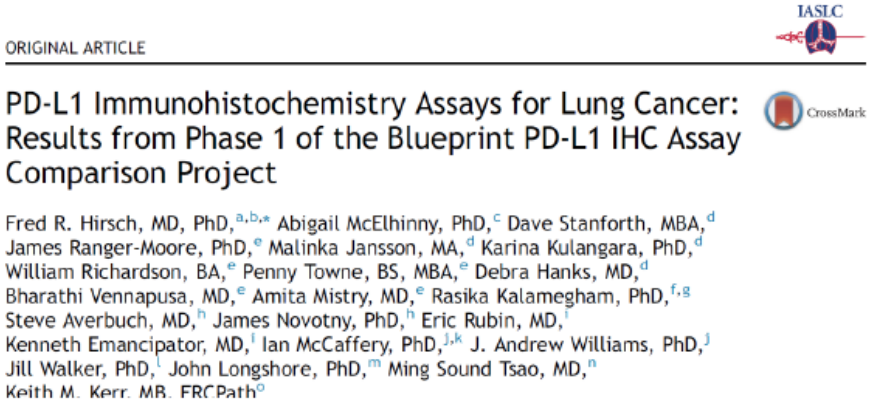
1. PD-L1 IHC
2. Tumor mutational burden (TMB)

Multiple FDA-Approved PD-L1 IHC Assays and Cutoffs: 22-C3, 28-8, SP-263, and SP-142 Assays

Agent	Pembrolizumab	Nivolumab	Durvalumab	Atezolizumab
Diagnostic Platform	Dako		Ventana	
Antibody	22-C3	28-8	SP-263	SP-142
Cut-off(s) being tested	TC[1] 1%, 50% CPS[3] 1, 10	TC 1%, 5% or 10%	TC[1] 25%	TC[1] or IC[2] 1%, 5%,10%

1) TC = tumor cell staining.
2) IC = infiltrating immune cell staining
3) Combined positive score (tumor and immune cell staining)

PD-L1 IHC Harmonization Effort – Blueprint Project



ORIGINAL ARTICLE

IASLC

PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project

Fred R. Hirsch, MD, PhD,[a,b,*] Abigail McElhinny, PhD,[c] Dave Stanforth, MBA,[d] James Ranger-Moore, PhD,[e] Malinka Jansson, MA,[d] Karina Kulangara, PhD,[d] William Richardson, BA,[e] Penny Towne, BS, MBA,[e] Debra Hanks, MD,[d] Bharathi Vennapusa, MD,[e] Amita Mistry, MD,[e] Rasika Kalamegham, PhD,[f,g] Steve Averbuch, MD,[h] James Novotny, PhD,[h] Eric Rubin, MD,[i] Kenneth Emancipator, MD,[j] Ian McCaffery, PhD,[j,k] J. Andrew Williams, PhD,[j] Jill Walker, PhD,[l] John Longshore, PhD,[m] Ming Sound Tsao, MD,[n] Keith M. Kerr, MB, FRCPath[o]

Goals:

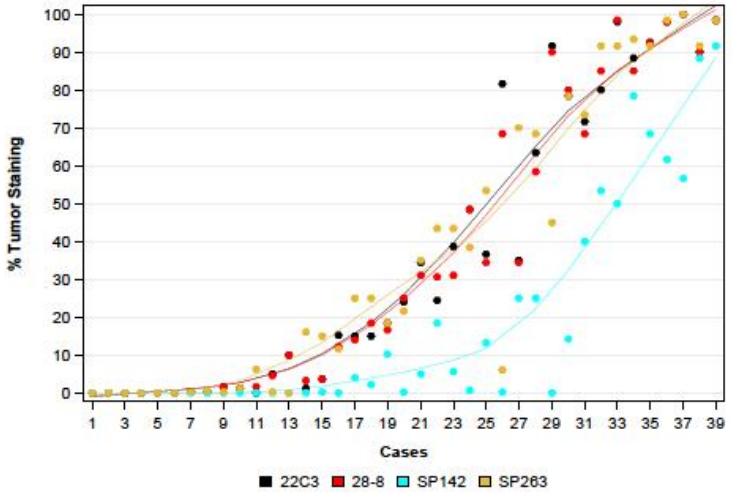
1. Compare analytical performance of 4 assays (22C3, 28-8, SP142, SP263) used as the staining protocols in corresponding clinical trials
2. Compare the treatment-determining scoring algorithm developed for each assay and used in clinical trials

