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Advances in Cancer Immunotherapy™

Immunotherapy Biomarkers in Head and Neck Cancer

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Disclosures

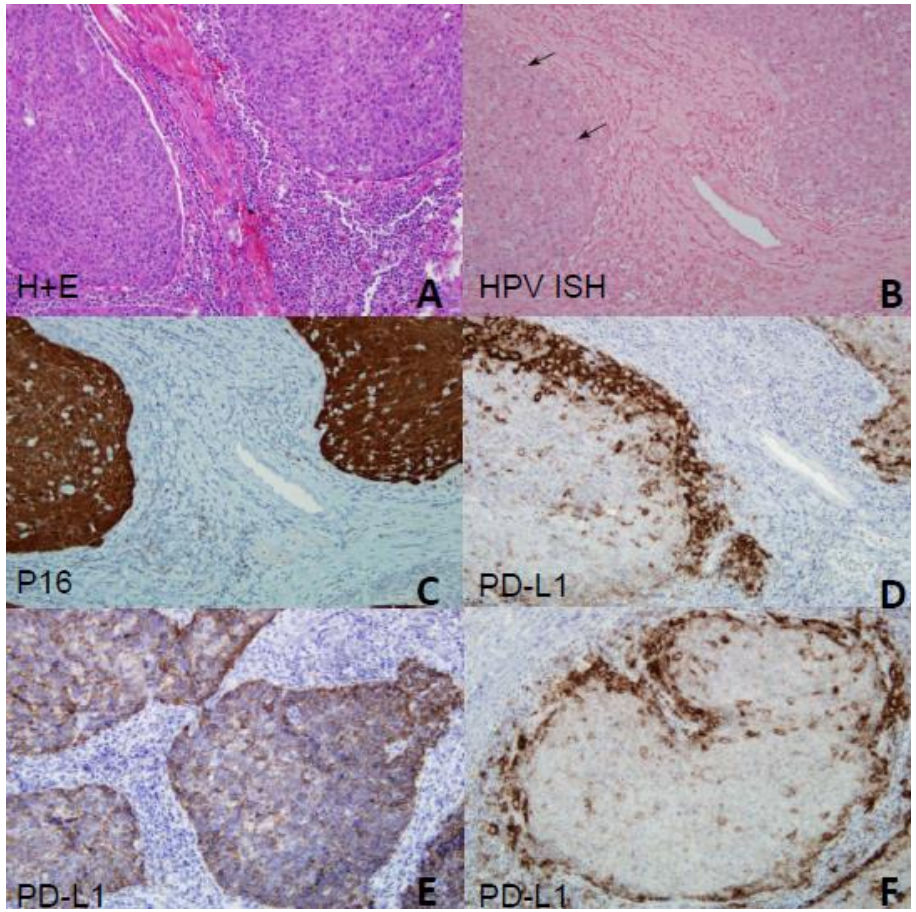
- Research Funds: Merck, Astra Zeneca
- Consulting – Rakuten Medical
- Advisory Board (Uncompensated) - Astra Zeneca
- I will be discussing non-FDA approved indications during my presentation.

Overview

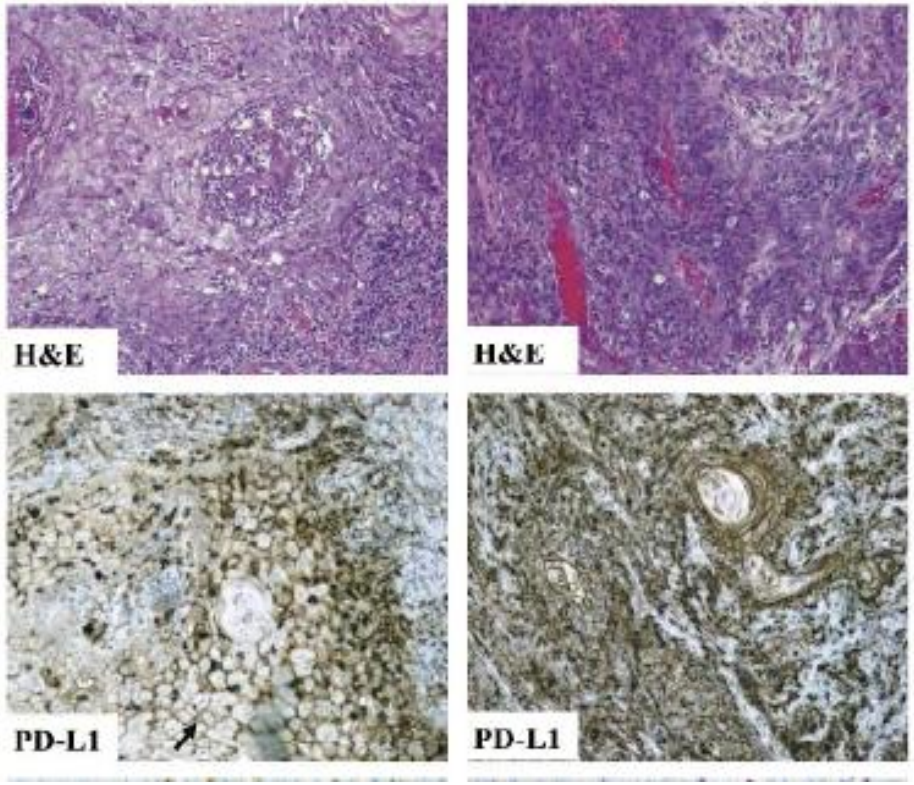
- PDL1 CPS
- TMB
- GEP
- SEMA4D

PD-L1 expression

14/20 (70%) of HPV+ HNSCC

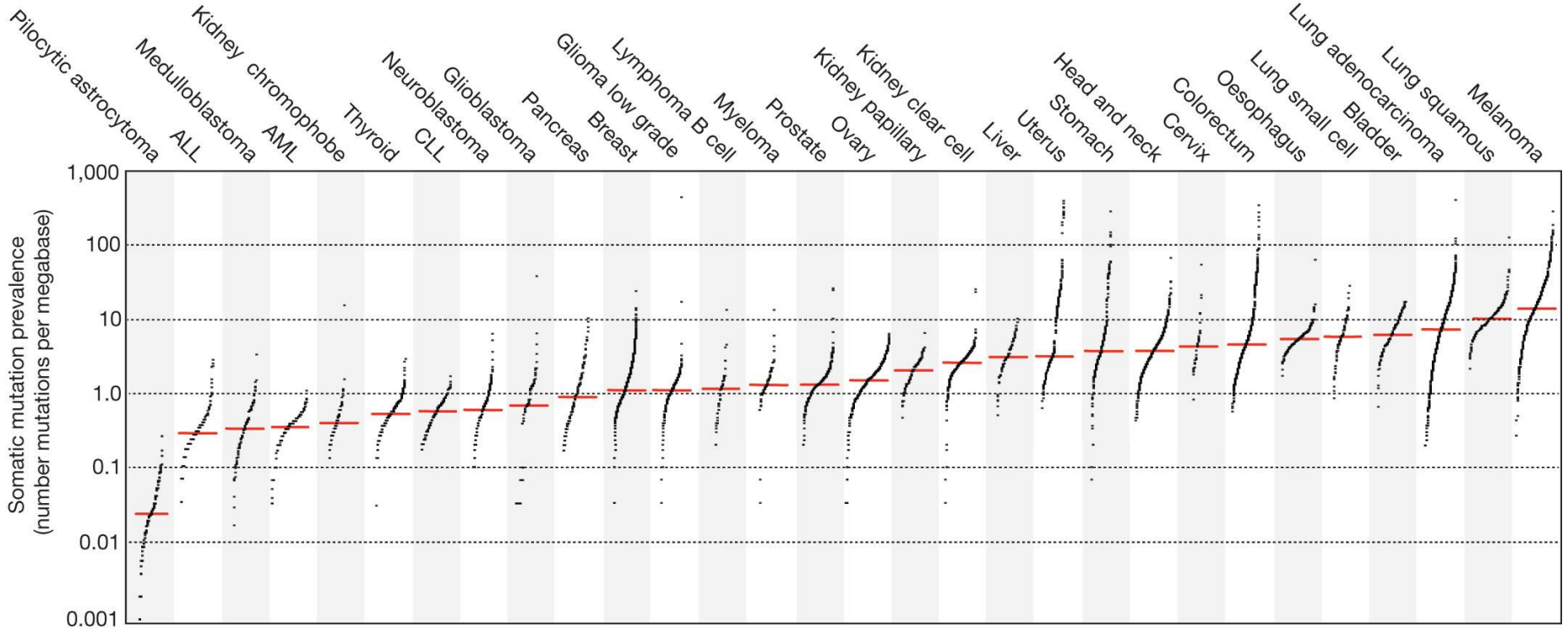


HPV- HNC: 2/7 (29%)



