Understanding the Rationale for Combining IO Agents

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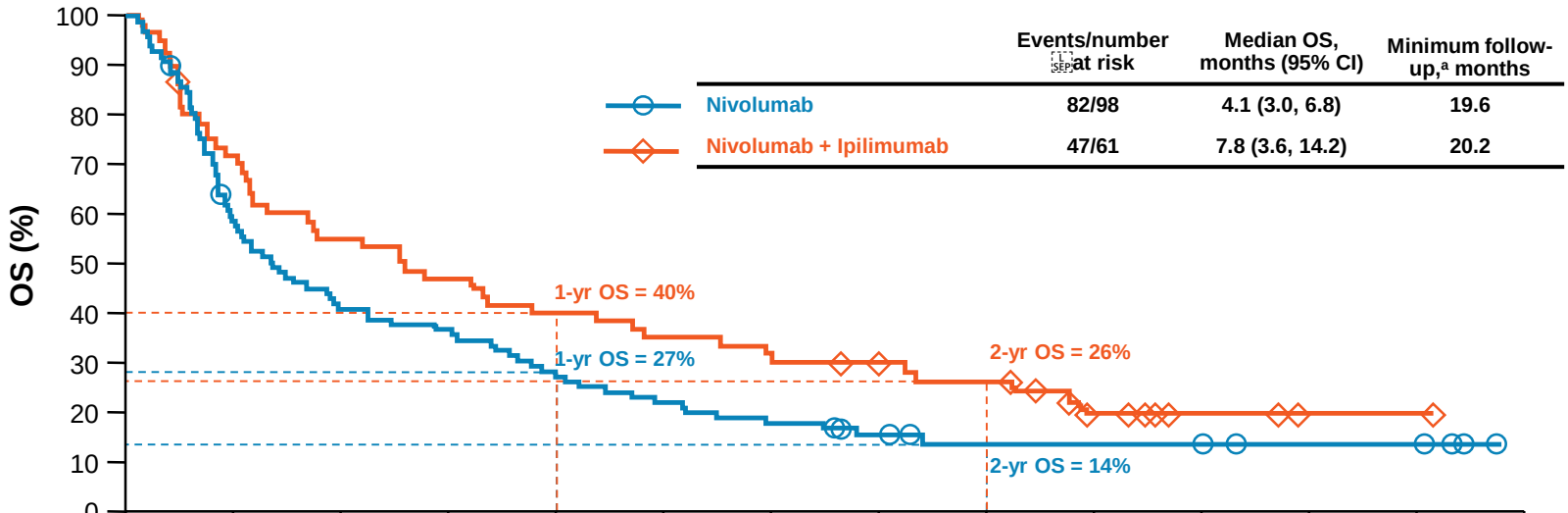
CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC
OS – Non-Randomized Cohort



	Events/number at risk	Median OS, months (95% CI)	Minimum follow-up,[a] months
Nivolumab	82/98	4.1 (3.0, 6.8)	19.6
Nivolumab + Ipilimumab	47/61	7.8 (3.6, 14.2)	20.2

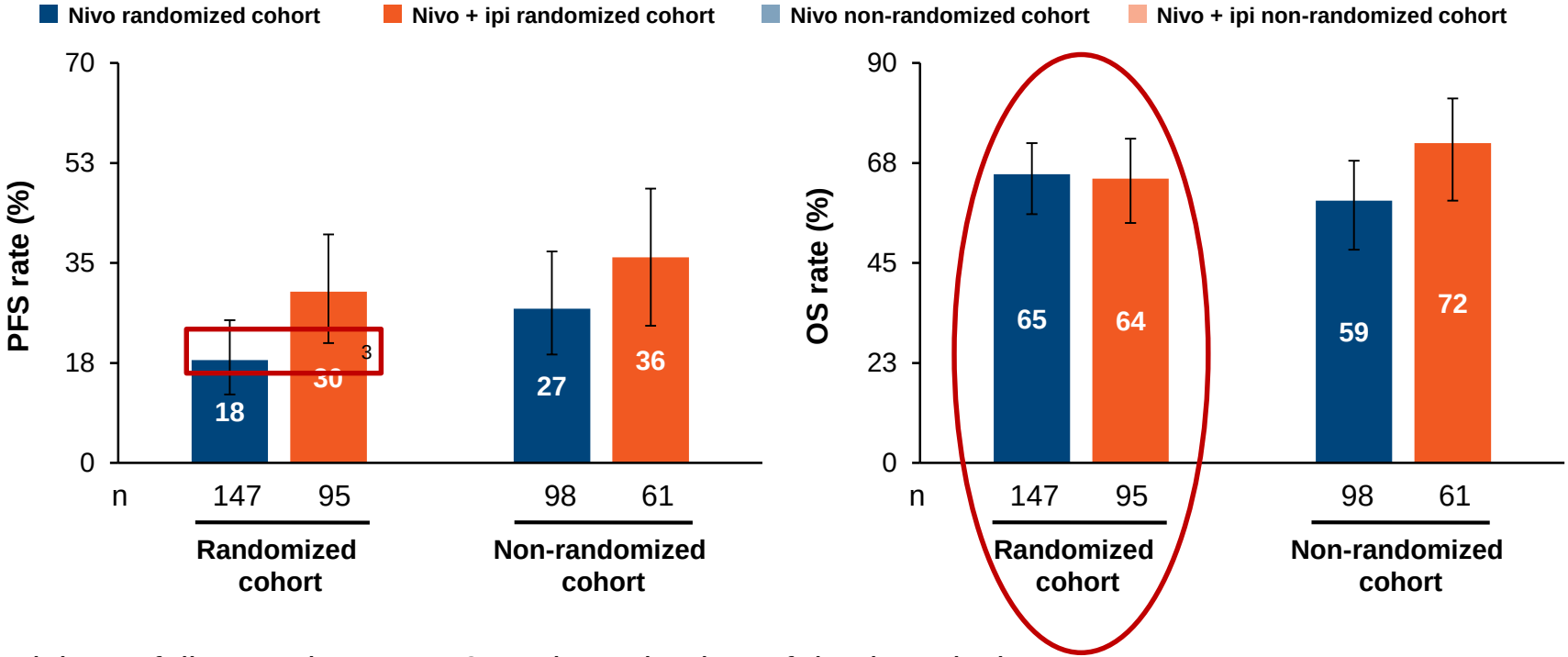
Number of patients at risk

Nivolumab	98	56	39	35	26	21	17	12	7	7	6	4	4	0
Nivolumab + Ipilimumab	61	43	33	28	24	21	19	16	14	7	3	1	1	0

[a]Between first dose and database lock; follow-up shorter for patients who died

Hellman MD et al. ASCO 2017

CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC
3-month PFS[a] and OS Rates

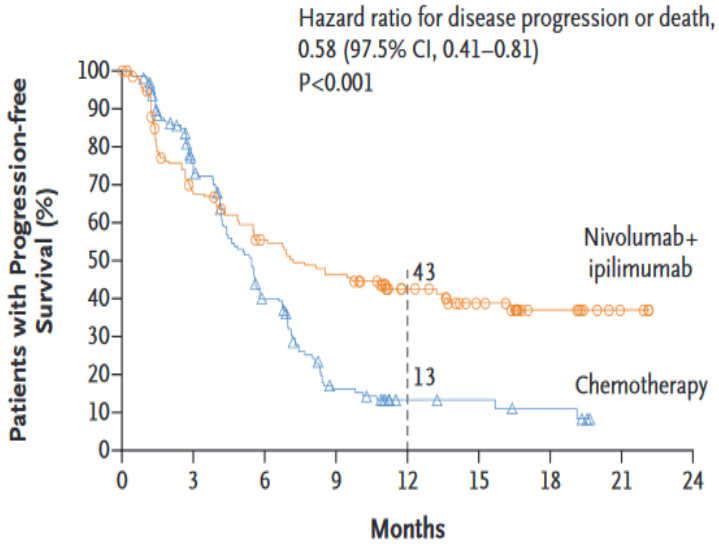


- Minimum follow-up time was 12 weeks at the time of database lock

Error bars indicate 95% CIs; [a]Per BICR; PFS = progression-free survival

Hellman MD et al. ASCO 2017

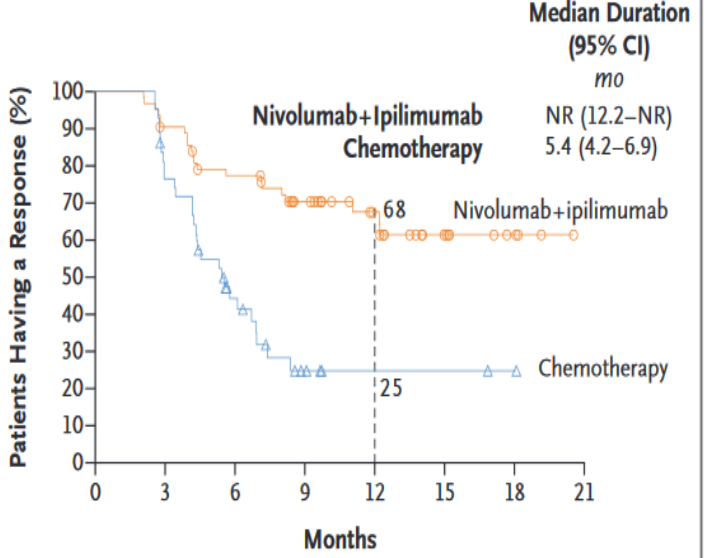
A Progression-free Survival



No. at Risk

Nivolumab + ipilimumab	139	85	66	55	36	24	11	3	0
Chemotherapy	160	103	51	17	7	6	4	0	0

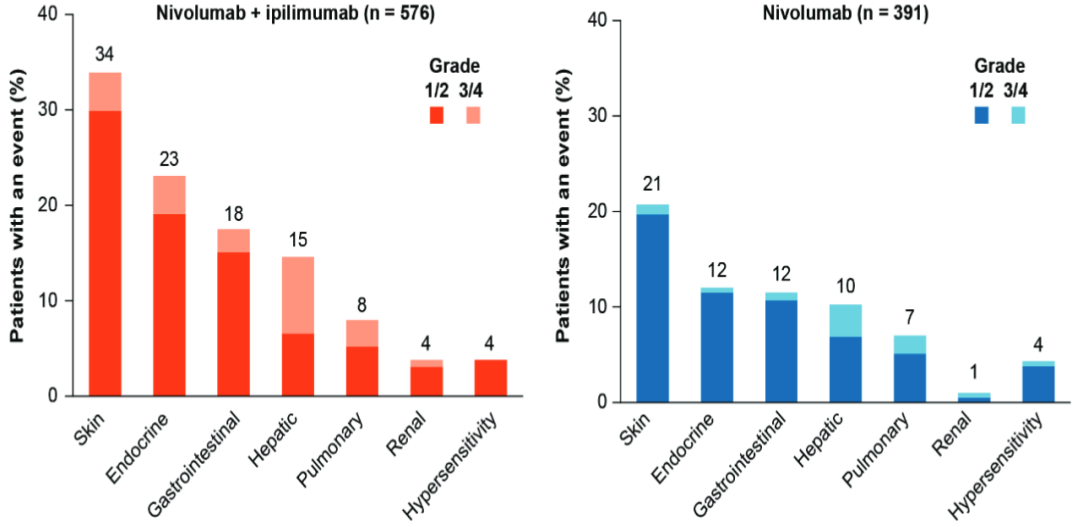
B Duration of Response



No. at Risk

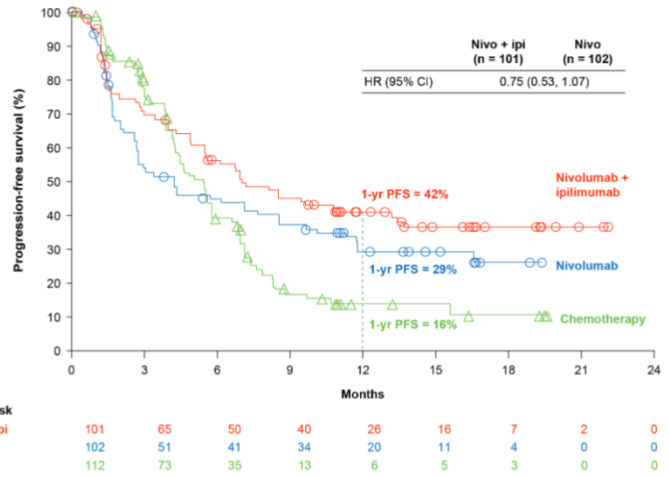
Nivolumab + ipilimumab	63	56	46	32	22	10	5	0
Chemotherapy	43	32	15	5	2	2	1	0