AACR
AstraZeneca
Bristol-Myers Squibb
Dako/Agilent
Genentech/Roche
IASLC
MSD
Ventana/Roche Tissue Diagnostics

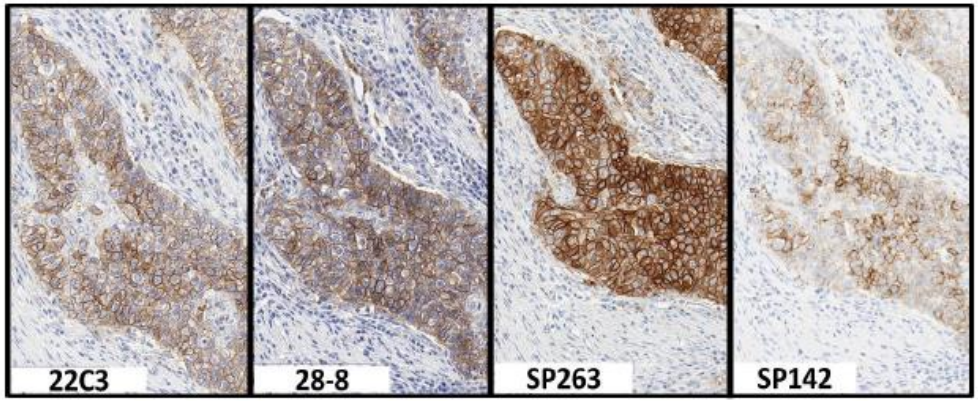
Journal of Thoracic Oncology 2016, Vol. 12 No. 2: 208-222

PD-L1 IHC Harmonization Effort – Blueprint Project

PD-L1 expression on tumor cells



Each dot represents the mean score of 3 pathologists



Conclusion 1: 3 assays showed similar staining characteristics for PD-L1 staining on tumor cells, but SP142 comparatively showed less tumor cells stained

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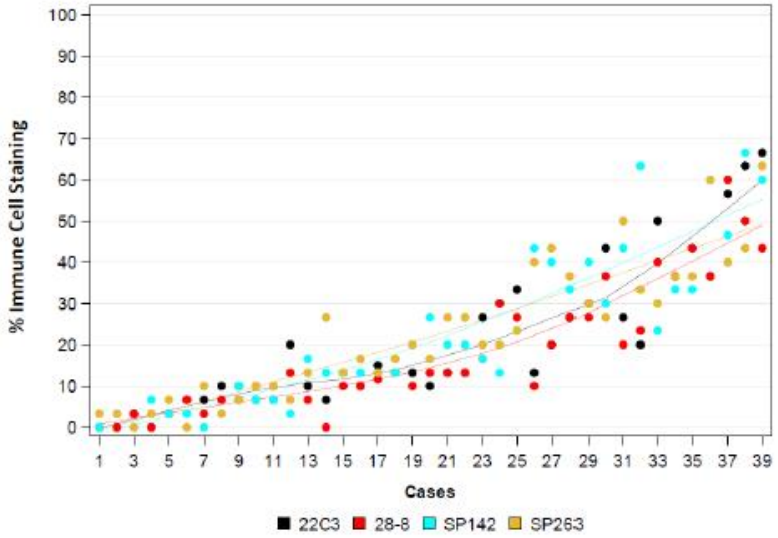
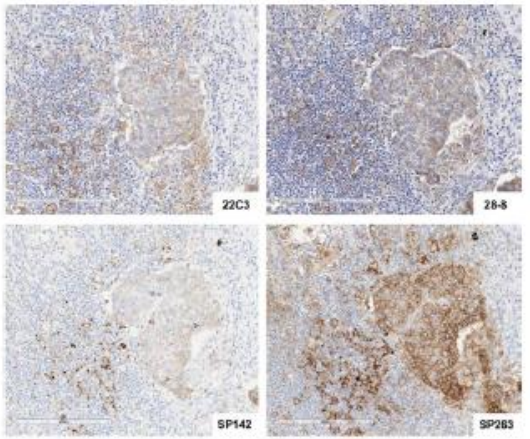
PD-L1 IHC Harmonization Effort – Blueprint Project

PD-L1 expression on immune cells



Each dot represents the mean score of 3 pathologists



Conclusion 2: All four assays showed immune cell staining, but with greater variability than tumor cell staining.