Lyford-Pike, et al. Can Res 2013
Malm, et.al. Head Neck, 2013

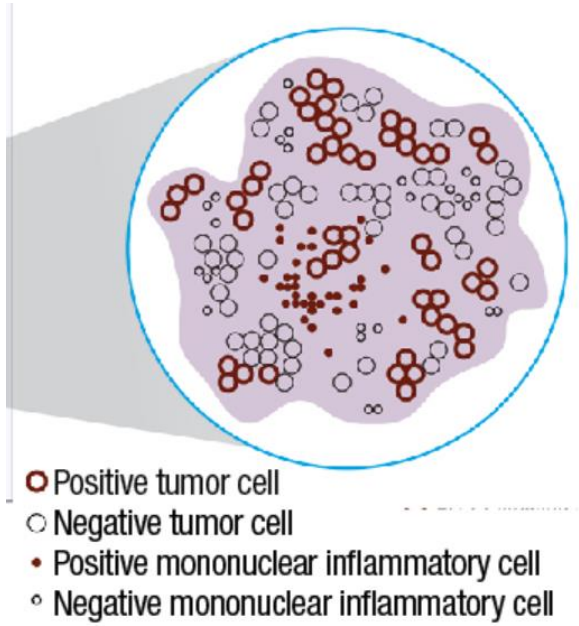
Mutational Load in SCCHN



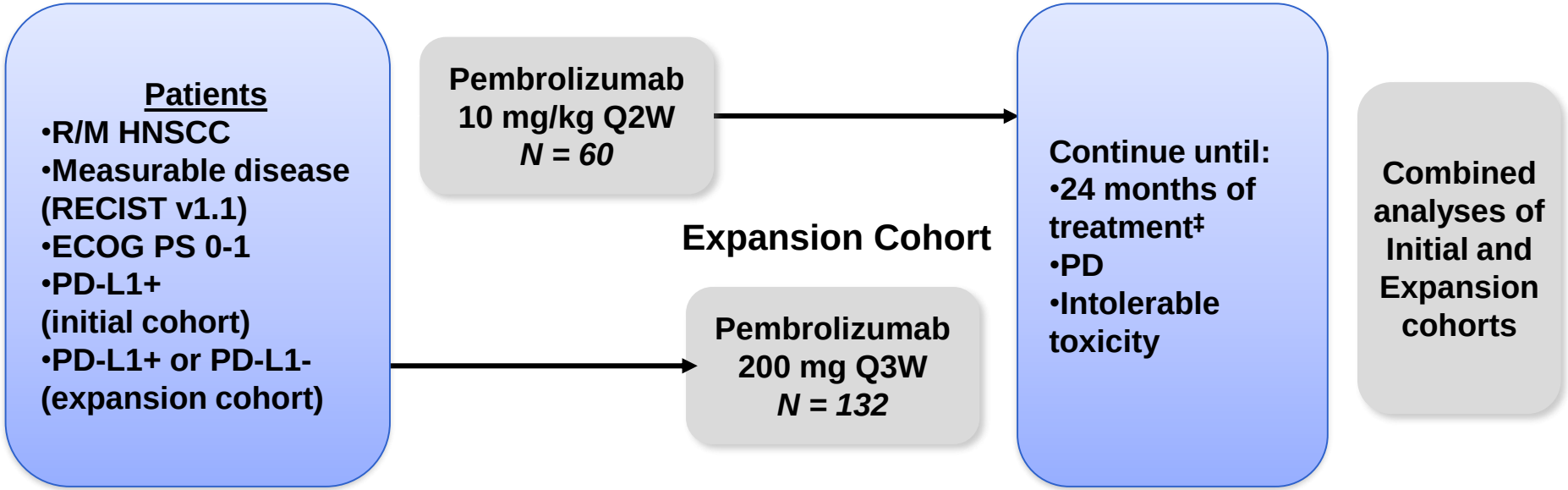
LB Alexandrov *et al. Nature* **000**, 1-7 (2013)
doi:10.1038/nature12477

TPS vs. CPS

- TPS – the percentage of tumour cells with membranous PD-L1 expression.
- CPS - the number of PD-L1-positive cells [tumor cells, lymphocytes, and macrophages] divided by the total number of tumor cells times 100.
- scores ranged from 0 to 100
- a cut-off of ≥1 is used to define the PD-L1 expression.



Phase 1b, Multi-cohort KEYNOTE-012 Trial

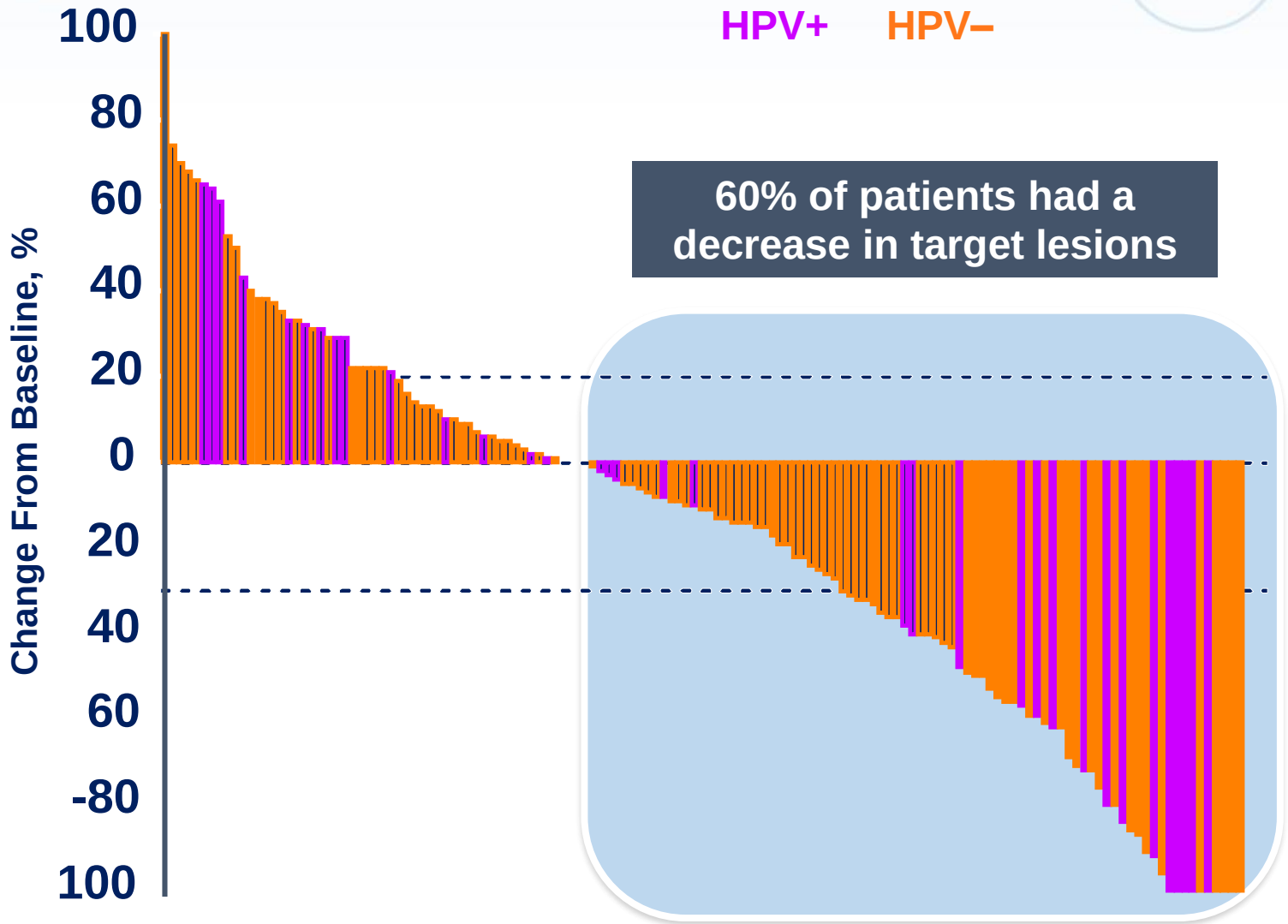


Response assessment: Every 8 weeks

Primary end points: ORR (RECIST v1.1, central imaging vendor), safety

Secondary end points: ORR (investigator), PFS, OS, response duration, ORR in HPV+ patients§