Figure S7. Treatment-Related Select Adverse Events[a] by Category With Nivolumab Plus Ipilimumab



[a]Select adverse events are those with potential immunologic etiology that require frequent monitoring/intervention

Figure S6. Progression-free Survival With Nivolumab Plus Ipilimumab Versus Nivolumab Monotherapy and Chemotherapy[a] in Patients With TMB ≥10 Mutations/Mb and ≥1% Tumor PD-L1 Expression



[a]HR (95% CI) = 0.62 (0.44, 0.88) for nivolumab + ipilimumab versus chemotherapy

CheckMate 012: Study Design (A-D)

Key eligibility criteria
- Stage IIIB or IV NSCLC
- Chemotherapy-naïve
- Prior *EGFR* TKI therapy allowed in patients with *EGFR* mutations

N = 56

→ Nivolumab 5 or 10 mg/kg IV Q3W
+
Histology-based platinum-doublet chemotherapy (four 21-day cycles)[a]

→ Continue nivolumab monotherapy until disease progression or unacceptable toxicity[b]

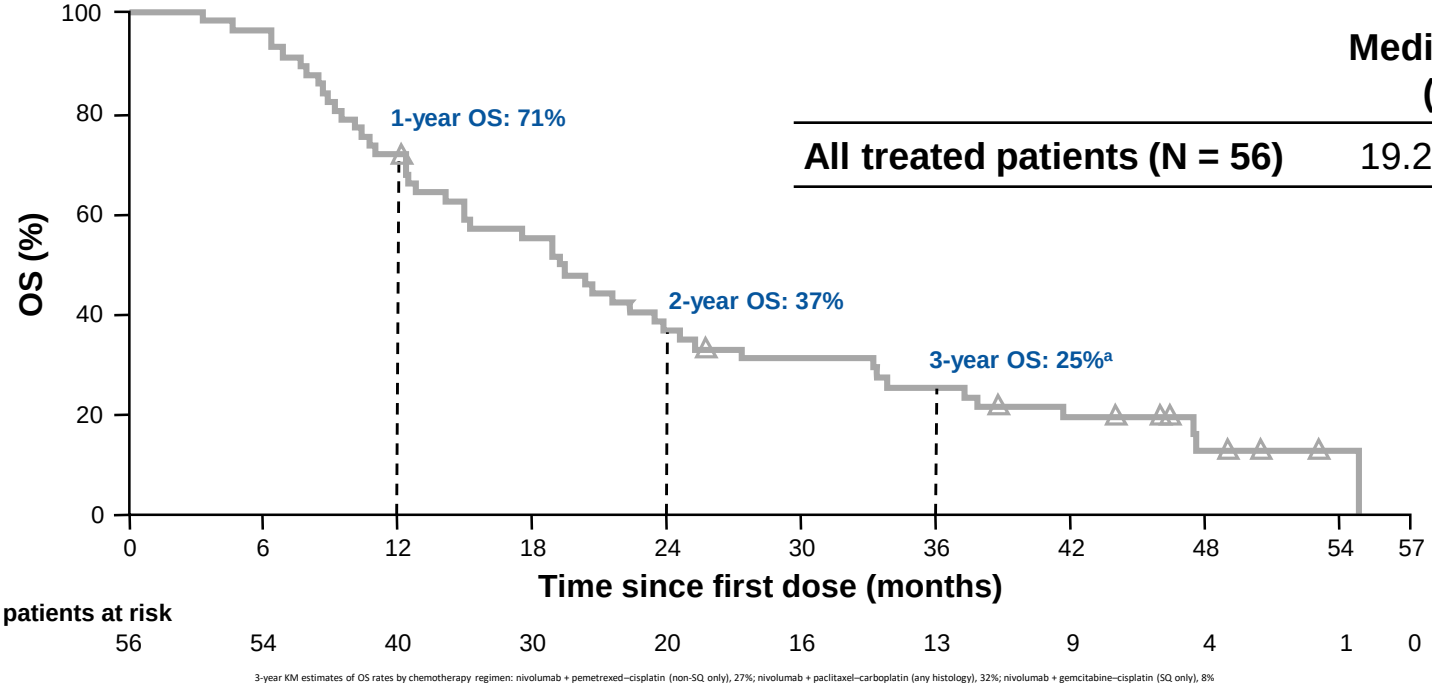
Primary objective: safety and tolerability
Secondary objectives: ORR and PFS rate at 24 weeks
Exploratory objective: OS

- Results based on a minimum survival follow-up of ~27 months were previously reported[1,c]
- This update is based on a minimum survival follow-up of ~45 months[d]

[a]Includes 15 patients treated with nivolumab 10 mg/kg + pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 on day 1 of each cycle, 15 patients treated with nivolumab 10 mg/kg + paclitaxel 200 mg/m^2 and carboplatin (AUC 6) on day 1 of each cycle, 14 patients treated with nivolumab 5 mg/kg + paclitaxel 200 mg/m^2 and carboplatin (AUC 6) on day 1 of each cycle, and 12 patients treated with nivolumab 10 mg/kg + gemcitabine 1250 mg/m^2 (days 1 and 8 of each cycle) and cisplatin 75 mg/m^2 (day 1 of each cycle); [b]Pemetrexed maintenance was not allowed; [c]March 2015 database lock for OS; September 2014 database lock for other endpoints; [d]September 2016 database lock.

AUC = area under the curve; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

CheckMate-012: 3 Year Estimate of OS

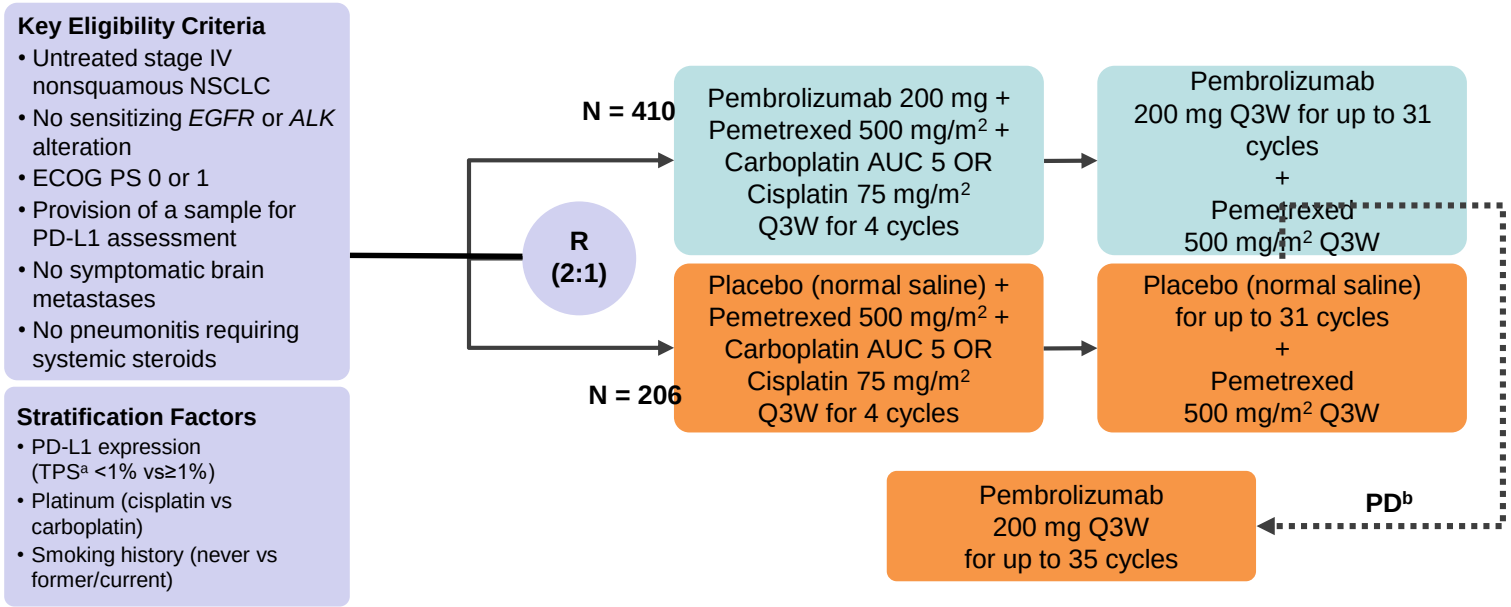


	Median OS, mo (95% CI)
All treated patients (N = 56)	19.2 (14.1, 23.8)

3-year KM estimates of OS rates by chemotherapy regimen: nivolumab + pemetrexed–cisplatin (non-SQ only), 27%; nivolumab + paclitaxel–carboplatin (any histology), 32%; nivolumab + gemcitabine–cisplatin (SQ only), 8%

[a]Between 2 and 3 years, there were 6 deaths due to disease and 1 patient was censored due to loss to follow-up; KM = Kaplan–Meier

KEYNOTE-189: Study Design



[a]Percentage of tumor cells with membranous PD-L1 staining assessed using PD-L1 IHC 22C3 pharmaDX assay. [a]Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.

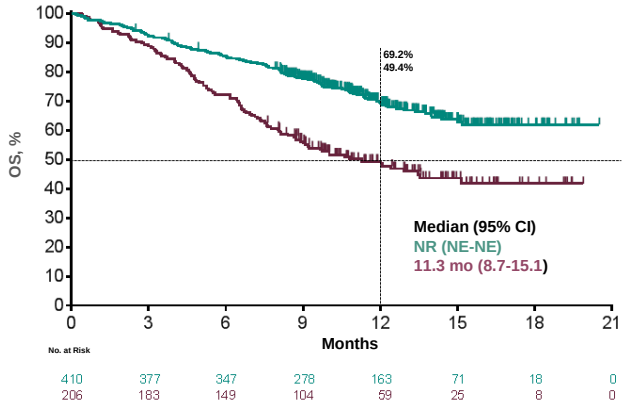
AUC, area under the plasma drug concentration-time curve; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD, progressive disease; TPS, tumor proportion score; Q3W, every 3 weeks

Gandhi L, et al. AACR 2018, Abstract CT075.

