PLENARY SYMPOSIUM 9
CLINICAL BREAKTHROUGH WITH IMMUNOTHERAPY: HEAD & NECK CANCER

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&
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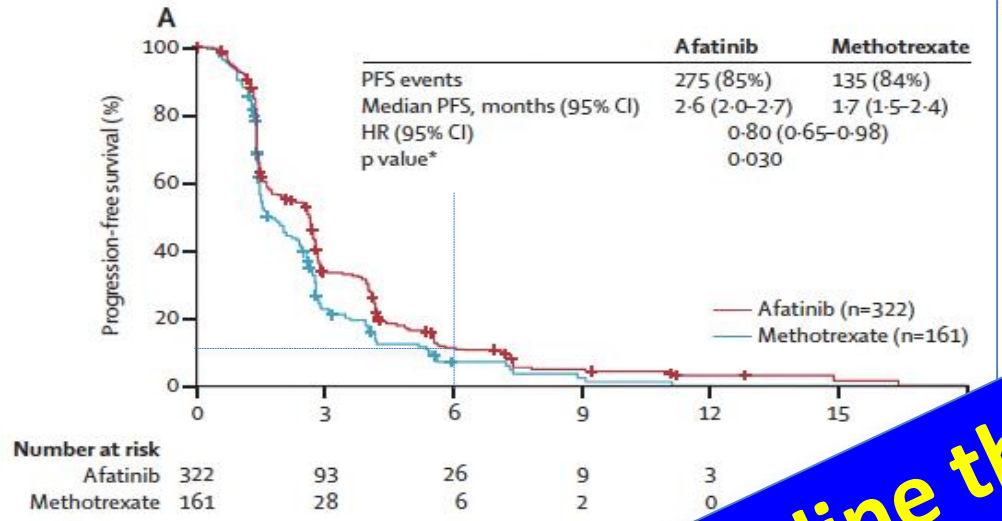
Declaration of conflict of interest

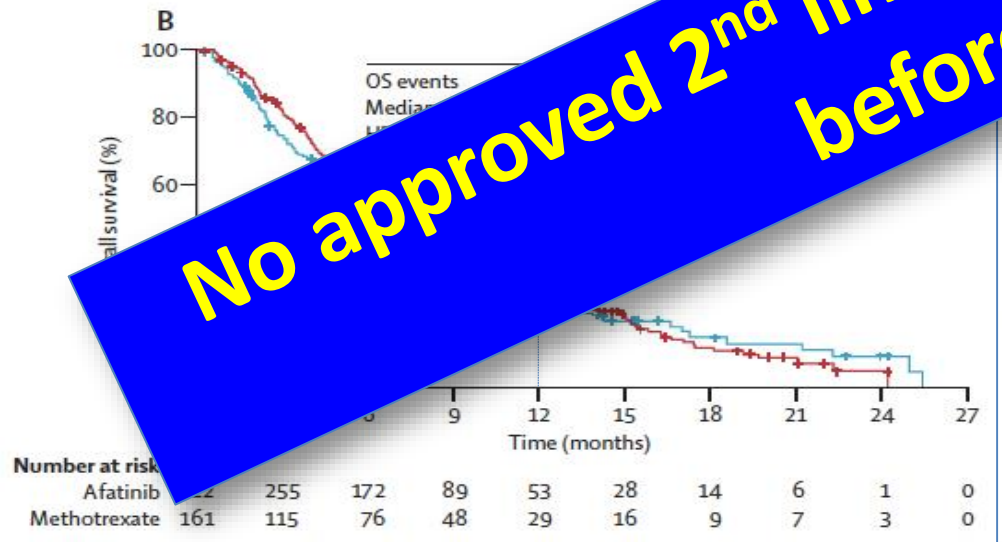
Type	Company
Employment full time/part time	None
Research Grant (P.I.; collaborator or consultant; pending and received grant)	Merck KGaA
Other research supports	None
Speaker Bureau/honoraria	MSD, BMS, Merck KGaA
Ownership interest (stock, stock-options, patent or intectual property)	Glaxo SK
Consultant/advisory board	MSD, BMS, Merck KGaA

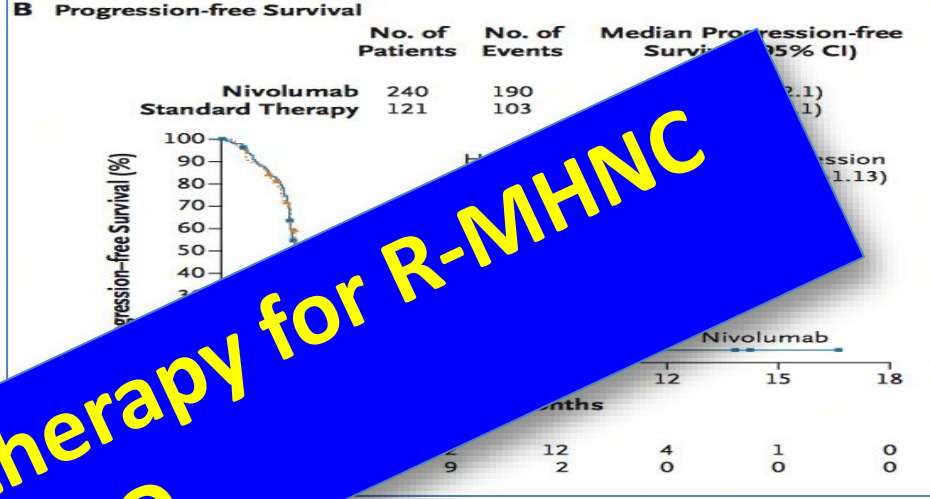
PROS…

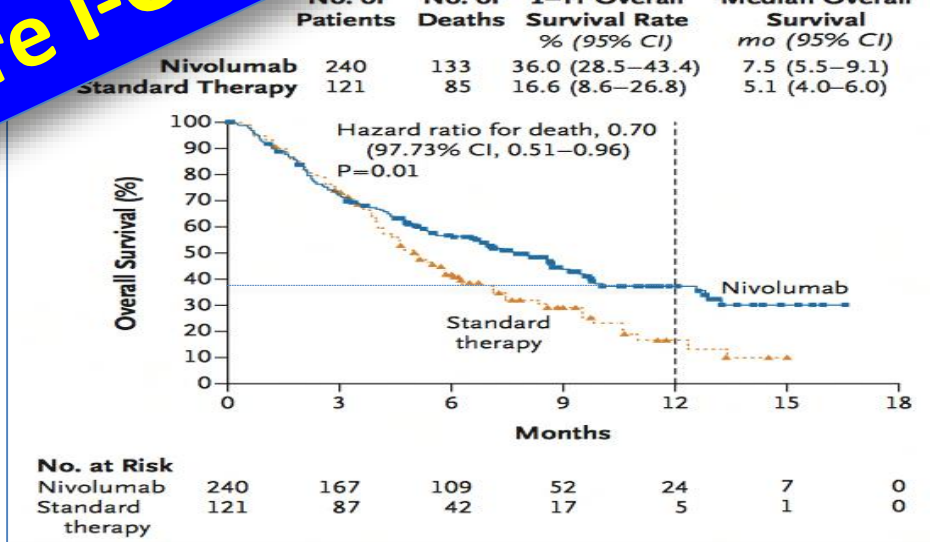
Unexpected survival in a (small) proportion of pts with heavily pre-treated RM-HNC

Very favourable toxic profile





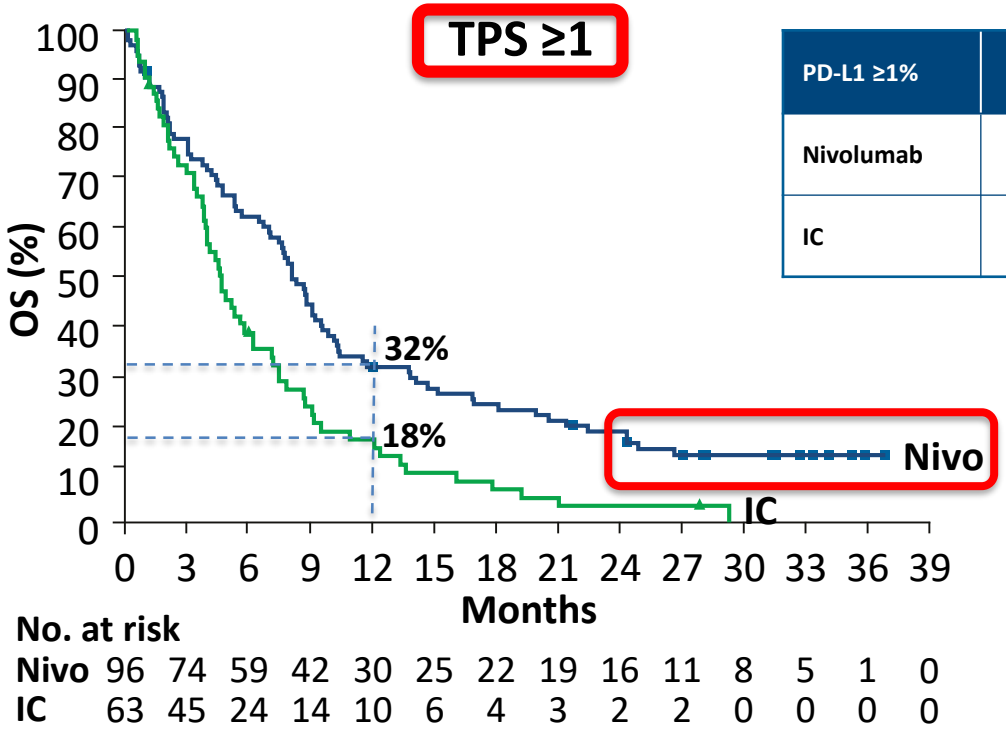




No approved 2nd line therapy for R-MHNC before I-O

OS in patients with tumor PD-L1 expression ≥1% (56% pts[1])

2-year follow-up (September 2017 data cutoff)



PD-L1 ≥1%	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab	8.2 (6.7, 9.5)	0.55 (0.39, 0.78)
IC	4.7 (3.8, 6.2)	

1) PD-L1 available in 159/261 pts

Treatment-Related AEs With Incidence ≥10%

	Pembrolizumab (N = 246)		SOC (N = 234)	
Event, n (%)	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Hypothyroidism	33 (13.4)	1 (0.4)	2 (0.9)	0
Fatigue	31 (12.6)	4 (1.6)	43 (18.4)	2 (0.9)
Diarrhea	20 (8.1)	4 (1.6)	24 (10.3)	1 (0.4)
Rash	19 (7.7)	1 (0.4)	34 (14.5)	1 (0.4)
Asthenia	18 (7.3)	1 (0.4)	28 (12.0)	4 (1.7)
Anemia	17 (6.9)	1 (0.4)	33 (14.1)	9 (3.8)
Nausea	12 (4.9)	0	29 (12.4)	1 (0.4)
Mucosal inflammation	9 (3.7)	1 (0.4)	30 (12.8)	5 (2.1)
Stomatitis	6 (2.4)	1 (0.4)	28 (12.0)	11 (4.7)
Neutrophil count decreased	3 (1.2)	1 (.4)	25 (10.7)	20 (8.5)
Alopecia	1 (0.4)	0	25 (10.7)	0

AEs did not change in updated analysis. Relationship to treatment was determined by the investigator.
Data cutoff date: May 15, 2017.

