ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

THE VALUE OF PD-L1 EXPRESSION AS PREDICTOR OF BENEFIT WITH IMMUNE CHECKPOINT INHIBITORS

Systematic review across solid tumours

Ahmad Awada, Luis Castelo-Branco, Emiliano Calvo, Irene Moreno, Karima Oualla, Ines Pires da Silva, Francesco Sclafani

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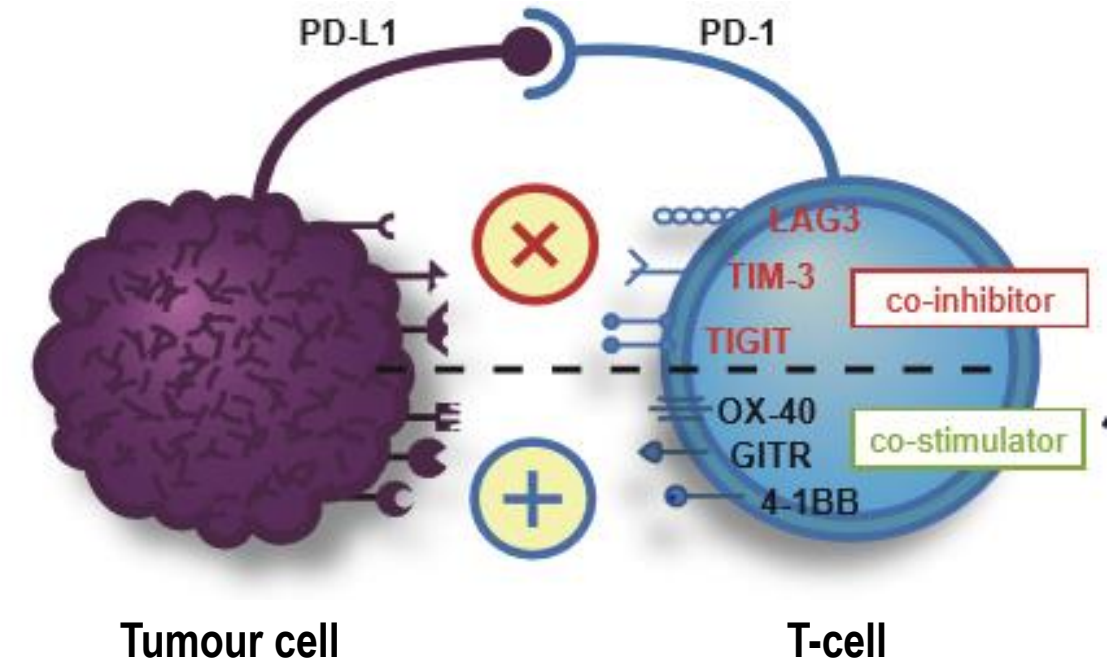
METHODOLOGY:

- Systematic review from Phase III clinical trials with Immune Checkpoint Inhibitors on different solid tumour settings and data available by PDL1 stratification
- Publications until July 2019

TOPICS

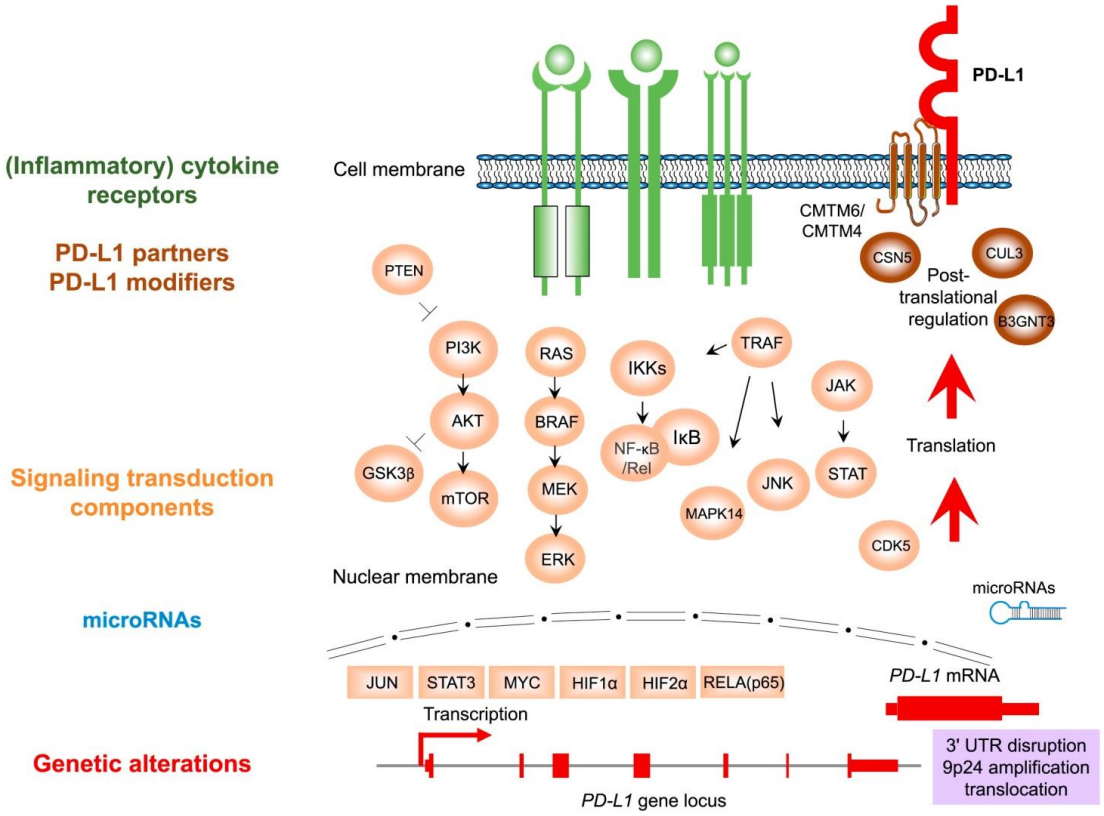
- Introduction
- Untreated NSCLC (Luis Castelo-Branco L; Ahmad Awada)
- Melanoma (Ines Pires da Silva)
- Head and Neck (Karima Oualla)
- Genito-Urinary (Irene Moreno; Emiliano Calvo)
- Gastro-Intestinal (Francesco Sclafani)

PD-L1 IS AN IMPORTANT INHIBITOR OF T-CELLS CITOTOXICITY



Castelo-Branco L, et al. Acta Med Port 2019 Apr;32(4):251-257

THERE ARE DIFFERENT REGULATORY MECHANISMS OF PD-L1 EXPRESSION AND IT IS VARIABLE OVER TIME



Reprinted from Immunity, 48 (3), Chong Sun et al, Regulation and Function of the PD-L1 Checkpoint, 434-452, copyright 2018, with permission from Elsevier.

PD-L1 ASSESSMENT BY DIFFERENT TECHNIQUES

Summary of PD-L1 monoclonal antibodies and technical aspects for evaluation and agencies' approvals in NSCLC

PD-L1 mAb clone	Ab host species	Automated platform	Checkpoint inhibitor (target)	PD-L1 scoring	Definition of positivity (cutoffs)	FDA status	EMA status
22C3	Mouse	Dako (Autostainer Link 48)	Pembrolizumab (PD-1)	TC	TC ≥1% (minimum of 100 TC)	Companion	CE mark
28-8	Rabbit	Dako (Autostainer Link 48)	Nivolumab (PD-L1)	TC	TC ≥1% (minimum of 100 TC)	Complementary	CE mark
SP142	Rabbit	Ventana (BenchMark ULTRA)	Atezolizumab (PD-L1)	TC, IC	TC ≥50% or IC ≥10% (minimum of 50 TC with associated stroma)	Complementary	CE mark
SP263	Rabbit	Ventana (BenchMark ULTRA)	Duravalumab (PD-L1)	TC	TC ≥25% (minimum of 100 TC)	FDA approval only for urothelial carcinoma	CE mark for nivolumab and pembrolizumab in NSCLC and durvalumab in urothelial carcinoma
73-10	Rabbit	Dako	Avelumab (PD-L1)	TC	TC ≥1% (minimum cells not defined)	FDA approval	NA

Teixidó C et al, Ther Adv Med Oncol. 2018, Vol. 10: 1–17

THE EXPRESSION OF PDL1 IN TUMOUR CELLS COULD BE ASSOCIATED WITH THE EFFICACY OF IMMUNE CHECKPOINT INHIBITORS IN SOLID TUMOURS?

PREVIOUSLY UNTREATED METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

UNTREATED STAGE IV NSCLC

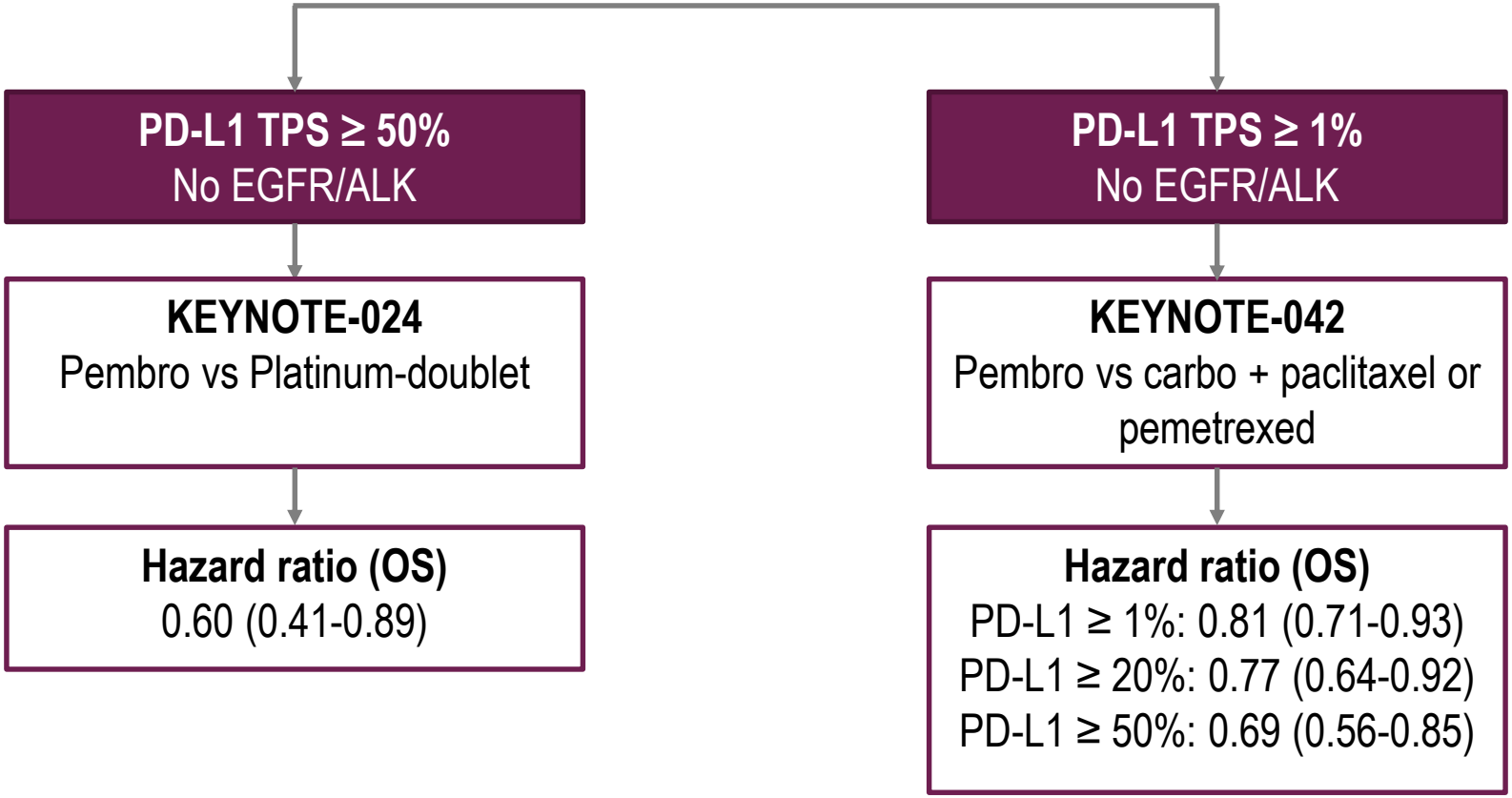
Immune Checkpoint Inhibitors (ICIs) Phase III clinical trials with results

ICIs only	ICIs + Chemotherapy
KEYNOTE-024	KEYNOTE-189
KEYNOTE-042	KEYNOTE-407
CHECKMATE-026	IMpower-150
CHECKMATE-227*	IMpower-130
	IMpower-131
	IMpower-132

*Includes also combination Nivo+IPI and Nivolumab + chemo

UNTREATED STAGE IV NSCLC

Histology agnostic – Pembrolizumab trials

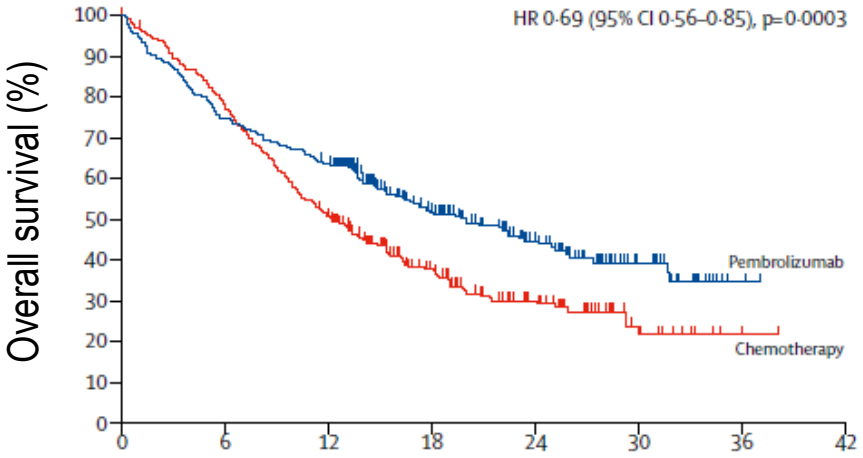


G Lopez ASCO 2018; M. Reck ESMO 2016.

PEMBRO VS CHEMO
UNTREATED NSCLC (KEYNOTE-042)

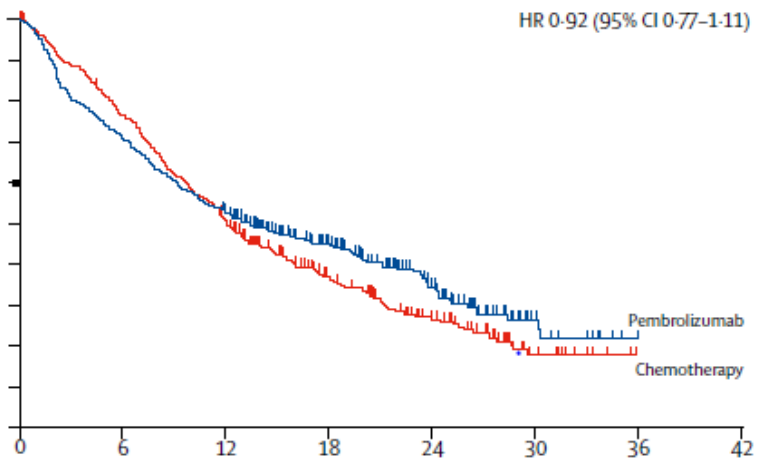
PD-L1 ≥50%

Benefit



PD-L1 1-49%

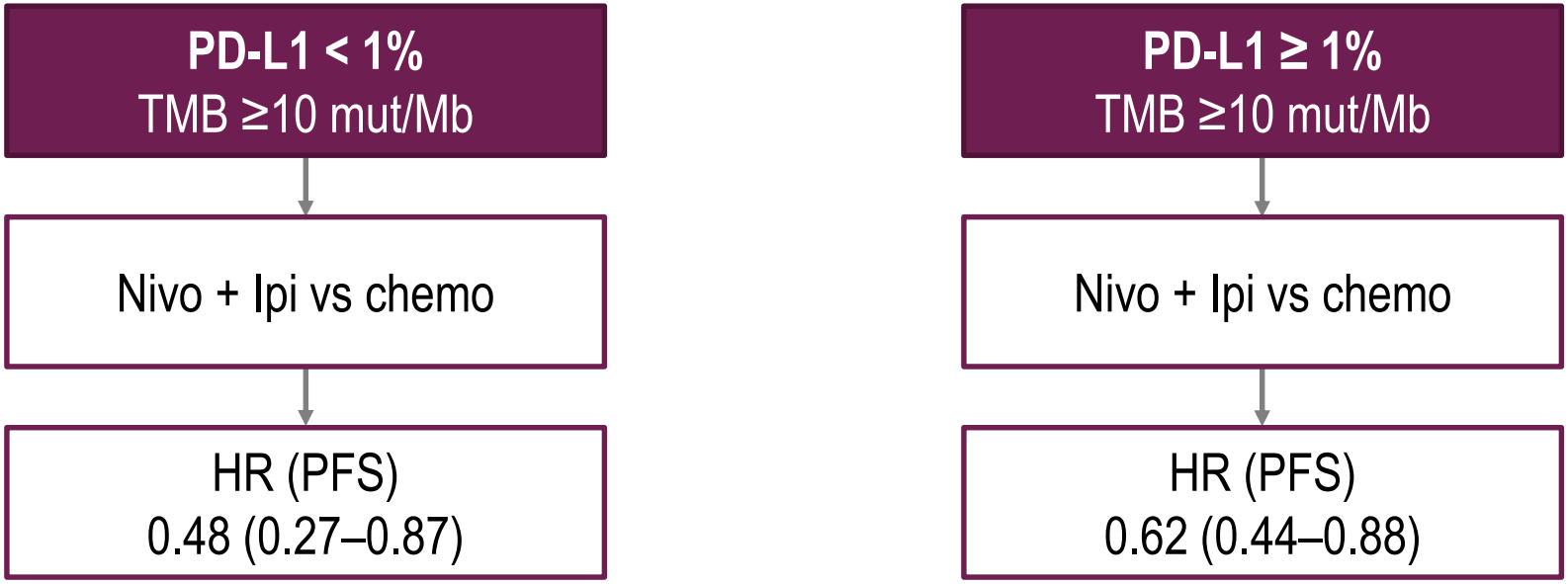
Non- Benefit



Reprinted from The Lancet, 393 (10183), Mok TSK, et al, Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial, 1819-1830, Copyright 2019, with permission from Elsevier.