WCLC 2018

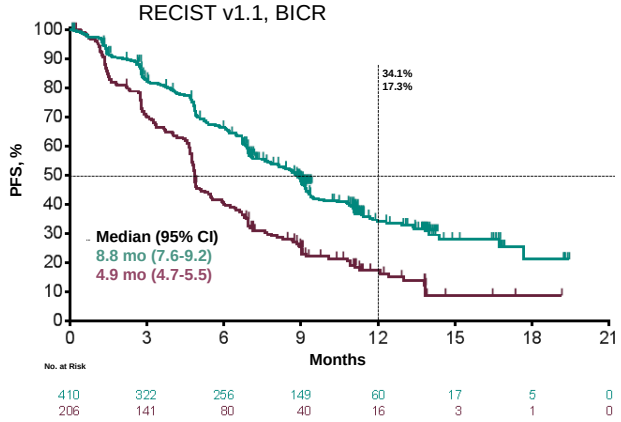
KEYNOTE-189: OS and PFS

Overall Survival



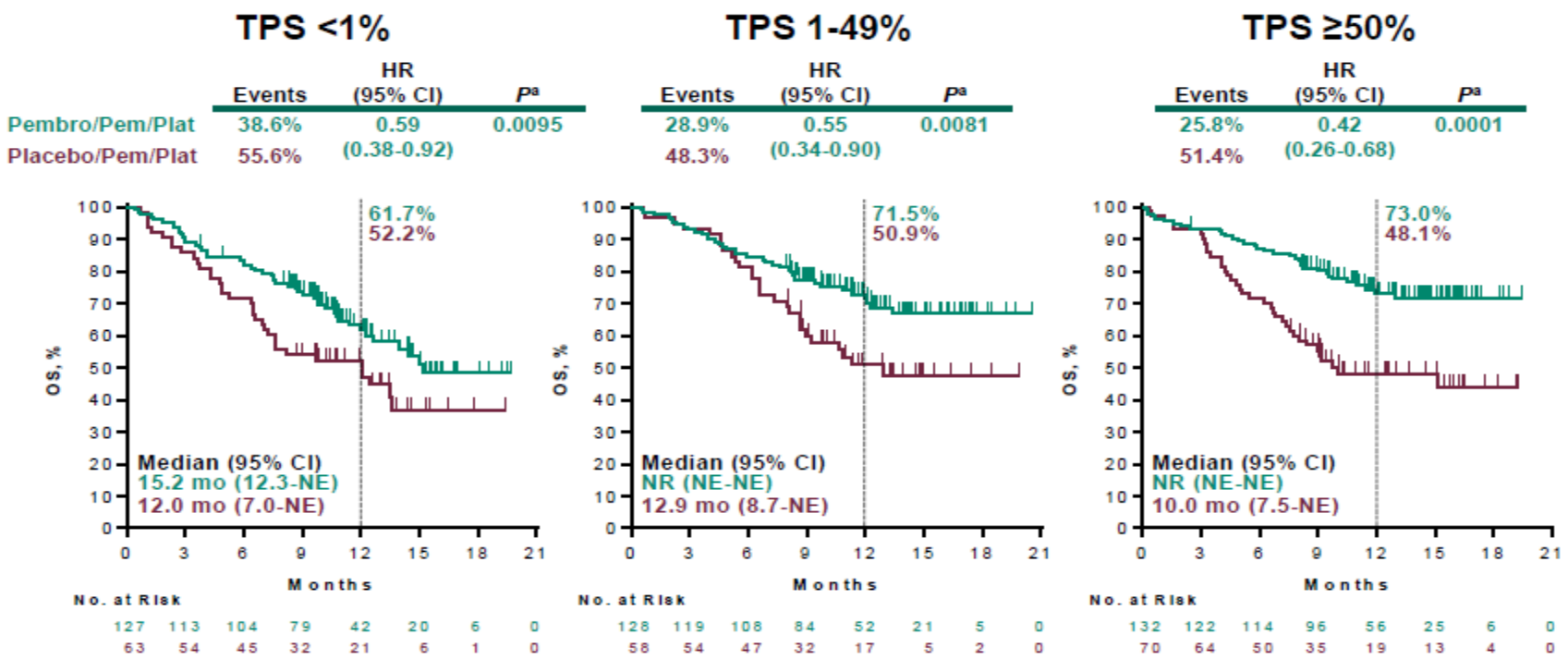
	Events	HR (95% CI)	*P*
Pembro/Pem/Plat	31.0%	0.49 (0.38-0.64)	<0.00001
Pembro/Pem/Plat	52.4%		

Progression-free Survival

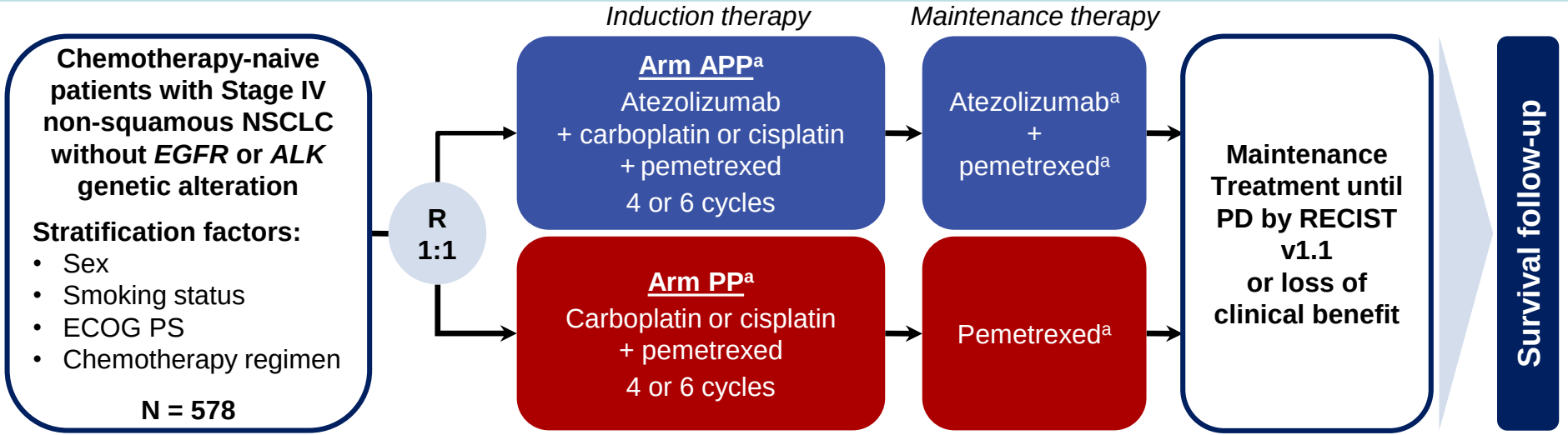


	Events	HR (95% CI)	*P*
Pembro/Pem/Plat	59.5%	0.52 (0.43-0.64)	<0.00001
Pembro/Pem/Plat	80.6%		

KEYNOTE-189: OS by PD-L1 status



IMpower 132: Study Design

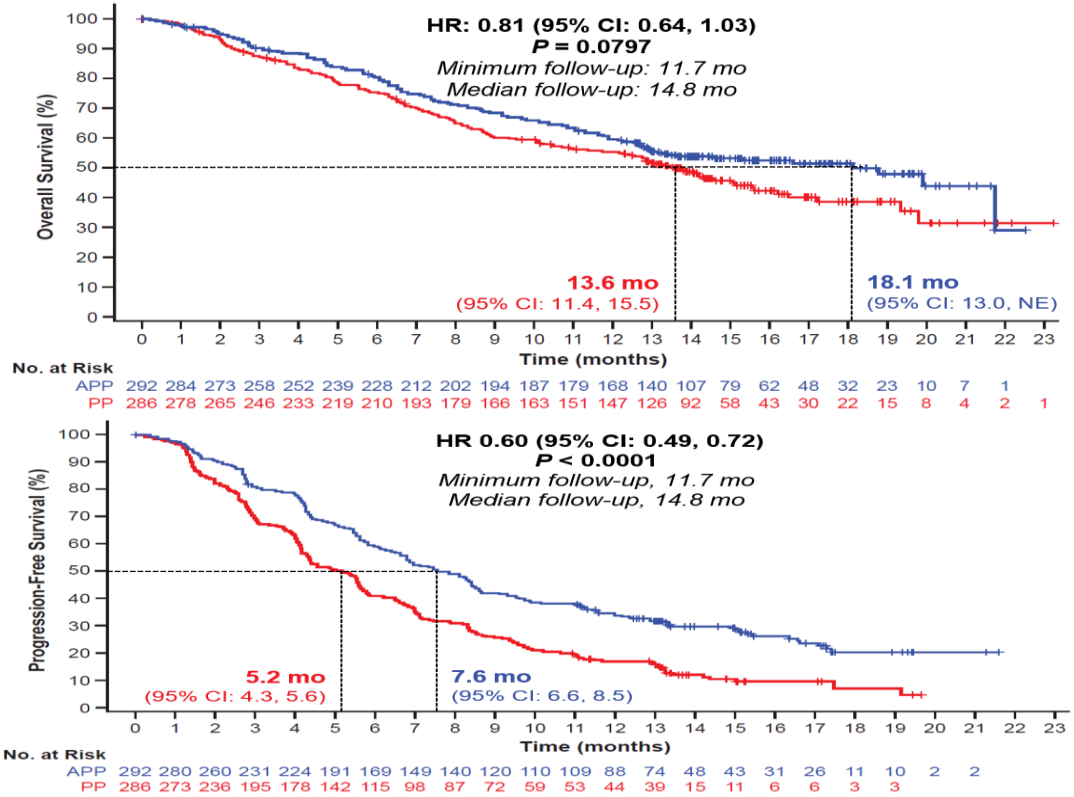


- Co-primary endpoints: INV-assessed PFS and OS
- Secondary endpoints: INV-assessed ORR and DOR, PRO and safety measures
- Exploratory analyses: clinical and biomarker subgroup analyses

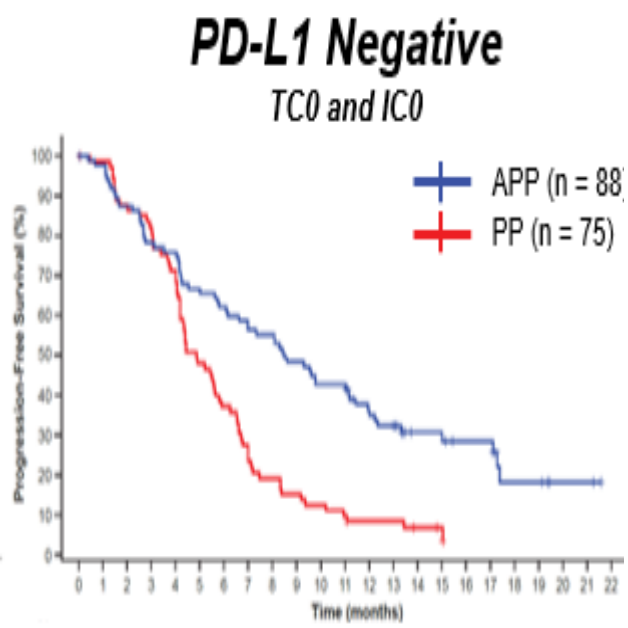
  Biomarker-evaluable tissue not mandatory for enrolment (was available from 60% of patients)