	Nivolumab (n = 236)		IC (n = 111)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE, n (%)	**146 (61.9)**	**36 (15.3)**	**88 (79.3)**	**40 (36.0)**
TRAEs in ≥15% of patients, n (%)				
Fatigue	**37 (15.7)**	**5 (2.1)**	**20 (18.0)**	**3 (2.7)**
Nausea	**22 (9.3)**	**0**	**23 (20.7)**	**1 (0.9)**
Anemia	**12 (5.1)**	**3 (1.3)**	**19 (17.1)**	**6 (5.4)**
Asthenia	**10 (4.2)**	**1 (0.4)**	**17 (15.3)**	**2 (1.8)**
Select TRAEs, n (%)				
Skin	**40 (16.9)**	**0**	**14 (12.6)**	**2 (1.8)**
Endocrine	**22 (9.3)**	**1 (0.4)**	**1 (0.9)**	**0**
Gastrointestinal	**20 (8.5)**	**1 (0.4)**	**17 (15.3)**	**2 (1.8)**
Hepatic	**7 (3.0)**	**2 (0.8)**	**5 (4.5)**	**1 (0.9)**
Pulmonary	**7 (3.0)**	**2 (0.8)**	**1 (0.9)**	**0**
Hypersensitivity/infusion reactions	**3 (1.3)**	**0**	**2 (1.8)**	**1 (0.9)**
Renal	**3 (1.3)**	**0**	**2 (1.8)**	**1 (0.9)**

Unexpected response with palliative conventional therapy in head and … noma after anti-programmed deat…

Dena… 2019:41;42-47

…Nivolumab

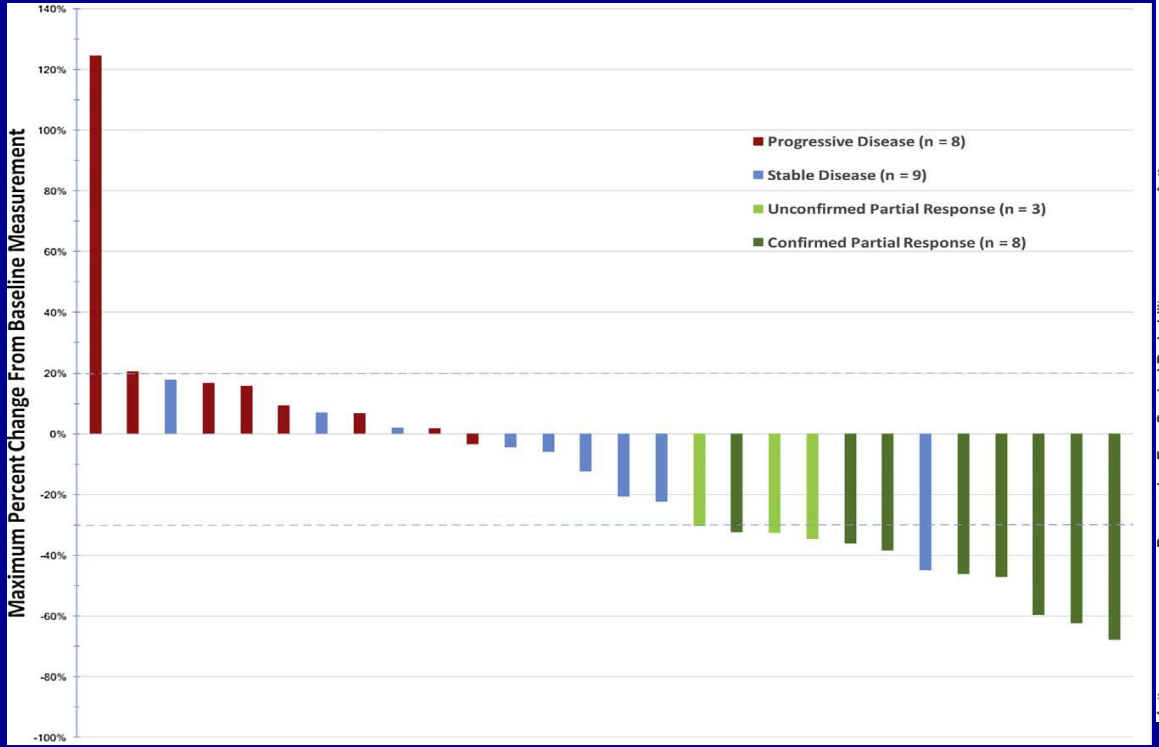
PD Nivolumab

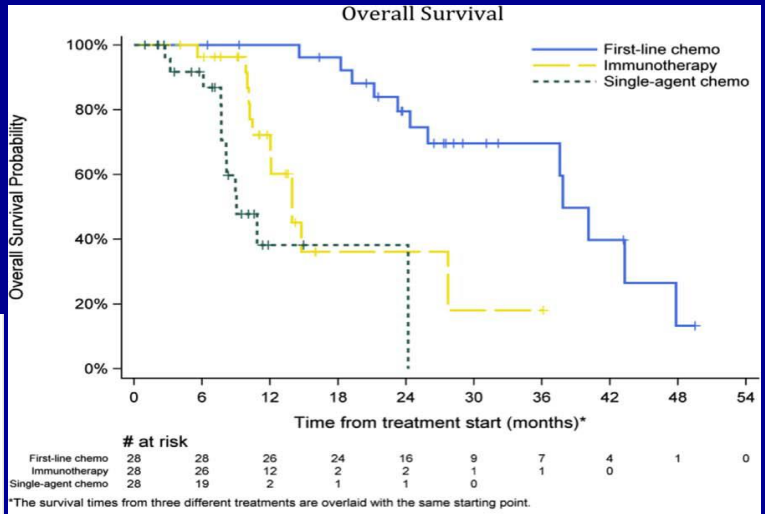
OR PCTXL

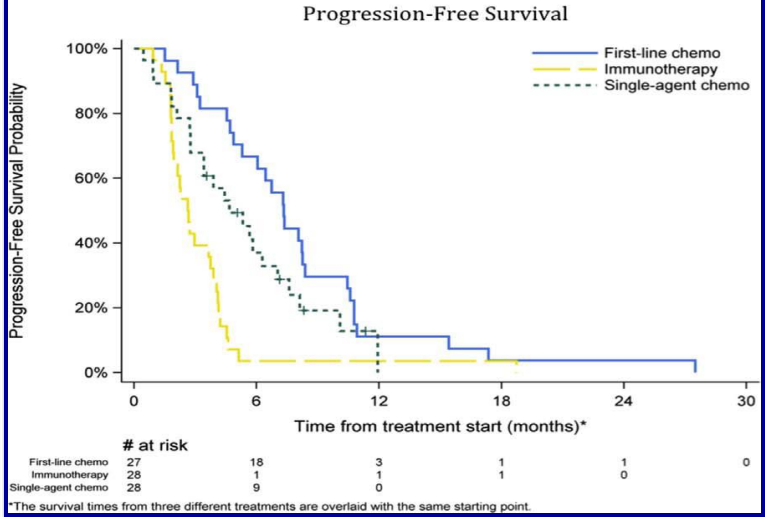
Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced non-small cell lung cancer

Gustavo Schvartsman[a], S. Andrew Peng[b], Giorgios Bis[c], J. Jack Lee[b], Marcelo F.K. Benveniste[d], Jianjun Zhang[e], Emily B. Roarty[e], Lara Lacerda[e], Stephen Swisher[f], John V. Heymach[e], Frank V. Fossella[e,*,1], William N. William[e,*,1]

Lung Cancer 2017







HNC - Subsequent therapy ASCO ‘18

Salvage Chemotherapy after Immunotherapy

Background

- Response to salvage therapy (control arm) ~ 6-10%

Checkmate-141

	Nivolumab (n = 240)	IC (n = 121)
ORR, % (95% CI)	13.3 (9.3, 18.3)	5.8 (2.4, 11.6)
Time to response, median (range), months	2.1 (1.8 to 7.4)	2.0 (1.9 to 4.6)
Duration of response, median (range), months	9.7 (2.8 to 32.8+)	4.0 (1.5+ to 11.3)

Ferris et al., AACR 2018

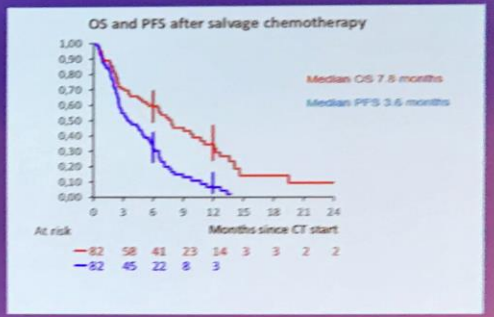
Keynote-040

Best Response, (%)	ITT Pembro N = 247	ITT SOC N = 248
ORR	36 (14.6)	25 (10.1)
CR	4 (1.6)	1 (0.4)
PR	32 (13.0)	24 (9.7)
SD	56 (22.7)	65 (26.2)
PD	108 (43.7)	97 (39.1)
NonCR/nonPD[b]	2 (0.8)	1 (0.4)
Not evaluable or assessable[c]	45 (18.2)	60 (24.2)

Soulieres et al., AACR 2018

Salvage Chemotherapy after Immunotherapy

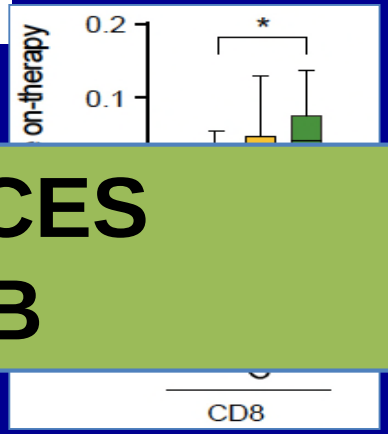
	N=82 (%)
Salvage chemotherapy	
Taxanes	46 (56%)
Platinum-based	30 (37%)
Cetuximab in combination	41 (50%)
Other	12 (15%)
ECOG PS at SCT	
0	11 (13%)
1	49 (60%)
2	21 (26%)
3	1 (1%)
Best response to SCT	
CR	3 (4%)
PR	22 (27%)
SD	22 (27%)
PD	35 (42%)
Number of lines after ICI	
1	55 (66%)
2	22 (27%)
≥3	6 (7%)



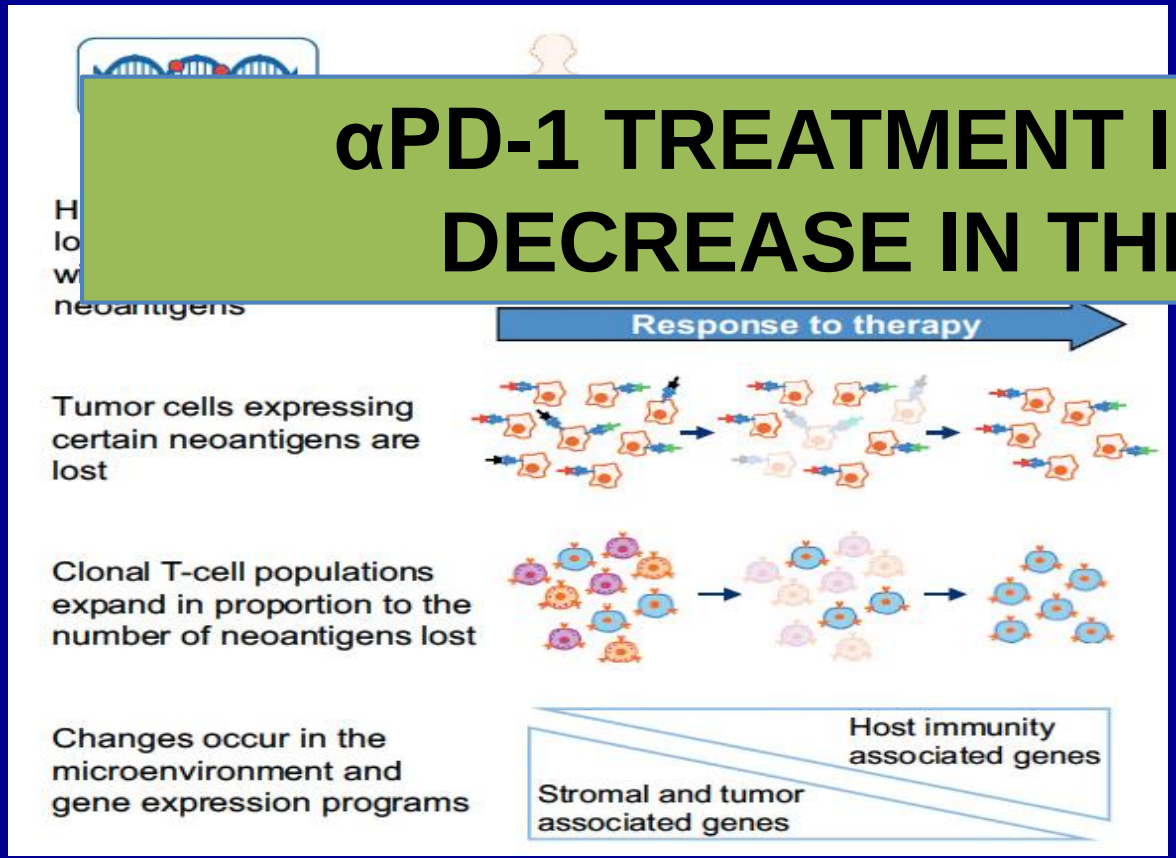
Saleh et al., ASCO 2018

Cell

Tumor and Microenvironment Evolution during Immunotherapy with Nivolumab



αPD-1 TREATMENT INDUCES DECREASE IN THE TMB



Mutation burden decreases with successful checkpoint blockade therapy in patients with melanoma, suggesting that selection against mutant neoepitopes may be a critical mechanism of action of Nivolumab.