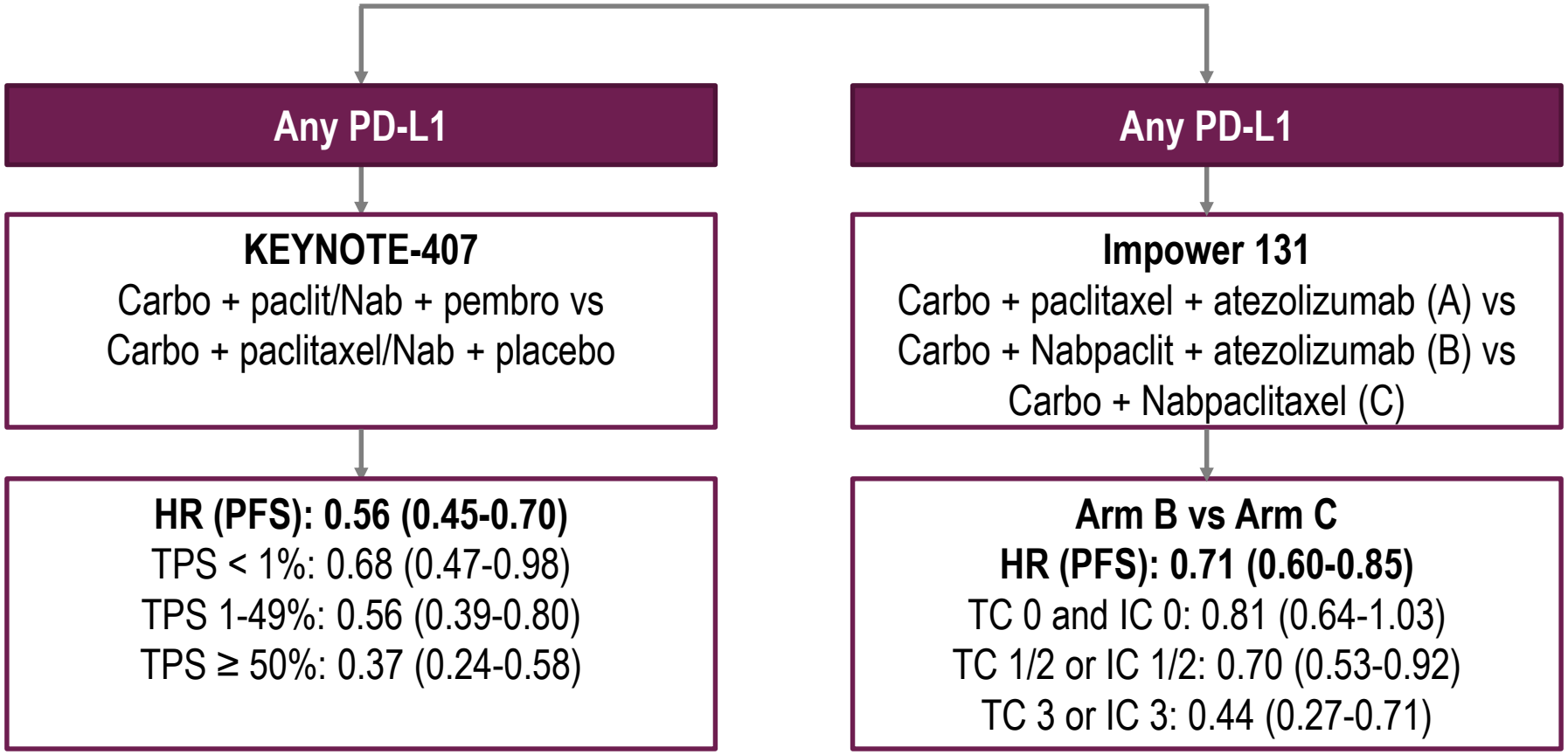
UNTREATED STAGE IV NSCLC

Histology agnostic – CheckMate 227 Trial – Results by PD-L1



H. Borghaei ASCO 2018. M.D. Hellmann NEJM 2018

UNTREATED STAGE IV NSCLC SQUAMOUS



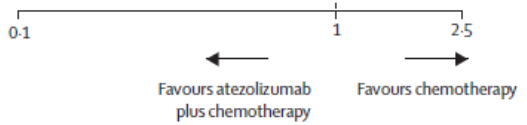
L Parez-Ares ASCO 2018; R Jotte ASCO 20185

IMPOWER130 - NON-SQUAMOUS NSCLC

Atezo + carbo + nab-paclitaxel vs Chemo

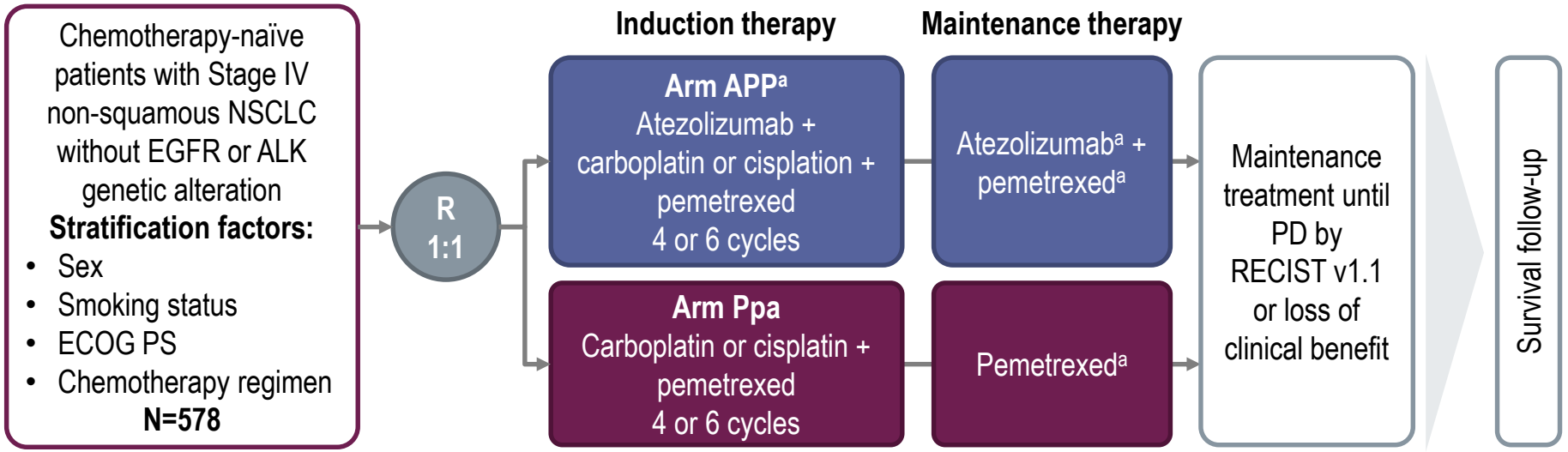
Forest plot of HR for PFS in the intention-to-treat wild-type population

	Atezolizumab plus chemotherapy group		Chemotherapy group		Hazard ratio (95% CI)
	Events/number of patients	Median progression-free survival, months	Events/number of patients	Median progression-free survival, months	
Sex					
Female	138/185	7·4	79/94	4·8	0·59 (0·45–0·78)
Male	209/266	6·4	119/134	5·6	0·67 (0·54–0·85)
Age					
<65 years	173/227	6·8	99/114	5·5	0·64 (0·5–0·82)
≥65 years	174/224	7·2	99/114	5·3	0·64 (0·5–0·82)
ECOG PS*					
0	142/189	7·9	78/91	5·6	0·59 (0·44–0·78)
1	205/261	6·1	119/136	5·0	0·68 (0·54–0·86)
2	..	NA	1/1	3·7	NA
Tobacco use history					
Never	43/48	8·1	16/17	4·6	0·63 (0·35–1·12)
Current or previous	304/403	6·9	182/211	5·5	0·64 (0·53–0·77)
No liver metastasis at enrolment	286/382	7·3	172/197	5·6	0·59 (0·49–0·71)
Liver metastasis at enrolment	61/69	4·2	26/31	4·4	0·93 (0·59–1·47)
PD-L1-high	61/88	6·4	41/42	4·6	0·51 (0·34–0·77)
PD-L1-low	96/128	8·3	52/65	6·0	0·61 (0·43–0·85)
PD-L1-negative	190/235	6·2	105/121	4·7	0·72 (0·56–0·91)
Intention-to-treat wild-type population	**347/451**	**7·0**	**198/228**	**5·5**	**0·64 (0·54–0·77)**



Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial, 924-937, Copyright 2019, with permission from Elsevier.

IMPOWER132 STUDY DESIGN



Co-primary endpoints: INV-assessed PFS and OS

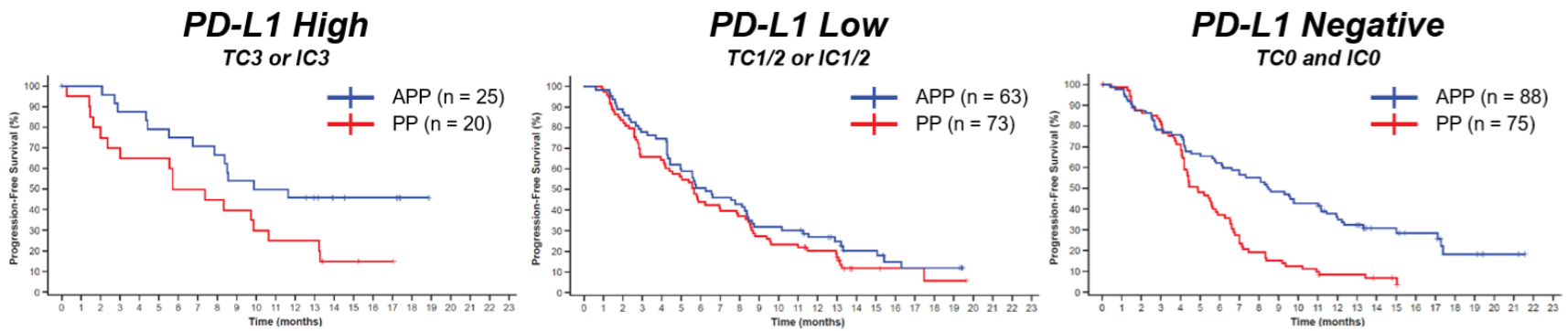
Secondary endpoints: INV-assessed ORR and DOR, patient-reported outcomes and safety measures

Exploratory analyses: Clinical and biomarker subgroup analyses

- Biomarker-evaluable tissue not mandatory for enrolment (was available from 60% of patients)

Papadimitrakopoulou VA. IMpower132: Efficacy & Safety. Presented at IASLC 19th World Conference on Lung Cancer, Toronto, Canada, September 2018.
[a]Atezolizumab: 1200 mg IV q3w; Carboplatin: AUC 6 mg/mL/min IV q3w; Cisplatin: 75 mg/m^2 IV q3w; Pemetrexed: 500 mg/m^2 IV q3w. NCT02657434. Data cutoff: May 22, 2018.

IMPOWER-132
PFS BY PD-L1 STATUS



	PD-L1 High (TC3 or IC3)		PD-L1 Low (TC1/2 or IC1/2)		PD-L1 Negative (TC0 and IC0)	
	APP	PP	APP	PP	APP	PP
ORR, %	72%	55%	38%	38%	44%	27%
CR | PR, %	0 | 72%	5% | 50%	2% | 37%	0 | 38%	2% | 42%	0 | 27%
Median DOR, mo	NE	7.2	7.2	7.2	10.1	4.2
12-month PFS	46%	25%	27%	20%	35%	8%
Median PFS, mo	10.8	6.5	6.2	5.7	8.5	4.9
HR[b] (95% CI)	0.46 (0.22, 0.96)		0.80 (0.56, 1.16)		0.45 (0.31, 0.64)	

APP, atezolizumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed.
[a] Overall HR 0.57 (0.45, 0.73) in biomarker-evaluable patients (60% of ITT). [b] Unstratified HR. Data cutoff: May 22, 2018.

Papadimitrakopoulou VA. IMpower132: Efficacy & Safety. Presented at IASLC 19th World Conference on Lung Cancer, Toronto, Canada. September 2018

SUMMARY OF RESULTS BY PDL1 SUBGROUPS

Trial	Tumour type	Interventions	Nº of patients	Main outcomes - results	Hazard Ratio (HR) by pdl1 stratification groups*	Trend for increased benefit with higher PDL1?
KEYNOTE-024	Advanced NSCLC and PD-L1 ≥ 50%	1 - Pembrolizumab 2 - Chemotherapy	305 (1:1)	mPFS 1 - 10.3 months 2 - 6.0 months	-	?
KEYNOTE-189	Metastatic nonsquamous NSCLC without sensitising EGFR or ALK mutations	1 - Chemo 2 - Chemo + Pembro	616 (2:1)	mOS at 12 months 1 – 69,2% 2 – 49,4% HR for death, 0.49 (0.38 to 0.64)	PDL1 < 1%: 0,59 PDL1 1-49%: 0,55 PDL1 ≥ 50 %: 0,42	Yes
IMPOWER-150	Nonsquamous NSCLC	1 - Atezo + Chemo 2 - Beva + Chemo 3 - Atezolizumab + Beva + Chemo	2 – 336 pts 3 – 356 pts	mPFS 2 – 6,8 months 3 - 8.3 months HR 0.59 (0.50–0.70)	TC0 and IC0: 0,77 TC0/1/2 and IC0/1/2: 0,68 TC1/2 or IC1/2: 0,56 TC1/2/3 or IC1/2/3: 0,50 TC3 or IC3: 0,39	Yes
KEYNOTE-042	Advanced NSCLC PD-L1 ≥ 50%	1 - Pembrolizumab 2 - Platinum based chemotherapy	1274 (1:1)	OS PDL1 ≥ 50% 20,0 vs 12,2 months PDL1 ≥ 20% 17,7 vs 13·0 months PDL1 ≥ 1% 16,7 vs 12,1 months	PDL1 ≥1% 0,81 PDL1 ≥20% 0,77 PDL1 ≥ 50% 0,69	Yes
Impower -130	Non-squamous NSCLC	1 - Atezo + Carbo + Nab-paclitaxel 2 - Carbo + Nab-paclitaxel	724 (2:1)	mOS 1 - 18,6mo; 2 – 13,9 mo mPFS 1 -7,0 mo vs 2 - 5,5 mo	PDL1 negative: 0,72 (0·56–0·91) PDL1 low: 0,61 (0·43–0·85) PDL1 High: 0,51 (0·34–0·77)	Yes
Impower -131	Stage IV squamous NSCLC	A - Atezo + Carbo + paclitaxel B - Atezo + Carbo + Nabpaclitaxel C - Carbo + Nabpaclitaxel	1021 (1:1:1)	mPFS B – 6,3mo C – 5,6 (HR, 0.715; P = 0.0001)	PDL1 neg: 0,81 (0,64-1,03) PDL1 low: 0,70 (0,53-0,92) Pdl1 high: 0,44 (0,27-0,71)	Yes
CHECKMATE-026	Untreated stage IV or recurrent NSCLC and PD-L1 ≥ 1%	1 - Nivolumab 2 - Platinum based chemotherapy	423 (1:1)	mPFS 1 - 4.2 months 2 - 5.9 months	Pdl1 ≥ 5%: 1,18 Pdl1 ≥ 50%: 1,07	NO
KEYNOTE-407	Metastatic squamous NSCLC	1 - Chemo + Pembro 2 - Chemo + placebo	559 (1:1)	mOS 1 - 15.9 months 2 - 11.3 months, HR 0.64 (0.49–0.85)	PDL1 < 1%: 0.61 PDL1 1–49%: 0.57 PDL1 > 50%: 0.64	NO
CHECKMATE-227	Stage IV or recurrent NSCLC that was not previously treated with chemotherapy.	Nivo Nivo + IPI Nivo +chemo Chemo	2220 (1:1:1:1)	1-year PFS (patients with high TMB) nivolumab+ipilimumab 42,6% chemotherapy 13.2%	PD-L1 < 1%; TMB ≥ 10 mut/Mb: 0,48 PD-L1 ≥ 1%; TMB ≥ 10 mut/Mb HR 0,62	NO
Impower-132	Stage IV non-squamous NSCLC without EGFR or ALK genetic alteration	1 - Atezo + platin + pemetrexed 2 - Platin + pemetrexed	578 (1:1)	12-mo PFS 1 – 33,7% 2 – 17%	PDL1 neg – HR 0.45 (0.31, 0.64) PDL1 low – HR 0.80 (0.56, 1.16) PDL1 high – HR 0.46 (0.22, 0.96)	NO

* HR from main outcome results

NSCLC AND PD-L1 EXPRESSION IMPLICATION FOR CLINICAL PRACTICE AND RESEARCH

Trend for increased benefit with ICIs alone on enriched PD-L1 NSCLC

On Combination ICI + chemo less importance of PD-L1 expression

Many uncertainties on the real value of PD-L1 for clinical practice with ICIs in untreated NSCLC

Important questions to be answered

- Why PD-L1 expression has a high value in some studies and low in others?
- PD-L1 expression combined with other biomarkers (eg. TMB; specific neo-antigens) for a score predictor of response in NSCLC?
- Are checkpoint inhibitors monotherapy better than combination with chemotherapy in PD-L1≥ 50% NSCLC untreated tumours?
- Chemo + ICI 1st line vs sequence of treatment, regardless PD-L1 expression?

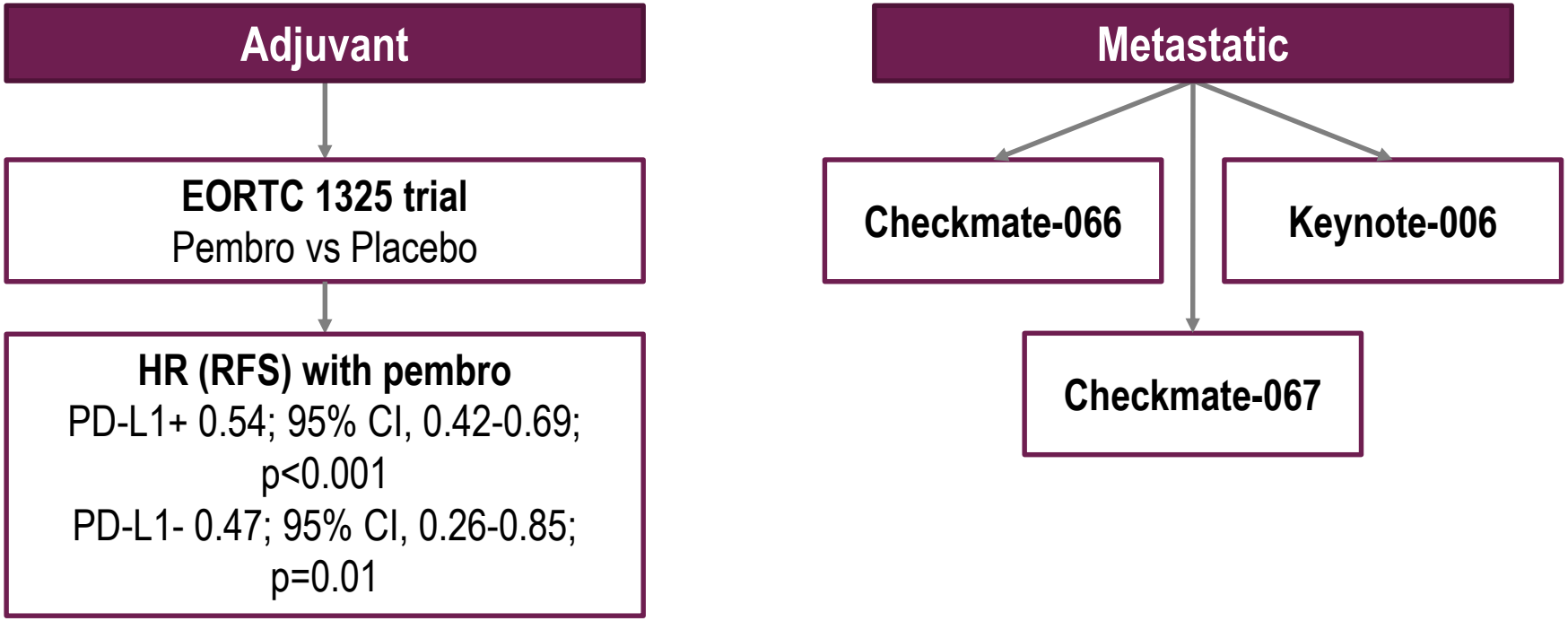
MELANOMA

PHASE III ICI TRIALS IN MELANOMA STRATIFIED BY PD-L1

Trial	Population	Drugs	Clinical outcome	Definition and % of PD-L1+ melanomas	Reference
EORTC 1325	Stage III resected melanoma No in-transit mets IIIA (N1a >1 mm)	(1) Pembrolizumab 200mg Q3W (n=514) (2) Placebo 200mg Q3W (n=505)	1-year RFS Pembro: 75.4% Placebo: 61.0% HR 0.57; 98.4% CI, 0.43-0.74; p<0.001	≥1% of PD-L1+ tumour and adjacent immune cells 83.7%	Eggermont AMM. et al, NEJM 2018
CM-066	Metastatic melanoma BRAF WT Treatment naïve	(1) Nivolumab 3mg/Kg Q2W + Placebo 1000mg/m^2 Q3W (n=210) (2) DTIC 1000mg/m^2 Q3W + Placebo 3mg/Kg Q2W (n=208)	mPFS Nivolumab + placebo: 5.1 months DTIC + placebo: 2.2 months HR 0.43; 95% CI, 0.34-0.56; p<0.001	≥5% of PD-L1+ tumour cells 35.4%	Robert C. et al, NEJM 2015
CM-067	Metastatic melanoma Treatment naïve	(1) Ipilimumab 3mg/Kg Q3W + Nivolumab 1mg/Kg Q3W (n=314) (2) Nivolumab 3mg/Kg Q2W (n=316) (3) Ipilimumab 3mg/Kg Q3W (n=315)	mPFS Ipilimumab + Nivolumab: 11.5 months* Nivolumab: 6.9 months Ipilimumab: 2.9 months* *HR 0.42; 95% CI 0.31-0.57; p<0.001	≥5% of PD-L1+ tumour cells 23.6%	Larkin J. et al, NEJM 2015
KN-006	Metastatic melanoma One prior line of treatment was allowed (except anti-PD(L)1 or anti-CTLA-4)	(1) Pembrolizumab 10mg/Kg Q2W (n=279) (2) Pembrolizumab 10mg/Kg Q3W (n=277) (3) Ipilimumab 3mg/Kg Q3W (n=278)	mPFS Pembrolizumab Q2W: 5.6 months Pembrolizumab Q3W: 4.1 months Ipilimumab: 2.8 months HR 0.61; 95% CI 0.50-0.75; p<0.001	≥1% of PD-L1+ tumour and adjacent immune cells 80%	Schachter J. et al. The Lancet 2017

RFS = recurrence-free survival. mPFS = median progression-free survival

PHASE III ICI TRIALS IN MELANOMA STRATIFIED BY PD-L1



HR = Hazard ratio; RFS = recurrence-free survival.