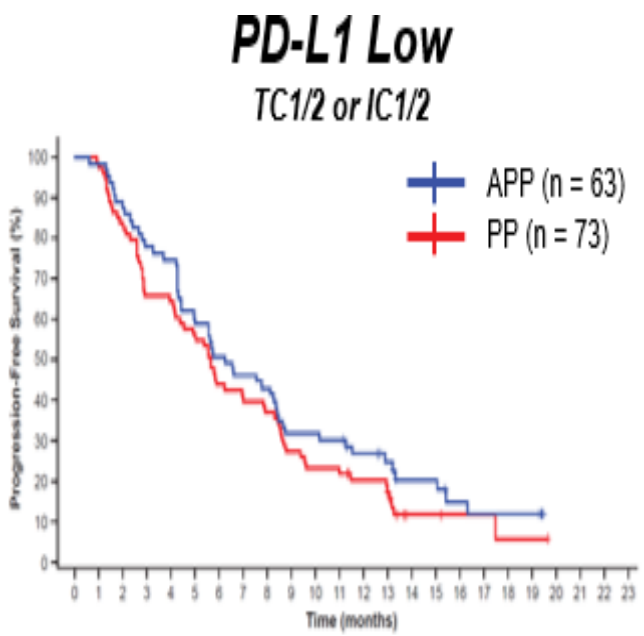
DOR, duration of response; INV, investigator; R, randomization; ORR, objective response rate; OS, overall survival; PD, progressive disease, PFS, progression-free survival; PRO, patient-reported outcomes. [a] Atezolizumab: 1200 mg IV q3w; Carboplatin: AUC 6 mg/mL/min IV q3w; Cisplatin: 75 mg/m^2 IV q3w; Pemetrexed: 500 mg/m^2 IV q3w. NCT02657434. Data cutoff: May 22, 2018

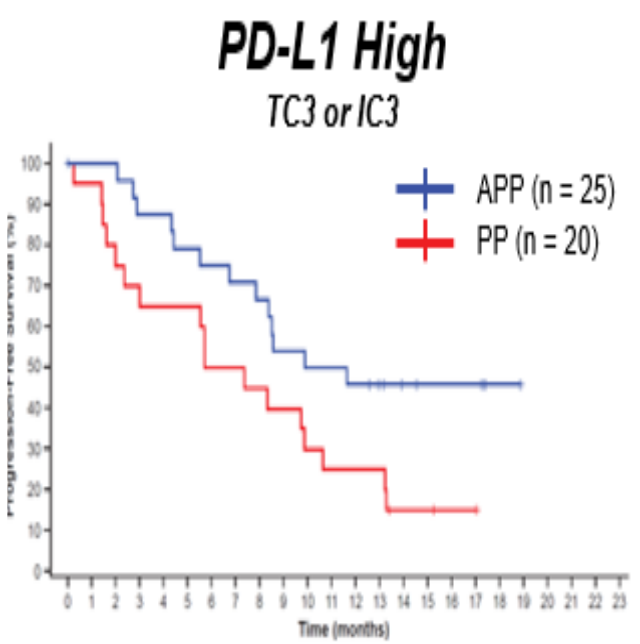
IMpower 132: OS (interim) and PFS



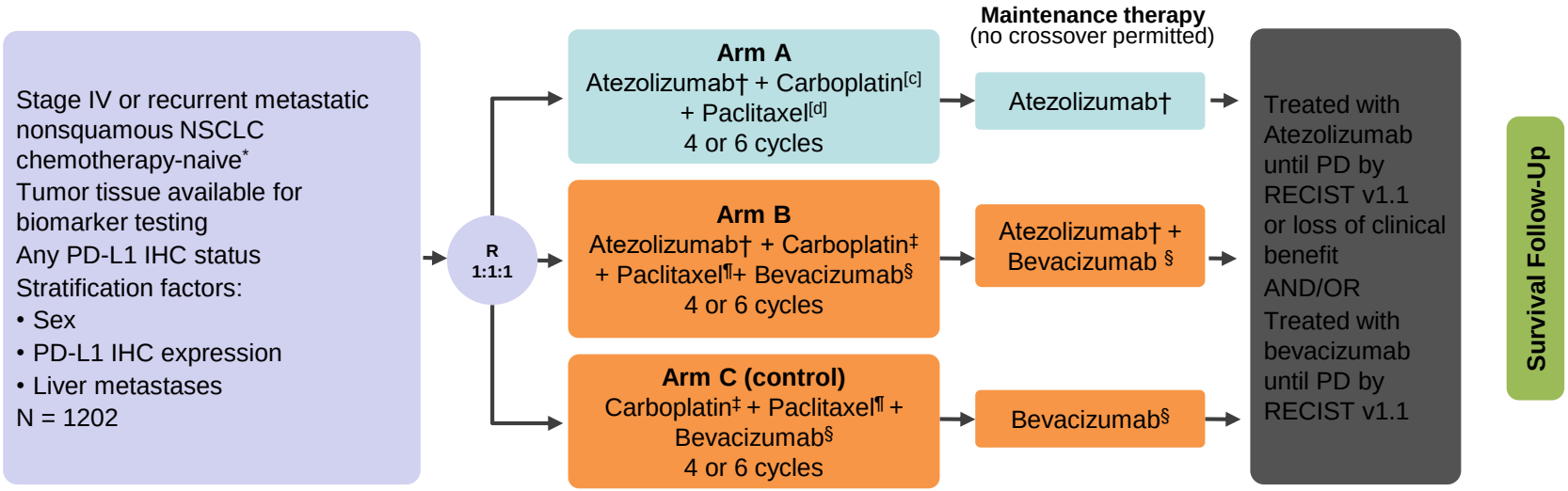
IMpower 132: PFS by PD-L1 status







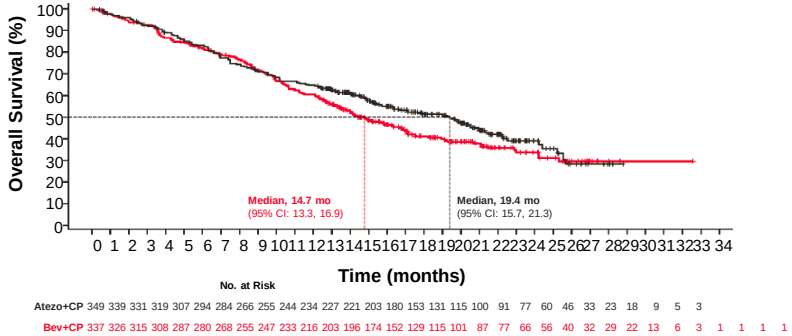
IMpower 150: Study Design



The principal question is to assess whether the addition of Atezolizumab to Arm C provides clinical benefit

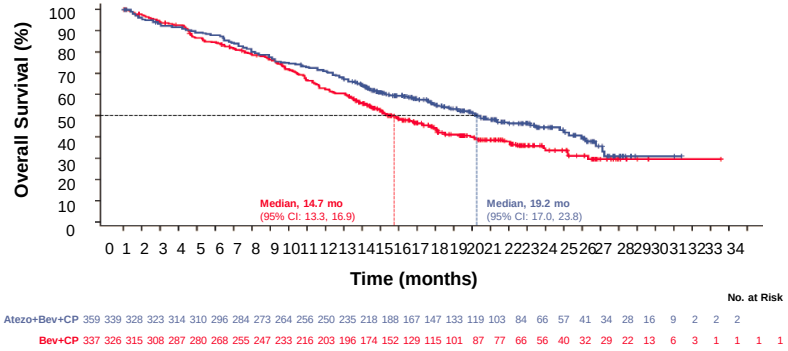
*Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. †Atezolizumab: 1200 mg IV every 3 weeks. ‡Carboplatin: AUC 6 IV every 3 weeks. ¶Paclitaxel: 200 mg/m^2 IV every 3 weeks. §Bevacizumab: 15 mg/kg IV every 3 weeks.
IHC, immunohistochemistry; PD, progressive disease; RECIST, Response Evaluation Criteria In Solid Tumors

IMpower 150: OS in WT population



Landmark OS, %	ARM A: atezo + CP	ARM C: bev + CP
12-month	65%	61%
18-month	51%	41%
24-month	39%	34%

HR[a], 088
(95% CI: 0.72, 1.08
P = 0.2041
Median follow-up: ~20 mo



Landmark OS, %	ARM B: atezo + bev + CP	ARM C: bev + CP
12-month	67%	61%
18-month	53%	41%
24-month	43%	34%

HR[a], 0.78
(95% CI: 0.64, 0.96
P = 0.0164
Median follow-up: ~ 20 mo

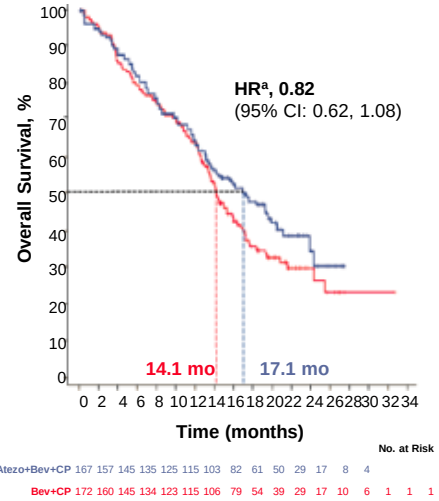
Atezo, Atezolizumab; Bev, Bevacizumab; CP, Carboplatin+ Paclitaxel; WT, wild type

Socinski M et al. ASCO Annual Meeting 2018, Abstract 9002;
Socinski M et al. N Engl J Med. 2018 ;378(24):2288-2301