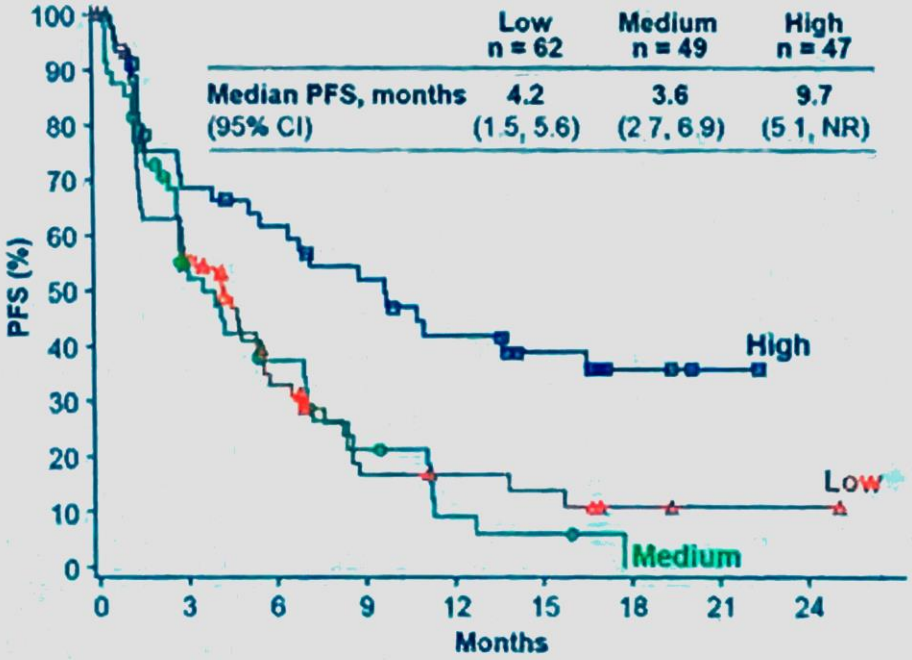
Riaz N (Chan T) et al: Cell 2017;171:934-949

AACR 2017

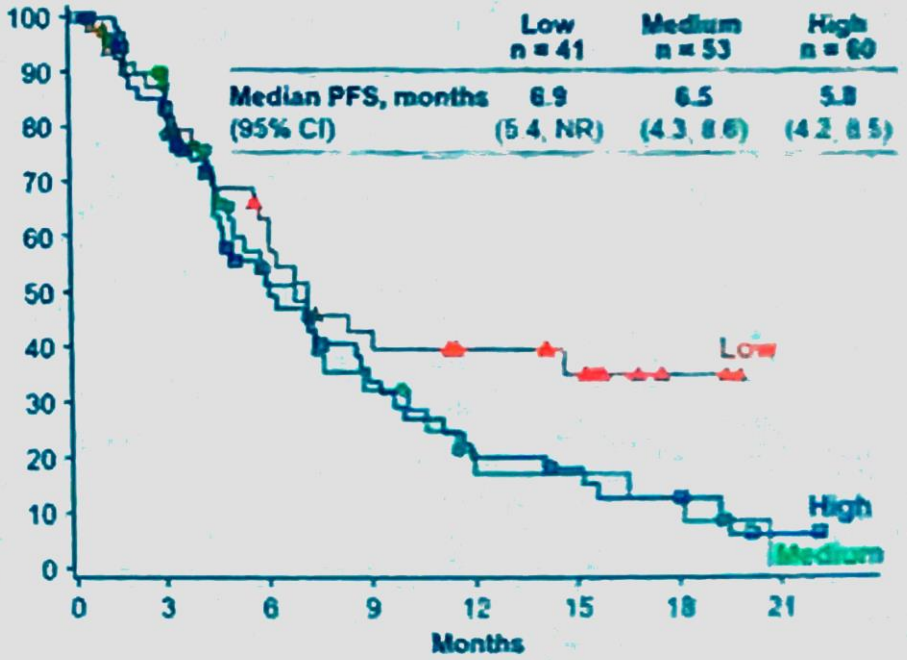
PFS by Tumor Mutation Burden Tertile

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

Nivolumab Arm



Chemotherapy Arm



- Data for patients with low and medium TMB were pooled in subsequent analyses

Carbone DP et al, NEJM 2017;376:2415-2426

ACTIVITY

CONS…

Checkmate 141		Keynote 040	
Nivo	SOC	Pembro	SOC
6	1	4	1
26	6	32	24
208	114	211	223

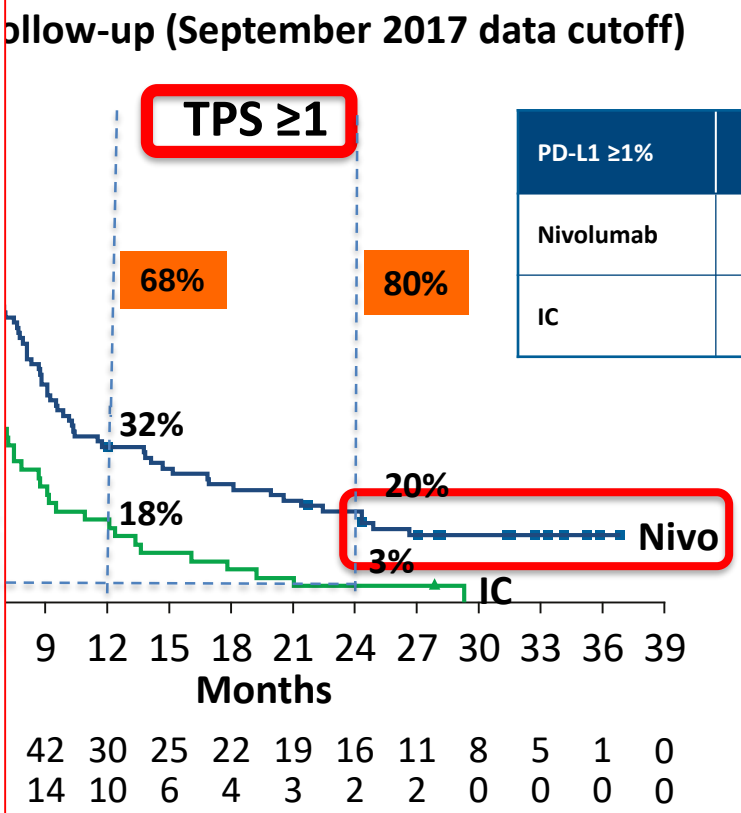
% (2.4 - 11.6)

14.6%

10.1%

ORR	AFATINIB	METHOTREXATE
CR	0	0
PR	33 (10%)	9 (6%)
No Resp	289	152

OS in patients with tumor PD-L1 expression ≥1% (56% pts[1])



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Nivolumab	8.2 (6.7, 9.5)	0.55 (0.39, 0.78)
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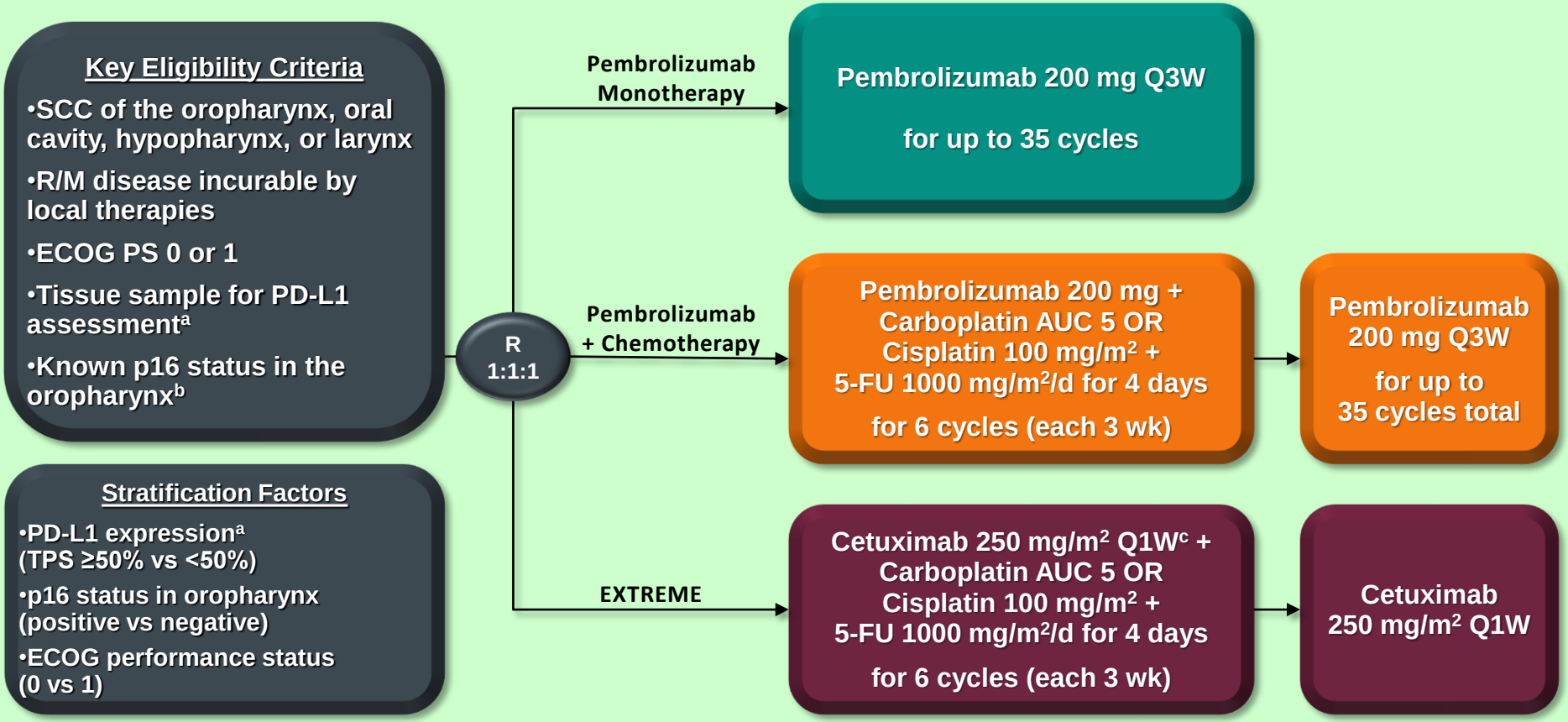
1) PD-L1 available in 159/261 pts