Eggermont AMM. et al, N Engl J Med 2018; 378:1789-1801.

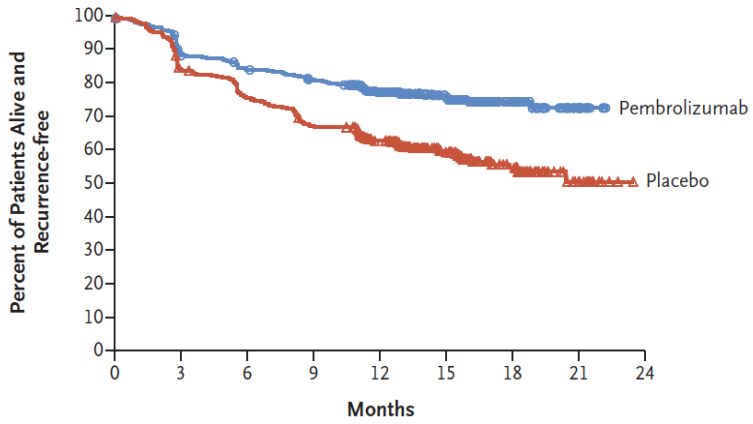
EORTC 1325 TRIAL ADJUVANT

Pembro vs placebo

Patients with PDL1-positive melanoma

	Total No.	No. with Event	Hazard Ratio (95% CI)
Pembrolizumab	428	102	0.54 (0.42–0.69)
Placebo	425	176	1.00

P<0.001 by stratified log-rank test

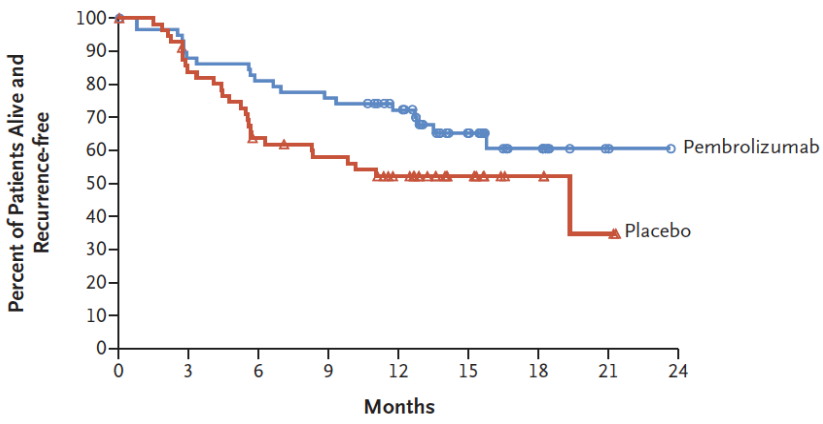


No. at Risk									
Pembrolizumab	428	370	350	333	266	156	61	13	0
Placebo	425	353	317	281	233	141	55	13	0

Patients with PDL1-negative melanoma

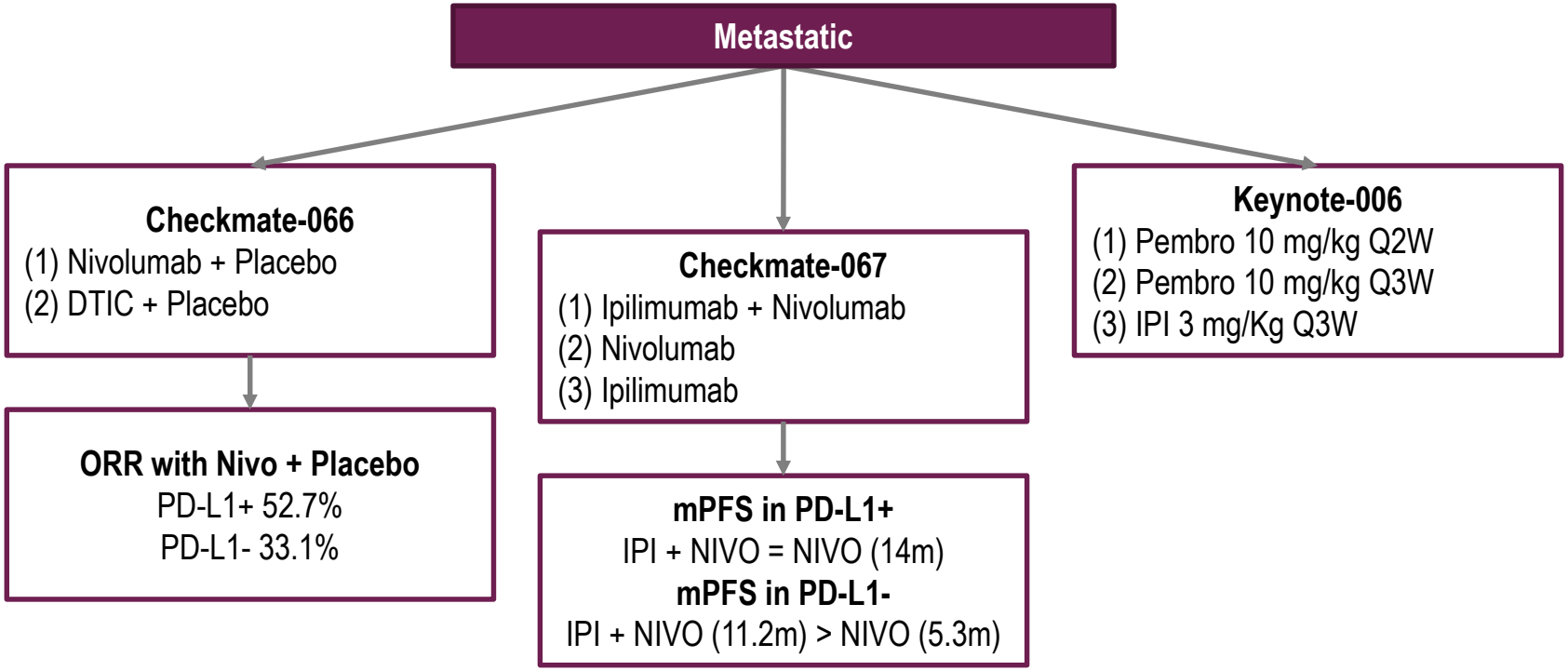
	Total No.	No. with Event	Hazard Ratio (95% CI)
Pembrolizumab	59	20	0.47 (0.26–0.85)
Placebo	57	27	1.00

P=0.01 by stratified log-rank test



No. at Risk									
Pembrolizumab	59	51	47	44	37	20	10	2	0
Placebo	57	46	34	30	23	12	5	2	0

PHASE III ICI TRIALS IN MELANOMA STRATIFIED BY PD-L1

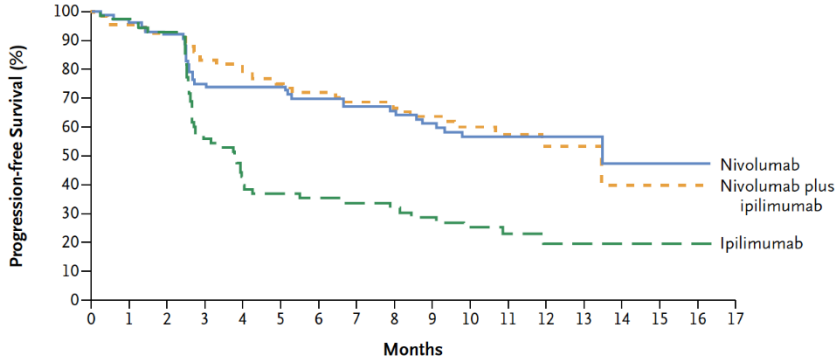


ORR = objective response rate; mPFS = median progression-free survival.

Robert C. et al, NEJM 2015; Larkin J. et al, NEJM 2015; Schachter J. et al. The Lancet 2017.

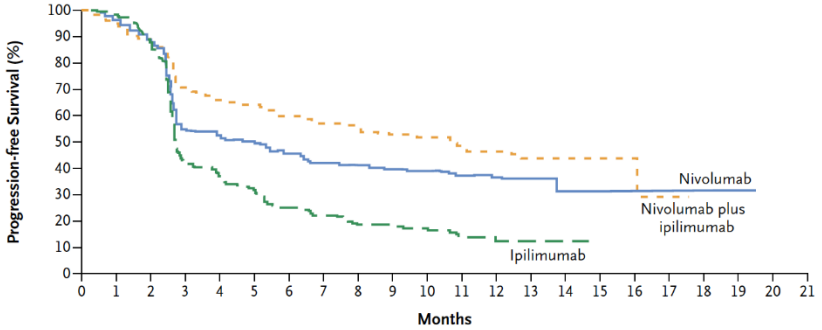
CHECKMATE-067
METASTATIC: IPI VS NIVO VS IPI+NIVO

PD-L1+ melanoma



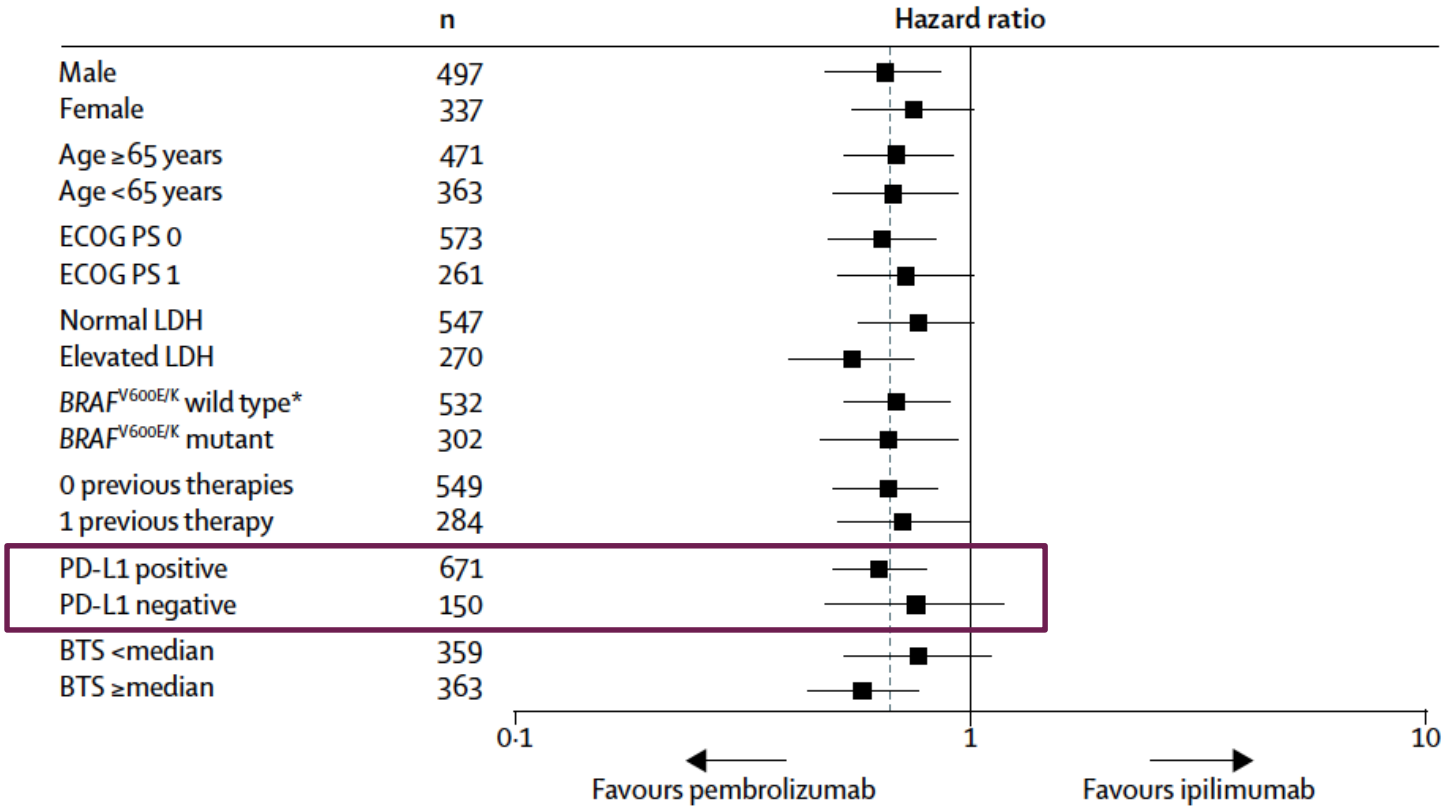
No. at Risk																	
Nivolumab	80	76	71	57	56	54	51	49	49	43	38	32	16	13	5	4	2	0
Nivolumab plus ipilimumab	68	63	61	53	52	47	44	42	42	39	34	24	16	12	3	1	1	0
Ipilimumab	75	69	66	40	33	24	22	21	21	17	16	15	9	6	3	2	2	0

PD-L1- melanoma



No. at Risk																					
Nivolumab	208	192	178	108	105	98	88	80	76	74	63	50	31	24	9	5	4	2	1	1	1	0
Nivolumab plus ipilimumab	210	195	181	142	134	123	112	106	105	96	88	79	42	36	13	9	6	2	1	0		
Ipilimumab	202	183	166	82	72	59	44	39	35	31	26	22	12	8	3	1	0					

KEYNOTE-006
METASTATIC: PEMBRO VS IPI



Reprinted from The Lancet,390 (10105), Schachter J. et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006), 1853-1862, Copyright 2017, with permission from Elsevier.

MELANOMA AND PD-L1 EXPRESSION

Implication for clinical practice and research

In melanoma, PD-L1 is not a good biomarker of response to immune checkpoint inhibitors

Challenges:

- Different antibodies and thresholds
- Intra & intertumour heterogeneity

The greatest benefit with the combination of nivolumab and ipilimumab versus nivolumab alone seems to occur in PD-L1- melanomas

HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC)

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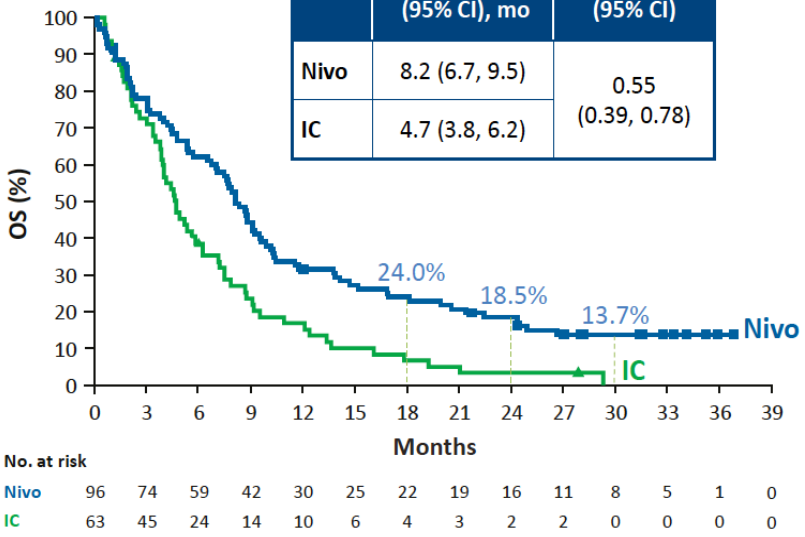
ESMO

CHECKMATE 141

HNSCC progression after platinum based therapy – Nivo vs Chemo

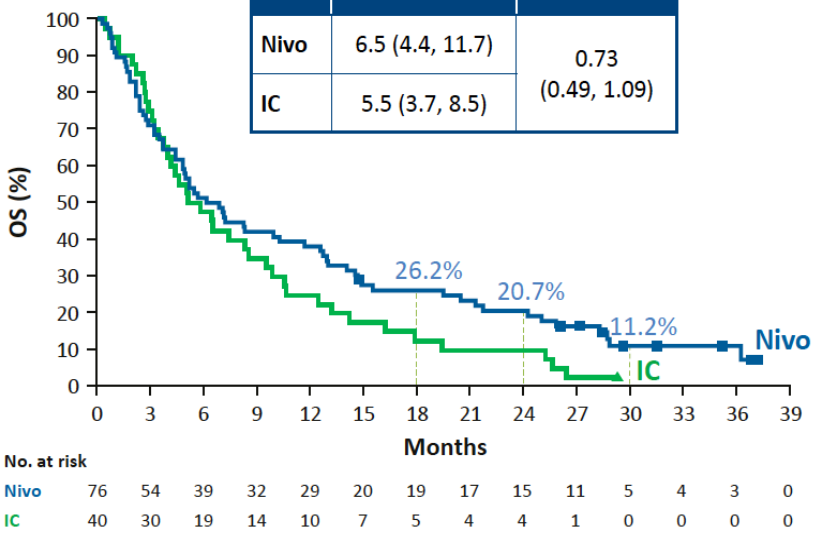
PD-L1 expressors (≥1%)
(57% of the tested patients)

	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)	



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)	



Reprinted from Oral Oncology, 81, Ferris RL, et al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumour PD-L1 expression, 45-51, Copyright 2018, with permission from Elsevier.
Ferris RL, et al. N Engl J Med. 2016;375(19):1856-1867. Gillison M, et al. J Clin Oncol. 2017;35(Suppl): Abstract 6019.

PHASE III KEYNOTE-040 STUDY

Key eligibility criteria

- SCC of the oral cavity, oropharynx, hypopharynx, or larynx
- PD after platinum-containing regimen for R/M HNSCC or recurrence or PD within 3-6 months of multimodal therapy using platinum[a]
- ECOG PS 0 or 1
- Known p16 status (oropharynx)[b]
- Tissue sample[c] for PD-L1 assessment[d]

Stratification factors

- ECOG PS (0 vs 1)
- p16 status (positive vs negative)
- PD-L1 TPS[d] (≥50% vs <50%)

R 1:1

Pembrolizumab 200 mg IV q3w for 2 y

Methotrexate 40 mg/m^2 qw[e]
OR
Docetaxel 75 mg/m^2 q3w
OR
Cetuximab 250 mg/m^2 qw[f]

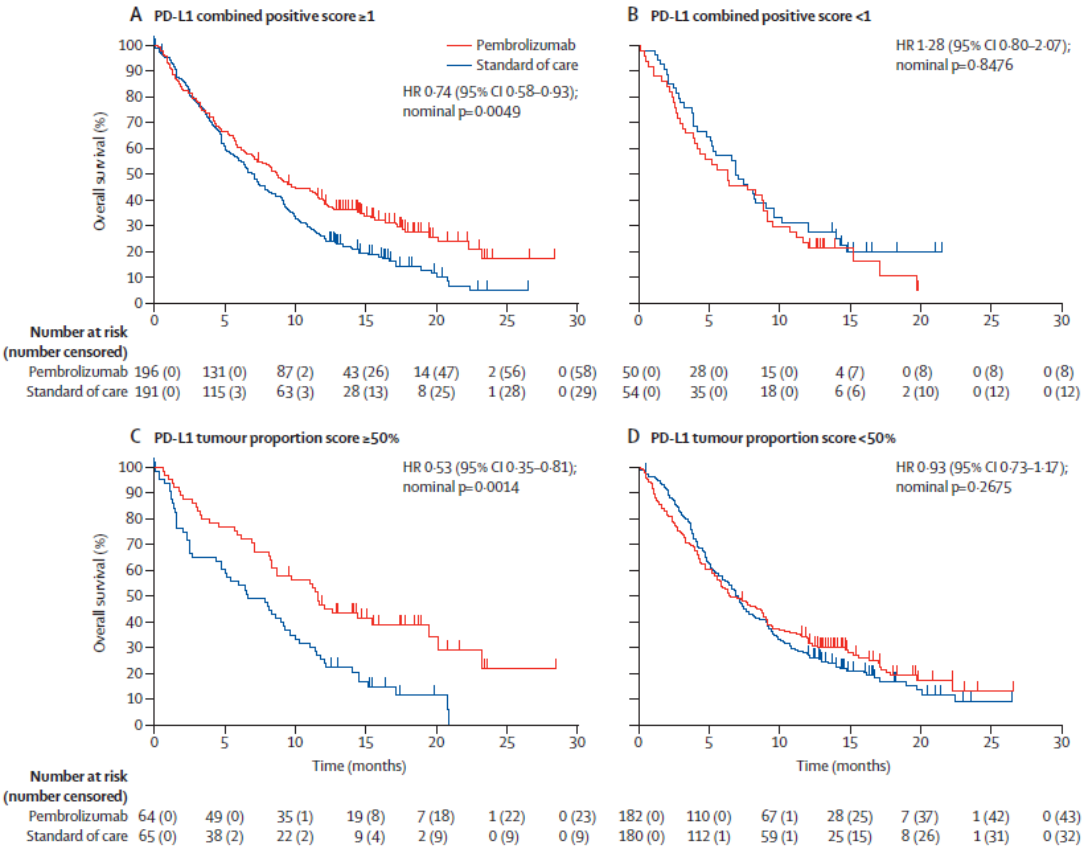
- Clinically stable patients with radiologic PD could continue treatment until imaging performed ≥4 wk later confirmed PD
- Crossover not permitted

[a]Limit of 2 prior therapies for R/M HNSCC. [b]Assessed using the CINtec p 16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Newly collected preferred. [d]Assessed using the PD-L1 IHC 22C3 pharmDx assay. TPS, tumour proportion score = % of tumour cells with membranous PD-L1 expression. [e]Could be increased to 60 mg/m^2 qw in the absence of toxicity. [f]Following a loading dose of 400 mg/m^2.