Seiwert et al. The Lancet Oncology 2016 17, 956-965DOI: (10.1016/S1470-2045(16)30066-3)
Chow et al. JCO 2016



Mehra et al. BJC 2018

Data cutoff date: Apr 26, 2016. Based on RECIST v1.1 per central imaging vendor review (waterfall plot). Includes patients who received ≥1 dose of pembrolizumab, had a baseline scan with measurable disease per R

PDL1 and ORR in KN012

Scoring Method	Expression Status	Number (%) positive	Responders/total n	ORR (%)	P value
TPS	PDL1 +	123 (65%)	22/123	18	0.461
TPS	PDL1-	65 (35%)	12/65	19	
CPS	PDL1 +	152 (81%)	32/152	21	0.023
CPS	PDL1 -	36 (19%)	2/36	6	

Mehra et al. Br J Cancer. 2018 Jul 17; 119(2): 153–159

Biomarker Analysis of 2 Studies

- 258 patients with HNSCC with available whole exome sequencing (WES) data:
  - KN-012 (phase 1b)[a,b]:
    - B1, **n=34** (PD-L1+, ≥1%, QualTek IHC[c])
    - B2, **n=73** (not PD-L1-selected)
  - KN-055 (phase II)[d]:
    - Platinum/cetuximab resistant, **n=151**

- Relationships of PD-L1 expression, GEP and TMB with response (BOR and PFS) to pembrolizumab were assessed
  - All patients and by HPV status (p16 and WES)
  - Other measures: neoantigen load, tumor clonality

a) Seiwert TY et al. Lancet Oncol 2016 17:956-965; b) Chow LQ et al. J Clin Oncol 2016; 34:3838-384. c) Includes PD-L1 presence in stroma; some patients had modified proportion score = 0 and were enrolled in the study. d) Bauml J et al. J Clin Oncol 35:1542-1549.

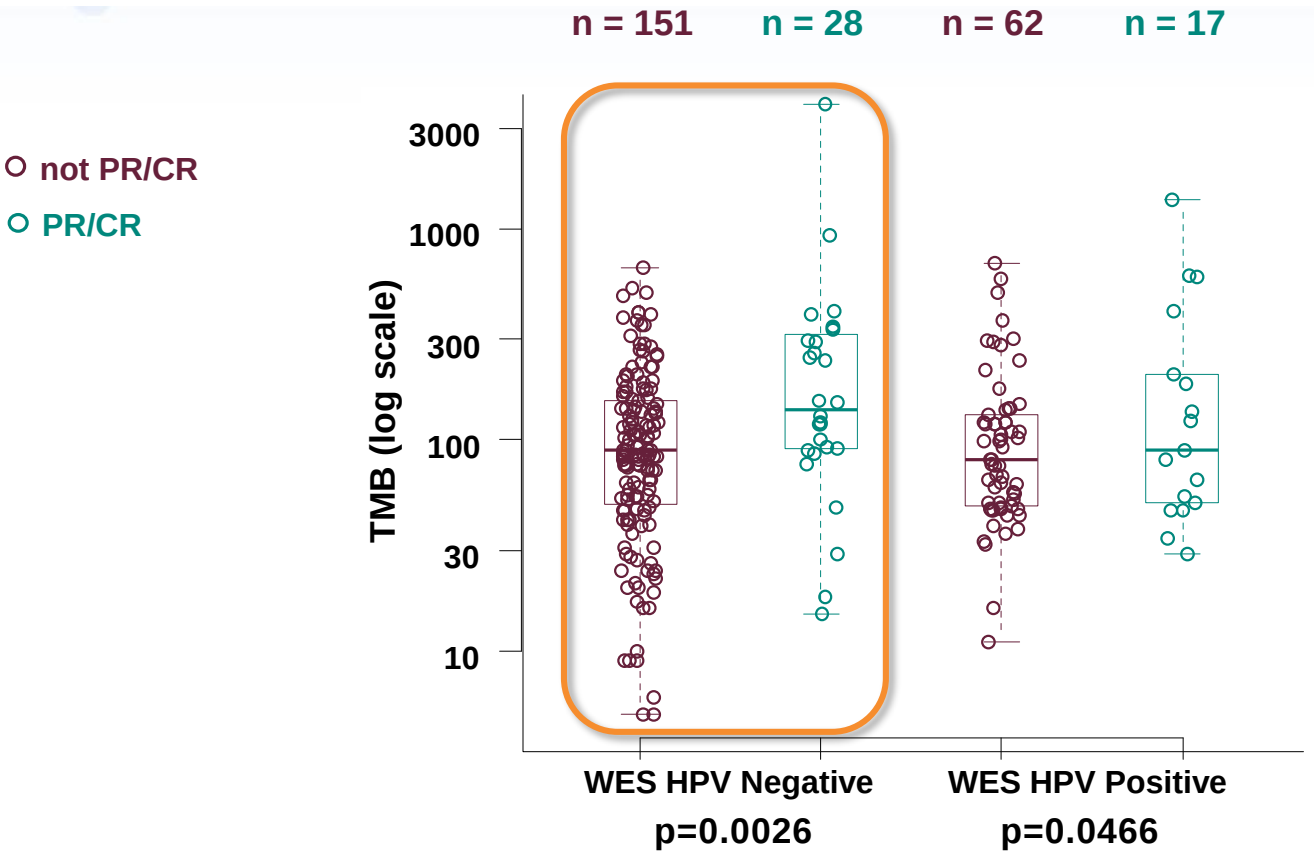
Baseline Characteristics

Characteristic, n (%)	Overall study cohort[a] (N=363)	WES[b] (N = 258)
Age, years, median (range)	61 (20, 90)	61 (25, 90)
Male	297 (82)	208 (81)
ECOG status (1 & 2)	258 (71)	178 (69)
Metastatic staging (M1)	321 (88)	231 (90)
Prior therapy		
0	37 (10)	25 (10)
1	80 (22)	49 (19)
2	113 (31)	93 (36)
≥3	133 (37)	91 (35)
HPV-positive p16 IHC	82 (23)	57 (22)
HPV-positive WES	-	79 (31)

- Patients with WES data had similar baseline characteristics to those in the overall population

a) Overall study cohort: KN-012 (n=192) + KN-055 (n=171); b) Patients with WES data available: KN-012 (n=107) and KN-55 (n=151) cohorts

Tumor mutational burden (TMB) vs Response



- TMB was significantly associated with BOR in all patients (p=0.0006)
- TMB association appears stronger in HPV negative patients