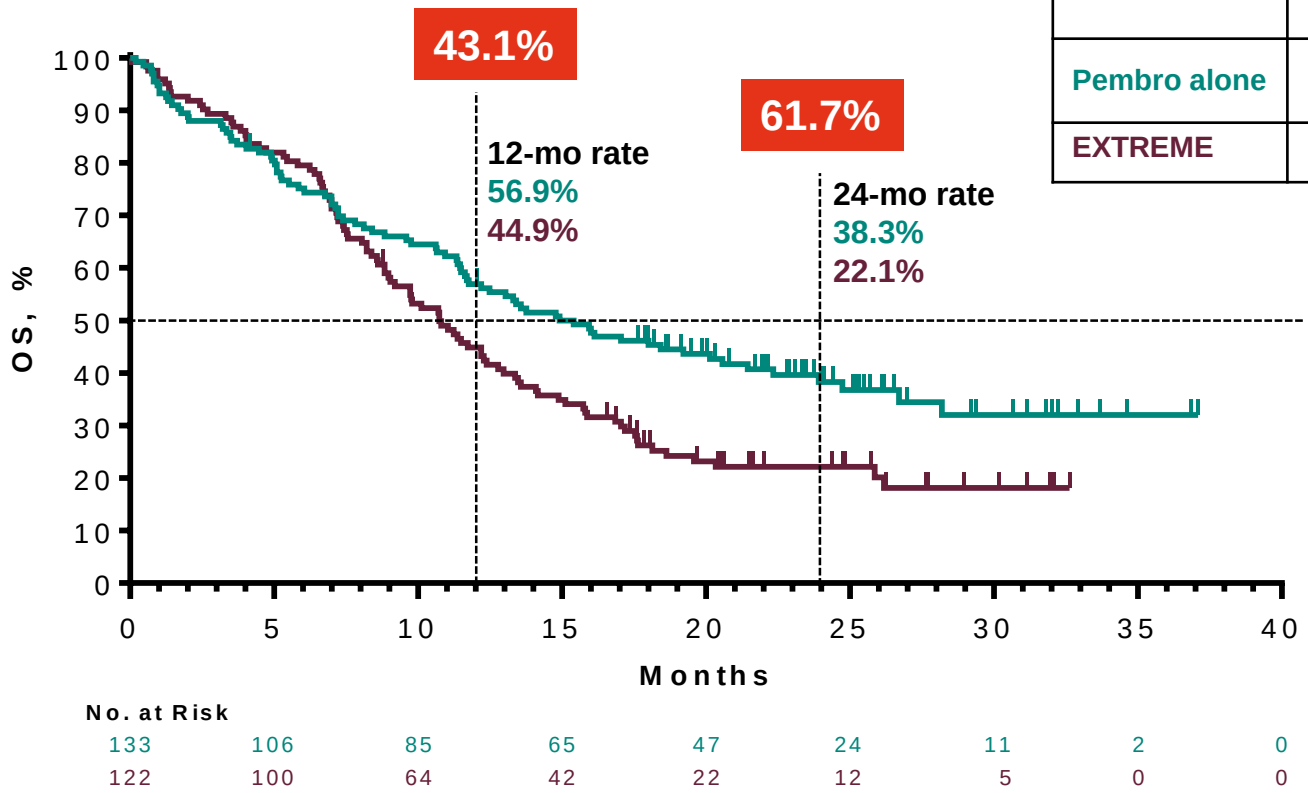
KEYNOTE-048 Study Design (NCT02358031)



[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 (42% pts)

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

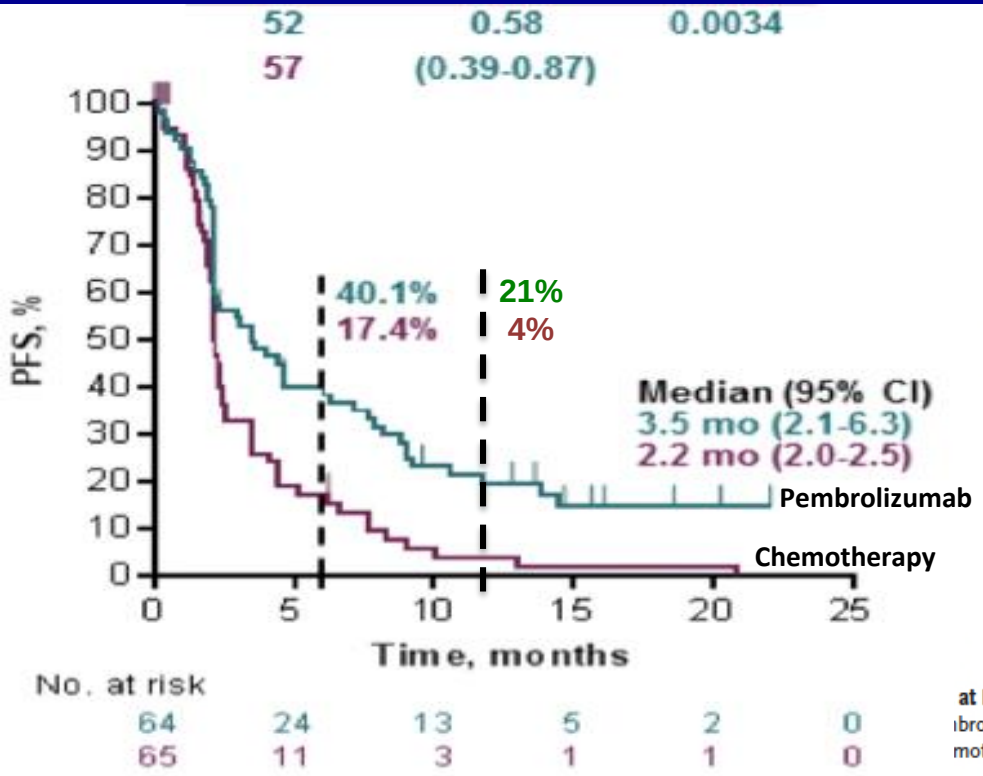


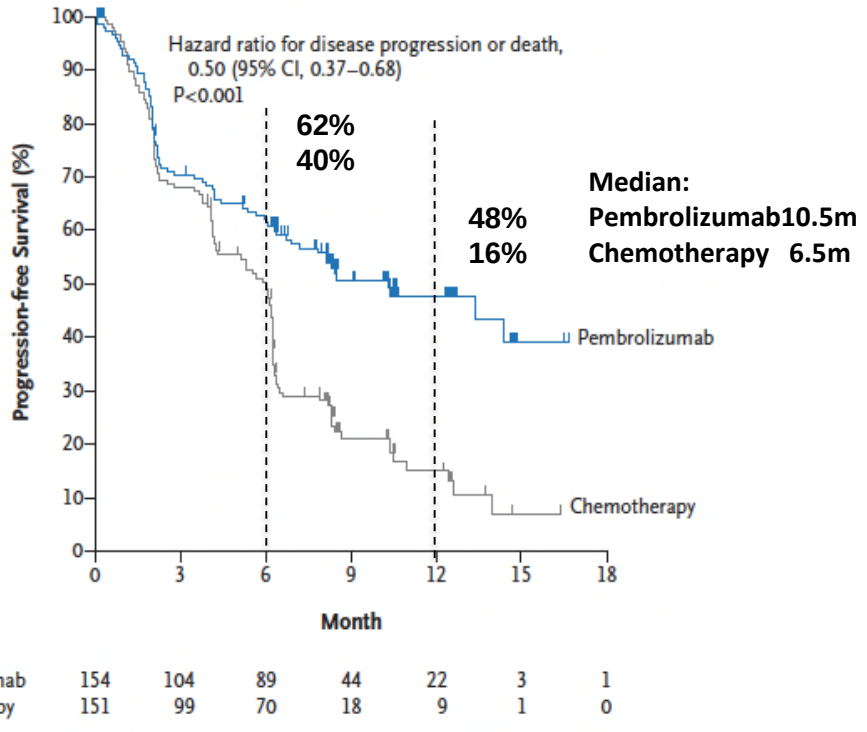
Median (95% CI)
14.9 mo (11.6-21.5)
10.7 mo (8.8-12.8)

Data cutoff date: Jun 13, 2018.

PROGRESSION-FREE SURVIVAL

PD-L1 > 50% (TPS)





KN040 AACR 2018 (HNC)

KN024 NEJM 2016 (NSCLC)

Clinical and Developmental Immunology
Volume 2010, Article ID 701657, 15 pages
doi:10.1155/2010/701657

Review Article

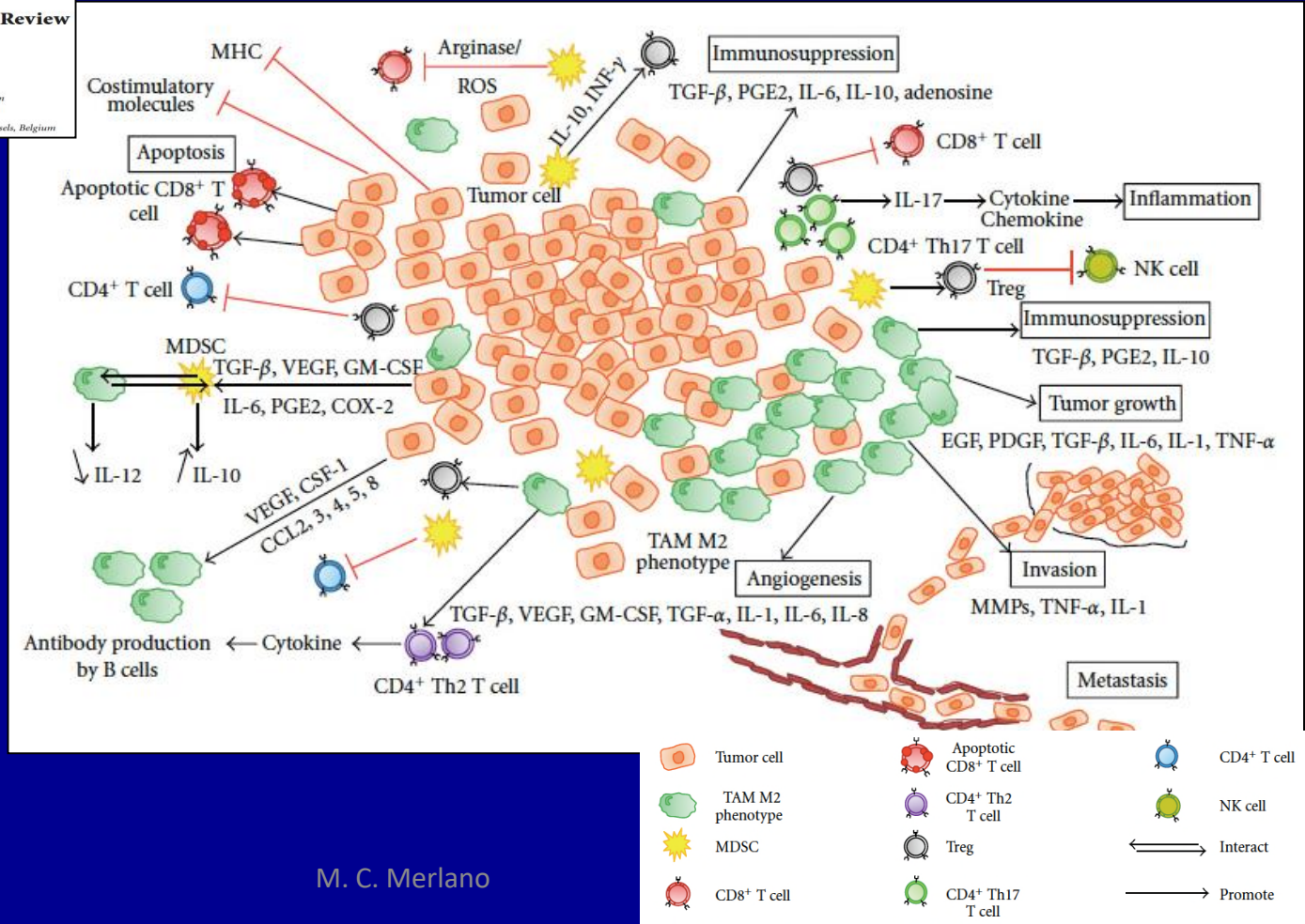
Immune Suppression in Head and Neck Cancers: A Review

Anaëlle Duray,[1] Stéphanie Demoulin,[2] Pascale Hubert,[3]
Philippe Delvenne,[2, 3] and Sven Saussez[1, 4]