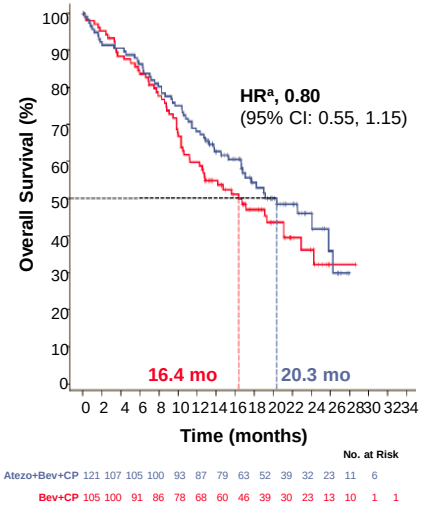
WCLC 2018

IMpower 150: OS by PD-L1 status

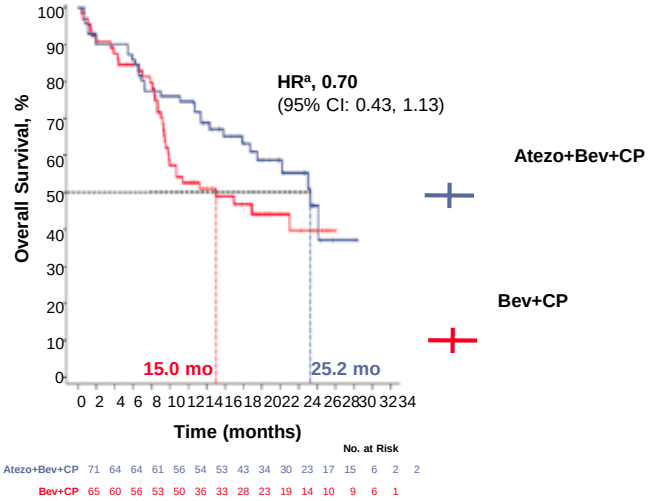
PD-L1-Negative
TC0 and IC0



PD-L1-Low
TC1/2 or IC1/2



PD-L1-High
TC3 or IC3

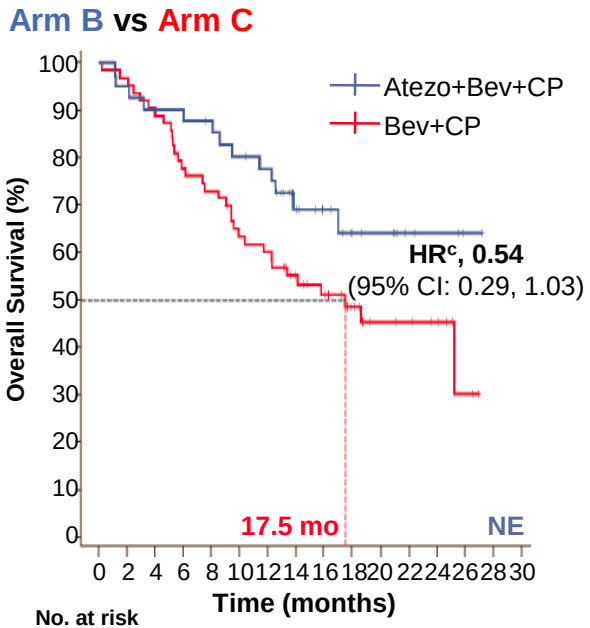


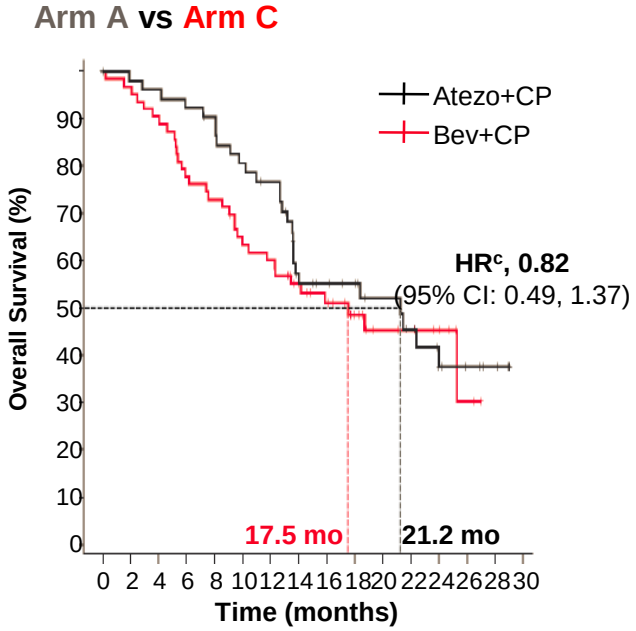
Atezo, Atezolizumab; Bev, Bevacizumab; CP, Carboplatin+ Paclitaxel; TC, tumour cell; IC, immune cell

Socinski M et al. ASCO Annual Meeting 2018, Abstract 9002;
Socinski M et al. N Engl J Med. 2018 ;378(24):2288-2301

WCLC 2018

IMpower 150: EGFR/ALK mutations





Atezo, Atezolizumab; Bev, Bevacizumab; CP, Carboplatin+ Paclitaxel.

Socinski M et al. ASCO Annual Meeting 2018, Abstract 9002;
Socinski M et al. N Engl J Med. 2018 ;378(24):2288-2301

WCLC 2018

KEYNOTE-407: Study Design

Key Eligibility Criteria

- Untreated stage IV NSCLC with squamous histology
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

Stratification Factors

- PD-L1 expression (TPS[a] <1% vs ≥1%)
- Choice of taxane (paclitaxel vs nab-paclitaxel)
- Geographic region (east Asia vs rest of world)

R (1:1)

Pembrolizumab 200 mg Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m^2 Q3W OR nab-Paclitaxel 100 mg/m^2 Q1W for 4 cycles (each 3 wk)

→ Pembrolizumab 200 mg Q3W for up to 31 cycles

Placebo (normal saline) Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m^2 Q3W OR nab-Paclitaxel 100 mg/m^2 Q1W for 4 cycles (each 3 wk)

→ Placebo (normal saline) Q3W for up to 31 cycles

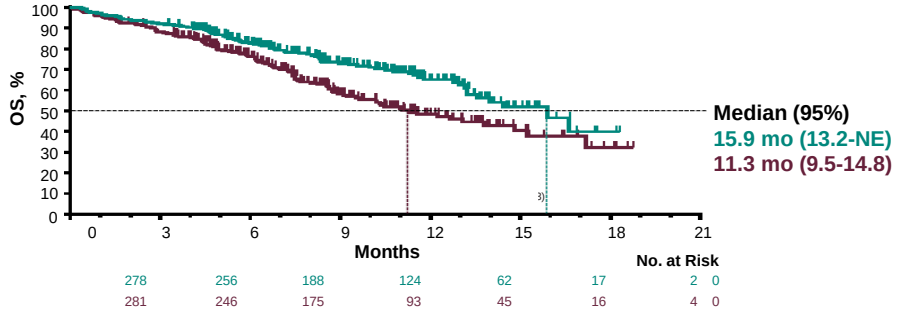
PD[b] → Optional Crossover[b] Pembrolizumab 200 mg Q3W for up to 35 cycles

End points:
Primary: PFS (RECIST v1.1, BICR) and OS
Secondary: ORR and DOR (RECIST v1.1, BICR), safety

BICR, blinded independent central radiologic review. [a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay.
[b]Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.

KEYNOTE-407: OS (interim) and PFS

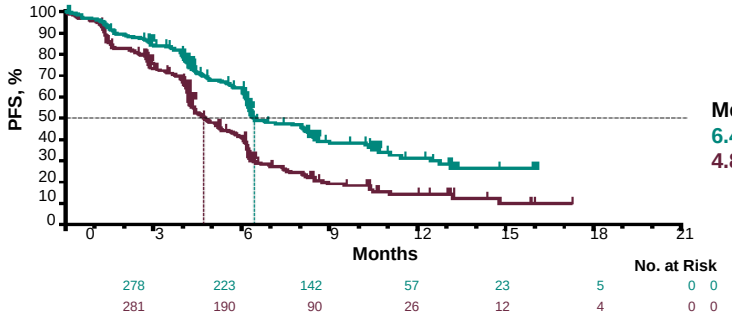
Overall Survival



Median (95%)
15.9 mo (13.2-NE)
11.3 mo (9.5-14.8)

	Events	HR (95% CI)	*P*
Pembro + Chemo	30.6%	0.64 (0.49-0.85)	0.0008
Placebo + Chemo	42.7%		

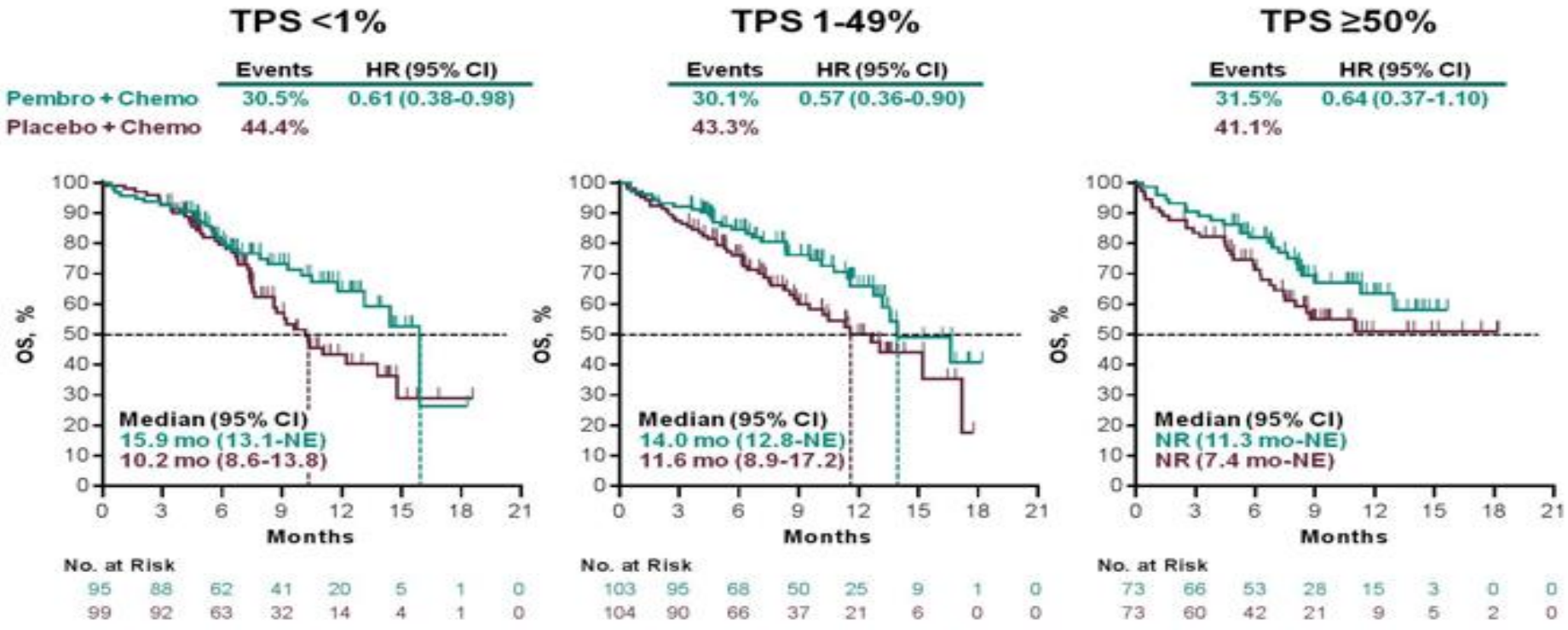
Progression-free Survival



Median (95% CI)
6.4 mo (6.2-8.3)
4.8 mo (4.3-5.7)