Cohen E, et al. Ann Oncol 2017;28(Suppl 5): abstract LBA45_PR.

KEYNOTE-040

Overall survival in the intention-to-treat populations according to PD-L1 expression category



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KEYNOTE-048 STUDY DESIGN (NCT02358031)

Key eligibility criteria

- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment[a]
- Known p16 status in the oropharynx[b]

Stratification factors

- PD-L1 expression[a] (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)

R 1:1:1

Pembrolizumab monotherapy

Pembrolizumab 200 mg IV q3w for up to 35 cycles

Pembrolizumab + chemotherapy

Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2/d for 4 days for 6 cycles (each 3 wk)

Pembrolizumab 200 mg q3w for up to 35 cycles total

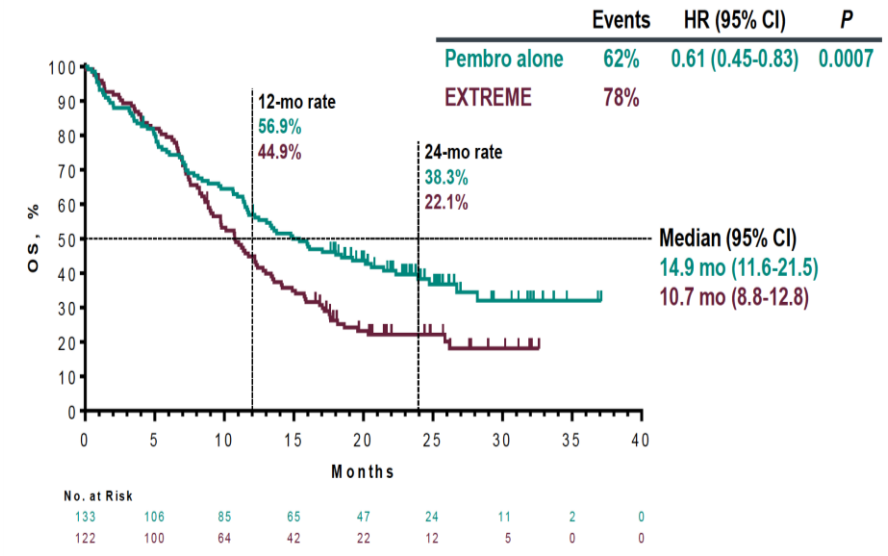
EXTREME

Cetuximab 250 mg/m^2 q1w[c] + Carboplatin AUC 5 OR Cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2/d for 4 days for 6 cycles (each 3 wk)

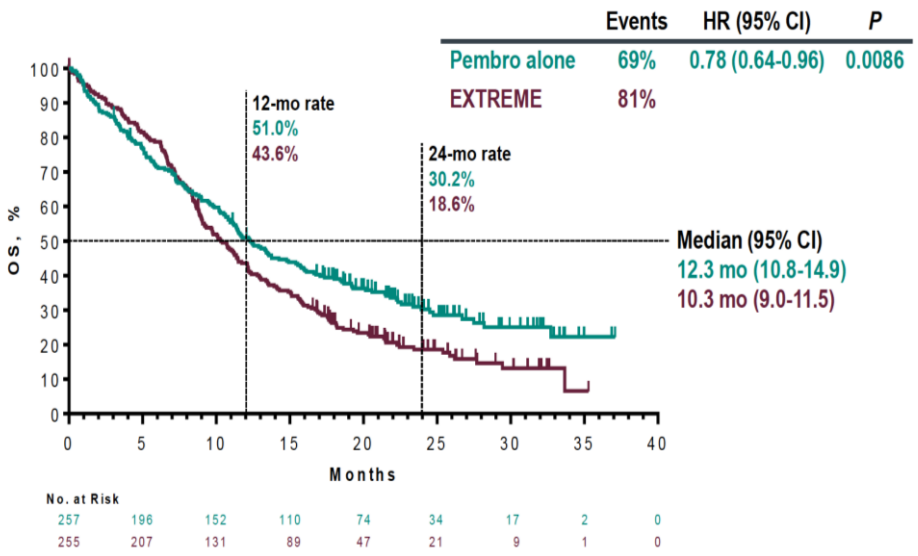
Cetuximab 250 mg/m^2 q1w

[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS, tumour proportion score = % of tumour 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/m^2. Burtness et al. Abstract #LBA8 PR. ESMO 2018.

Overall survival: P vs E, CPS ≥20 population



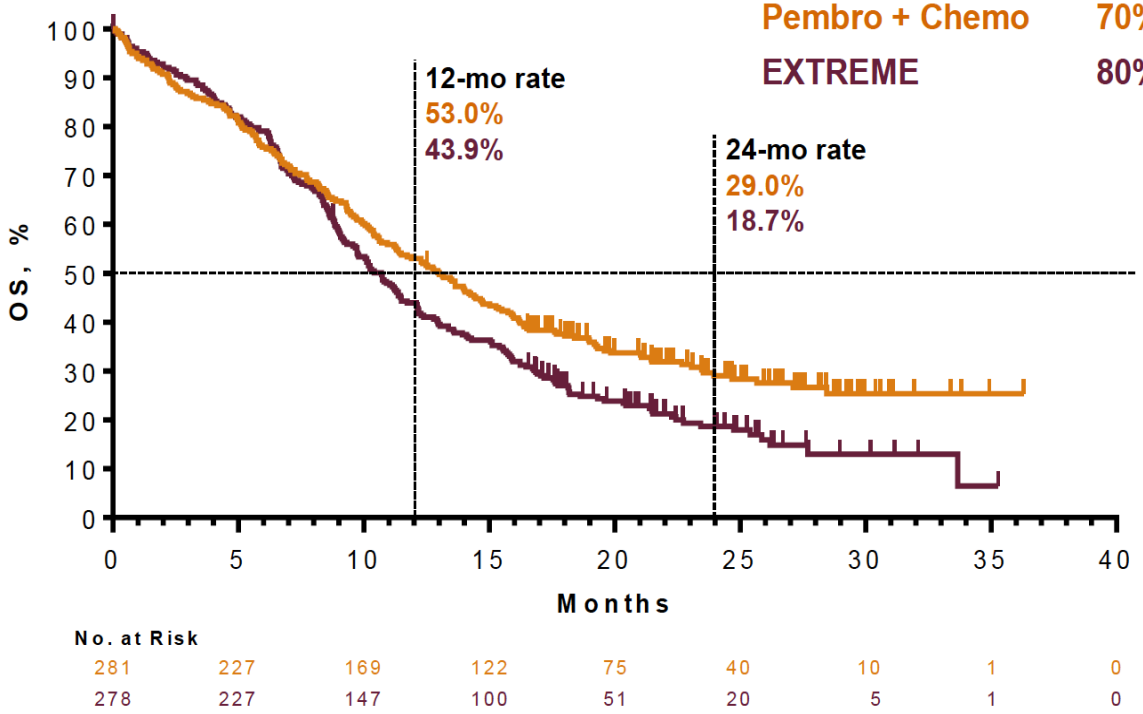
Overall survival: P vs E, CPS ≥1 population



Burtness B, et al. Abstract #LBA8 PR. ESMO 2018. By permission of Prof B. Burtness .

OVERALL SURVIVAL: P+C VS E, TOTAL POPULATION

	Events	HR (95% CI)	*P*
Pembro + Chemo	70%	0.77 (0.63-0.93)	0.0034
EXTREME	80%		



Burtness B, et al. Abstract #LBA8 PR. ESMO 2018. By permission of Prof B. Burtness..

PHASE III TRIALS TESTING ICIS IN RECURRENT/METASTATIC HNSCC BY PD-L1 STATUS

Trial	Tumour type	Interventions	Nº of patients	PD-L1 Expression location	Cut-off	HR for OS Overall	HR for OS PD-L1+	HR for OS PD-L1-	PDL-1 a relevant biomarker?
Checkmate-141	Metastatic HNSCC in 2nd line	Nivolumab vs chemotherapy	240	TCs	>1%	0.68	0.55	0.73	Yes
KEYNOTE-040	Metastatic HNSCC in 2nd line	Pembrolozumab vs chemotherapy	247	TCs+Ics (CPS) TCs (TPS)	CPS >1 TPS >50%	0.80 (P 0.016)	CPS ≥1 0.74 TPS ≥50% 0.53	CPS <1 1,28 TPS <50% 0.93	Yes
KEYNOTE-048	Metastatic HNSCC in 1st line	1. Pembro vs chemo	882	TCs+Ics (CPS)	CPS >1% CPS >20%	0.77 (P 0.0086)	0.78 0.61	Ø Ø	Yes for monotherapy
		2. Pembro + chemo vs chemo			CPS >1% CPS >20%		0.71 0.69	Ø Ø	No for combination with chemotherapy

OS: overall survival; HR: hazard ratio; TCs: tumour cells; Ics: immune cells; CPS:number of PD-L1-positive cells divided by total number of tumour cells 100; TPS: percentage of tumour cells with membranous PD-L1 expression Ø, data no available

IMPLICATION OF PD-L1 EXPRESSION AND CHALLENGES IN CLINICAL PRACTICE FOR HNSCC

- **KEYNOTE-048** – Better OS with pembro monotherapy in first line HNSCC and trend for more benefit with higher PD-L1 expression (CPS ≥20% vs ≥1%)
- Benefit on combination pembro + chemo regardless PDL-1 expression
- **KEYNOTE-040** – Improved OS with higher pdl1 expression
- **CHECKMATE-141** – Trend for more benefit with higher PD-L1 expression
- No firm conclusion on the value of pdl1 for clinical practice with ICIs in HNSCC
  - Trend for relevance on ICI monotherapy but lower importance on combination ICI+ chemo
- Other different biomarkers under investigation: HPV status, tumour immune infiltration, TMB, etc.

RENAL CARCINOMA

POSITIVE PHASE III TRIALS WITH CPI IN METASTATIC RENAL CANCER

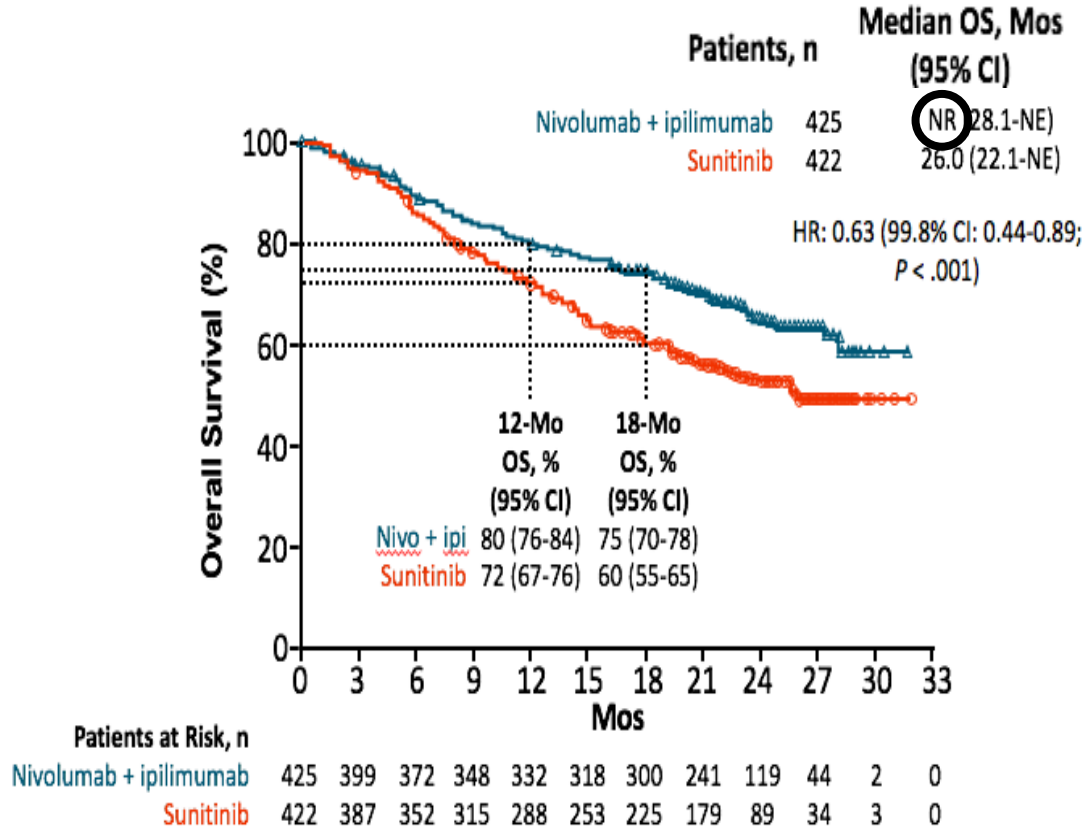
Trial	Setting	Interventions	No. pts	Main outcomes results	Adverse events	PDL1 stratification
CHECKMATE-214	Ph III, 1st line Intermediate-bad prognostic (Including sarcomatoid)	A. Nivo (3 mg/kg)-Ipi (1 mg/kg) B. Sunitinib	1096 (1:1)	**OS.** N-I: Not Reached (NR)/S: 26 m **PFS.** N-I: 11,6 m/S: 8,4 m **ORR.** N-I: 42%./S: 27%	**Any grades:** N-I: 93%; S: 97% **G3/G4:** N-I: 46%; S: 63%	No (regardless PDL1 status)
IMMOTION 151	Ph III, 1st line (Including sarcomatoids)	A. Atezo + Beva B. Sunitinib	915 (1:1)	**OS.** PDL1+: All: A-B 34 m vs S: 32,7 m A-B 33,6 m vs S: 34,9 m **PFS.** PDL1+: All: A-B 11,2 m vs S: 7,7 m. A-B 11,2 m vs S: 8,4 m **ORR.** PDL1+: All: A-B 43% vs S: 35%. A-B 37% vs S: 33%	**Any grades:** A-B: 93%/S: 97% **G3/G4:** A-B: 46%/S: 63% AEs-Discontinuation: 5% (A-B) vs 8% (S)	Yes <1% vs ≥1%, assessed by ICH- VENTANA PD-L1 SP142 assay
JAVELIN RENAL 101	Ph III 1st line	A. Avelumab + Axitinib B. Sunitinib	886 (1:1)	**OS.** PDL1+: All: A-A NR vs S: NR A-A NR vs S: NR **PFS**. PDL1+: All: A-A 13,8 m vs S: 7,2 m. A-A 13,8 m vs S: 8,4 m **ORR.** PDL1+: All: A-A 55,2% vs S: 25,5%. A-A 51,4% vs S: 25,7%	**Any grades:** A-A: 99,5% S: 99,3% **G3/G4:** A-A: 71,2% S: 71,5%	Yes <1% vs ≥1%, assessed by ICH- VENTANA PD-L1 (SP263) assay

POSITIVE PHASE III TRIALS WITH CPI IN METASTATIC RENAL CANCER

Trial	Setting	Interventions	No pts	Main outcomes results	Adverse events	Pdl1 stratification
KEYNOTE-426	Ph III, 1st line (including sarcomatoid features)	1. Pembro + Axitinib 2. Sunitinib	1062 (1:1)	**OS:** P-A: NR S: NR **PFS:** P-A 15,1 m S: 10,1 m **ORR:** P-A 59,3% S: 35,7%	**Any grades:** -P-A: 98,4% -S: 99,5% **G3/G4:** -P-A: 75,8% -S: 70,6%	• No results so far • Assessed by IHC 22C3 pharmDx assay (CPS)
CHECKMATE-025	Ph III 2nd/3rd line	1. Nivo 2. Everolimus	821 (1:1)	**OS:** PDL1+: N 21,8 m vs E: 18,8 m All: N 25 m vs E: 19 m -> PDL1 <1%: N 27,4 m vs E 21,2 m **PFS:** N: 4,6 m E: 4,4 m **ORR:** N: 25% vs E: 5%	**Any grades:** -N: 79% -E: 88% **G3/G4:** -N: 19% -E: 39%	• Yes, but just OS • Assessed by Dako PD-L1 ICH staining

1ST LINE: CHECKMATE 214

Intermediate/Poor risk prognostic group



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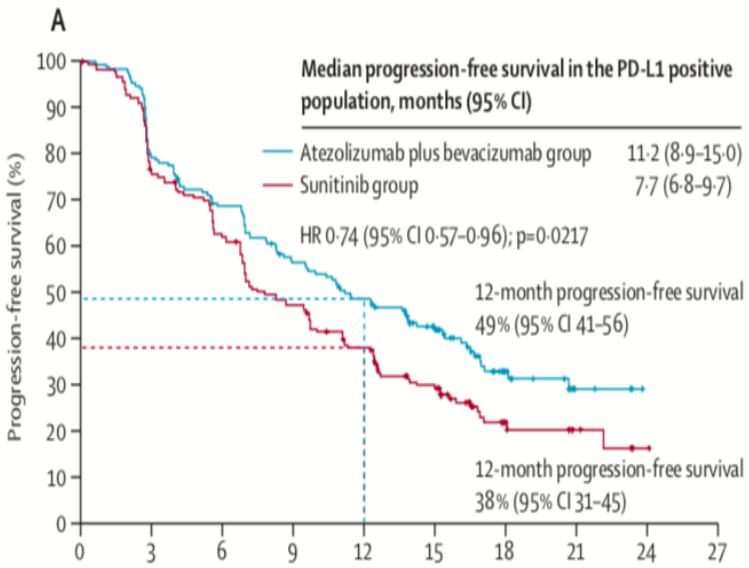
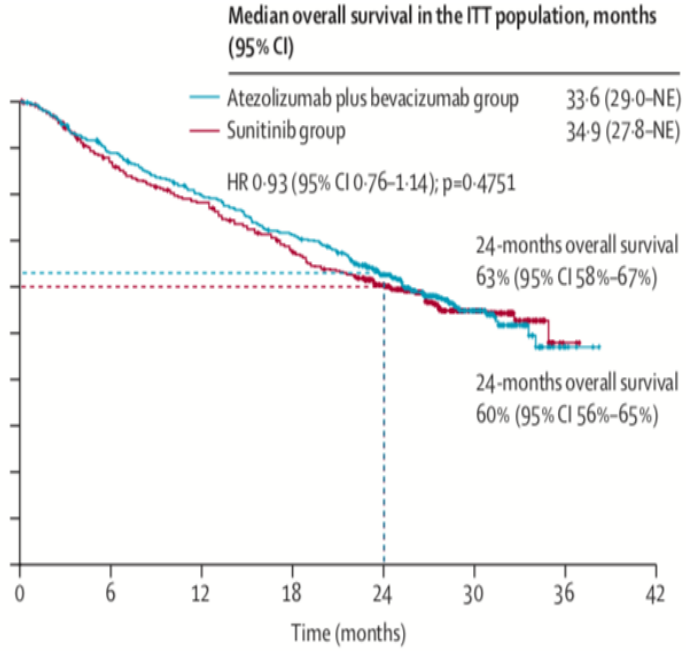
1ST LINE: IMMOTION 151: ATEZO+BEVA

PFS in PDL1+ cohort



Number at risk (number censored)										
Atezolizumab plus bevacizumab group	178 (0)	137 (5)	117 (7)	94 (9)	79 (11)	55 (26)	22 (49)	5 (64)	..	..
Sunitinib group	184 (0)	135 (5)	110 (6)	83 (7)	64 (10)	44 (17)	15 (37)	7 (44)	1 (49)	..