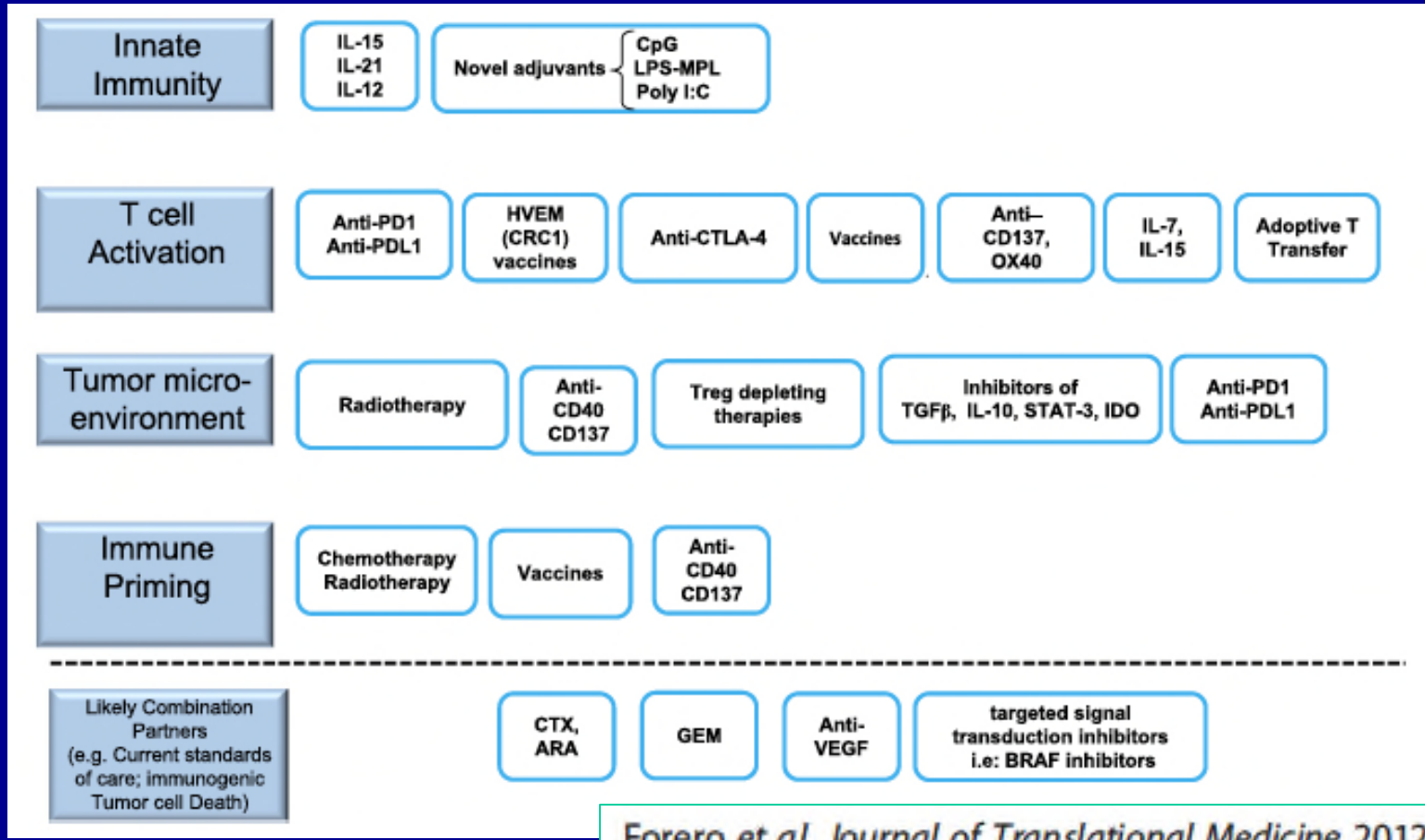
[1] Laboratory of Anatomy, Faculty of Medicine and Pharmacy, University of Mons, 7000 Mons, Belgium
[2] Department of Pathology, CHU Sart-Tilman, University of Liège, 4000 Liège, Belgium
[3] Belgian National Fund for Scientific Research (FNRS), 1000 Brussels, Belgium
[4] Department of Oto-Rhino-Laryngology, CHU Saint-Pierre, Université Libre de Bruxelles, 1000 Brussels, Belgium

The Head and Neck Cancer evasion machinery

- Disruption of Antigen Presenting Machinery
- High amount of TGF β
- High levels of galectin-1
- Abundance of Treg
- Production of VEGF, PGE2, IL-10
- TAM Φ M2



Combination therapy in H-NC



Forero *et al. Journal of Translational Medicine* 2012, **10**:108

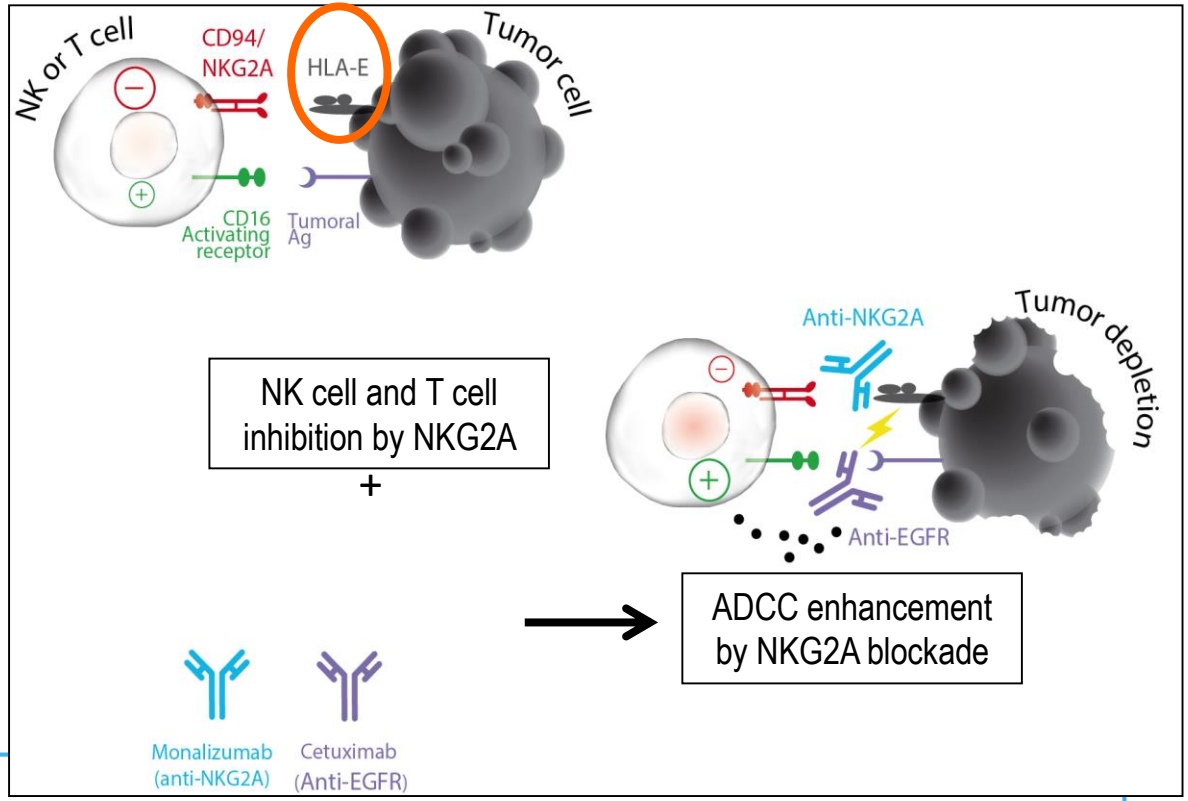
TARGETING NKG2A

Background

Monalizumab:

first-in-class humanized IgG_4
Targeting NKG2D on NK
and tumor infiltrating $CD8^+$.

blocks binding of CD94/NKG2A to HLA-E
reducing inhibitory signaling and thereby
unleashing NK and T cell responses.



Hypothesis:

Dual targeting with the combination of monalizumab and cetuximab will provide greater antitumor activity than cetuximab alone

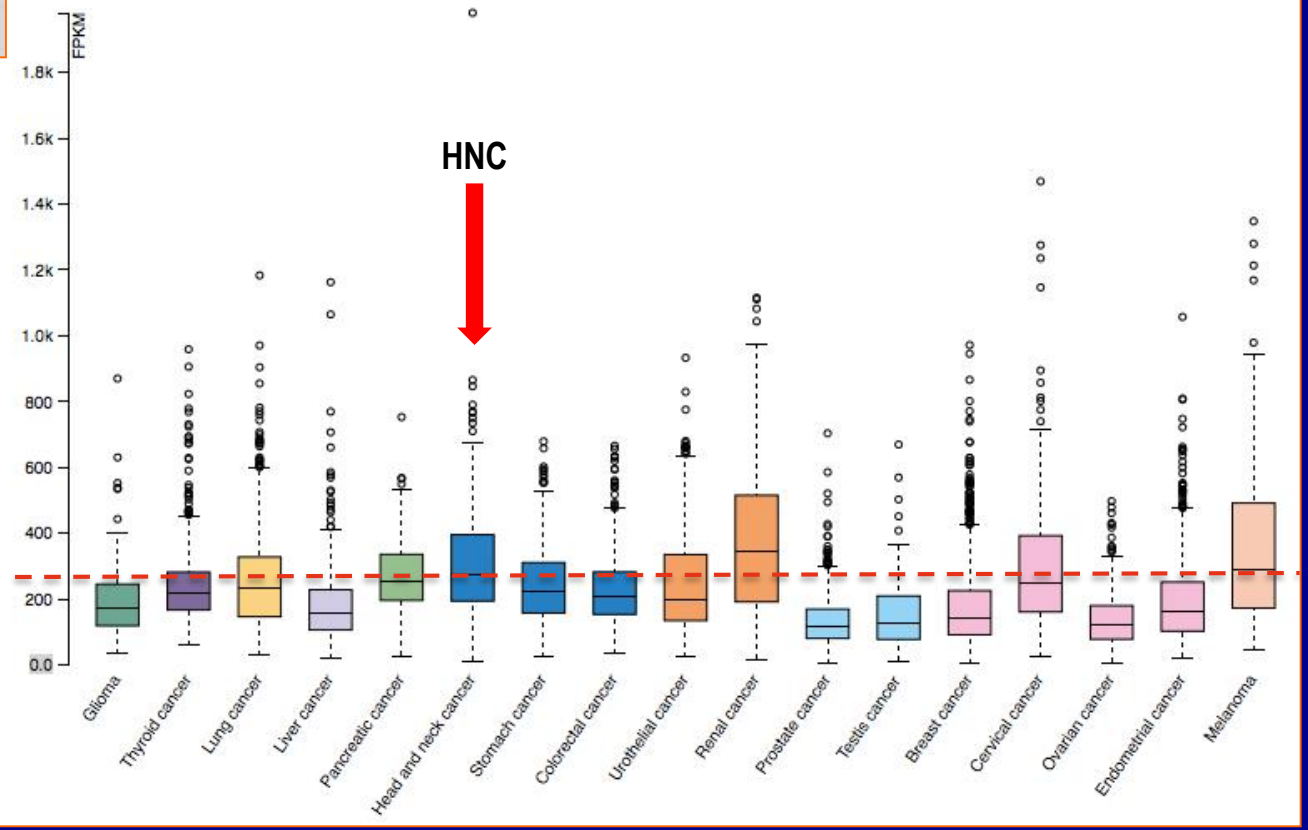
GENERAL INFORMATION	
Gene name	HLA-E
Gene description	Major histocompatibility complex, class I, E
Protein class	Predicted membrane proteins
Predicted localization	Membrane
Number of transcripts	1

THE HUMAN PROTEIN ATLAS

SSION OVERVIEW

taset

RNA cancer category: Expressed in all



78 – 83% of HNC express HLA-E[1]

1) Silva TG et al 2012

Study DESIGN

- Multicenter single arm study to evaluate cetuximab plus monalizumab
- Cohort expansion in R/M SCCHN (NCT02643550)

Key eligibility criteria

- R/M SCCHN, HPV(+) or HPV(-)
- PD after platinum-based CT
- Maximum of 2 prior systemic regimens for R/M disease
- Prior IO allowed*

Treatment

Monalizumab
(10mg/kg Q2W)
+ cetuximab
(approved dosage)

until progression or unacceptable toxicity

Primary objective

- ORR (RECIST 1.1)