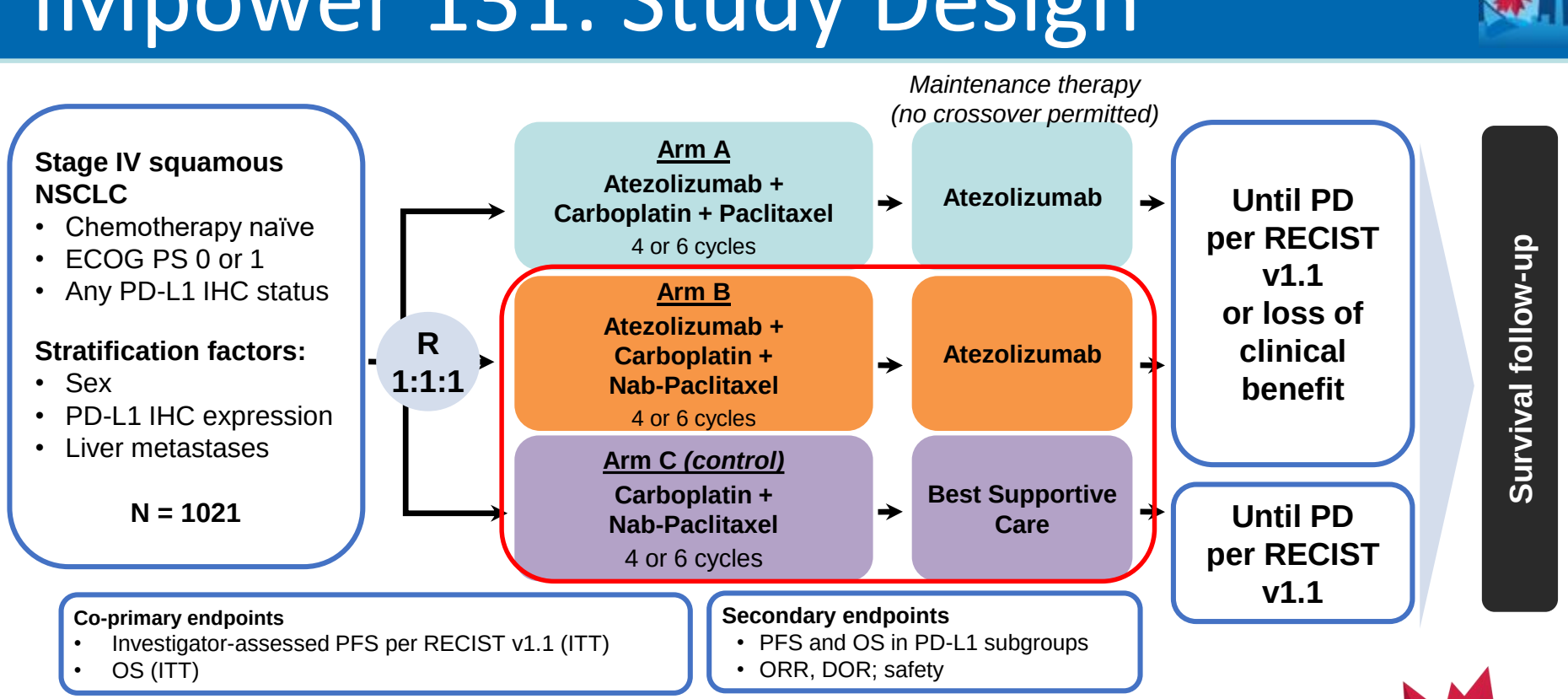
	Events	HR (95% CI)	*P*
Pembro + Chemo	54.7%	0.56 (0.45-0.70)	<0.0001
Placebo + Chemo	70.1%		

KEYNOTE-407: OS by PD-L1 status



Paz-Ares L, et al. ASCO 2018. Abstract 105.

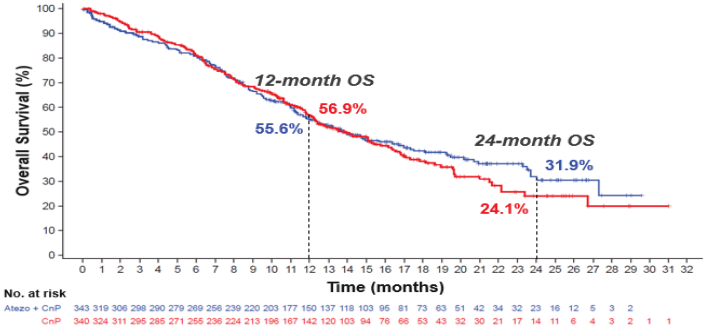
IMpower 131: Study Design



Atezolizumab 1200 mg IV q3w; carboplatin AUC 6 IV q3w; nab-paclitaxel 100 mg/m^2 IV qw; paclitaxel 200 mg/m^2 IV q3w.
[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance to treatment with ≥ 1 approved targeted therapies. Testing for *EGFR* mutation or *ALK* translocation was not mandatory.[b] PD-L1 expression was evaluated using the VENTANA SP142 IHC assay.

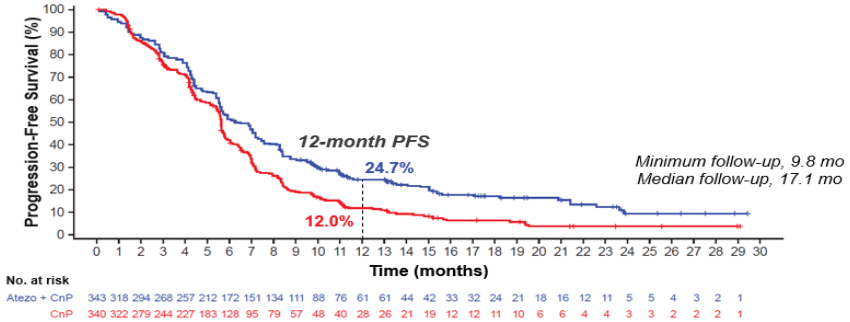
IMpower 131: OS (interim) and PFS

Overall Survival (interim)



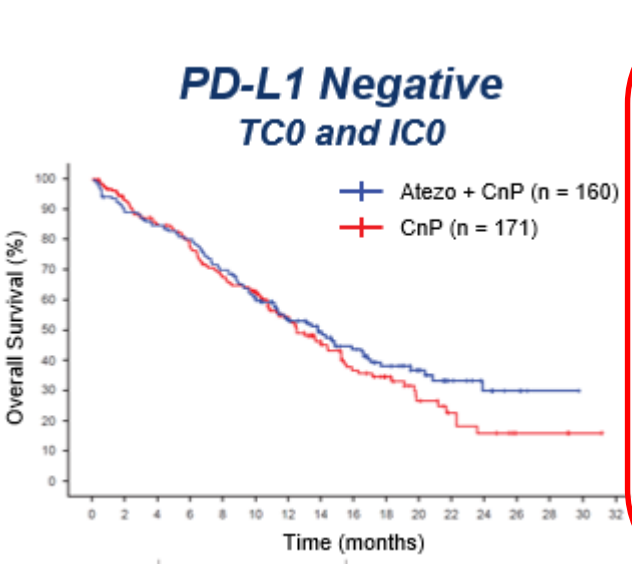
	Arm B: Atezo + CnP	Arm C: CnP
Median OS (95% CI), mo	14.0 (12.0, 17.0)	13.9 (12.3, 16.4)
HR[a] (95% CI) *P* value	0.96 (0.78, 1.18) 0.6931	

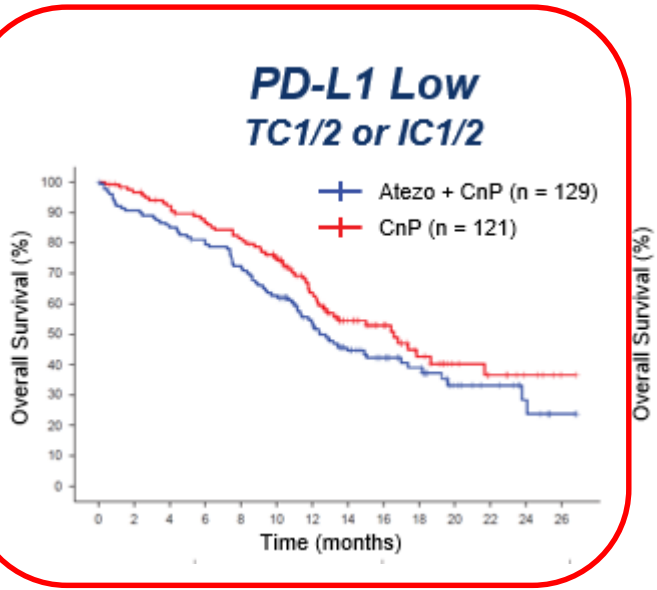
Progression-free Survival

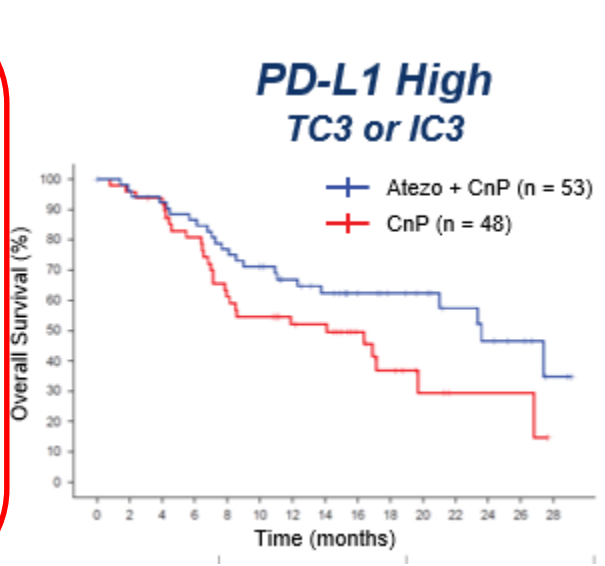


	Arm B: Atezo + CnP	Arm C: CnP
Median PFS (95% CI), mo	6.3 (5.7, 7.1)	5.6 (5.5, 5.7)
HR[a] (95% CI) *P* value	0.71 (0.60, 0.85) 0.0001	