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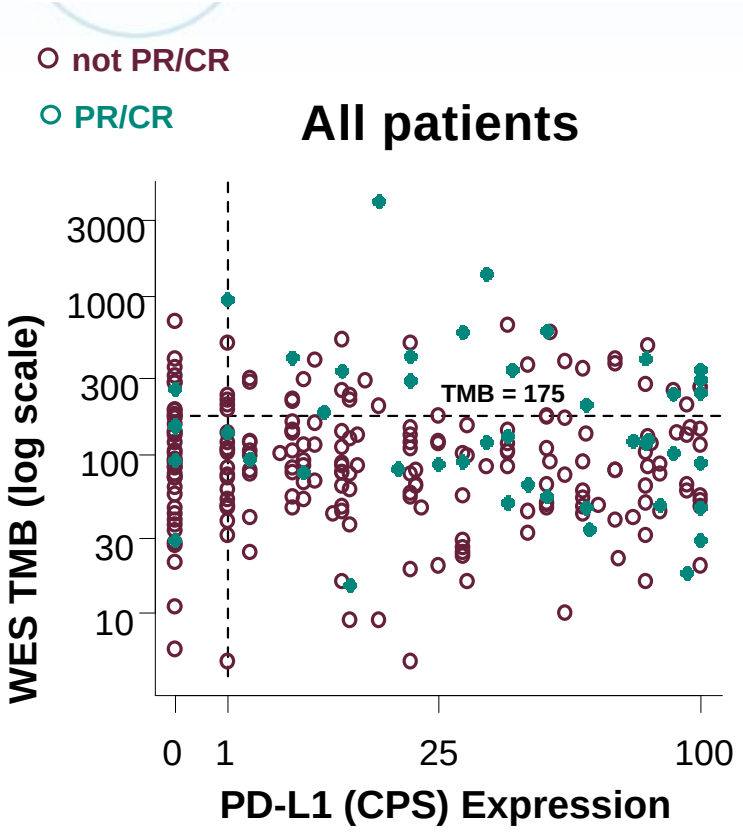
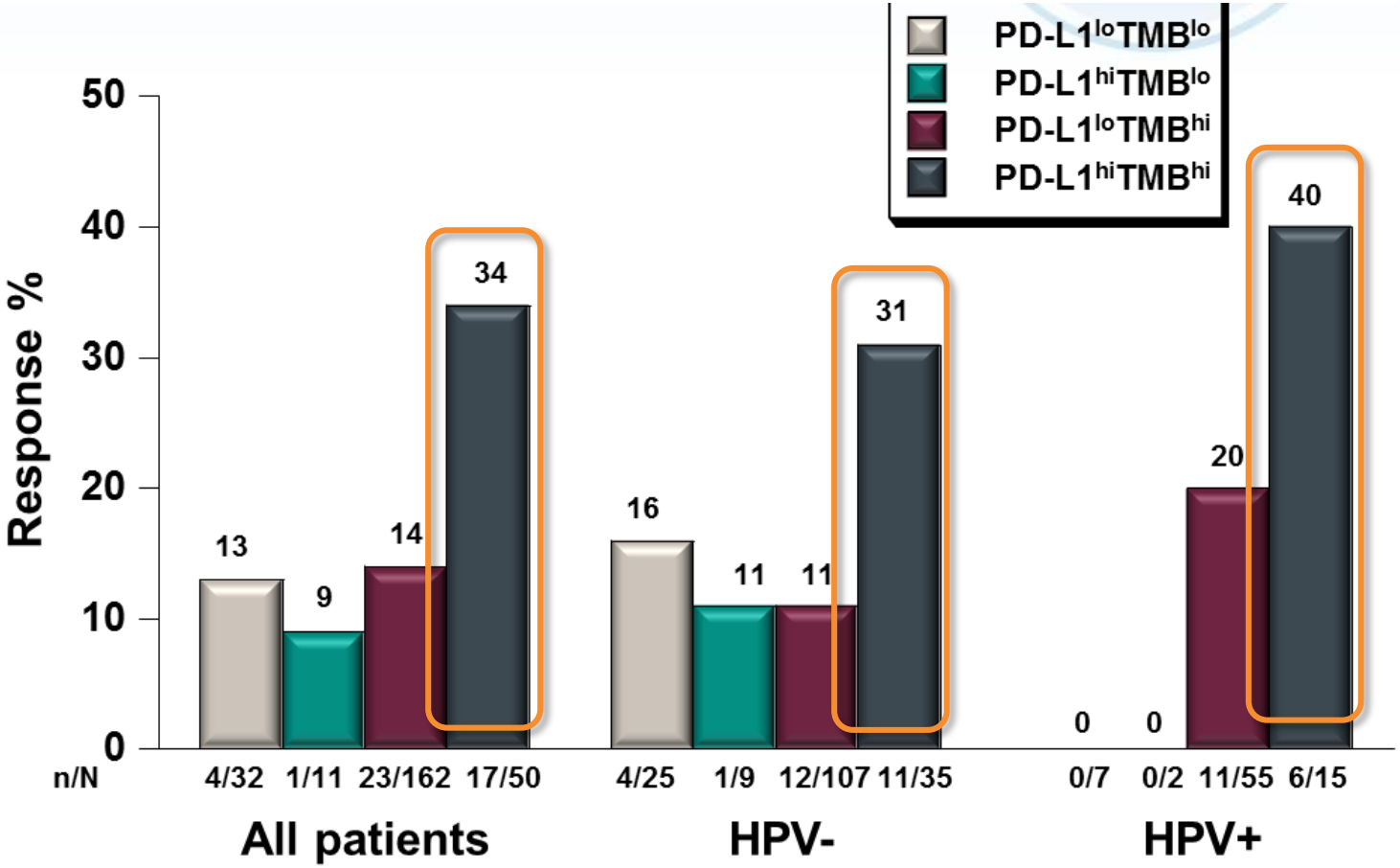
PR=partial response; CR=complete response

PD-L1 and TMB response rates (BOR)

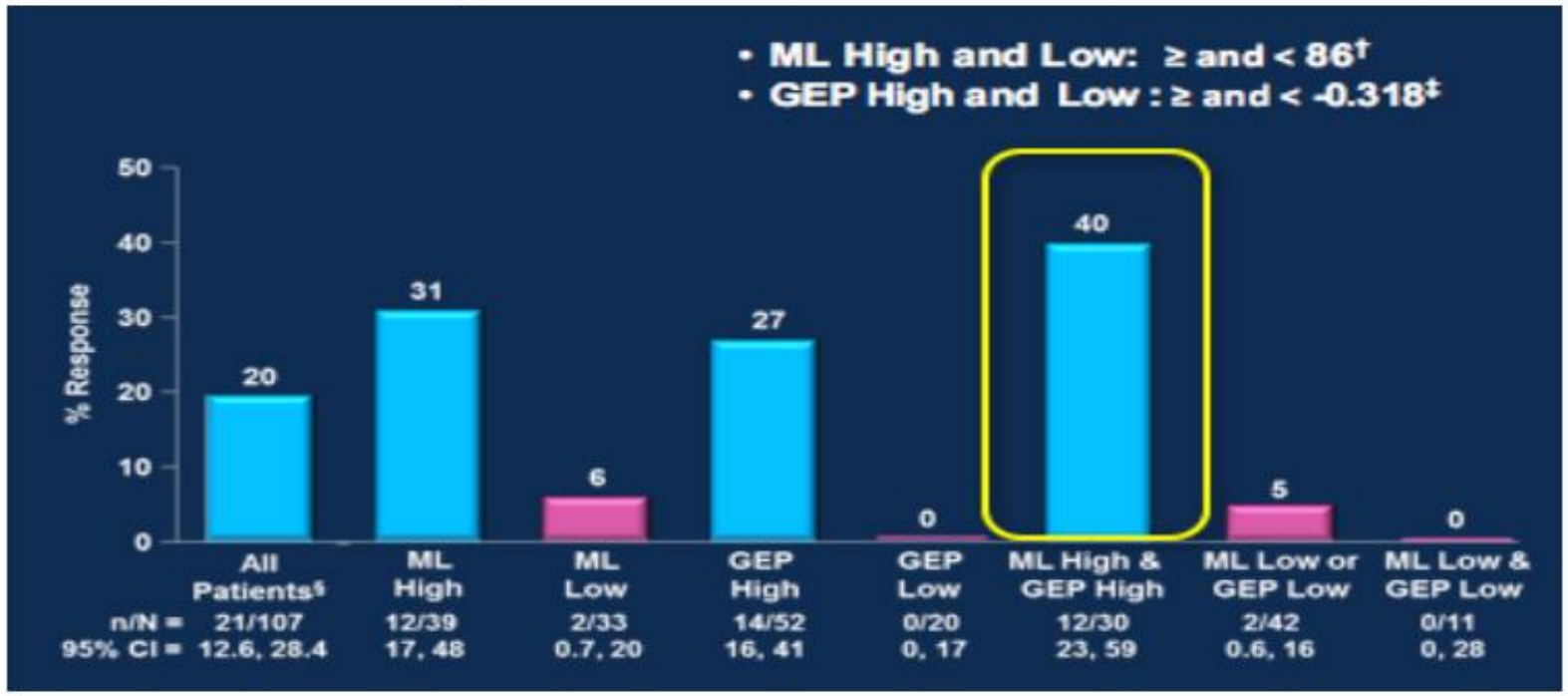




- Response rates were higher in those who had PDL1+ and TMB across all patients and in both HPV subgroups than those with low levels of both

Dashed horizontal line is the clinically applicable TMB threshold (TMB ≥175 mutations per exome) derived using GEP and TMB data from the pan tumor cohort (Panda A et al. Precision Oncol. 2017). Dashed vertical line is PD-L1 CPS ≥1. PD-L1 CPS high (hi) and low (lo): ≥1 and 0; TMB hi and lo: ≥ and < 175.