Journal of Thoracic Oncology 2016, Vol. 12 No. 2: 208-222

PD-L1 IHC Harmonization Effort – Blueprint Project

Harmonization of assays: Overall percent agreement when assays are applied to clinical cut-off of other assays

Assay clone used for staining	Number of cases and overall percentage of agreement (concordant with index assay scoring algorithm)							
	22C3	1%TPS	28-8	1% TPS	SP142	TC1/IC1	SP263	25% TPS
22C3	38/38	100%	36/38	94.7%	33/38	86.6%	34/38	89.5%
28-8	36/38	94.7%	38/38	100%	31/38	81.6%	33/38	86.8%
SP142	24/38	63.2%	24/38	63.2%	38/38	100%	25/38	65.8%
SP263	34/38	89.5%	34/38	89.5%	33/38	86.8%	38/38	100%

Journal of Thoracic Oncology 2016, Vol. 12 No. 2: 208-222

TMB as a Predictive Biomarker for Immune Checkpoint Inhibitors

- TMB measures mutations in a tumor (per megabase)
  - Used as a surrogate of neoantigen load
- High levels of TMB (TMB-high) have been correlated with efficacy of antibodies targeted to immune checkpoints CTLA-4, PD-1, and PD-L1
- High microsatellite instability (MSI-H) is a subtype of TMB-high
  - Pembrolizumab provides durable responses in patients with MSI-H cancers and is approved in several countries, including the US, Japan, and Australia, for the treatment of previously treated MSI-H advanced solid tumors

Fancello L et al. *J Immunother Cancer* 2019;7:183. 2. Stenzinger A et al. *Genes Chromosomes Cancer*. 2019;58:678-88. 3. Marcus L et al. *Clin Cancer Res* 2019;25:3753-8.

Multiple Assays under Development for Evaluation of Tumor Mutational Burden

Laboratory	Panel name	# genes	Total region covered (Mb)	TMB region covered∞ (Mb)	Type of exonic mutations included in TMB estimation	Published performance characteristics [Ref]
ACT Genomics	ACTOnco+	440	1.8	1.12	non-synonymous^, synonymous	NA
AstraZeneca	AZ600	607	1.72	1.72	non-synonymous, synonymous	NA
Caris	SureSelect XT	592	1.60	1.40	non-synonymous	Vanderwalde et al., 2018 [38]
Foundation Medicine	FoundationOne CDx™ *	324	2.20	0.80	non-synonymous, synonymous	Frampton et al., 2013[39] Chalmers et al., 2017[25] Fabrizio et al., 2018[40] U.S. FDA SSED[31]
Guardant Health	GuardantOMNI&	500	2.15	1.00	non-synonymous, synonymous	Quinn et al., 2018[41]
Illumina	TSO500 (TruSight Oncology 500)	523	1.97	1.33	non-synonymous, synonymous	NA
Memorial Sloan Kettering Cancer Center	MSK-IMPACT™ %	468	1.53	1.14	non-synonymous	Cheng et al., 2015[42], Zehir et al. 2017[30], U.S. FDA [32]
NeoGenomics	NeoTYPE® Discovery Profile for Solid Tumors	372	1.10	1.03	non-synonymous, synonymous	NA
Personal Genome Diagnostics	PGDx elio tissue complete	507	2.20	1.33	non-synonymous, synonymous	Wood et al., 2018[43]
QIAGEN	QIAseq TMB panel	486	1.33	1.33	non-synonymous, synonymous	NA
Thermo Fisher Scientific	Oncomine™ Tumor Mutation Load Assay	409	1.70	1.20	non-synonymous	Chaudhary et al., 2018[44] & Endris et al., 2018[35]