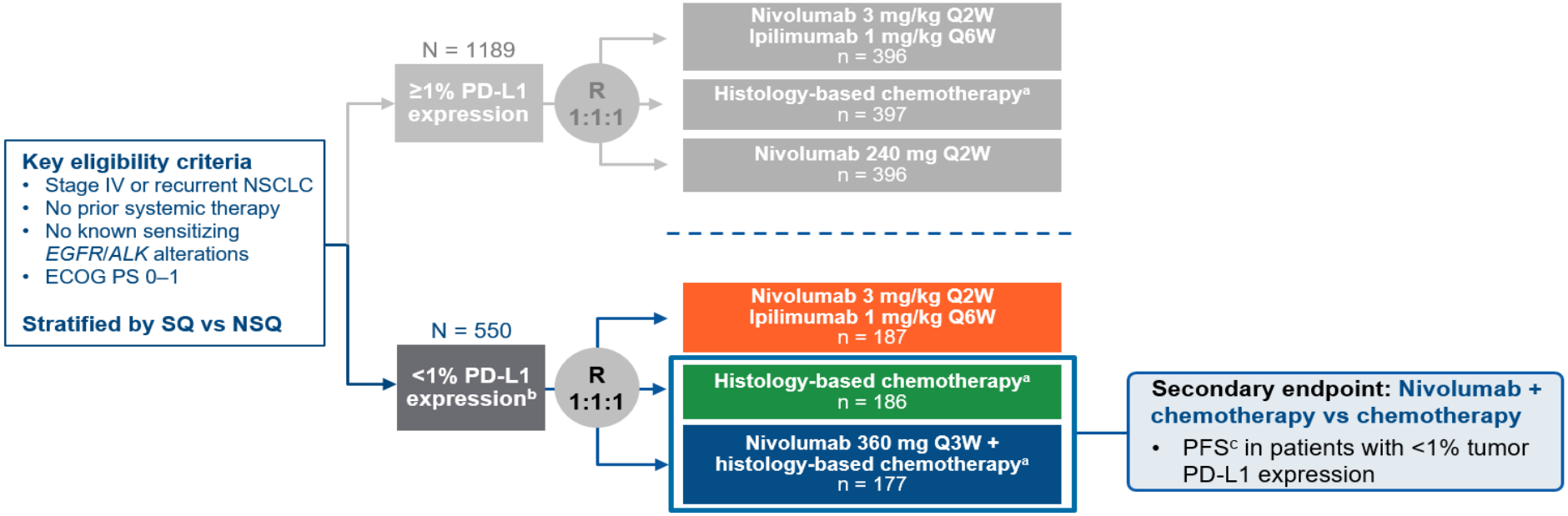
IMpower 131: OS by PD-L1 status







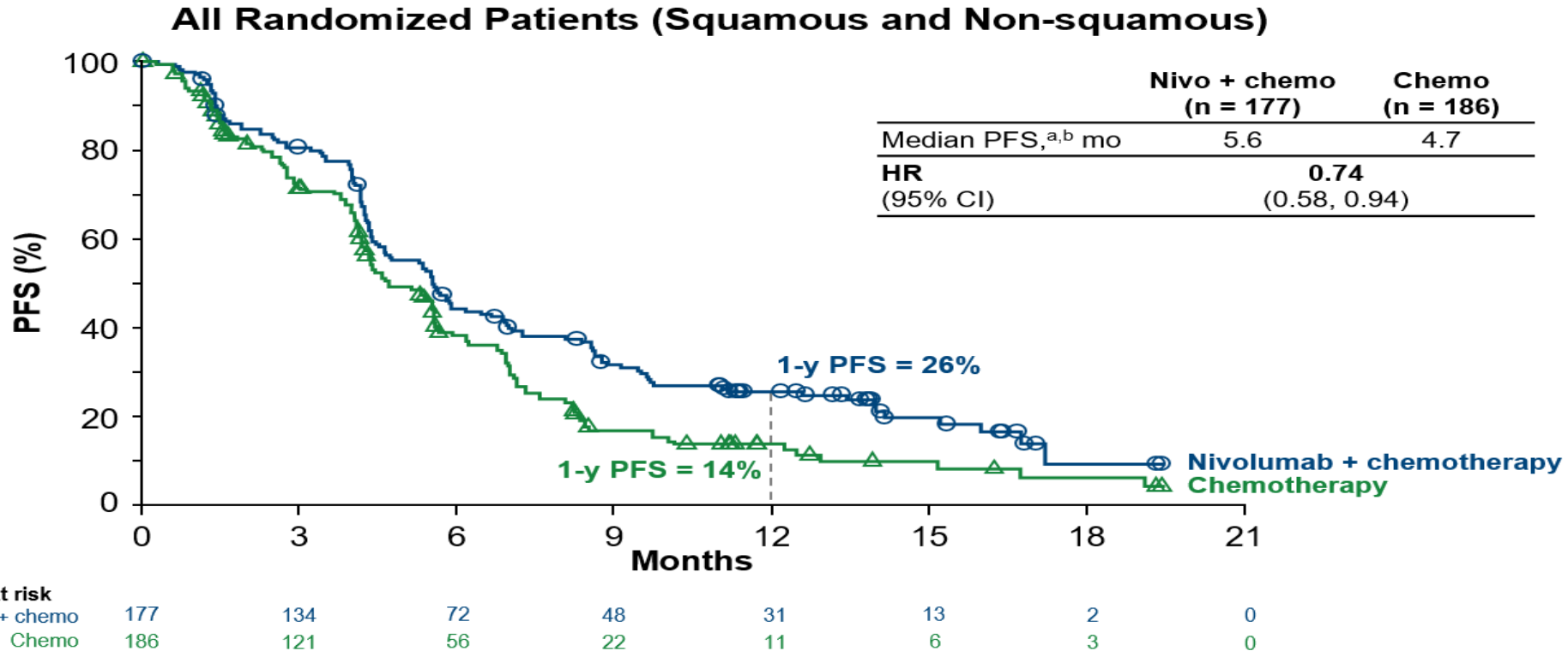
CheckMate 227: Study Design



- Co-primary endpoints: OS in PD-L1–selected populations and PFS[c] in TMB-selected populations treated with nivolumab + ipilimumab vs chemotherapy

[a]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles; [b]One patient was randomized with <1% tumor PD-L1 expression in IVRS, but was subsequently found to have ≥1% tumor PD-L1 expression; [c]Per BICR

CheckMate 227: PFS in PD-L1 neg



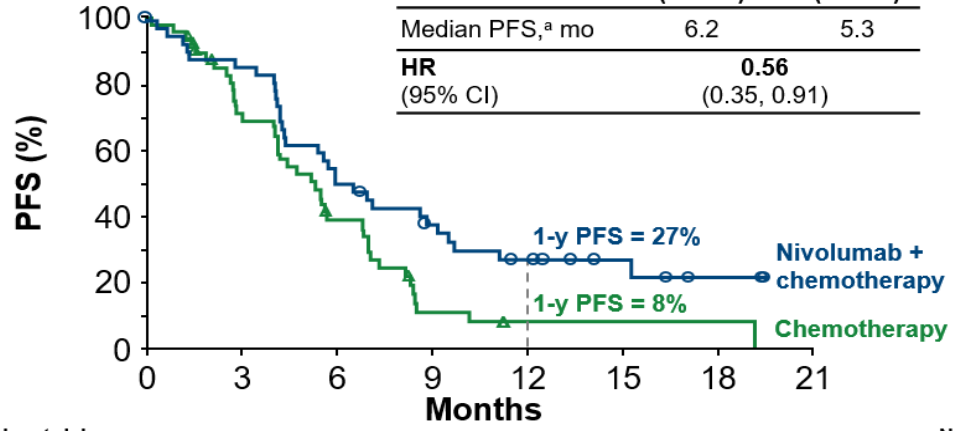
	Nivo + chemo (n = 177)	Chemo (n = 186)
Median PFS,[a,b] mo	5.6	4.7
HR (95% CI)	**0.74** (0.58, 0.94)	

[a]95% CI: nivo + chemo (4.6, 6.7 mo), chemo (4.3, 5.6 mo); [b]In the nivo + ipi arm (n = 187), median (95% CI) PFS was 4.4 (3.1, 6.0), 1-y PFS was 29%, and HR vs chemo was 0.79 (0.62, 1.01)

CheckMate 227: PFS in PD-L1 neg by TMB

TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression

	Nivo + chemo (n = 43)	Chemo (n = 48)
Median PFS,[a] mo	6.2	5.3
HR (95% CI)	**0.56** (0.35, 0.91)	

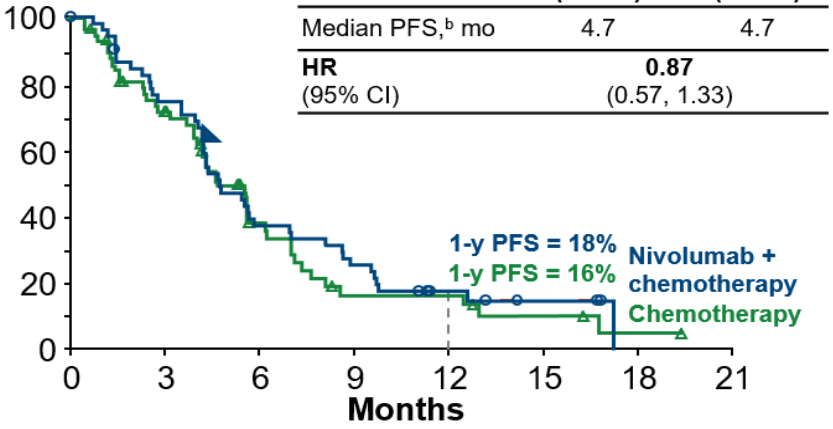


No. at risk

Nivo + chemo	43	36	21	14	9	5	2	0
Chemo	48	30	16	4	1	1	1	0

TMB <10 mut/Mb and <1% Tumor PD-L1 Expression

	Nivo + chemo (n = 54)	Chemo (n = 59)
Median PFS,[b] mo	4.7	4.7
HR (95% CI)	**0.87** (0.57, 1.33)	



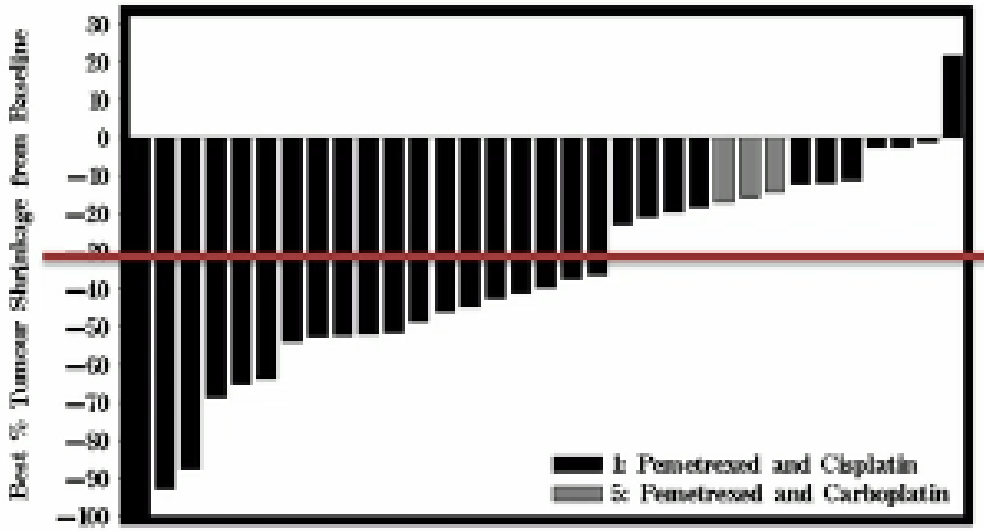
No. at risk

Nivo + chemo	54	38	19	13	6	3	0	0
Chemo	59	39	16	6	6	3	1	0

- TMB ≥10 mut/Mb: ORR was 60.5% with nivo + chemo and 20.8% with chemo
- TMB <10 mut/Mb: ORR was 27.8% with nivo + chemo and 22.0% with chemo

[a]95% CI: nivo + chemo (4.3, 9.1 mo), chemo (4.0, 6.8 mo); [b]95% CI: nivo + chemo (4.2, 6.9 mo), chemo (3.9, 6.2 mo)

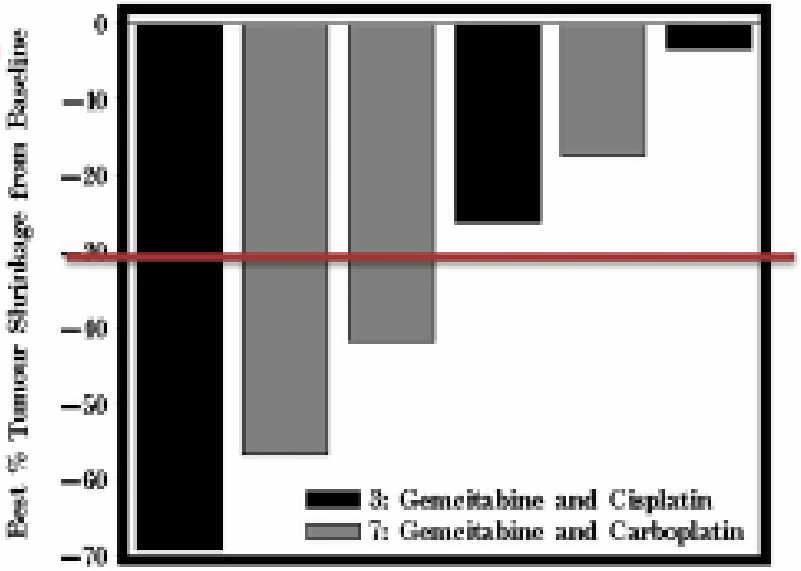
CCTG IND 226: Plt doublet + PD-L1 and CTLA-4