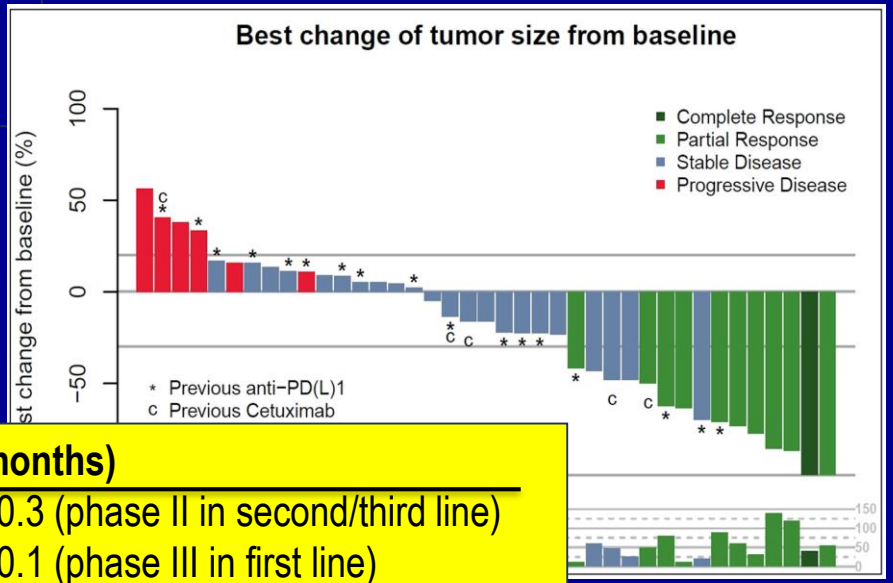
Secondary objectives

- Safety
- DoR, PFS, OS

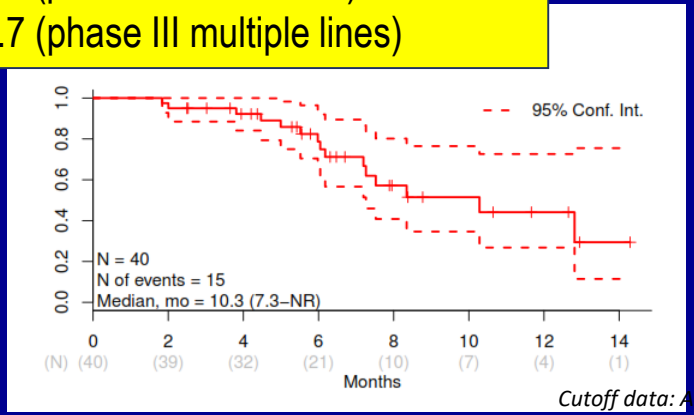
* prior cetuximab allowed if in locally advanced disease with no PD for at least 4 months

KEY RESULTS of monalizumab and cetuximab

KEY RESULTS	n (%) CI
Complete Response (CR)	1 (2.5%)
Partial response (PR)*	10 (25%)
Stable disease	22 (55%)
Overall Response Rate (ORR)	2
Median PFS	5.(
Median OS	10.



mOS	(months)
Monalizumab	10.3 (phase II in second/third line)
Extreme	10.1 (phase III in first line)
CheckMate-141	7.7 (phase III multiple lines)



Safety data:

- Good safety profile of the combination
- No potentiation of the cetuximab related AEs by monalizumab

Cutoff data: Aug 31, 2018

Targeting TLRs

MUNICH 2018 ESMO congress

PHASE 1B/2, OPEN LABEL, MULTICENTER STUDY OF INTRATUMORAL SD-101 IN COMBINATION WITH PEMBROLIZUMAB IN ANTI-PD-1 TREATMENT NAÏVE PATIENTS WITH RECURRENT OR METASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC)

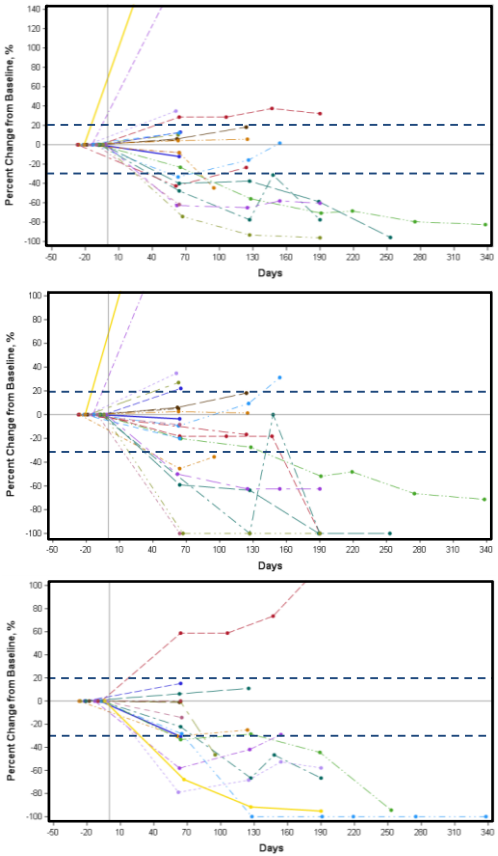
Abstract 1050PD

Ezra Cohen, et al.

EFFICACY

	8 mg	2 mg
mITT patients, n*	**22**	**2**
Objective response rate, n (%)	6 (27.3)	
95% confidence interval	(16, 56)	
Best overall response, n (%)		
Complete response	0	
Partial response	6 (27.3)	
Stable disease	4 (18.2)	2 (100)
Progressive disease	10 (45.5)	
Time to response (months)		
Median (min, max)	2.1 (2.0, 4.2)	
Duration of response (months)		
Median (min, max)	3.6+ (0.0, 6.9)	

Percent Change From Baseline for Target Lesions: SD-101 8 mg



All Target Lesions

Injected Target Lesions

ABSCOPAL EFFECT!!!

Non-Injected Target Lesions

Cohen E, et al. Abstract 3560

- The combination of SD-101 and pembrolizumab was well tolerated, consistent with previous reports
  - No evidence of an increased incidence or severity of Aes and immune-related AEs over pembrolizumab monotherapy
  - AEs associated with SD-101 were mainly mild to moderate injection-site reactions and flu-like symptoms that were manageable with over-the-counter medications
- The combination therapy showed promising efficacy in patients with HNSCC, with an ORR of 27.3%
  - Responses were observed in both SD-101 injected and non-injected lesions
  - Responses were observed in both PD-L1 negative and positive tumors

Cohen E, et al. Abstract 3560

JAMA Oncology | Brief Report

Effect of Adding Motolimod to Standard Combination Chemotherapy and Cetuximab Treatment of Patients With Squamous Cell Carcinoma of the Head and Neck

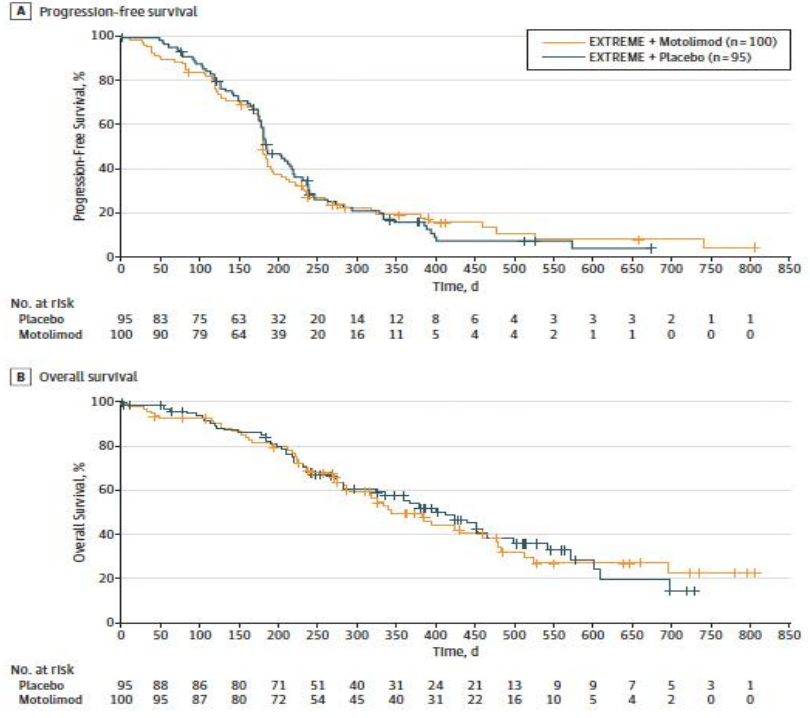
The Active8 Randomized Clinical Trial

Robert L. Ferris, MD, PhD; Nabil F. Saba, MD; Barbara J. Gitlitz, MD; Robert Haddad, MD; Ammar Sukari, MD; Prakash Neupane, MD; John C. Morris, MD; Krzysztof Misiukiewicz, MD; Julie E. Bauman, MD, MPH; Moon Fenton, MD, PhD; Antonio Jimeno, MD; Douglas R. Adkins, MD; Charles J. Schneider, MD; Assuntina G. Sacco, MD; Keisuke Shirai, MD; Daniel W. Bowles, MD; Michael Gibson, MD, PhD; Tobenna Nwizu, MD; Raphael Gottardo, PhD; Kristi L. Manjarrez, BS; Gregory N. Dietsch, PhD; James Kyle Bryan, MD; Robert M. Hershberg, MD, PhD; Ezra E. W. Cohen, MD

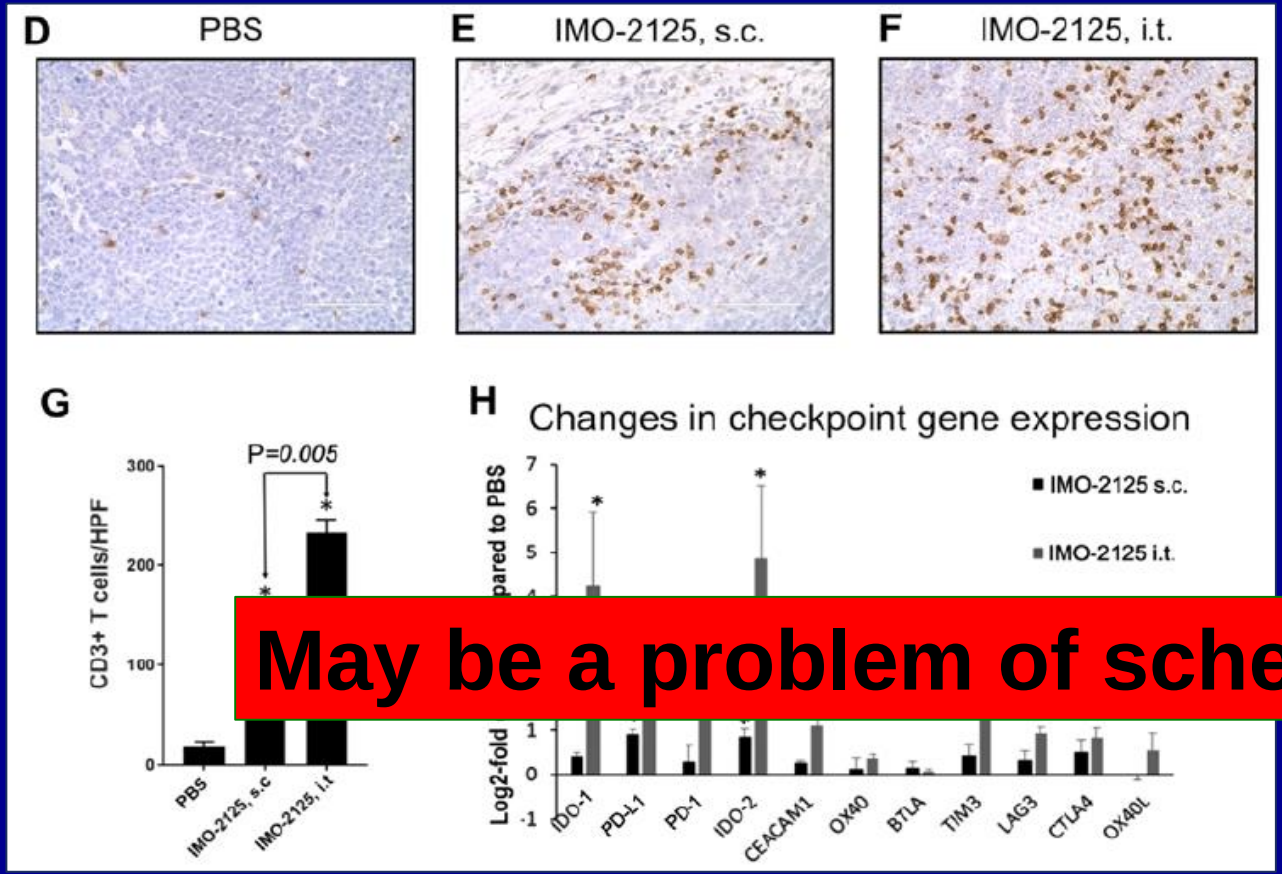
Methods

P-F-Cmab + six 21-day cycles of weekly subcutaneous motolimod (3 mg/m2) or placebo.