OS in ITT cohort

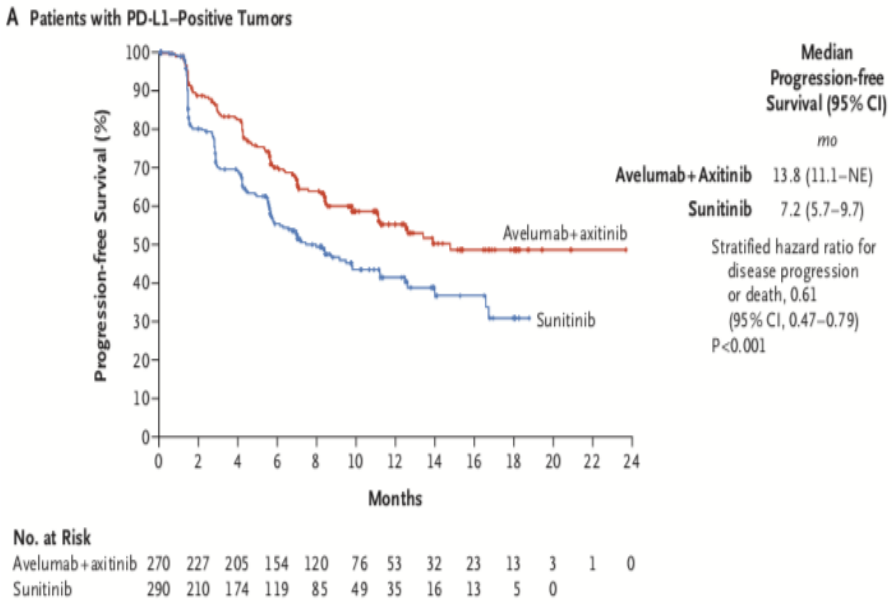


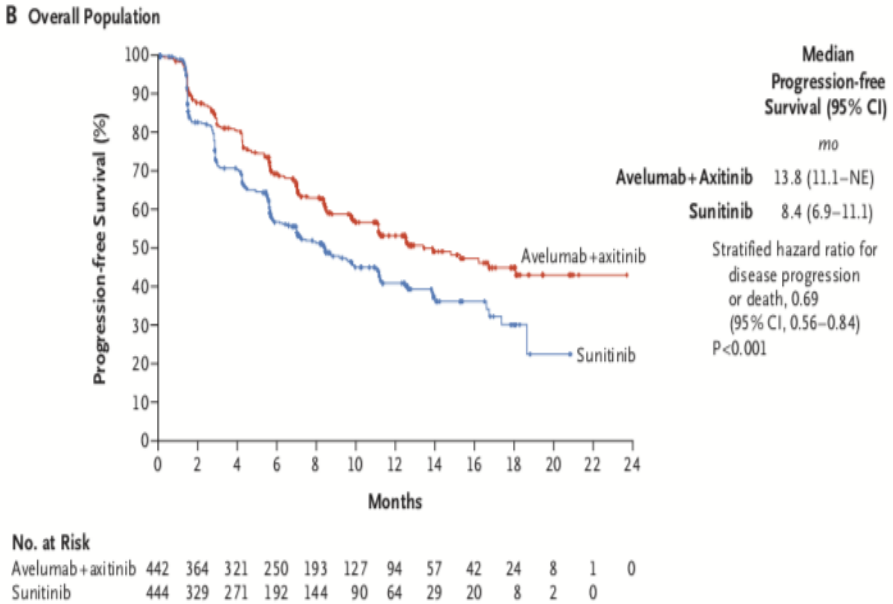
	454 (0)	429 (2)	398 (6)	372 (8)	352 (10)	333 (10)	314 (11)	294 (14)	240 (48)	155 (118)	85 (181)	33 (229)	6 (254)	.. ..
	461 (0)	423 (12)	386 (16)	360 (18)	344 (20)	317 (22)	294 (24)	273 (26)	223 (63)	141 (135)	85 (187)	29 (241)	2 (267)	.. ..

1ST LINE: JAVELIN RENAL 101: AVELUMAB + AXI

OS NOT REACHED

- PD-L1 expression (≥1% immune cells) associated with the longest PFS in the A+Ax arm and the shortest in the S arm (HR: 0,63)
- High-CD8+ cells extended PFS in the A+Ax arm and the reduced in the S arm

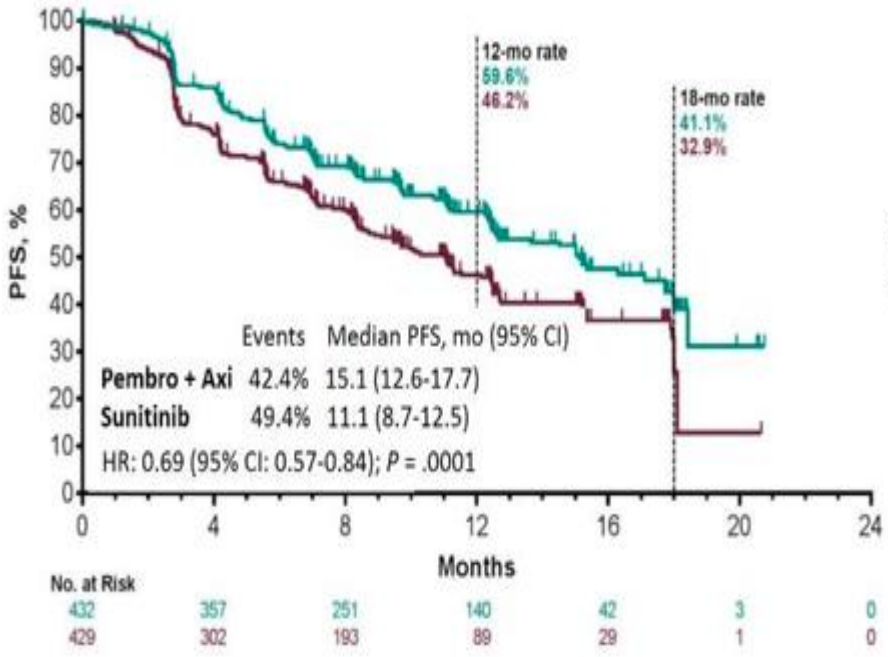




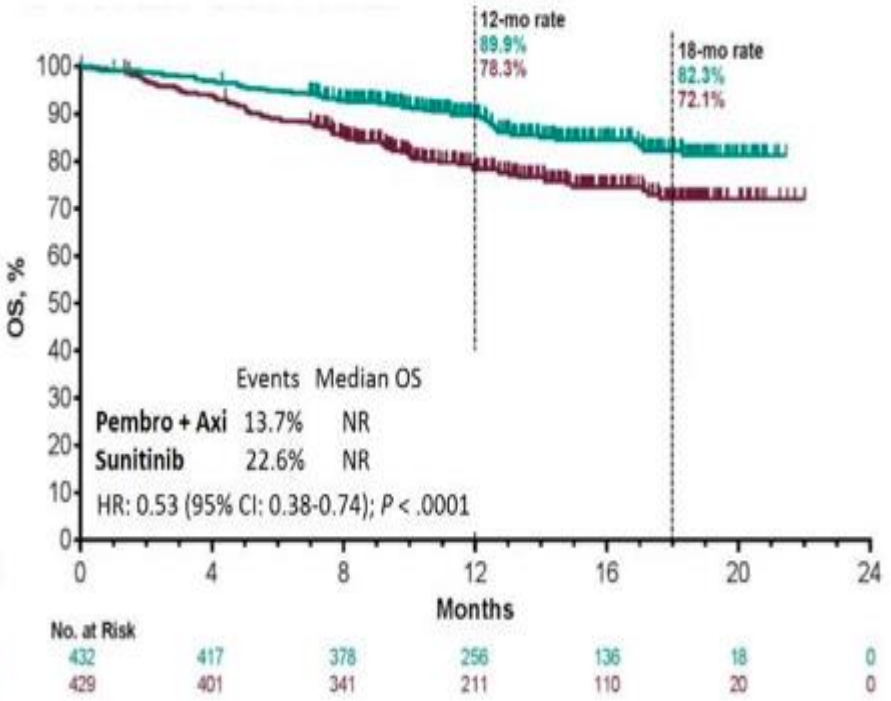
From N Engl J Med 2019, Motzer RJ, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma 380(12)., 1103-1115 Copyright © (2019) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Motzer. NEJM, 2019/ESMO 2018. Abstract LBA6. Choueiri. ASCO 2019. Abstract 101.

1ST LINE: KEYNOTE 426: PEMBRO + AXI

PFS in ITT population



OS in ITT population



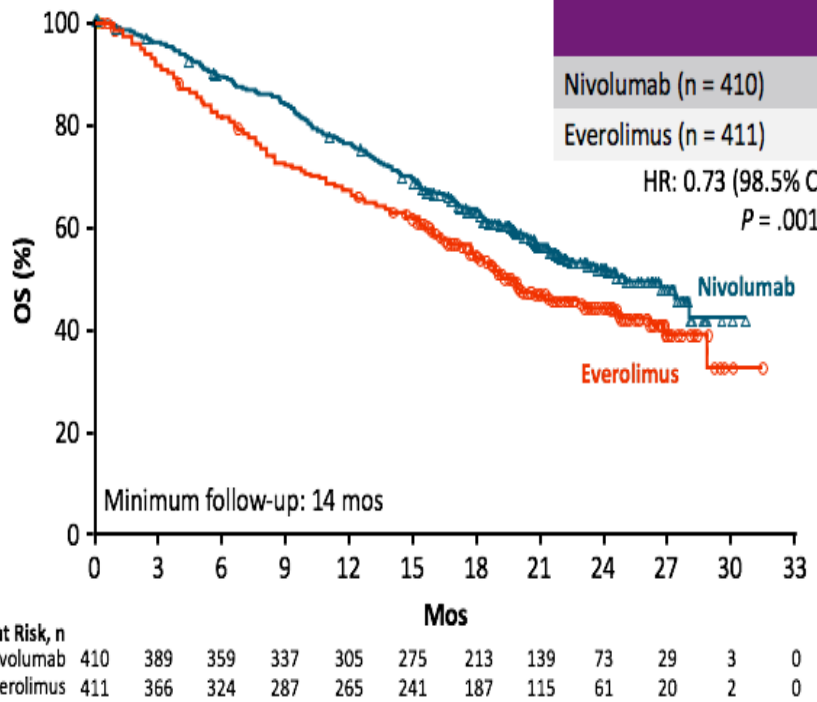
From N Engl J Med 2019, Rini BI, et al.Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma 380., 1116-1127 Copyright © (2019) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Rini, NEJM 2019/Powles, Genitourinary Cancers Symposium, 2019. Abstr 543.

2ND LINE: CHECKMATE 025: NIVO

Exploratory analysis of OS by subgroups

Metastatic RCC with ≤2 prior antiangiogenic therapies and ≤3 total prior systemic regimens (N=821)

- Nivolumab 3 mg/kg IV every 2 wks
- Everolimus 10 mg PO daily



From N Engl J Med 2015, Motzer RJ, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma, 373(19)., 1803-1813 Copyright © (2015) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

RENAL CELL CARCINOMA AND PD-L1 EXPRESSION

Learned lessons for clinical practice

CPI has been rapidly adopted into the routine care of patients

CPI: opportunity of long term survival

CPI: treatment-free survival – QoL (against TKIs)

New approaches needed: Subsequent treatments, perioperative strategy, new combinations

Better understanding of the immunological effects of TKIs and mTOR inhibitors (sequence)

Clinical trials with IO agents need to use IO endpoints

Selecting patients: Searching for new biomarkers

UROTHELIAL CARCINOMA

POSITIVE PHASE III TRIALS WITH CPI IN METASTATIC UROTHELIAL CANCER

Trial	Setting	Interventions	No patients	Main outcomes results	Adverse events	PDL1 stratification
IMVIGOR-210	Ph II Cohort 1: 1st line, cisplatin-ineligible *PDL1>5%	Atezolizumab	119 (cohort 1)	**OS:** 15,9 m **PFS:** 2,7 m **ORR:** IC2/3: 23% (9% CR)	Any: 66% G3/G4: 16%	Yes - Assessed by SP142 assay (Ventana, AZ, USA). - IC0 (<1%), IC1 (≥1% but <5%), and IC2/3 (≥5%).
KEYNOTE-052	Ph II 1st line, cisplatin-ineligible * CPS > 10%	Pembrolizumab	370	**OS:** 11,95 m **PFS:** 2,3 m **ORR:** 28,9 (8,1% CR)	Any: 62% G3/G4: 19%	Yes -Assessed by Dako 22C3 assay, CPS. -PD-L1 cut-off to define a positive level at which responses were most enriched.
IMVIGOR-211	Ph III 2nd line (after platinum)	1. Atezolizumab 2. Chemotherapy-CT (investigator choice): - Vinflunine - Paclitaxel - Docetaxel	467 (931 in total)	**OS:** Atezo: 8,9 m; IC2/3: 11,1 m **CT:** IC2/3: 10,6 m **PFS:** Atezo: 2,4 m; CT: 4,2 m **ORR:** Atezo:13,4%; IC2/3: 23% (7% CR) **CT:** 13,4%; IC2/3: 21,6%	Any: -Atezo: 69%; IC2/3: 75% -Chemo: 89%; IC 2/3: 88% G3/G4: Atezo: 20%	Yes - Assessed by VENTANA SP142 PD-L1 IHC assay. -IC0 (<1%), IC1 (≥1% but <5%), and IC2/3 (≥5%)
CHECKMATE-275	Ph II 2nd line (after platinum)	Nivolumab	265	**OS:** 8.7 m PDL1< 1%: 5,95 m; PDL1 >1%: 11,3 m **PFS:** 2 m **ORR:** 19,6% PDL1 <1%: 16,1%; PDL1 >1%: 23,8%; PDL1 >5%: 28,4%	Any: 64% G3/G4: 18%	Yes - Assessed by Dako PD-L1 IHC 28-8 pharmDx kit - ≥1% or ≥5% tumour cell membrane staining

POSITIVE PHASE III TRIALS WITH CPI IN METASTATIC UROTHELIAL CANCER

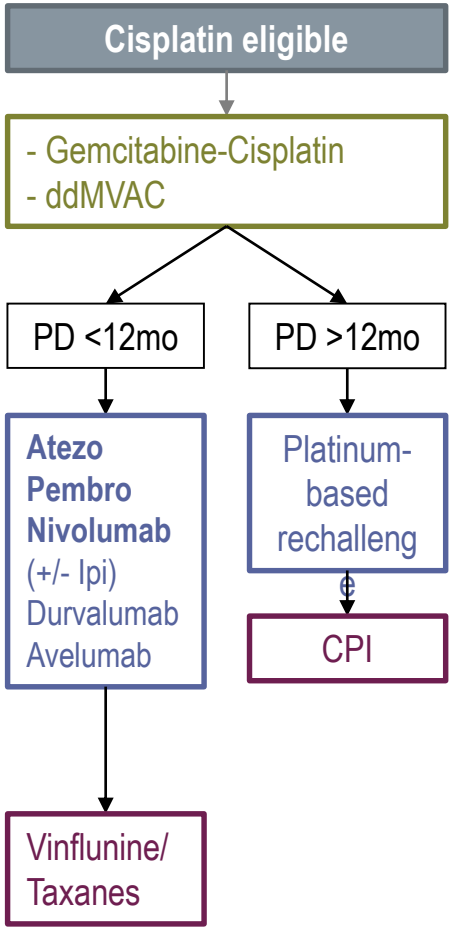
Trial	Setting	Interventions	No patients	Main outcomes results	Adverse events	PDL1 stratification
STUDY 1108	Ph I/II 2nd line (after platinum)	Durvalumab	191	. OS 18,2, m PDL1 high: 20 m PDL1 low/negative: 8,1 m . PFS 1,5 m PDL1 high: 2,1 m PDL1 low/negative: 1,4 m . ORR 17,8% PDL1 high: 27,6% PDL1 low/negative: 5,1%	Any: 60,7% G3/G4: 6,8%	Yes - Assessed by SP-263 anti-PD-L1 assay (Ventana Medical Systems) - Enrollment regardless PDL1 status (although there was some point that it was) - PDL1 high: ≥25%
JAVELIN SOLID TUMOURS	Ph Ib 2nd line (after platinum)	Avelumab	249	. OS 6,5 m PDL1 >5%: 8,2 m PDL1 <5%: 6,2 m . PFS 6,3 m (by inmune-related response), 1,5 m PDL1 >5%: 11,9 m PDL1 <5%: 6,1 m . ORR 17%	Any: 67% G3/G4/G5: 10,8%	Yes - Assessed by Dako PD-L1 IHC73-10 pharmDx assay - PD-L1 cutoff of 5% or higher. - Mutational load established by RNASeq
KEYNOTE-045	Ph III 2nd line (after platinum)	1. Pembrolizumab-P 2. Chemotherapy-CT: - Vinflunine - Paclitaxel - Docetaxel	542 (748)	. OS (CPS>10%) P: 10,3 m; CT: 7,4 m . PFS (CPS>10%) P: 2,1 m; CT: 3,3 m . ORR (CPS>10%) P: 21,1% ; CT: 11,4%	Any: P: 60,9% C: 90,2% G3/G4/G5: P: 15% C: 49,4%	Yes, - Assessed by PD-L1 IHC 22C3 pharmDx assay (Dako North America)

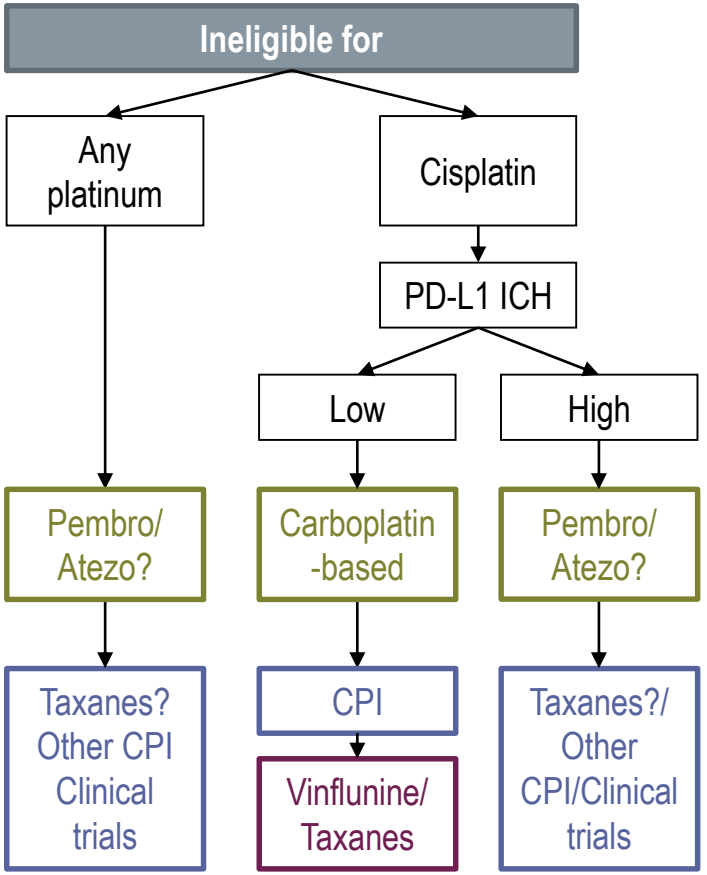
ADVANCED UC: TREATMENT ALGORITHM

1st LINE

2nd LINE

3rd LINE





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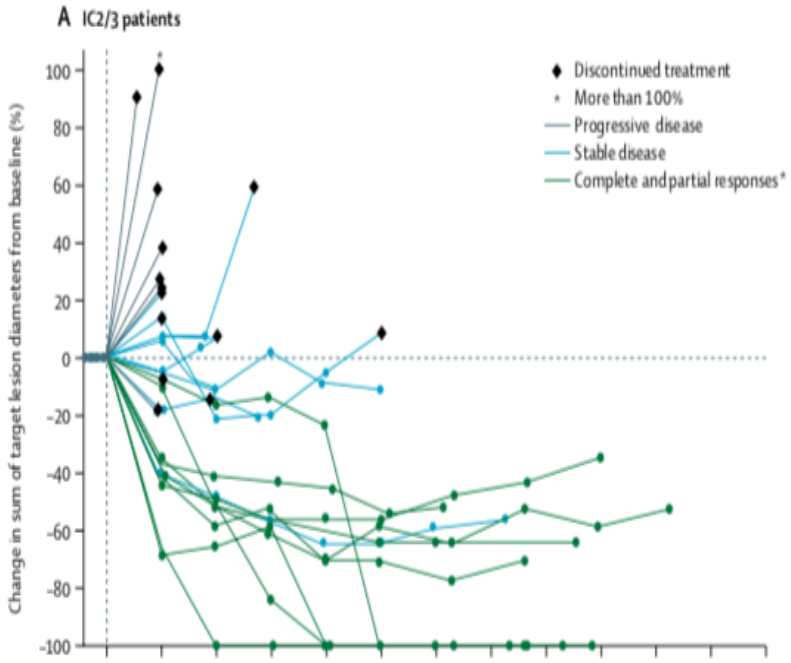
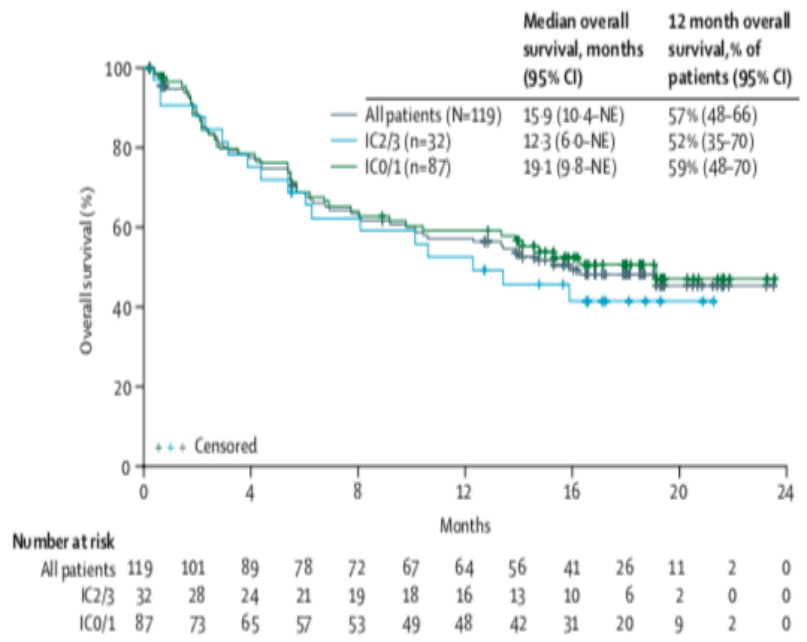
1ST LINE-INELIGIBLE PD-L1 >5% ATEZOLIZUMAB: IMVIGOR 210