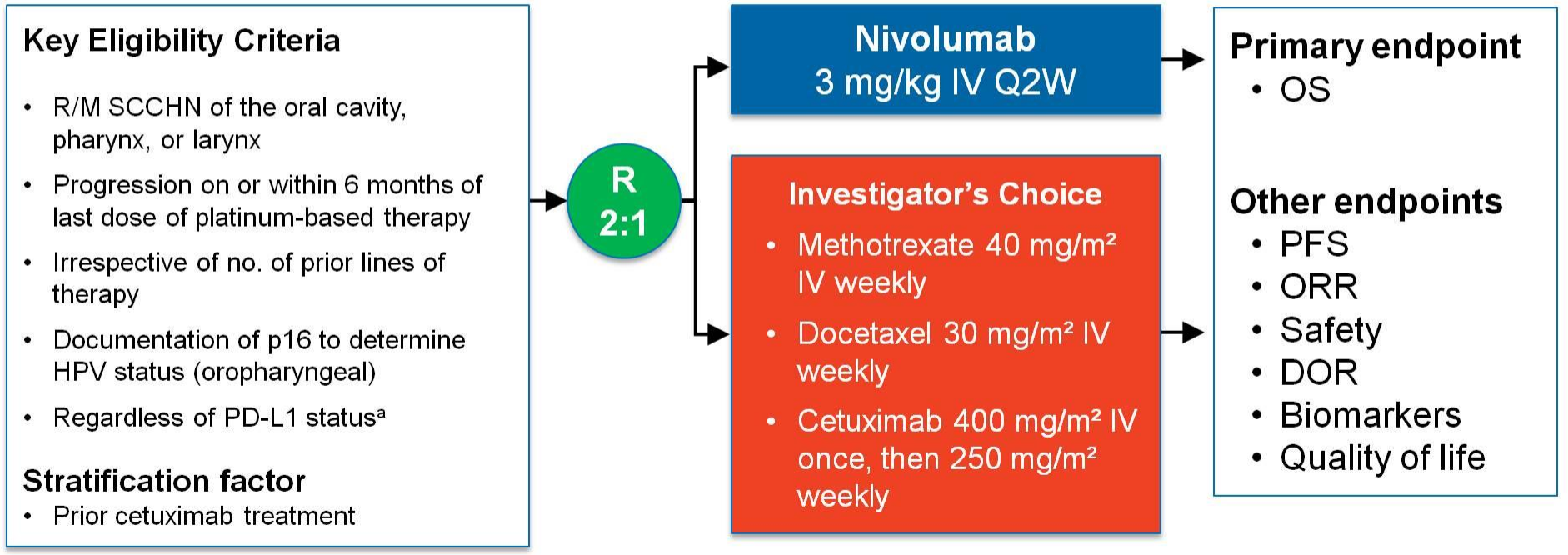
Combined GEP/ML



Haddad et al ASCO 2017

Phase 3 CheckMate 141 Study Design
Nivolumab in R/M SCCHN After Platinum Therapy

Randomized, global, phase 3 trial of the efficacy and safety of nivolumab vs investigator's choice in patients with R/M SCCHN



[a]Tissue required for testing

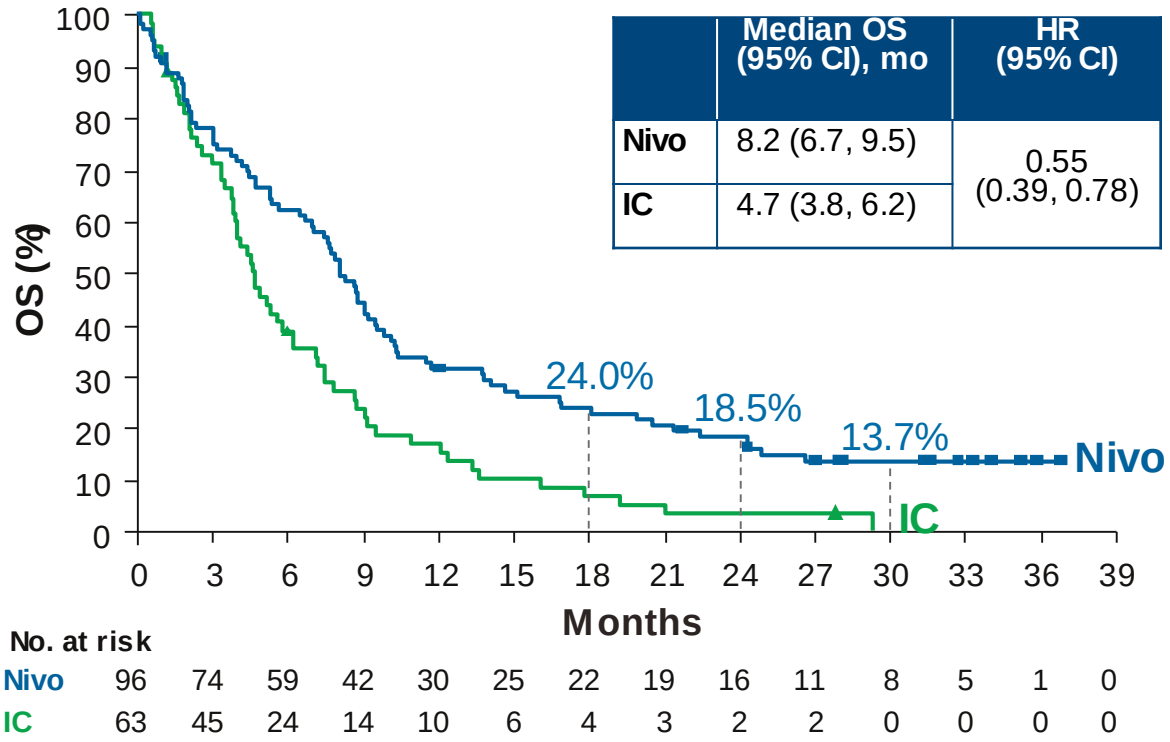
DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

Presented By Robert Ferris at 2016 ASCO Annual Meeting

OS Benefit Across PD-L1 Expressors and Non-Expressors

- OS rates at 18, 24, and 30 months were similar in both groups
  - PD-L1 expressors: nivolumab continued to provide OS benefit, with 45% reduction in risk of death vs IC
  - PD-L1 non-expressors: nivolumab resulted in 27% reduction in risk of death vs IC