Figure 2. Kaplan-Meier Analyses of Progression-Free Survival and Overall Survival in the Intent-to-Treat Population



TLR9 Agonist IMO-2125. s.c. = sub-cutaneous; i.t. = intra-tumor



Intra-tumor delivery extends antitumor immune response to uninjected distal tumors resulting in a systemic efficacy

May be a problem of scheduling?

Wang D et al, Int. J. Oncol. 2018

Targeting TME

ONCOIMMUNOLOGY
2017, VOL. 6, NO. 1, e1257453 (5 pages)
http://dx.doi.org/10.1080/2162402X.2016.1257453

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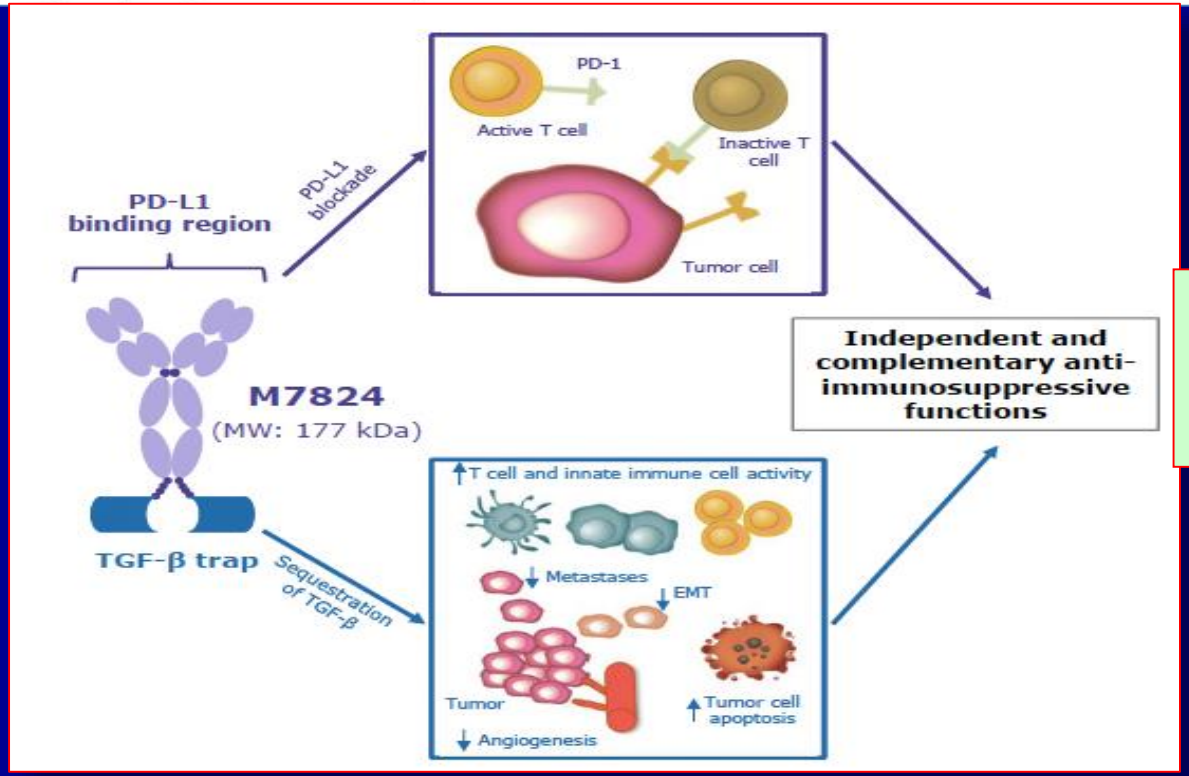
POINT OF VIEW

OPEN ACCESS

Novel TGF-β inhibitors ready for prime time in onco-immunology

Armand de Gramont[a], Sandrine Faivre[b], and Eric Raymond[c]

[a]AFR Oncology, Boulogne-Billancourt, France; [b]Medical Oncology, Hôpitaux Universitaires Paris Nord Val de Seine (HUPVNS), Université Paris 7, Paris, France; [c]Medical Oncology, Groupe Hospitalier Paris Saint-Joseph, Paris, France

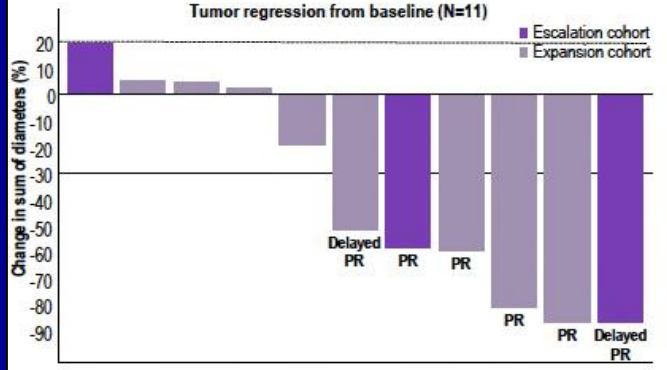


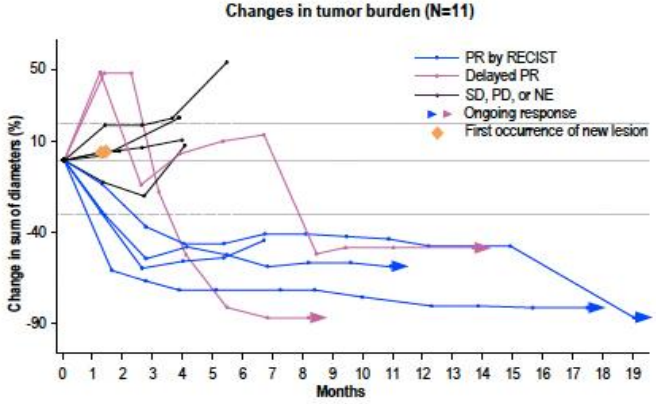
Double anti-immunosuppressive effects, but, possibly, also a reduced toxicity due to concentration in inflamed areas

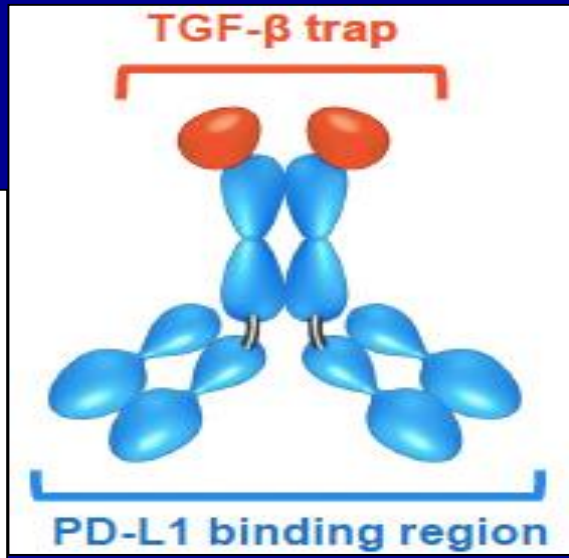
M7824 (MSB0011359C), A BIFUNCTIONAL FUSION PROTEIN TARGETING TGF-β AND PD-L1, IN PATIENTS WITH ADVANCED SCCHN: RESULTS FROM A PHASE 1 COHORT

B.C. Cho[1], A. Daste[2], A. Ravaud[2], S. Salas[3], N. Isambert[4], E. McClay[5], A. Awada[6], C. Borel[7], L.S. Ojalvo[8], C. Helwig[9], P.A. Rolfe[8], J.L. Gulley[10], N. Penel[11]

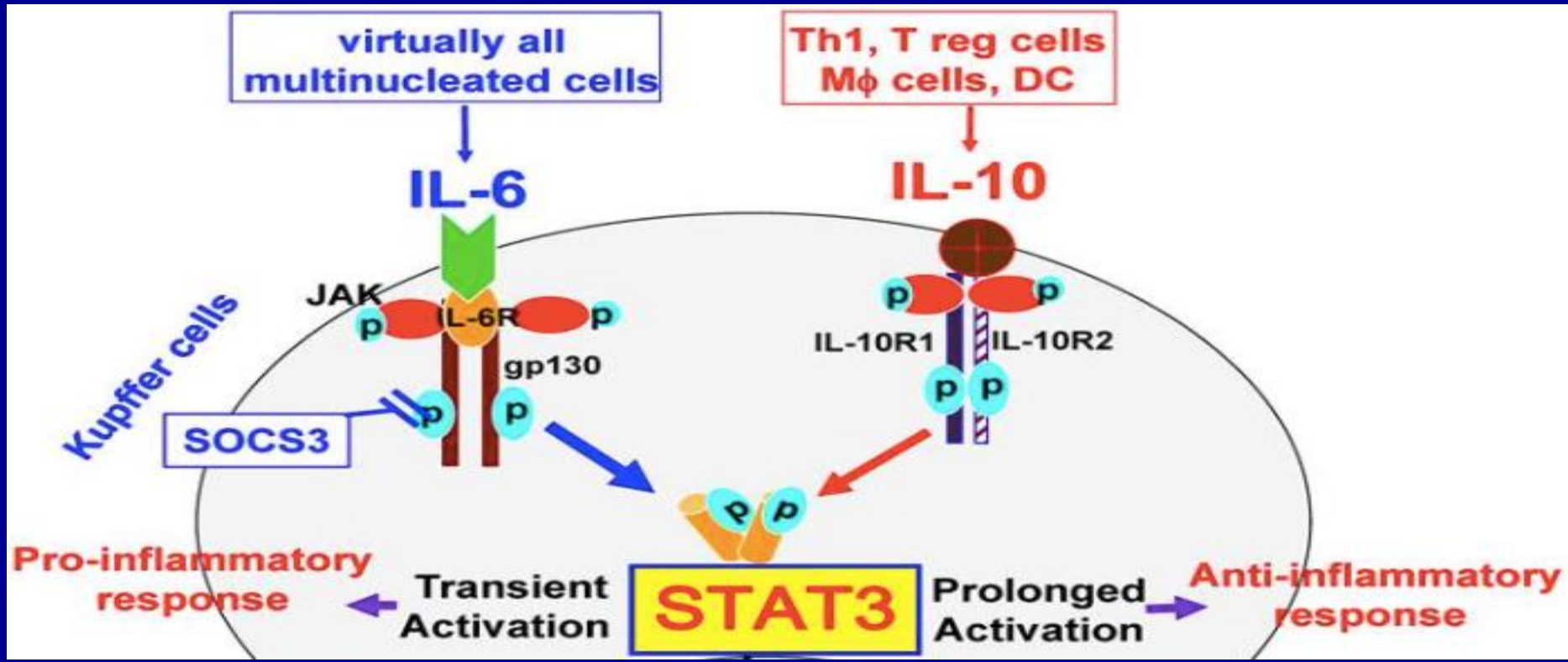
CLINICAL ACTIVITY BY INVESTIGATOR (HPV+ SCCHN)