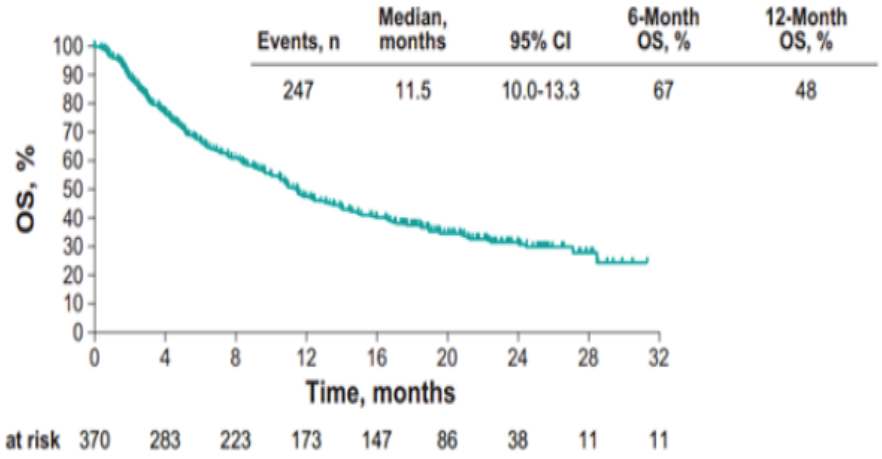
ORR IC2/3 28% (23% all groups)
Median OS: 15,9 months (95% CI 6.6-9.3) for the entire cohort of pts

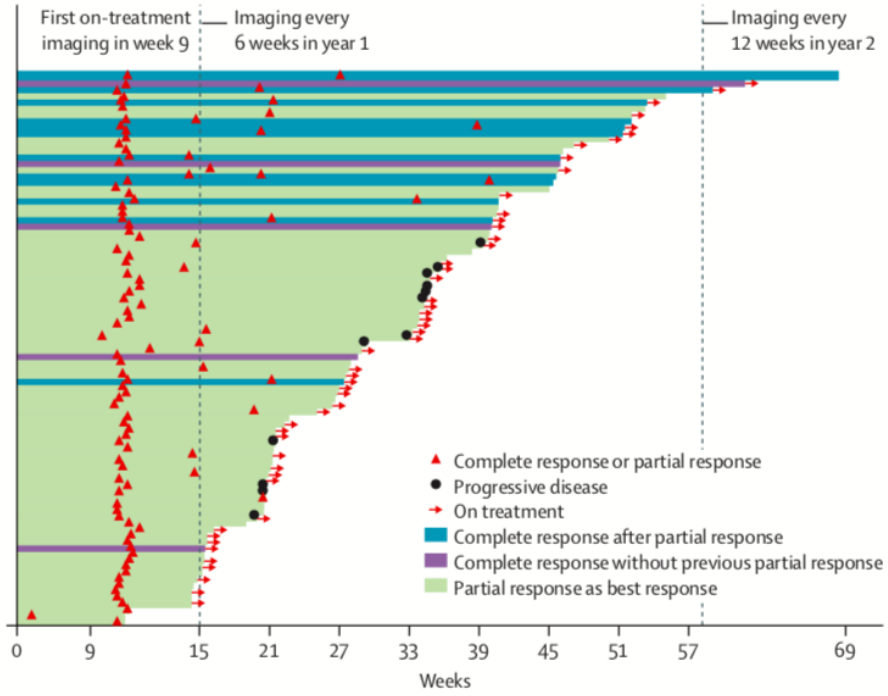
Restriction by **PDL1 status** in previously untreated patients: **Decreased survival in patients with** low PDL-1 expression



Rosenberg J, et al. The Lancet, 2016, 387(10031) 2016: 1909-1920
Reprinted from The Lancet,, 389 (10064), Balar AV, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial: 67-76. Copyright 2017, with permission from Elsevier.

1ST LINE-INELIGIBLE CPS >10% PEMBROLIZUMAB: KN 052





Updated results:

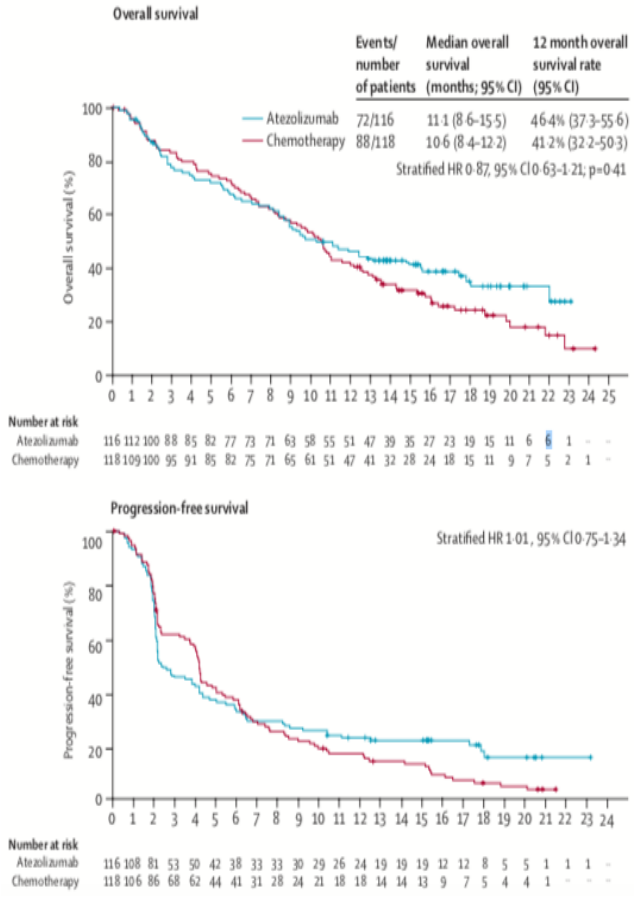
OS: 11.95 m

PFS: 2.3 m

ORR: 28.9 (8.1% CR)

Reprinted from The Lancet Oncol, 18 (11), Balar AV, et al, First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study, 1483-1492, copyright 2017, with permission from Elsevier.
By permission of Dr Vuky J, J Clin Oncol 2018;36(suppl).; Presented at ASCO 2018; Abstract 4524.

2ND LINE
ATEZOLIZUMAB: IMVIGOR 211



Negative results:

- PD-L1+: More favourable outcome with **both** CT and atezolizumab
- PD-L1 assay disparities

	IC2/3 population		ITT population	
	Atezolizumab group (n=116)	Chemotherapy group (n=118)	Atezolizumab group (n=467)	Chemotherapy group (n=464)
Progression-free survival				
Patients with event (%)*	93 (80%)	105 (89%)	407 (87%)	410 (88%)
Median (months; 95% CI)	2·4 (2·1–4·2)	4·2 (3·7–5·0)	2·1 (2·1–2·2)	4·0 (3·4–4·2)
Objective response†				
Number of evaluable patients	113	116	462	461
Number of patients with response (%, 95% CI)	26 (23·0%, 15·6–31·9)	25 (21·6%, 14·5–30·2)	62 (13·4%, 10·5–16·9)	62 (13·4%, 10·5–16·9)
Best overall response†				
Complete response	8 (7%)	8 (7%)	16 (3%)	16 (3%)
Partial response	18 (16%)	17 (15%)	46 (10%)	46 (10%)
Stable disease	23 (20%)	37 (32%)	92 (20%)	162 (35%)
Progressive disease	47 (42%)	30 (26%)	240 (52%)	150 (32%)
Missing or unevaluable	17 (15%)	24 (21%)	68 (15%)	87 (19%)
Duration of response†				
Patients with event (%)*	10/26 (38%)	20/25 (80%)	23/62 (37%)	49/62 (79%)
Median (months; 95% CI)	15·9 (10·4–NE)	8·3 (5·6–13·2)	21·7 (13·0–21·7)	7·4 (6·1–10·3)

Reprinted from The Lancet, 391 (10122), Powles T, et al, Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial, 748-757, copyright 2018, with permission from Elsevier.

2ND LINE
NIVOLUMAB: CHECKMATE 275

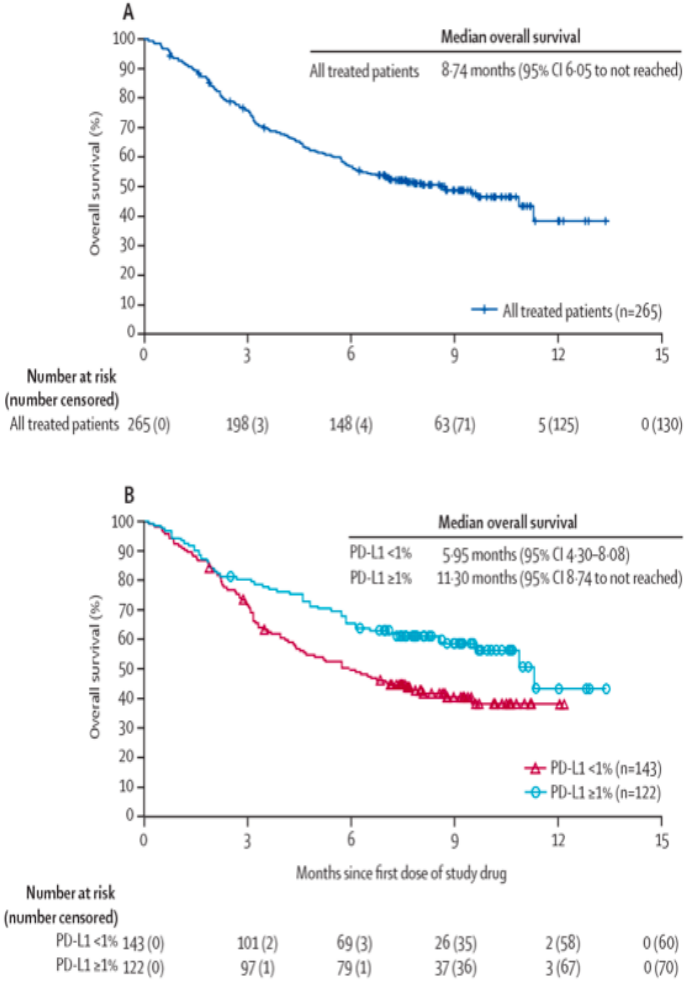
5% of CR in second-line setting!

Open-label, single-arm, Phase 2 study

- Metastatic or locally advanced mUC
- Disease progression on prior platinum-based therapy
- Evaluable PD-L1 tumour tissue sample[a]

→ Nivolumab 3 mg/kg IV every 2 wk N=270 → Treat until progression[b] or unacceptable toxicity

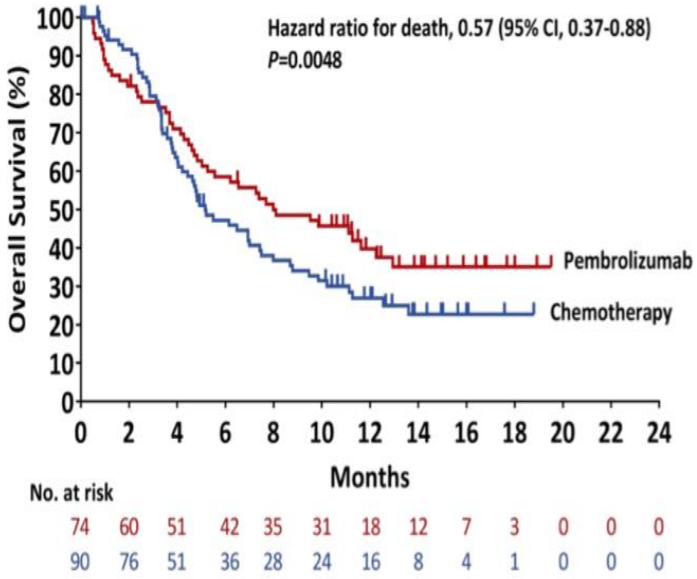
Binded independent review committee (BIRC) assessment of response using RECIST v1.1



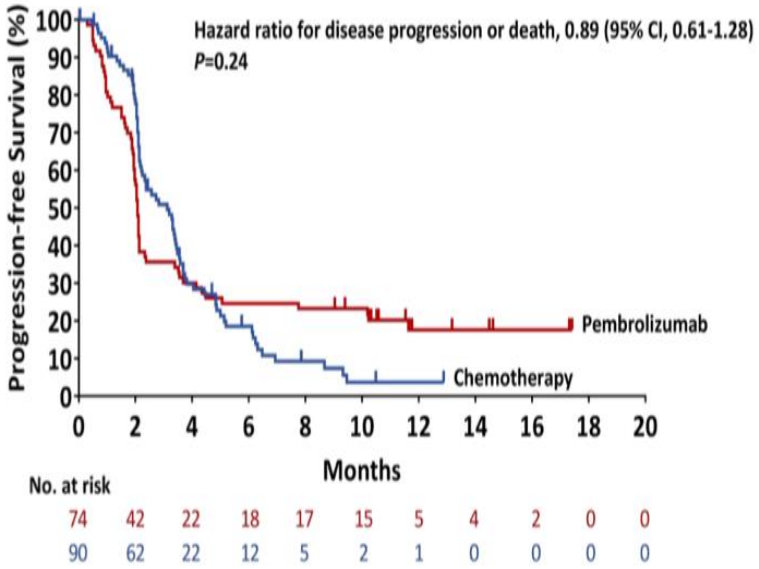
Reprinted from The Lancet Oncol, 18 (3), Sharma P, et al, Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial, 312-322, copyright 2017, with permission from Elsevier.

2ND LINE
PEMBROLIZUMAB: KEYNOTE 045

Overall Survival in PD-L1 Combined Positive Score (CPS) ≥10 population

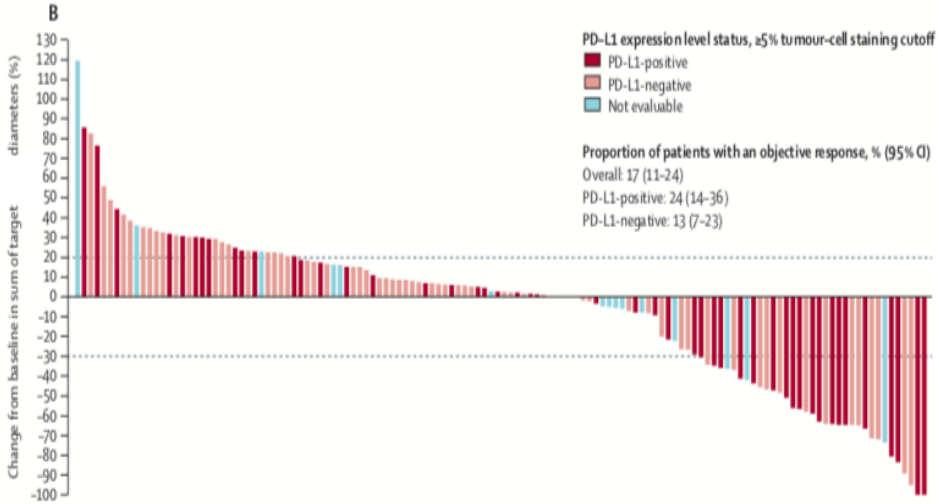


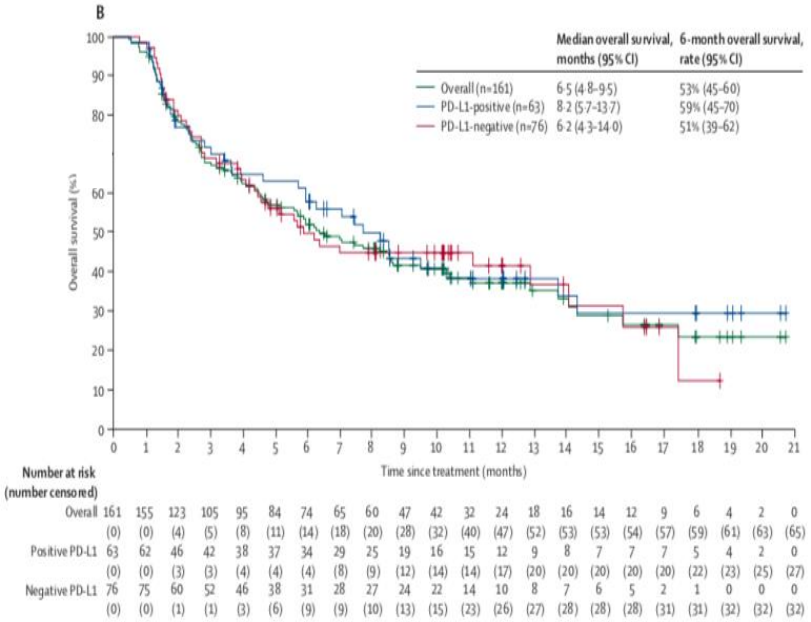
Progression-Free Survival in PD-L1 CPS ≥10 population



Median OS: Pembro 10.3 m vs CT 7.4 m
ORR: Pembro 21.1% vs CT 11.4%

2ND LINE
AVELUMAB: JAVELIN SOLID TUMOUR





Phase 1b, UC cohort (n=249)
Single-arm, multicenter trial

2ND LINE
DURVALUMAB: STUDY 1108

	PD-L1 high	PD-L1 low/negative	Total
No. of patients (events)	98 (30)	79 (35)	191 (68)
Median OS (95% CI), mo	20 (11.6-NE)	8.1 (3.1-NE)	18.2 (8.1-NE)
OS rate, % (95% CI)			
6 mo	72 (62-80)	51 (38-63)	64 (56-71)
9 mo	66 (53-77)	41 (21-60)	57 (47-66)
12 mo	63 (49-74)	41 (21-60)	55 (44-65)
Median PFS (95% CI), mo	2.1 (1.4-2.8)	1.4 (1.3-1.5)	1.5 (1.4-1.9)
PFS rate, % (95% CI)			
6 mo	31 (22-41%)	8 (3-16%)	22 (16-28)
9 mo	25 (16-35%)	8 (3-16%)	18 (12-25)
12 mo	21 (13-31%)	8 (3-16%)	16 (10-23)

- Median time to response: 1.41 mo (range 1.2-7.2)
- Median duration of response (DOR) in as-treated population: Not reached (17/34 responders -50%- had a response lasting at least 6 mo and 26 -76.5%- had an ongoing response at data cut off
- Tumour shrinkage and Deep durable changes were seen in both PD-L1 subgroups
- Median PFS 1.5 mo (95% CI, 1.4-1.9), median OS 18.2 mo (95% CI, 8.1-Not estimable -NE-)

Data retrieved from Powles, JAMA Oncol, 2017

UROTHELIAL CELL CARCINOMA AND PD-L1 EXPRESSION

Learned lessons for clinical practice

- CPIs have shown long-term durable response and tolerable safety profiles
- However, ORR with CPI just around 25-30%
- Combination of different agents (antiPD1/PD-L1 + chemotherapy, antiangiogenics, etc.) / New drugs: M7824 (TGFß, Sanjeev Mariathasan, Nature 2018) are needed
- There is controversy between PD-L1 expression and ORR
- New biomarkers to guide therapy and develop novel combination therapies

PREVIOUSLY UNTREATED OESOPHAGO-GASTRIC CANCER

FIRST LINE ADVANCED OR METASTATIC OESOPHAGO-GASTRIC CANCERS

Pembrolizumab trials

KEYNOTE-062
Pembro vs chemotherapy

Gastric or OGJ ADC

Hazard ratio (PFS)
PD-L1 CPS ≥1: 1.66 (1.37-2.01)
PD-L1 CPS ≥10: 1.10 (0.79-1.51)

Hazard ratio (OS)
PD-L1 CPS ≥1: 0.91 (0.69-1.18)
PD-L1 CPS ≥10: 0.69 (0.49-0.97)

KEYNOTE-062
Pembro + chemo vs chemotherapy

Gastric or OGJ ADC

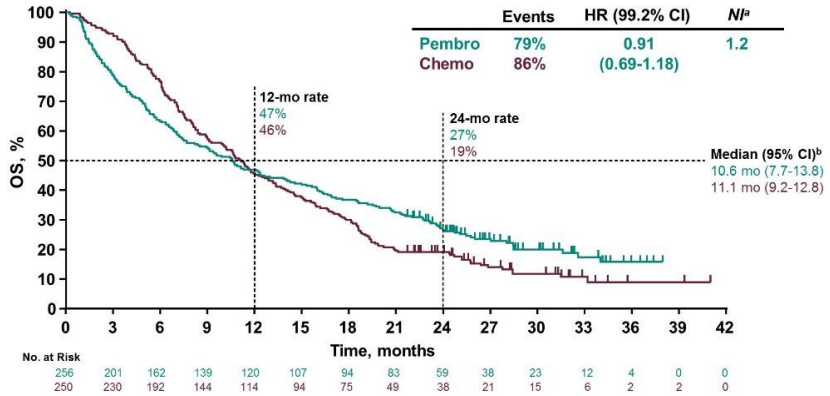
Hazard ratio (PFS)
PD-L1 CPS ≥1: 0.84 (0.70-1.02)
PD-L1 CPS ≥10: 0.73 (0.53-1.00)

Hazard ratio (OS)
PD-L1 CPS ≥1: 0.85 (0.70-1.03)
PD-L1 CPS ≥10: 0.85 (0.62-1.17)

Tabernero J, *et al,* ASCO 2019.