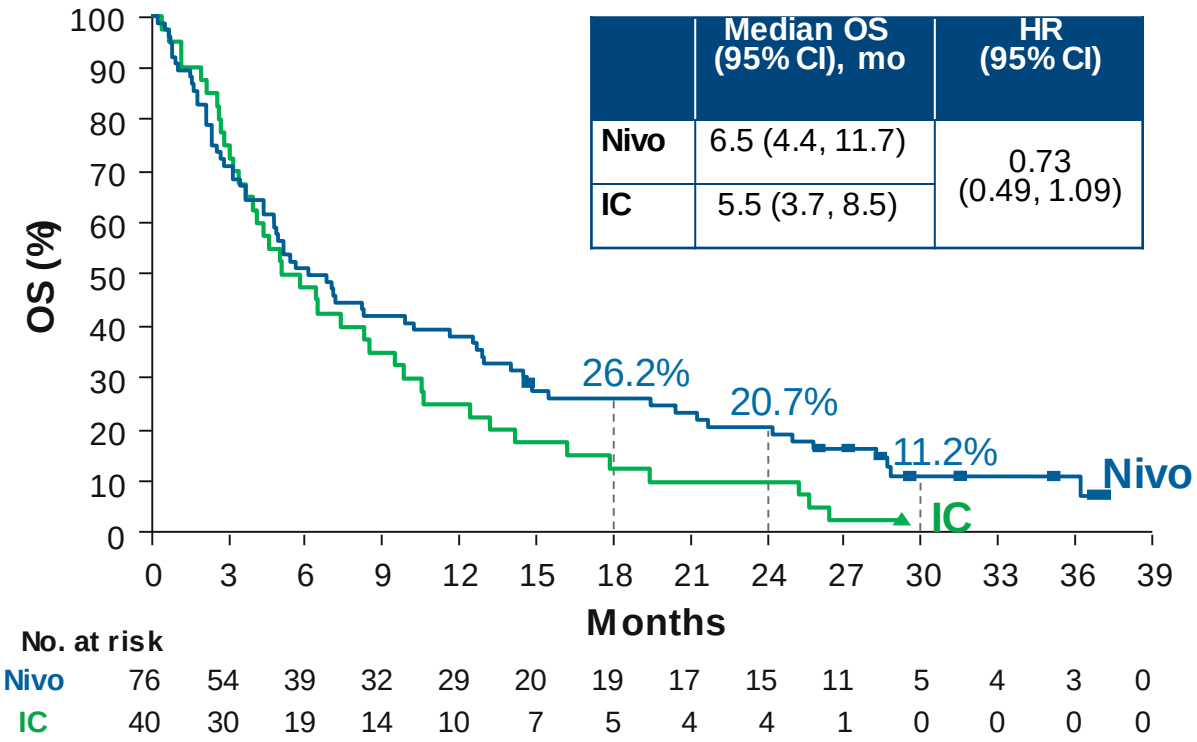
PD-L1 Expressors (≥1%)



	Median OS (95% CI), mo	HR (95% CI)
Nivo	8.2 (6.7, 9.5)	0.55 (0.39, 0.78)
IC	4.7 (3.8, 6.2)	

No. at risk														
Nivo	96	74	59	42	30	25	22	19	16	11	8	5	1	0
IC	63	45	24	14	10	6	4	3	2	2	0	0	0	0

PD-L1 Non-Expressors (<1%)



	Median OS (95% CI), mo	HR (95% CI)
Nivo	6.5 (4.4, 11.7)	0.73 (0.49, 1.09)
IC	5.5 (3.7, 8.5)	

No. at risk														
Nivo	76	54	39	32	29	20	19	17	15	11	5	4	3	0
IC	40	30	19	14	10	7	5	4	4	1	0	0	0	0

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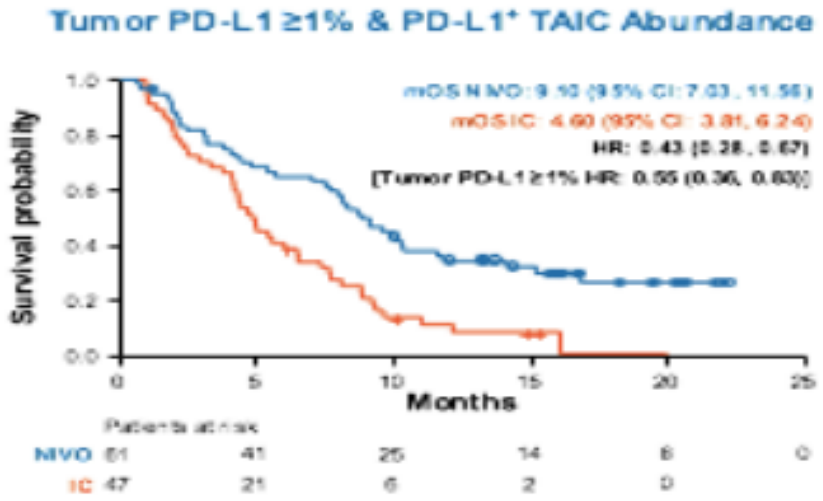
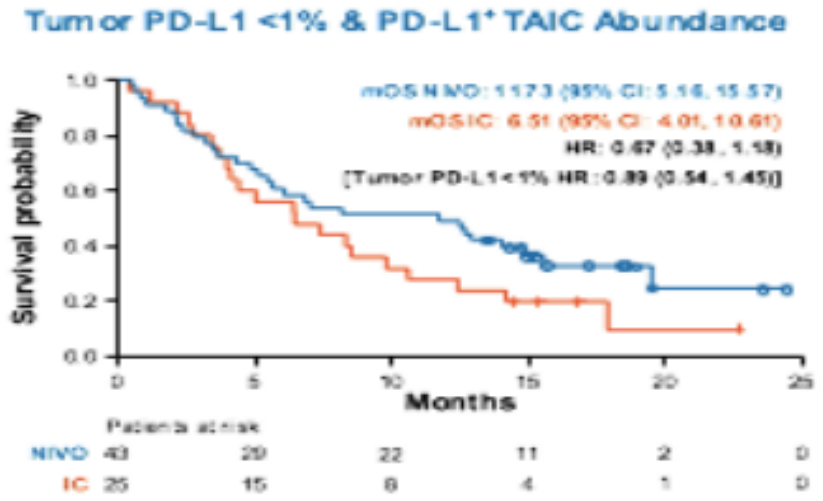
Symbols represent censored observations