- Various studies evaluating TMB as a predictive marker for IO treatments have used different scoring approaches and cutoffs, making direct comparisons of the assays difficult
- Ongoing effort led by the Friends of Cancer Research, with inclusion of FDA, and several Pharma and Diagnostics companies, to create a set of standards for the calculation, validation, and reporting of TMB

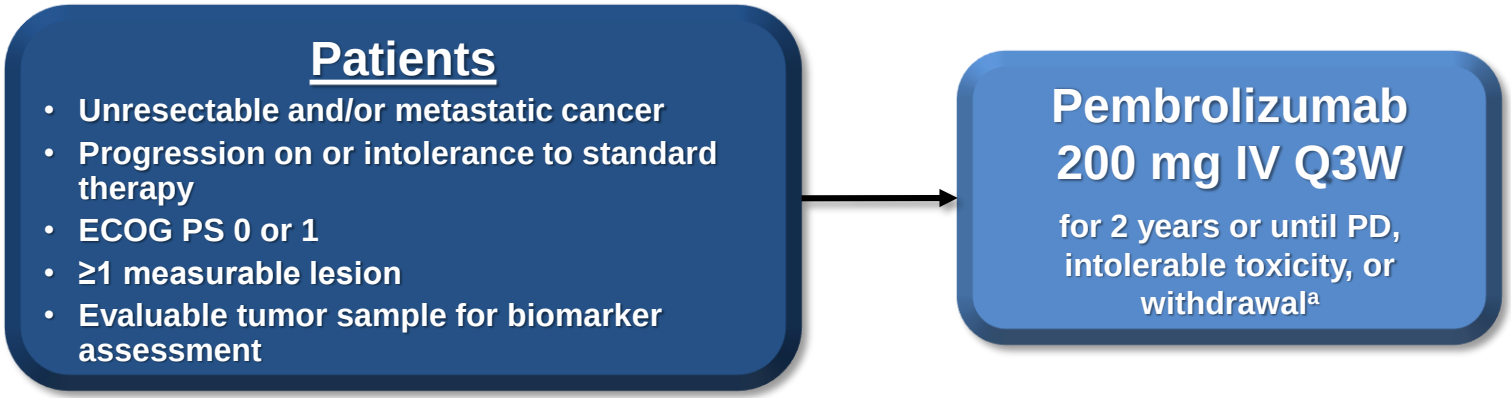
Friends of Cancer Research TMB Harmonization Project

- Involves several diagnostic, academic, and pharma groups, NCI, FDA
- Identified a set of reference standards consisting of 10 well-characterized human-derived lung and breast tumor-normal matched cell lines
- Compared the correlation between TMB scores calculated using whole exome sequencing (WES) and individual diagnostic company gene panels
- The set of reference standards spanned a clinically meaningful TMB range (4.3 to 31.4 mut/Mb)
- Across laboratories, there was a good correlation between panel-TMB and WES-TMB.
  - Spearman R values ranged from 0.56-0.97 with slopes ranging from 0.58-1.16
  - Some laboratories had consistently over- or underestimated TMB values
- These results support the need for alignment to a reference control
- Future studies aim to validate reference standard material using formalin-fixed paraffin-embedded human tumor samples

https://www.focr.org/blog/engaging-innovation/tmb-harmonization-working-group-meeting

Merino, et al; J Clin Oncol 37, 2019 (suppl; abstr 2624)

Evaluation of TMB in KEYNOTE-158 (NCT02628067): Phase 2 Multicohort Study of Pembrolizumab for Select Previously Treated Advanced Solid Tumors



Included cancers

- Cohort A: anal squamous cell carcinoma
- Cohort B: biliary adenocarcinoma
- Cohort C: well or moderately differentiated neuroendocrine tumors
- Cohort D: endometrial carcinoma
- Cohort E: cervical squamous cell carcinoma
- Cohort F: vulvar squamous cell carcinoma
- Cohort G: small-cell lung cancer
- Cohort H: malignant pleural mesothelioma
- Cohort I: papillary or follicular thyroid carcinoma
- Cohort J: salivary gland carcinoma
- Cohort K: MSI-H solid tumors, excluding colorectal cancer (cohort excluded from this analysis)

[a]Clinically stable patients could remain on pembrolizumab until PD was confirmed on a second imaging assessment performed ≥4 weeks later. Patients who completed pembrolizumab treatment with SD or better and subsequently experienced PD were eligible to resume pembrolizumab for ≤1 year.