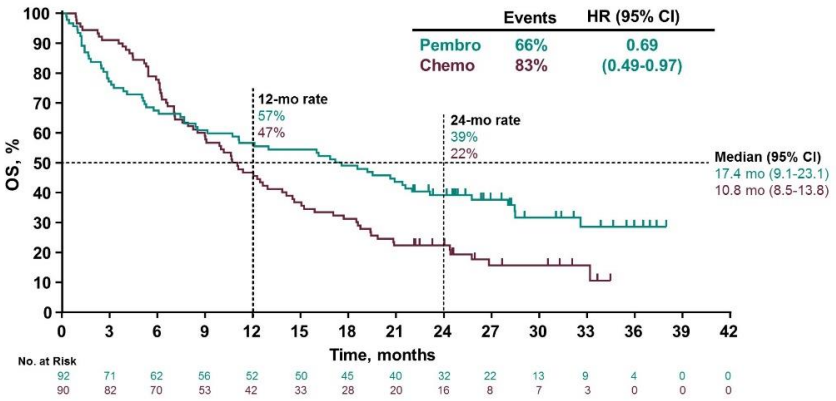
PEMBRO VS CHEMO
1ST LINE GASTRIC/OGJ (KEYNOTE-062)

Overall survival: P vs C (CPS ≥1)



[a]NI, non-inferiority margin; [b]HR (95% CI) = 0.91 (0.74-1.10), *P* = 0.162 for superiority of P vs C; Data cutoff: March 26, 2019.

Overall survival: P vs C (CPS ≥10)



Data cutoff: March 26, 2019.

Tabernero J, *et al,* ASCO 2019.. By permission of Prof J. Tabernero.

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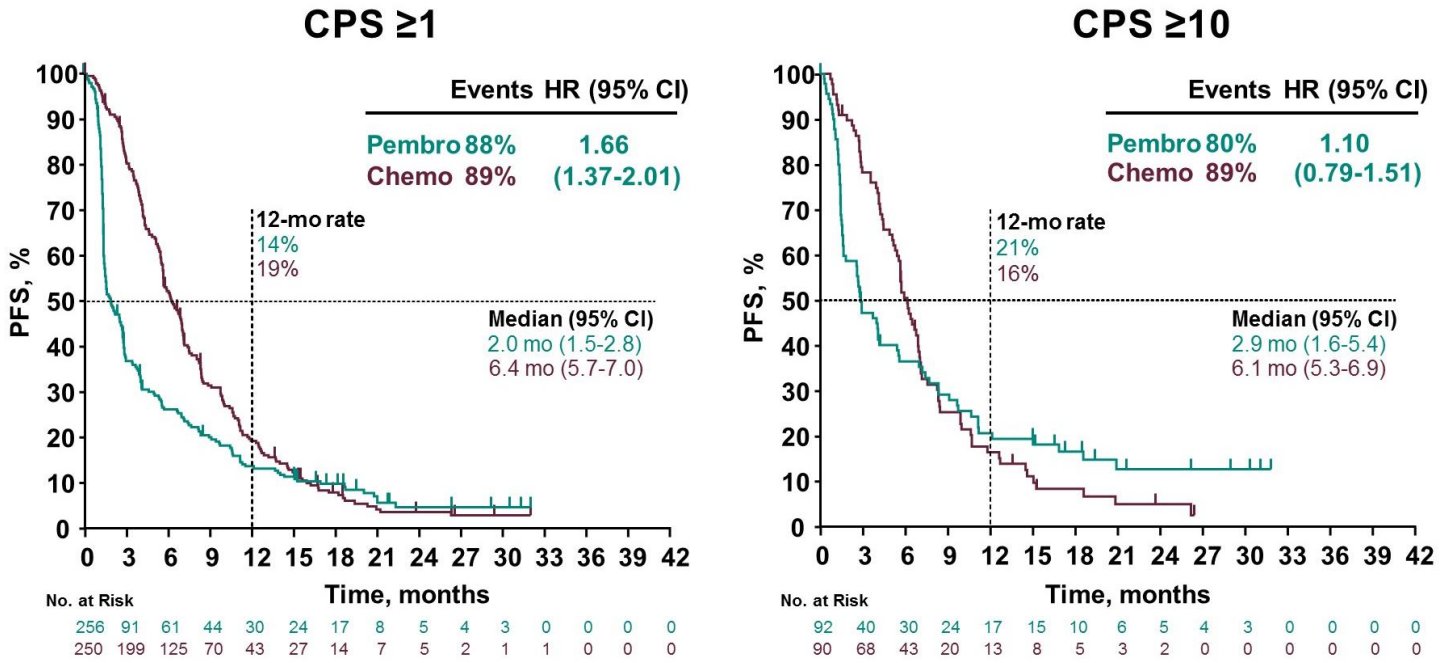
ESMO

PEMBRO VS CHEMO
1ST LINE GASTRIC/OGJ (KEYNOTE-062)

Progression-free survival: P vs C

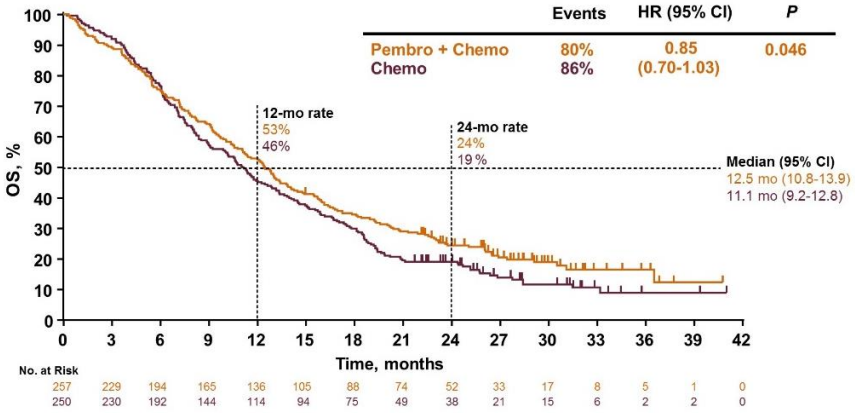


PFS assessed per RECIST v1.1 by blinded independent central review (final analysis of PFS occurred at IA2); Data cutoff: Sept 28, 2018.

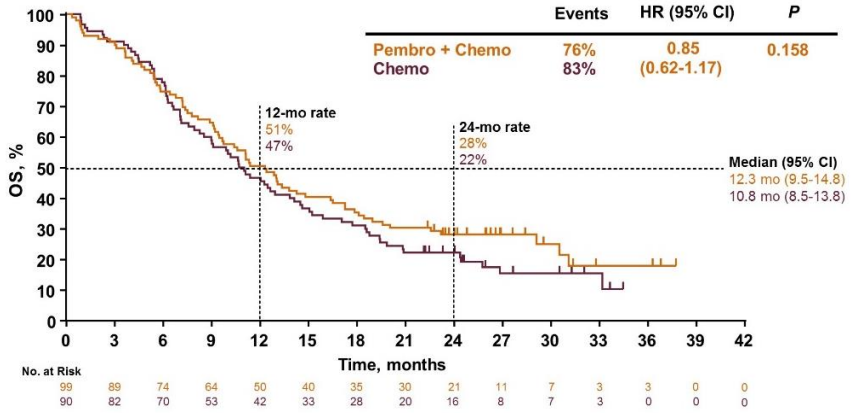
Tabernero J, *et al,* ASCO 2019. By permission of Prof J. Tabernero.

PEMBRO + CHEMO VS CHEMO
1ST LINE GASTRIC/OGJ (KEYNOTE-062)

Overall survival: P+C vs C (CPS ≥1)



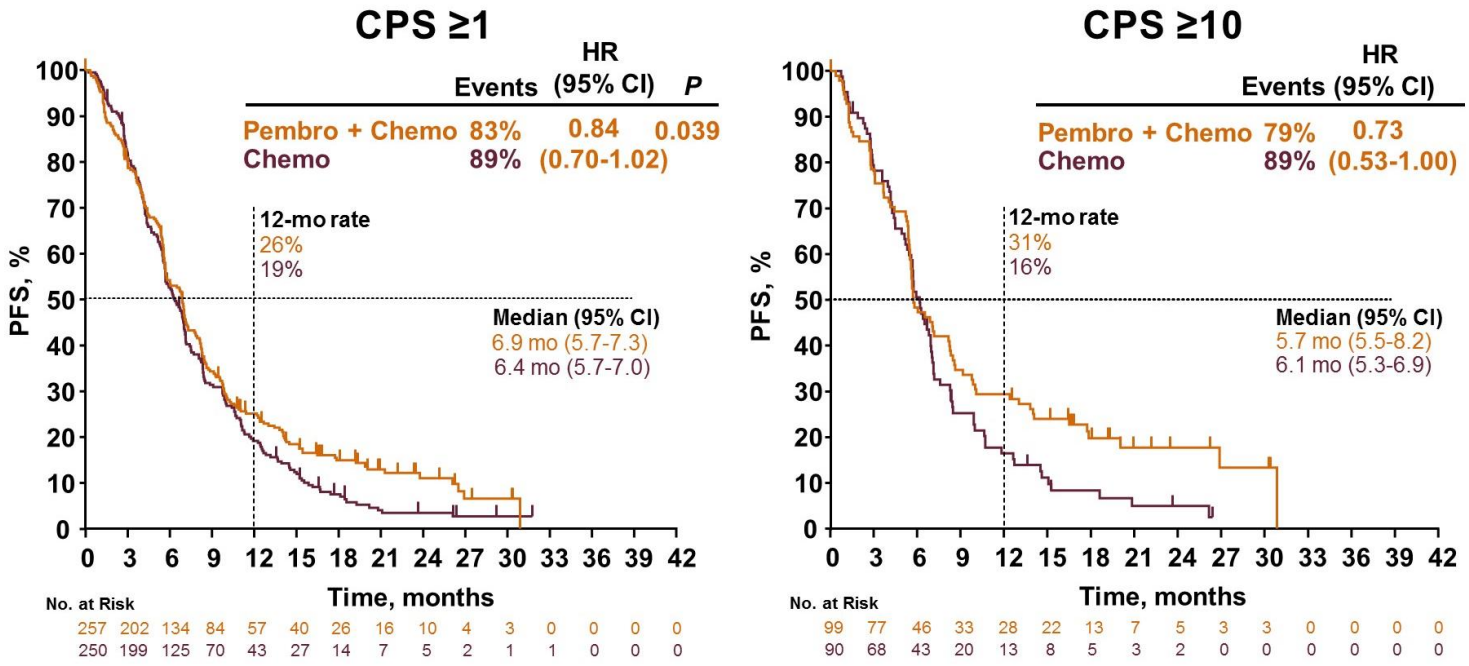
Overall survival: P+C vs C (CPS ≥10)



Data cutoff: March 26, 2019. Tabernero J, *et al,* ASCO 2019. By permission of Prof J. Tabernero.

PEMBRO + CHEMO VS CHEMO
1ST LINE GASTRIC/OGJ (KEYNOTE-062)

Progression-free survival: P+C vs C



PFS assessed per RECIST v1.1 by blinded independent central review (final analysis of PFS occurred at IA2); Data cutoff: Sept 28, 2018.

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TRIALS WITH ICI AND PD-L1

Subgroups untreated oesophago-gastric cancer patients

Trial	Tumour type	Interventions	Nº of patients	Main outcomes results	PdI1 stratification Results (HR)*	PdI1 good predictor of response?
KEYNOTE-062	Advanced/metastatic gastric or gastro-oesophageal adenocarcinoma	1- Pembrolizumab 2- Pembrolizumab + chemotherapy 3- Chemotherapy	763 (1:1:1)	mOS (CPS ≥ 1) 1 – 10.6 months 3 – 11.1 months HR (1 vs 3): 0,91 (0,69-1,18) p=na mPFS (CPS ≥ 1) 1 – 2.0 months 3 – 6.4 months HR (1 vs 3): 1,66 (1,37-2,01) p=na mOS (CPS ≥ 1) 2 – 12.5 months 3– 11.1 months HR (2 vs 3): 0,85 (0,70-1,03) p=0.046 mPFS (CPS ≥ 1) 2 – 6.9 months 3 – 6.4 months HR (2 vs 3): 0,84 (0,70-1,02) p=0.039	1 vs 3 CPS ≥ 10: HR OS 0,69 (0.49-0.97) 1 vs 3 CPS ≥ 10: HR PFS 1,10 (0.79-1.51) 2 vs 3 CPS ≥ 10: HR OS 0,85 (0.62-1.17) 2 vs 3 CPS ≥ 10: HR PFS 0.73 (0.53-1.00)	Yes?

PREVIOUSLY TREATED OESOPHAGO-GASTRIC CANCER

SECOND LINE ADVANCED OR METASTATIC OESOPHAGO-GASTRIC CANCERS

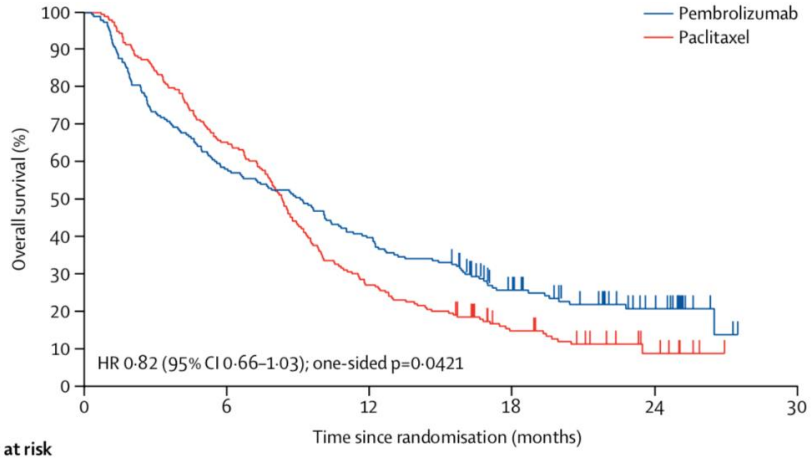
Pembrolizumab trials

KEYNOTE-181 Pembro vs chemotherapy	KEYNOTE-061 Pembro vs paclitaxel
Oesophageal or OGJ SCC and ADC	**Gastric or OGJ ADC**
Hazard ratio (OS) PD-L1 CPS any: 0.85 (0.72-1.01) PD-L1 CPS ≥ 10: 0.67 (0.50-0.89)	**Hazard ratio (OS)** PD-L1 CPS < 1: 1.20 (0.89-1.63) PD-L1 CPS ≥ 1: 0.82 (0.66-1.03) PD-L1 CPS ≥ 10: 0.64 (0.41-1.02)

Shah M et al, ASCO 2019; Shitara K et al, Lancet 2018

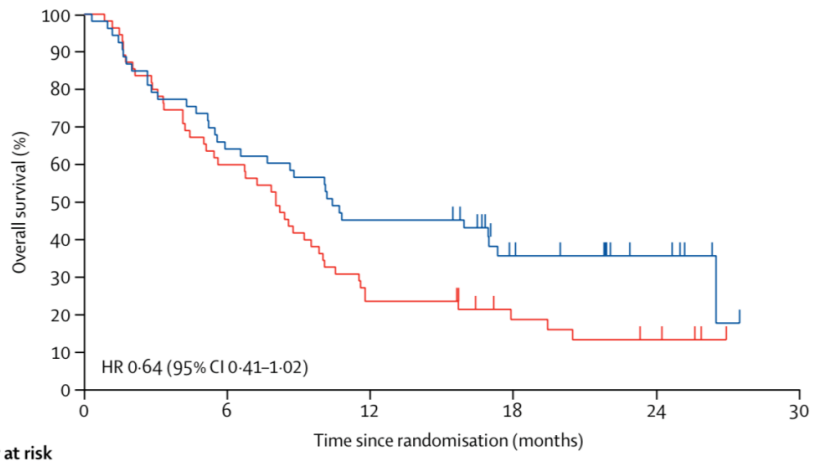
PEMBRO VS PACLITAXEL 2ND LINE GASTRIC/OGJ (KEYNOTE-061)

PD-L1 CPS ≥ 1
No benefit



Number at risk (censored)						
Pembrolizumab	196 (0)	114 (0)	78 (0)	39 (12)	14 (31)	0 (45)
Paclitaxel	199 (0)	130 (0)	54 (0)	23 (8)	7 (17)	0 (24)

PD-L1 CPS ≥ 10
Benefit?