CM141 – Tumor and Immune cells

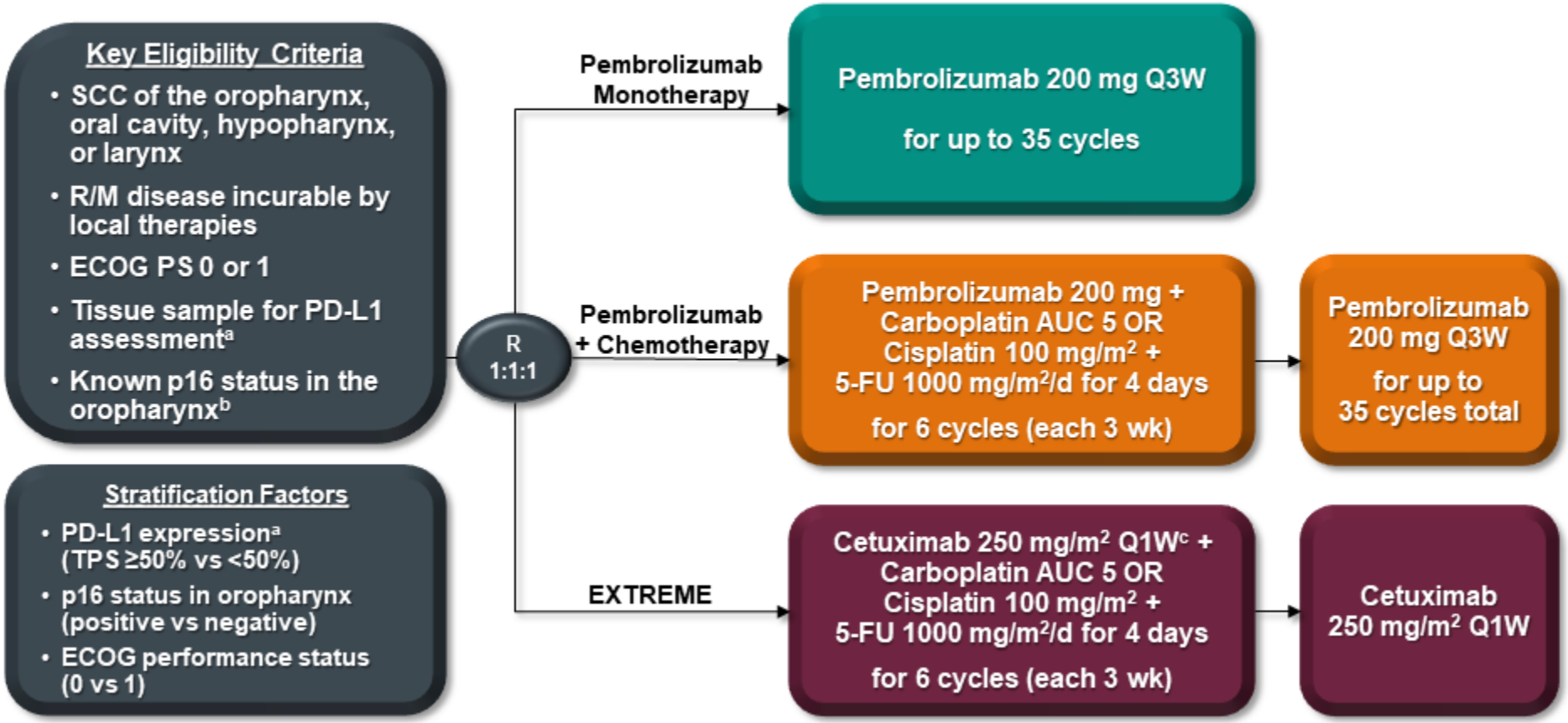




Ferris et al AACR 2017

Burtness KN048 ESMO 2018

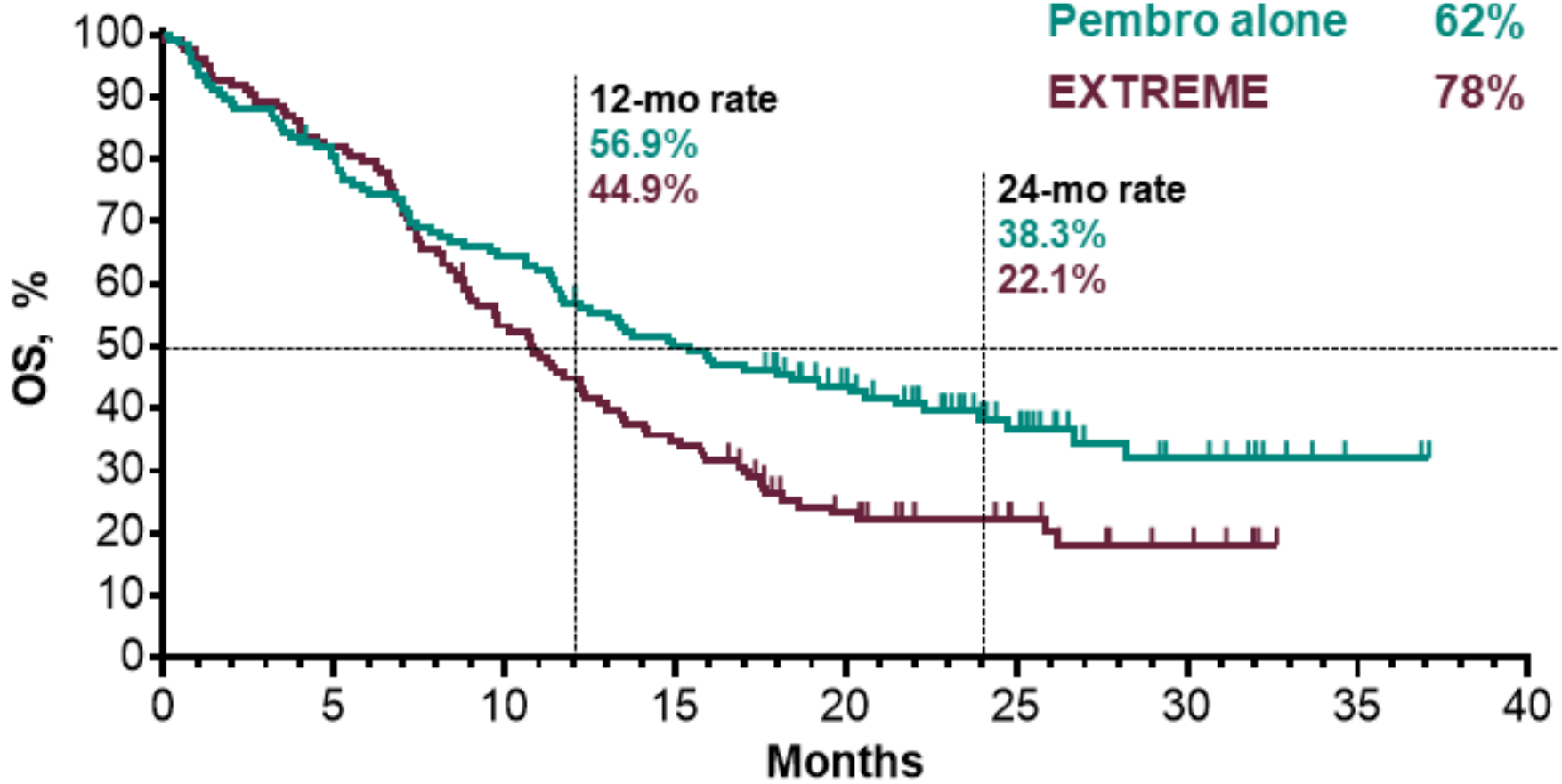
KEYNOTE-048 Study Design (NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Overall Survival: P vs E, CPS ≥20 Population

	Events	HR (95% CI)	*P*
Pembro alone	62%	0.61 (0.45-0.83)	0.0007
EXTREME	78%		



Median (95% CI)
14.9 mo (11.6-21.5)
10.7 mo (8.8-12.8)

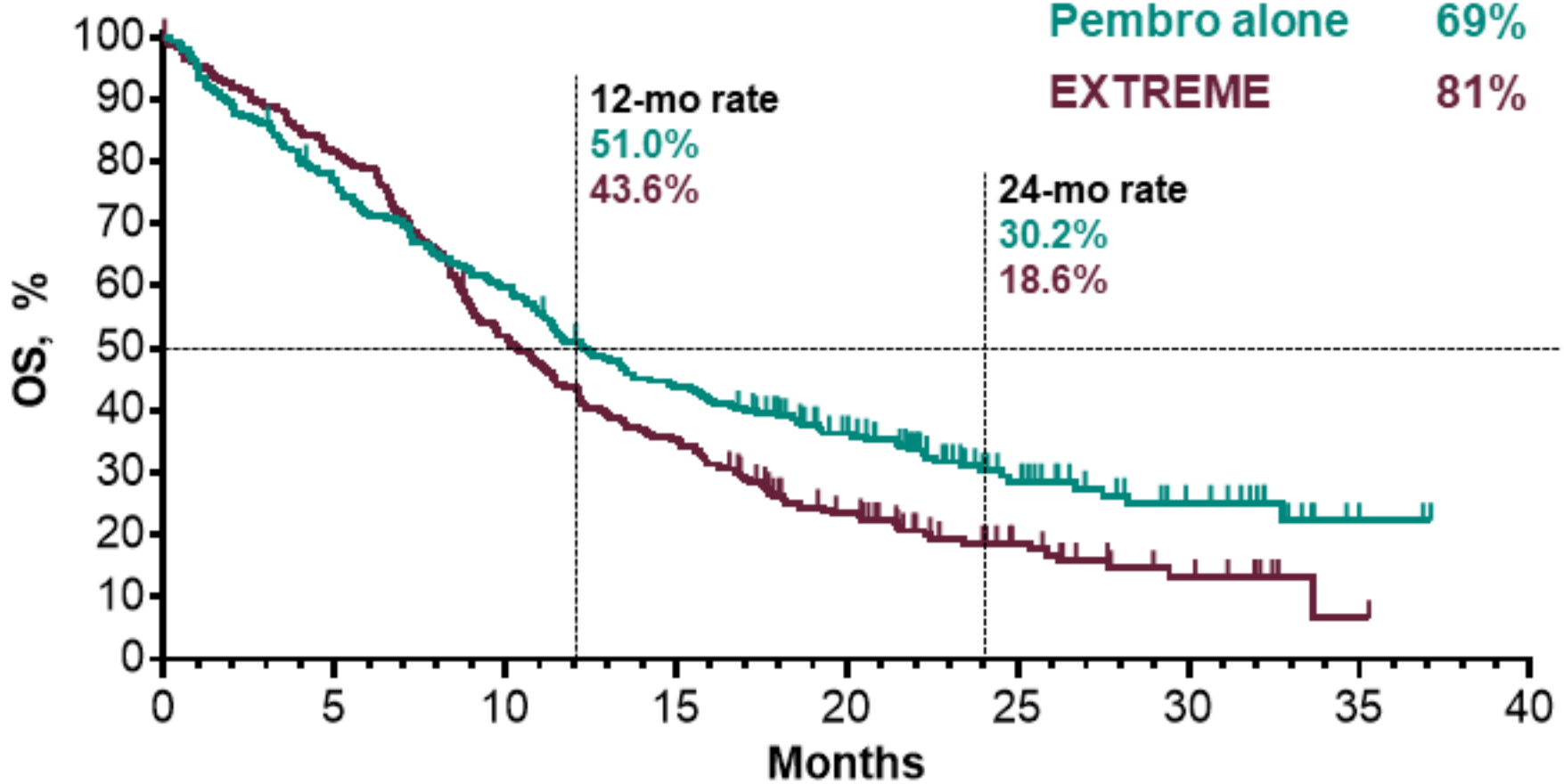
No. at Risk

133	106	85	65	47	24	11	2	0
122	100	64	42	22	12	5	0	0

Data cutoff date: Jun 13, 2018.