KN-158 End Points and Assessments

Protocol-Specified Study End Points

- Primary: ORR assessed per RECIST v1.1 by independent central review
- Secondary: DOR and PFS assessed per RECIST v1.1 by independent central review, OS, safety
- Exploratory: relationship between TMB and efficacy

Study Assessments

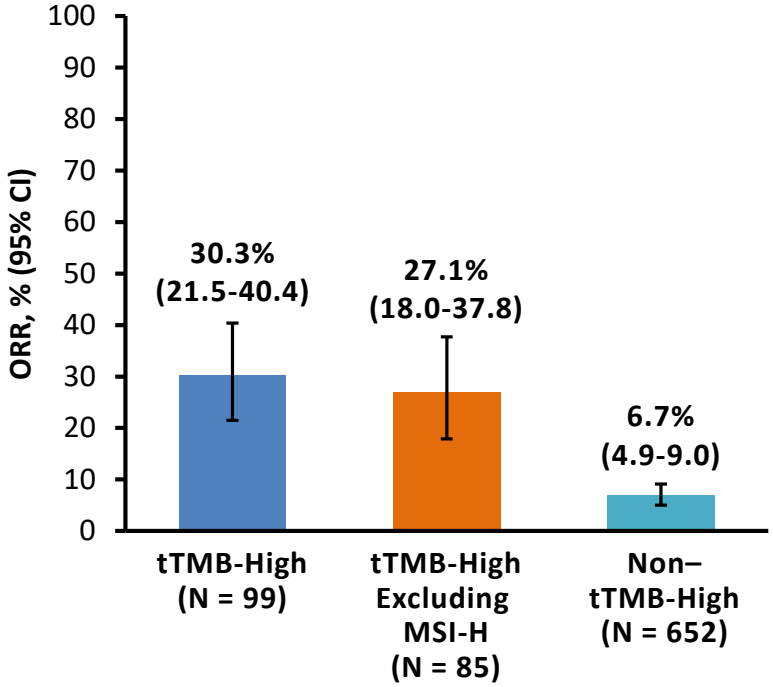
- Response: assessed every 9 weeks for the first 12 months and every 12 weeks thereafter
- AEs and laboratory abnormalities: monitored throughout treatment and for 30 days (90 days for serious AEs) thereafter
  - Graded per NCI CTCAE version 4.0

Biomarker Assessments

- TMB
  - Assessed in FFPE tumor samples (tissue TMB, or tTMB) using the FoundationOne CDx™ assay (version 3.3)
  - TMB-high defined as ≥10 mut/Mb (prespecified[a])
- MSI
  - Determined retrospectively by PCR of 5 mononucleotide loci[b] performed at a central laboratory
  - MSI-H defined as allelic loci size shifts in ≥2 of 5 analyzed loci

[a]Cutpoint was prespecified before the TMB results were correlated with outcomes.
[b]BAT25, BAT26, NR21, NR24, and Mono27.