Number at risk (censored)						
Pembrolizumab	53 (0)	34 (0)	24 (0)	13 (7)	6 (14)	0 (19)
Paclitaxel	55 (0)	33 (0)	13 (0)	7 (4)	4 (5)	0 (9)

THIRD LINE ADVANCED OR METASTATIC OESOPHAGO-GASTRIC CANCERS

Nivolumab trials

ATTRACTION-2
Nivo vs placebo

↓

Gastric or OGJ
ADC

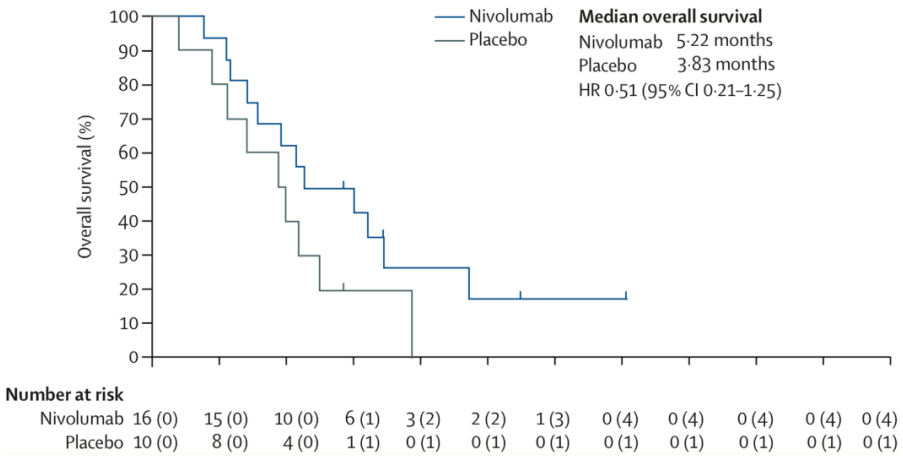
↓

Hazard ratio (OS)
PD-L1 any: 0.63 (0.51-0.78)
PD-L1 < 1%: 0.72 (0.49-1.05)
PD-L1 ≥ 1%: 0.51 (0.21-1.25)

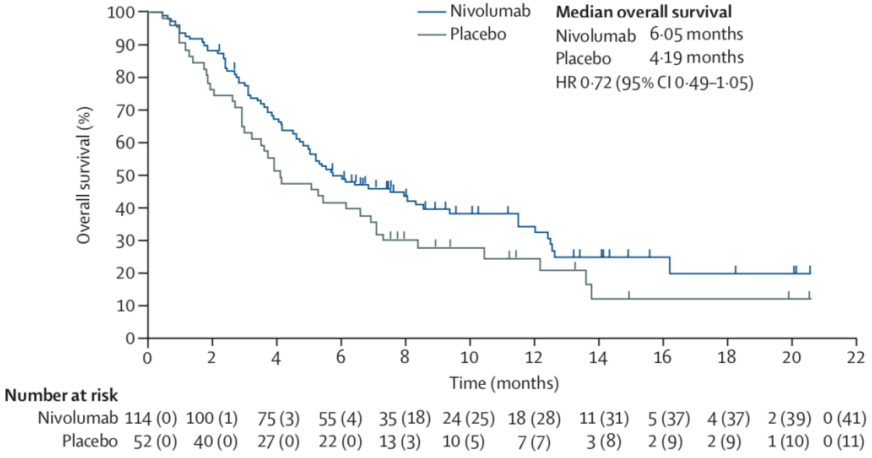
Kang YK et al, Lancet 2017

NIVOLUMAB VS PLACEBO 3RD LINE GASTRIC/OGJ (ATTRACTION-2)

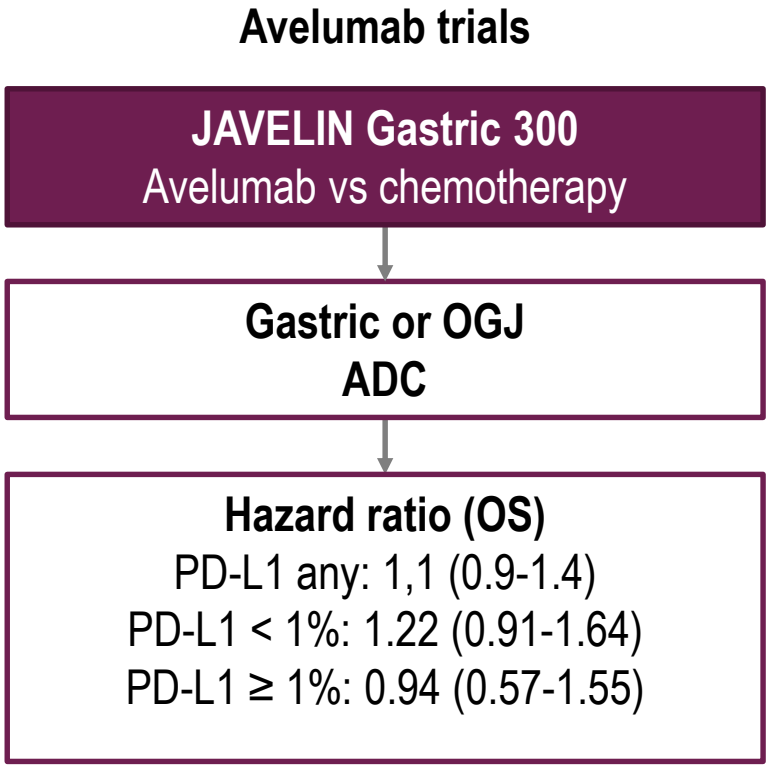
PD-L1 ≥ 1%



PD-L1 < 1%



THIRD LINE ADVANCED OR METASTATIC OESOPHAGO-GASTRIC CANCERS

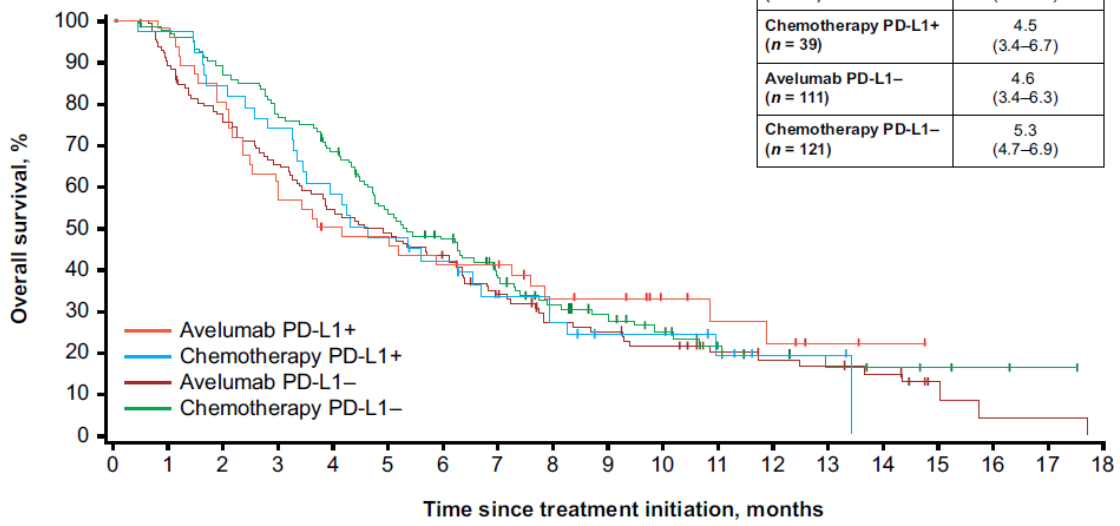


Bang YG et al, Ann Oncol 2018.

AVELUMAB VS CHEMO 3RD LINE GASTRIC/OGJ (JAVELIN GASTRIC 300)

PD-L1 ≥ 1% versus PD-L1 < 1%

	Median OS, months (95% CI)
Avelumab PD-L1+ (*n* = 46)	4.0 (2.5–7.6)
Chemotherapy PD-L1+ (*n* = 39)	4.5 (3.4–6.7)
Avelumab PD-L1– (*n* = 111)	4.6 (3.4–6.3)
Chemotherapy PD-L1– (*n* = 121)	5.3 (4.7–6.9)



Number at risk																			
Avelumab PD-L1+	46	45	37	28	22	21	18	17	12	11	7	5	4	2	1	0	0	0	0
Chemotherapy PD-L1+	39	37	32	28	22	18	15	11	9	6	6	5	2	2	0	0	0	0	0
Avelumab PD-L1–	111	99	84	71	59	53	47	33	24	22	18	13	11	10	8	3	1	1	0
Chemotherapy PD-L1–	121	116	106	92	80	62	53	38	28	23	17	11	7	5	4	3	2	1	0

TRIALS WITH ICI AND PD-L1 SUBGROUPS PRE-TREATED OESOPHAGO-GASTRIC CANCER PATIENTS

Trial	Tumour type	Interventions	Nº of patients	Main outcomes results	Pdl1 stratification Results (HR)*	Pdl1 good predictor of response?
KEYNOTE-061	Advanced/metastatic gastric or gastro-oesophageal adenocarcinoma	1 – Pembrolizumab 2- Paclitaxel	592 (1:1)	mOS (PD-L1 CPS ≥ 1) 1 – 9.1 months 2 - 8.3 months HR 0,82 (0,66-1,03) p=0.0421	PD-L1 CPS ≤ 1: 1,20 (0,89-1,63) PD-L1 CPS ≥ 1: 0,82 (0,66-1,03) PD-L1 CPS ≥ 10: 0,64 (0,41-1,02)	Yes?
KEYNOTE-181	Advanced/metastatic oesophageal or gastro-oesophageal junction squamous cell carcinoma or adenocarcinoma	1 – Pembrolizumab 2- Investigator-choice (Paclitaxel, Docetaxel, or Irinotecan)	628 (1:1)	mOS (PD-L1 CPS ≥ 10) 1 – 9.3 months 2 – 6.7 months HR 0.67, (0,50-0,89), p=0.0029	PD-L1 CPS any: 0,85 (0,72-1,01) PD-L1 CPS ≥ 10: 0,67 (0,50-0,89)	Yes?
ATTRACTION-2	Advanced/metastatic gastric or gastro-oesophageal junction adenocarcinoma	1 – Nivolumab 2 – Placebo	493 (2:1)	mOS (PD-L1 unselected) 1 – 5,26 months 2 - 4.14 months HR 0.63, (0.51-0.78), p<0.0001	PD-L1 ≥ 1%: 0.51 (0.21-1.25) PD-L1 < 1%: 0.72 (0.49-1.05)	See comments
JAVELIN GASTRIC 300	Advanced/metastatic gastric or gastro-oesophageal junction adenocarcinoma	1 – Avelumab 2- Investigator-choice (Paclitaxel, Irinotecan, or Best supportive care)	371 (1:1)	mOS (PD-L1 unselected) 1 – 4,6 months 2 – 5,0 months HR 1,1 (0.9-1.4), p=0.81	PD-L1 ≥ 1%: 0.94 (0.57-1.55) PD-L1 < 1%: 1.22 (0.91-1.64)	See comments

OESOPHAGO-GASTRIC CANCER AND PD-L1 EXPRESSION

Implication for clinical practice and research

Main findings or subgroup analyses of all randomised phase III trials completed so far (KEYNOTE-061, KEYNOTE-062, KEYNOTE-181, ATTRACTION-2 and JAVELIN Gastro 300) suggest some consistent association between PD-L1 expression and increased benefit from immune checkpoint inhibitors.

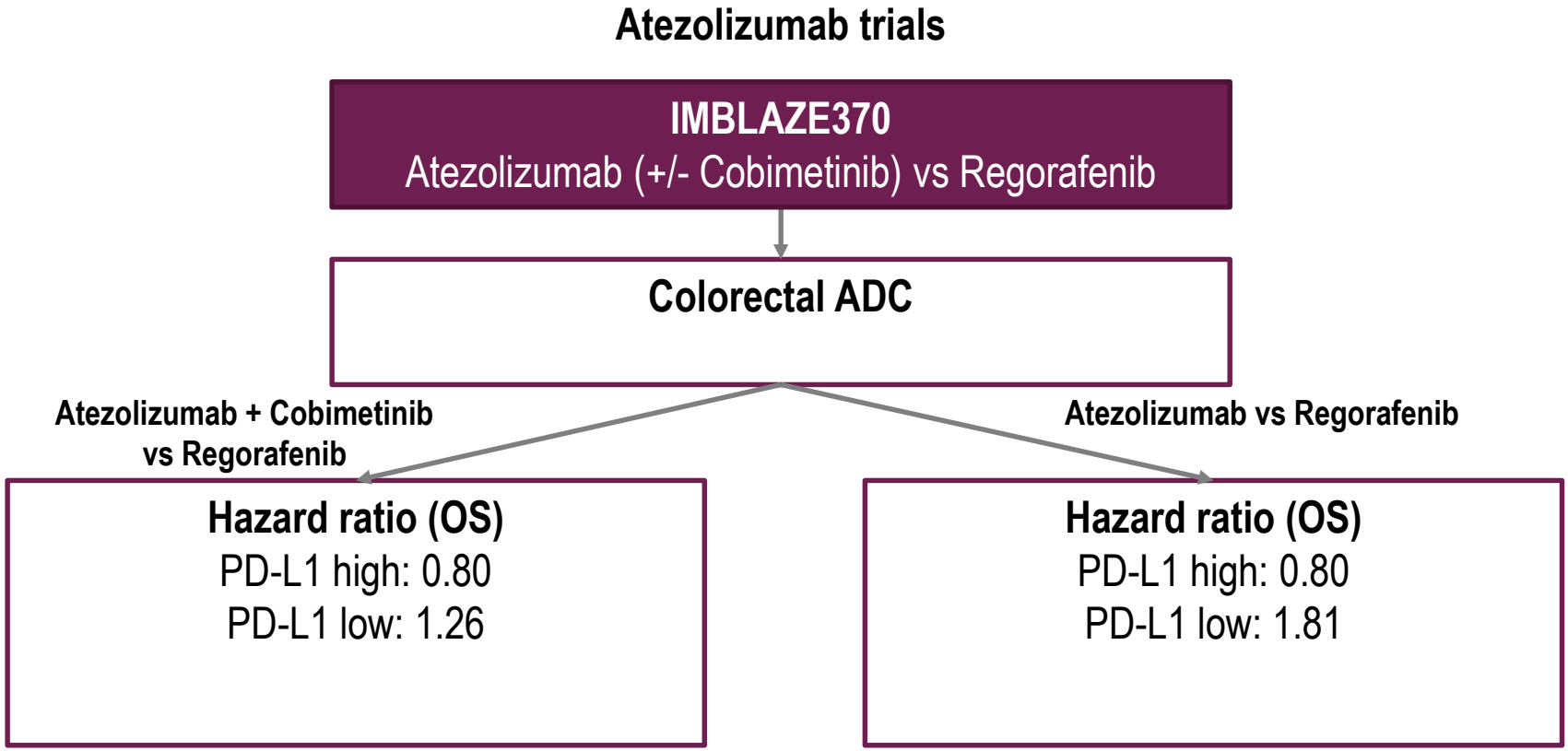
Heterogeneity, however, exists between these trials in terms of assay for PD-L1 expression, PD-L1 scoring system, definition of PD-L1 positivity, timing of PD-L1 testing (retrospective vs prospective). Furthermore the small numbers of subgroup analyses and the lack of interaction tests do not allow drawing final conclusions.

Important questions to be answered

- Which are the optimal PD-L1 scoring system and cut-off value for PD-L1 positivity?
- What is the impact of the site/timing of PD-L1 testing on PD-L1 status and its prediction of treatment benefit?
- What is, if any, the added value of PD-L1 testing in patients with MSI-H tumours or tumours with high TMB?
- Does the potential predictive power of PD-L1 expression change if immune checkpoint inhibitors are given in combination with chemotherapy or other agents?
- What are the most appropriate outcome measures/endpoints to assess the clinical benefit from immune checkpoint inhibitors?

PREVIOUSLY TREATED COLORECTAL CANCER

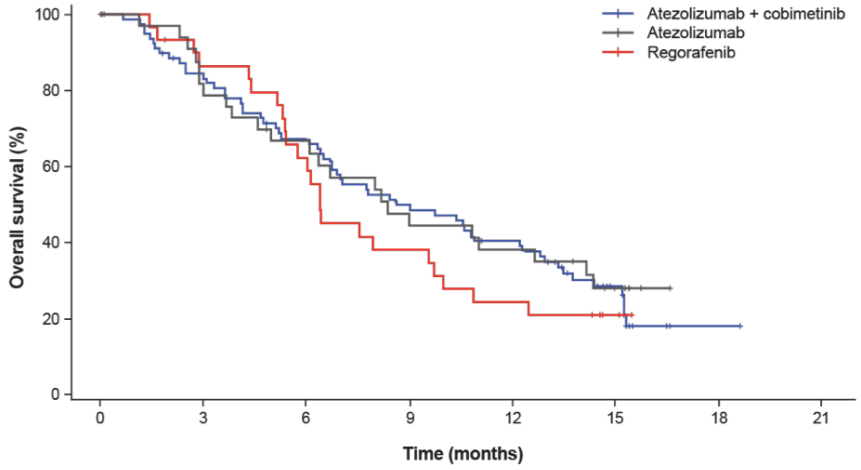
THIRD LINE ADVANCED OR METASTATIC COLORECTAL CANCER



Eng C et al, Lancet Oncol 2019. HR = Hazard ratio. Score for PD-L1 expression unknown.

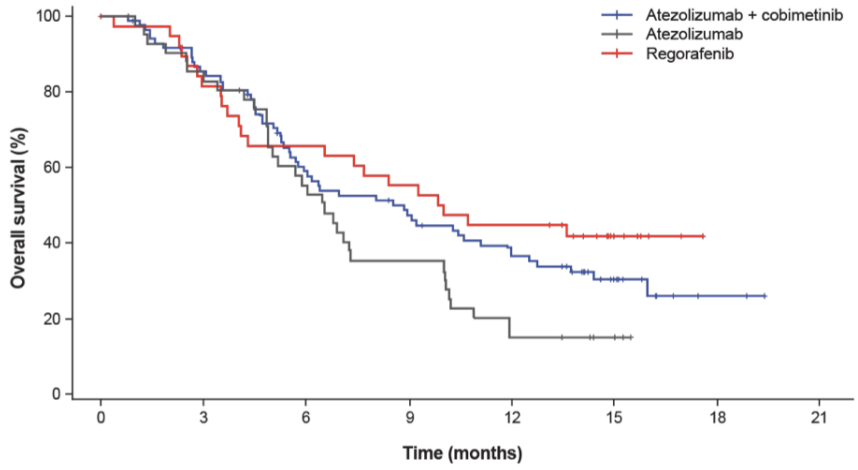
ATEZOLIZUMAB +/- COBIMETINIB VS REGORAFENIB ≥ 3RD LINE - IMBLAZE370

Atezolizumab +/- Cobimetinib vs Regorafenib in PD-L1 high



Number at risk							
Atezolizumab + cobimetinib	79	64	50	37	29	12	1
Atezolizumab	35	27	21	15	12	6	
Regorafenib	31	25	18	11	7	2	

Atezolizumab +/- Cobimetinib vs Regorafenib in PD-L1 low



ber at risk							
cobimetinib	84	69	46	36	27	12	2
ezolizumab	42	35	22	14	6	3	
legorafenib	40	31	25	21	17	7	

TRIALS WITH ICI AND PD-L1 SUBGROUPS

Pre-treated colorectal cancer patients

Trial	Tumour type	Interventions	Nº of patients	Main outcomes results	PdI1 stratification Results (HR)*	PDL1 good predictor of response?
IMblaze370	Advanced/metastatic colorectal adenocarcinoma	1 – Atezolizumab + cobimetinib 2- Atezolizumab 3 - Regorafenib	363 (2:1:1)	mOS (PD-L1 any) 1 – 8.87 months 2 – 7.10 months 3 – 8.51 months HR (1 vs 3): 1,00 (0,73-1,38) p=0.99 HR (2 vs 3): 1,19 (0,83-1,71) p=0.34	1 vs 3 PD-L1 < 1%: 1,26 PD-L1 ≥ 1%: 0,80 2 vs 3 PD-L1 < 1%: 1,81 PD-L1 ≥ 1%: 0,80	Yes?

COLORECTAL CANCER AND PD-L1 EXPRESSION

Implication for clinical practice and research

The impact of PD-L1 expression on the clinical benefit from immune checkpoint inhibitors in colorectal cancer is difficult to assess.

Only one randomised phase III study has been completed so far (IMblaze370) and the results appear to suggest a possible association between PD-L1 expression and increased benefit from immune checkpoint inhibitors.

Important questions to be answered

- Can PD-L1 (high) expression identify a subgroup of MSS colorectal cancer patients who might be sensitive to immune checkpoint inhibitors? More data are needed
- Is PD-L1 testing of any value in patients with MSI-H tumours or tumours with high TMB?
- Which are the optimal PD-L1 scoring system and cut-off value for PD-L1 positivity?
- What is the impact of the site/timing of PD-L1 testing on PD-L1 status and its prediction of treatment benefit?

FINAL CONCLUSIONS

Implication for clinical practice and research

Although not a perfect biomarker, there is a trend for increased benefit with ICIs on enriched PDL1 solid tumours

But on Combination ICI + chemo pdl1 expression seems to be less relevant

There are still many uncertainties on the real value of PDL1 for clinical practice with ICIs in solid tumours

Important questions to be answered

- Why PDL1 expression has a high value in some studies and low in others?
- More data on cut-off value for PDL1 expression and how it changes over time?
- Combine PDL1 expression with other biomarkers (eg. TMB; specific neo-antigens, etc)?
- To identify best strategies with ICIs in low/negative PDL1 tumours?
- Are ICIs alone a better strategy for enriched PDL1 subgroups and combo ICI+chemo better on lower/negative PDL1 expression subgroups?

THANK YOU!

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