Overall Survival: P vs E, CPS ≥1 Population

	Events	HR (95% CI)	*P*
Pembro alone	69%	0.78 (0.64-0.96)	0.0086
EXTREME	81%		



Median (95% CI)
12.3 mo (10.8-14.9)
10.3 mo (9.0-11.5)

No. at Risk

257	196	152	110	74	34	17	2	0
255	207	131	89	47	21	9	1	0

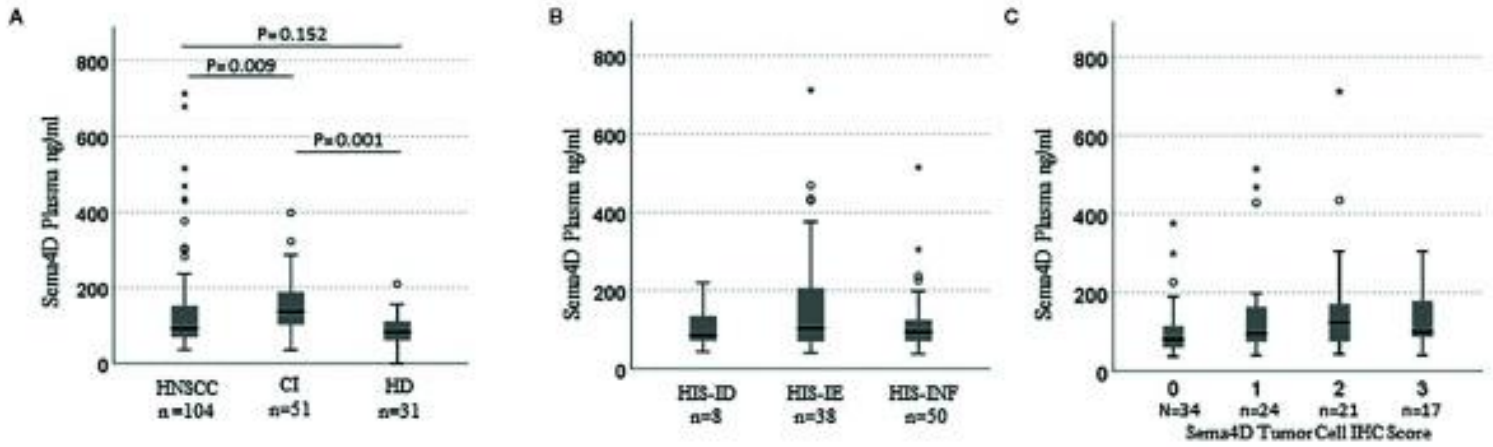
Data cutoff date: Jun 13, 2018.

Sema4D

- Semaphorin D – glycoprotein on tumor and immune cells which is membrane bound or soluble
- Expressed by T cells
- Enhances B cell responses and maturation of APCs
- High levels of soluble Sema4D is noted in chronic inflammatory conditions

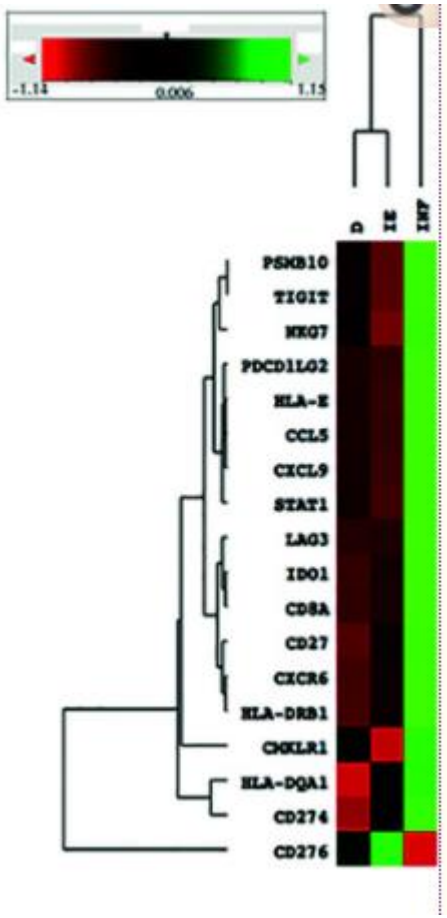
Kikutani et al Nat Rev Immunol 2003
Yoshida et al. Arthritis Rheumatol. 2015 Jun; 67(6):1481-90.

sSema4D and tissue expression



Younis et al. Front Immunol 2021; 12

Sema4D is associated with non-inflamed profile



HsS4D in plasma is associated with HIS-IE.

		Plasma		Total	p-value
		LsS4D	*HsS4D		
HIS	ID	7	1	8	
		87.5%	12.5%	100.0%	
	IE	22	16	38	0.007
		57.9%	42.1%	100.0%	
	INF	43	7	50	
		86.0%	14.0%	100.0%	
	Total	72	24	96	
		75.0%	25.0%	100.0%	

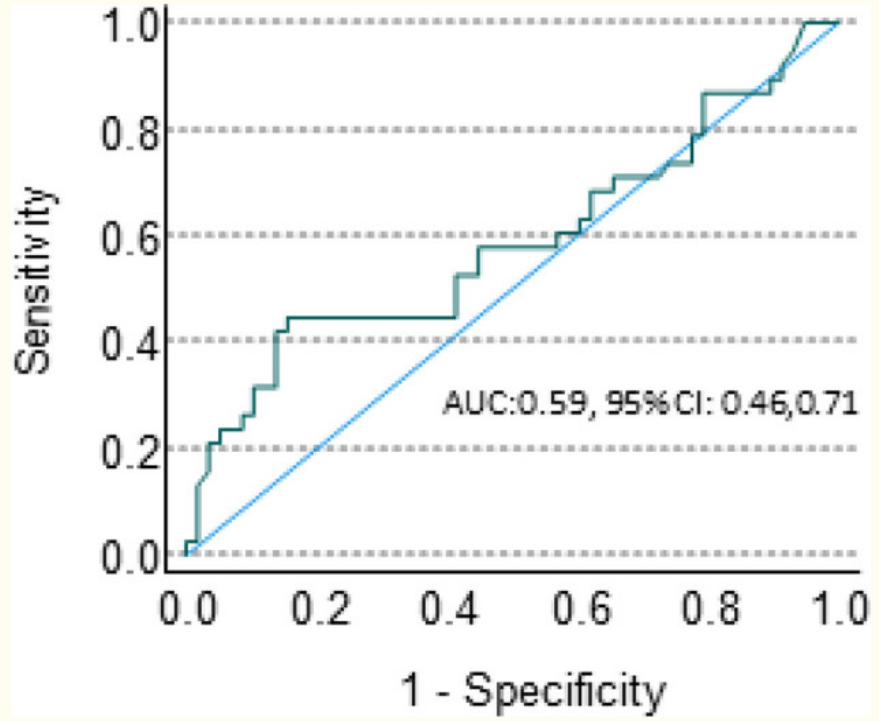


Figure 7

Younis et al. Front Immunol 2021; 12

Conclusions

- PDL1 CPS is the current clinically validated biomarker for determining immunotherapy based treatment selection for SCCHN
- Mutation burden and GES signatures are active areas of further study and based on retrospective data is associated with a response
- Novel biomarkers of immune response are under study for head and neck cancer.