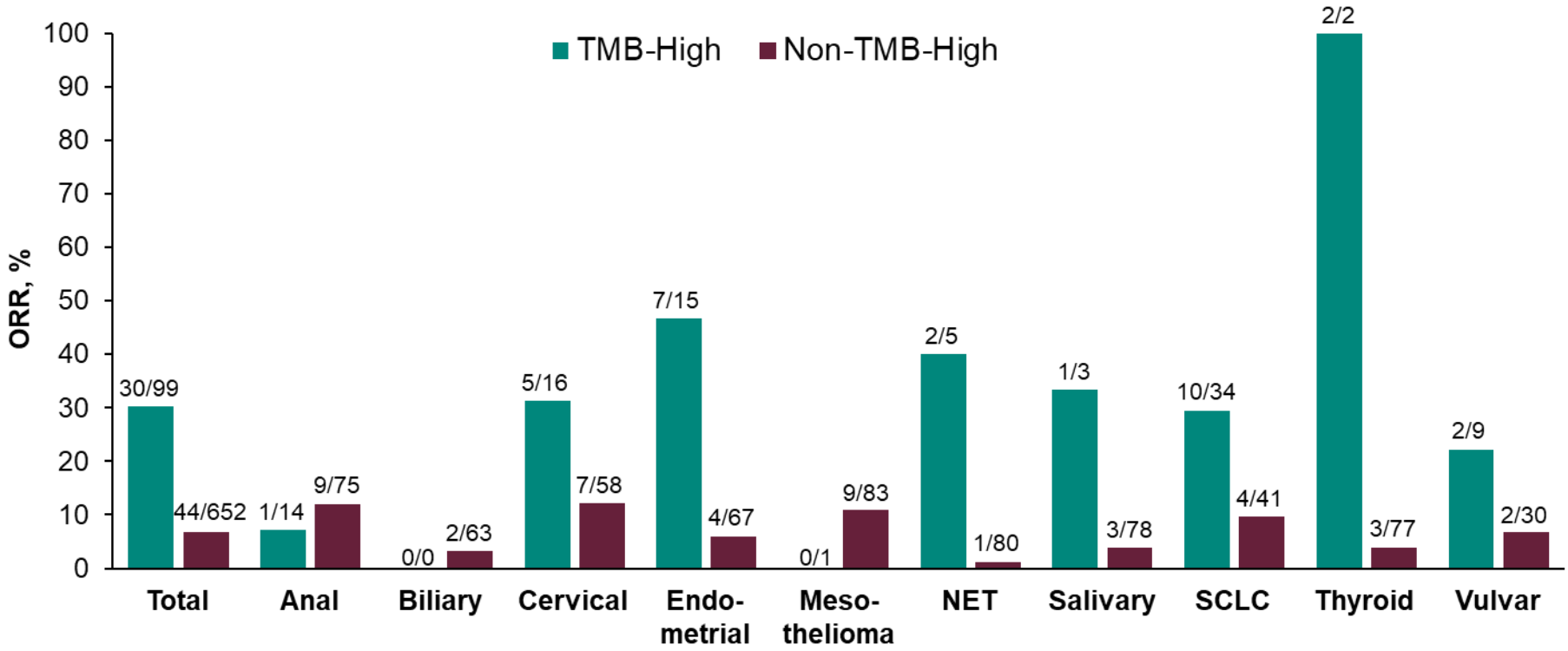
Confirmed Best Overall Response
(RECIST v1.1, Independent Central Review)



Best Response	tTMB-High N = 99	tTMB-High Excl. MSI-H N = 85	Non–tTMB-High N = 652
CR	4.0%	3.5%	1.7%
PR	26.3%	23.5%	5.1%
SD	14.1%	15.3%	33.6%
Non-CR/ non-PD	0%	0%	0.5%
PD	46.5%	48.2%	50.3%
Not evaluable[a]	0%	0%	2.3%
Not assessed[b]	9.1%	9.4%	6.6%