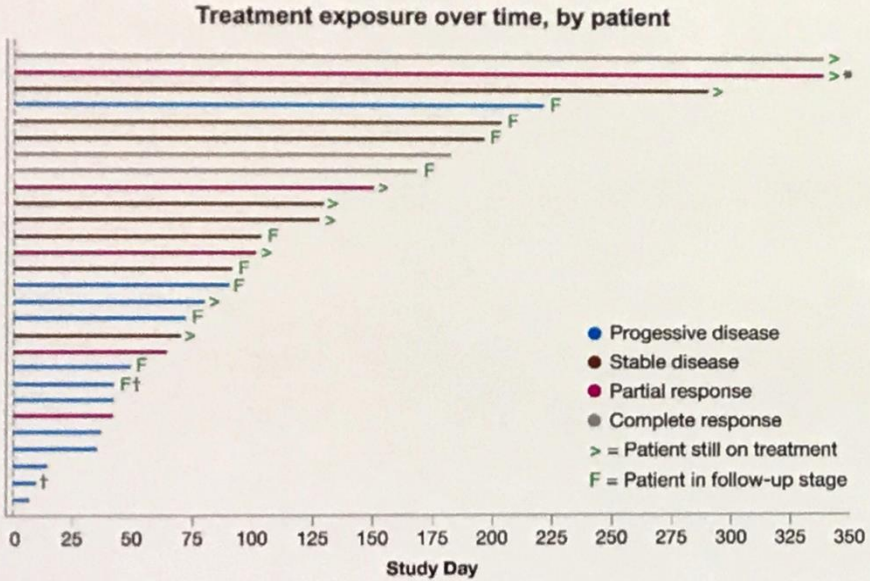
STAT-3

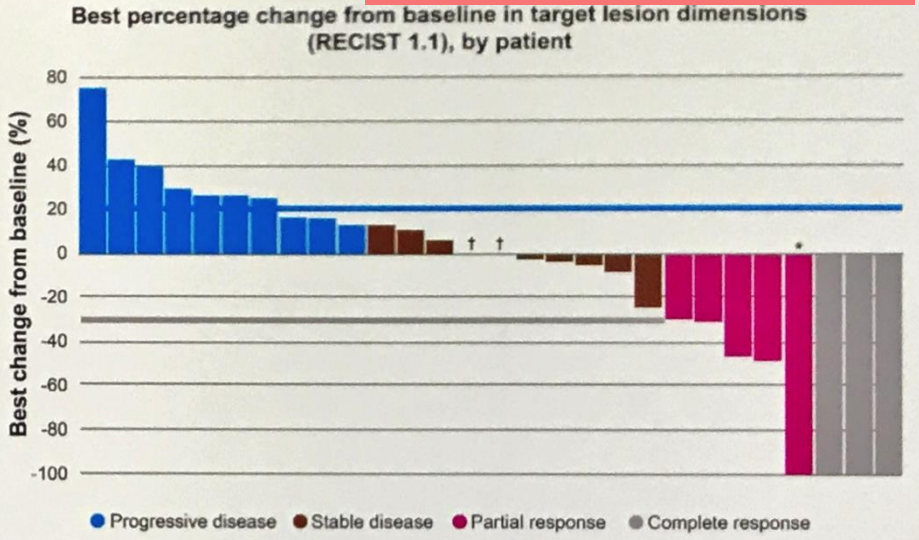


Wang H et al. Int J Biol Sci 2011; 7(5):536-550. doi:10.7150/ijbs.7.536

EXPOSURE AND BEST RESPONSE PLOTS BY PATIENT OVER TIME: AZD9150 + DURVALUMAB IN PD-(L)1 NAÏVE PATIENTS

The SCORE STUDY





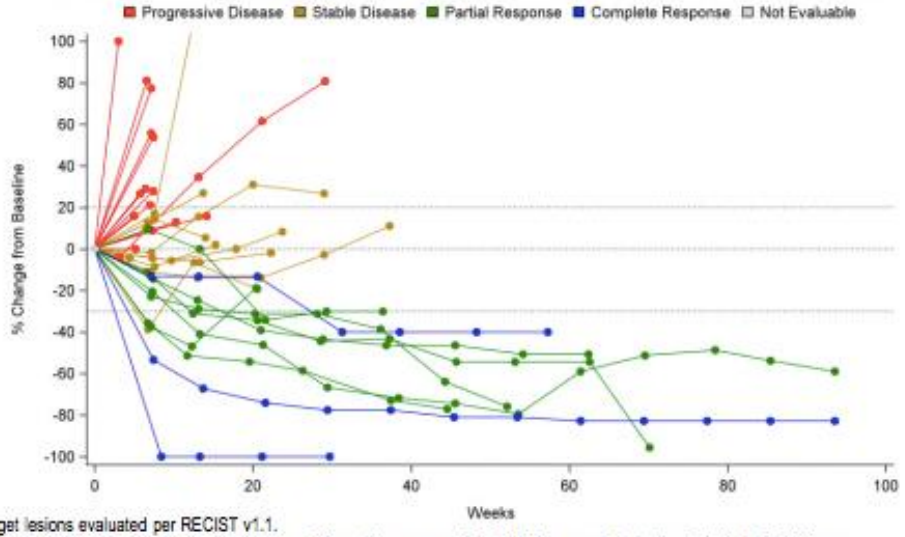
Plots shows 28 patients who were evaluable at data cut-off date 20 July 2017, unvalidated data by best response. Each bar represents a subject in Arm B3. All RECIST CRs represented as –100% change.
*A CR in target lesions; †Only baseline tumour measurement available.
CR=complete response; PD-(L)1=programmed death-(ligand) 1; RECIST=Response Evaluation Criteria In Solid Tumors.

Cohen EE, ESMO 2017

RESPONSE RATE DOUBLES WITH DANVATIRSEN + DURVALUMAB VS DURVALUMAB MONOTHERAPY IN PD-L1 NAIVE PATIENTS

- Response rate, including complete responses in 2L+ immunotherapy treatment naive patients with R/M HNSCC

Percent change in target lesions over time in 2L+ IO-naive R/M-HNSCC



Target lesions evaluated per RECIST v1.1.
CR, complete response; IO, immuno-oncology; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Sui L, et al. Presented at: Multidisciplinary Head and Neck Cancers Symposium; February 15-17, 2018; Scottsdale, AZ [abstract 1].
2. Zandberg DP, et al. Presented at ESMO 2017. *Ann Onc.* (2017) 28 (suppl_5): v372-v394. 10.1093/annonc/mdx374.
3. Ferris RL, et al. *N Engl J Med.* 2016;375:1858-1867.
4. Cohen E, et al. Presented at: European Society for Medical Oncology Annual Meeting; September 8-12, 2017; Madrid, Spain [abstract LBA45_PR].

Treatment	N	ORR (%)
SCORES		
Durvalumab + danvatirsen	44[a]	23% (3 CR, 7%; 7 PR, 16%)
Danvatirsen monotherapy	13[b]	0%
Durvalumab + AZD5069	21[c]	5% (1 PR)
OTHER STUDIES		
Durvalumab (CONDOR: PD-L1 low)[1]	65	9% (6 PR)
Durvalumab (HAWK: PD-L1 high)[2]	111	16% (17 PR, 15%; 1 CR, 1%)
Nivolumab[3]	240[1]	13% (6 CR, 2.5%)
Pembrolizumab (all PD-L1, KEYNOTE-040)[4]	247	14.6% (CR 1.6%)

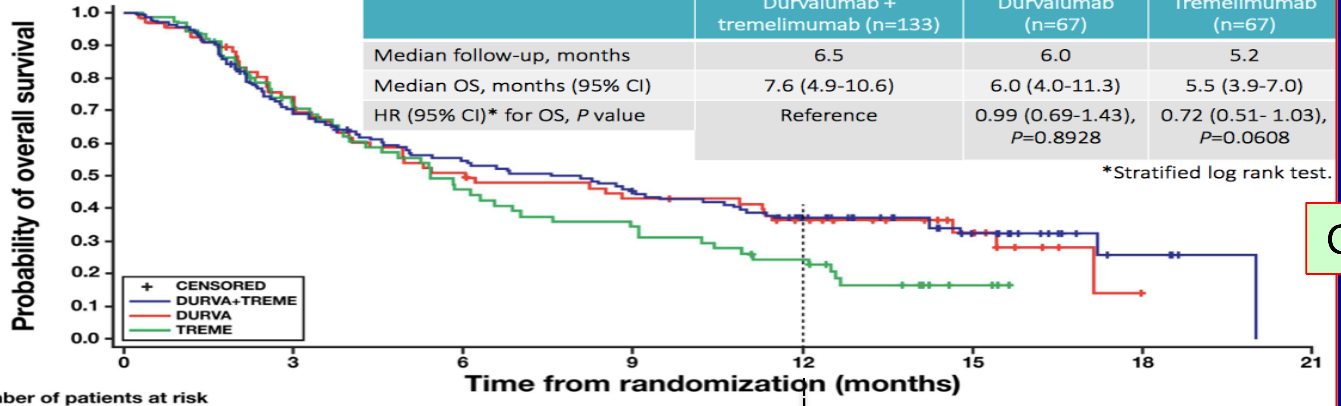
Data cutoff: 12 July 2018
[a]SCORES 2L + RM HNSCC patients (Arm B3)
[b]SCORES 1L and 2L+ RM HNSCC patients (Arm B5)
[c]SCORES 1L and 2L+ patients (Arm B4)

Combination ICIs

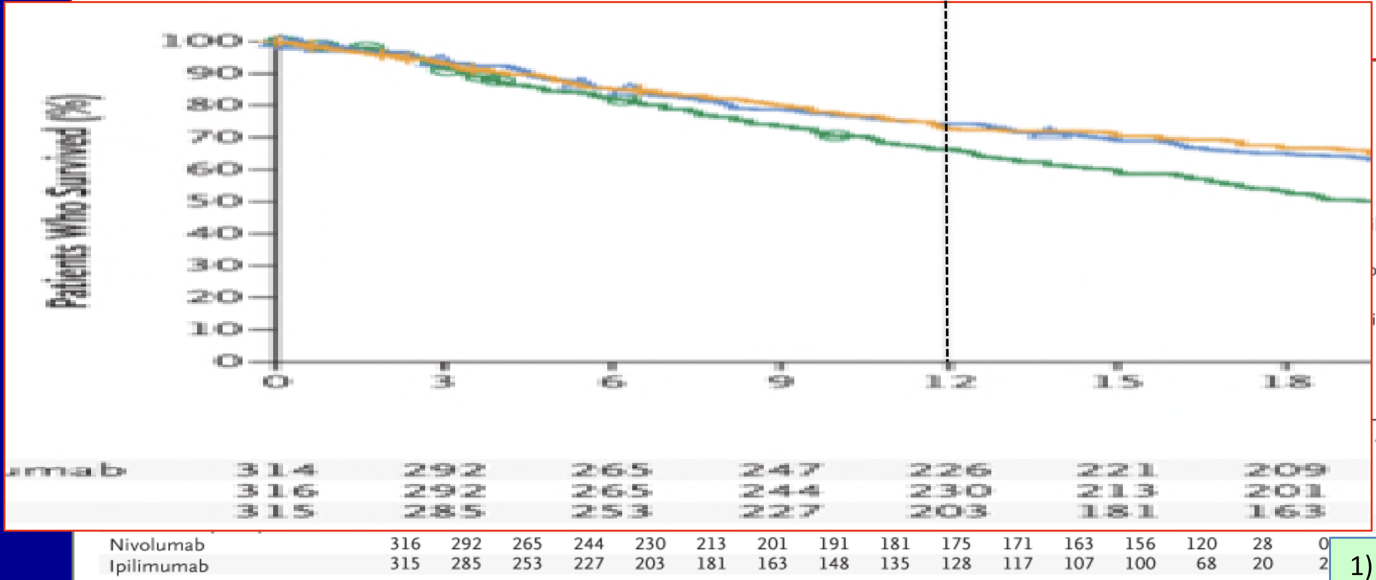
Overall Survival

	Durvalumab + tremelimumab (n=133)	Durvalumab (n=67)	Tremelimumab (n=67)
Median follow-up, months	6.5	6.0	5.2
Median OS, months (95% CI)	7.6 (4.9-10.6)	6.0 (4.0-11.3)	5.5 (3.9-7.0)
HR (95% CI)* for OS, *P* value	Reference	0.99 (0.69-1.43), *P*=0.8928	0.72 (0.51- 1.03), *P*=0.0608

*Stratified log rank test.



CONDOR



Checkmate 067[1]

1) Wolchok JD et al, NEJM 2017

In conclusion

Inhibition of the PD-L1 / PD-1 axis shows a clear but limited benefit in head and neck cancer

TME and evasion mechanisms might be different from those in MM and NSCLC

Very preliminary data suggest that combination therapy may fulfil the gap, but we are at the beginning of the way

Combination therapy should take into account also the immune effect of conventional treatment i.e chemotherapy, radiotherapy and targeted therapy (not faced in the present talk due to time limitation)

Thank You!