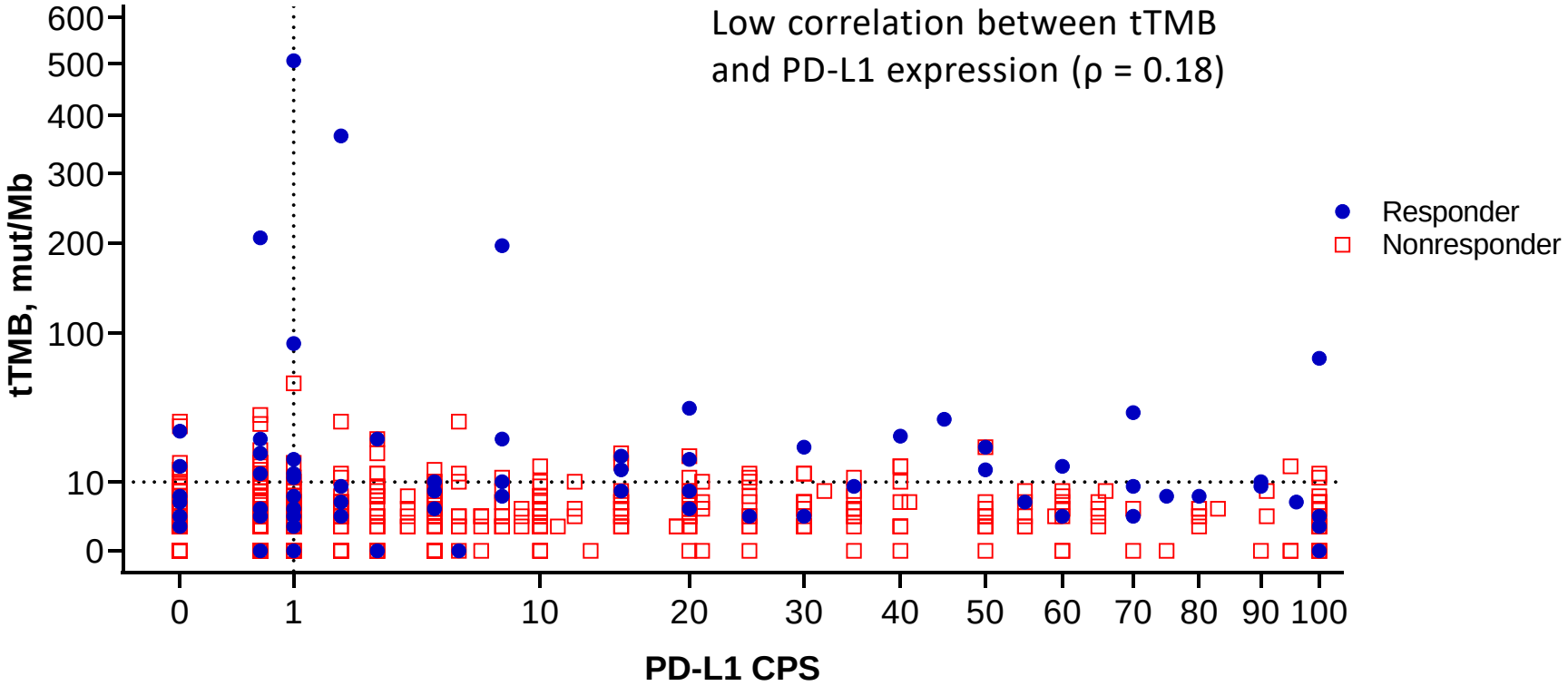
[a]Patients who did not have a post-baseline imaging assessment evaluable for response. [b]Patients who did not have post-baseline imaging.
Data cutoff date: December 6, 2018.

Confirmed ORR by Tumor Type
(RECIST v1.1, Independent Central Review)



Bars are labelled with the number of participants with response out of the total number of participants with that tumor type.
Data cutoff date: December 6, 2018.

Relationship Between tTMB and PD-L1



tTMB and PD-L1 CPS were graphed on a square root scale.
Data cutoff date: December 6, 2018.

TMB Summary

- TMB-high status assessed in tumor tissue is associated with a clinically meaningful improvement in the efficacy of pembrolizumab monotherapy in participants with previously treated solid tumors
- The benefit in the tTMB-high subgroup was not driven by MSI-H status, and responses were observed across tumor types
- Median duration of response was not reached with a median follow-up of ~1 year
- There was low correlation of tTMB and PD-L1 expression
- The safety profile in the tTMB-high subgroup was tolerable and consistent with that previously observed for pembrolizumab monotherapy
- Data suggest that tTMB may predict efficacy of pembrolizumab monotherapy in participants with previously treated advanced solid tumors

Conclusions

- Innovative approaches should continue to be pursued to enable rapid drug development and access for advanced cancer populations
- Project Orbis is a good example of international regulatory collaboration that may facilitate patient access to new treatments
- Continued collaboration is needed to simplify use of predictive biomarkers, particularly where selection of a cutoff is required