Above: Pem-Platinum cohorts (n=33 evaluable)

Right: Gem-Platinum cohorts (n=6 evaluable)

Interim Responses



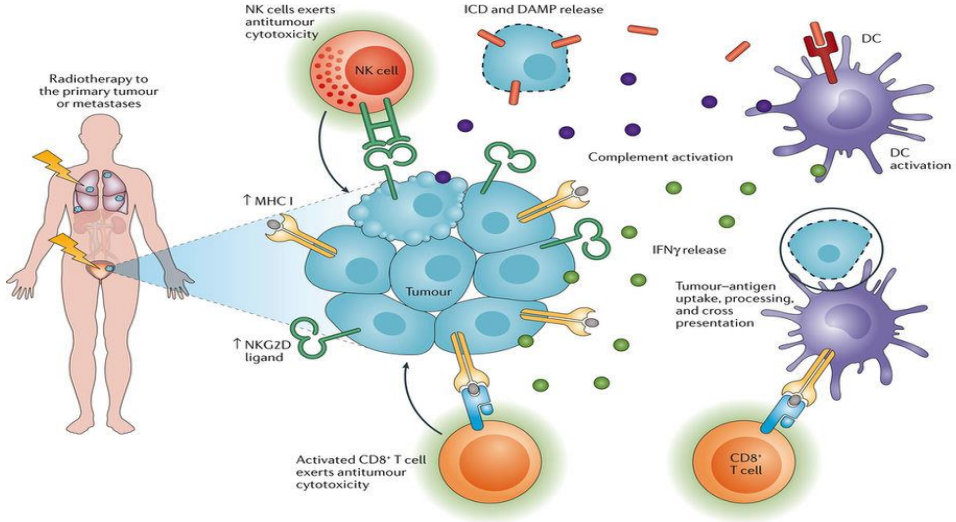
Conclusions

- PD-(L)1 inhibitors plus chemotherapy offer additive benefits when combined with chemotherapy
- The durability of the benefit is yet to be defined and requires further long term follow up
- The side effect profile is manageable with no obvious amplification or suppression of IO or chemotherapy classic toxicities
- The influence of PD-L1 tumour status on PFS and OS is still an open question with discrepant results between trials
- Better biomarkers are needed to help identify which patients would benefit from the combination of chemotherapy and immune checkpoint inhibitors

Why combining IO and RT in the advanced NSCLC setting?

- Poor survival <5% for stage IIIB/IV disease
- IO SOC in first and second-line treatment for advanced NSCLC
- RT induces immunomodulatory effects in the local tumour microenvironment,
  - Some (*but limited*) clinical evidence that RT not only provides local tumour control, but also influences systemic control
  - Supporting a synergistic combination approach with IO to improve systemic control
- Potential for RT to overcome resistance to immune checkpoint blockade
- →making tumours '*sensitive again*' to IO

Immunogenic effects of radiotherapy

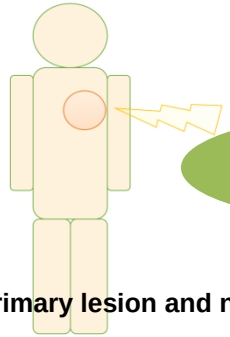


RT enhances immune recognition of tumour

- Promotes the release of tumour neoantigens
- Enhances MHC class I expression
- Upregulates chemokines & cell-adhesion molecules
- Promotes dentritic cell activation
- Promotes antigen processing/ presentation
- Promotes priming of CD8+ T-cells

In theory, this should lead to an abscopal effect

However…. immunosuppression dominates…

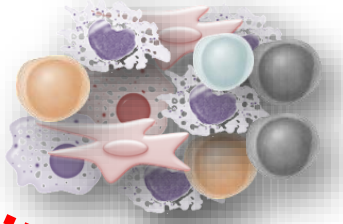


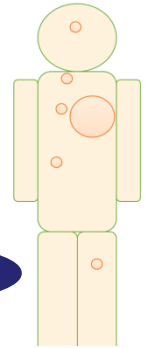
Primary lesion and nodes

1.Immunogenic cell death

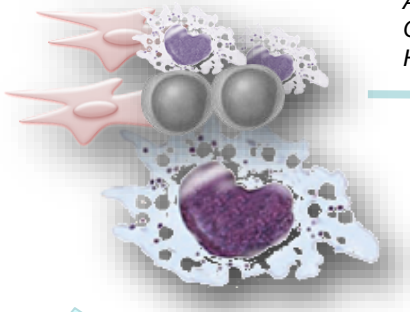
2. Inflammatory cytokine response

All tumour sites
Including micrometastasis

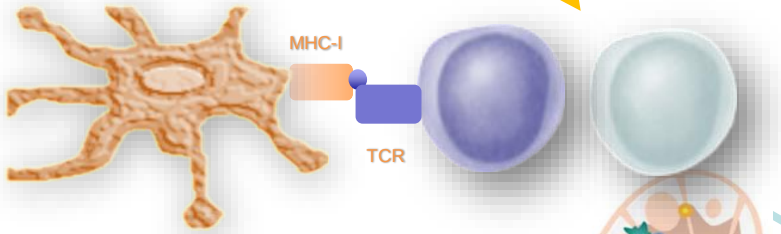




3. Anti-PD(L)-1

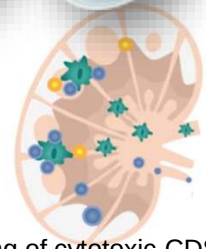


ATP
Calreticulin
HMGB1



↑ Target cell lysis
↑ Lymphocyte motility
↑ TCR signalling

Recruitment & maturation of DC
Engulfment of tumour AGs by DC



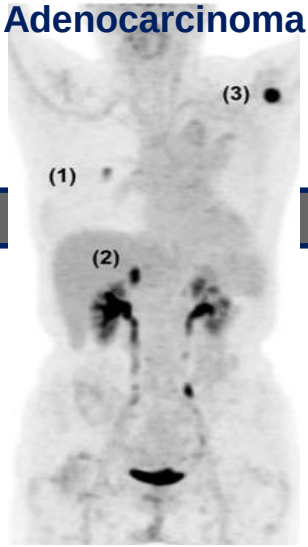
Cross-priming of cytotoxic CD8 T cells

Homing of T cells

+ Concurrent chemotherapy

→abscopal effect is rare

The abscopal effect



Does the combination of RT/IO provide an opportunity to boost abscopal response rates?

Siva et al Cancer Letters 2015

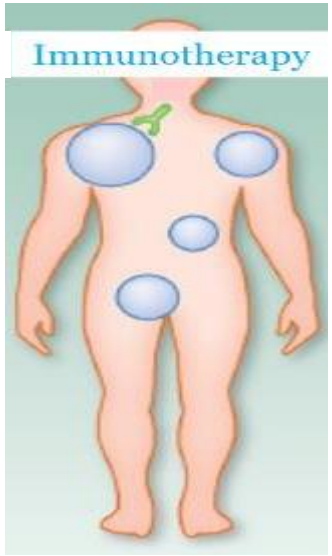
Abscopal effect of RT and IO - Clinical data

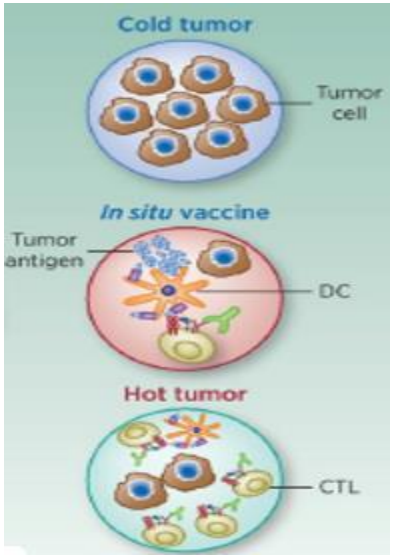
Pub. Year	♀♂	Age	Histology	Primary site	Treatment of primary	RT treated sites	Treatment + RT Dose / fractions	Non-irradiated abscopal regression	Time until abscopal response	PFS after response*
2014	M	74	Adenocarci-noma	Lung	Resection	Supraclavi-cular LN	BCG-vaccine 58 Gy/29x	Lung M+	6 m	47 m
2013	M	64	Adenocarci-noma	Lung	CT (PD)	Hepatic M+	Ipilimumab 30 Gy/5x	Liver M+ / Bone M+ / Lung M+	3 m	5 m
2012	M	57	Melanoma	Arm	Wide excision / axillary dissection	Hepatic M+	Ipilimumab 54Gy/3x	Cutaneous M+	6 m	6 m
2012	M	67	Melanoma	Scalp	CT (PD)	Brain M+	Ipilimumab SRT**	Nodal M+	NR	NR
2012	F	33	Melanoma	Upper back	Wide excision	Paraspinal M+	Ipilimumab 28,5 Gy/3x	Splenic M+ / hilar LN	4 m	6 m

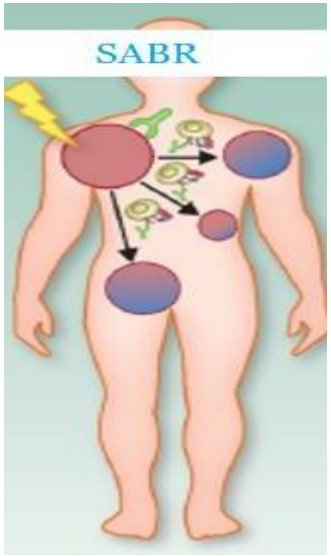
Reynders et al. Cancer Treat Rev 2015

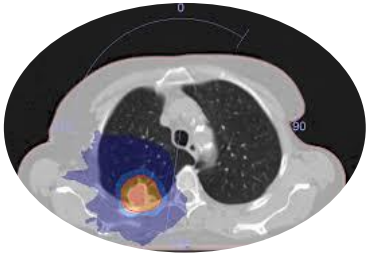
The promise of SBRT & IO

'Cold' tumour refractory to IO









***In situ* vaccination with SABR to 'warm' tumour and enhance effect of immunotherapy**

Randomized phase II study of pembrolizumab after SBRT versus pembrolizumab alone in patients with advanced non-small cell lung cancer: The PEMBRO-RT study

Study objective: To investigate the efficacy and safety of pembrolizumab after SBRT compared with pembrolizumab alone in patients with advanced NSCLC

Key patient inclusion criteria
- Advanced NSCLC
- >2L therapy
- Any PD-L1 status

(n=74)

R 1:1

SBRT to a single tumour site 3x 8 Gy within 7 days prior to 1st cycle of Pembrolizumab 200 mg q3w (n=38)

Stratification
- Smoking status

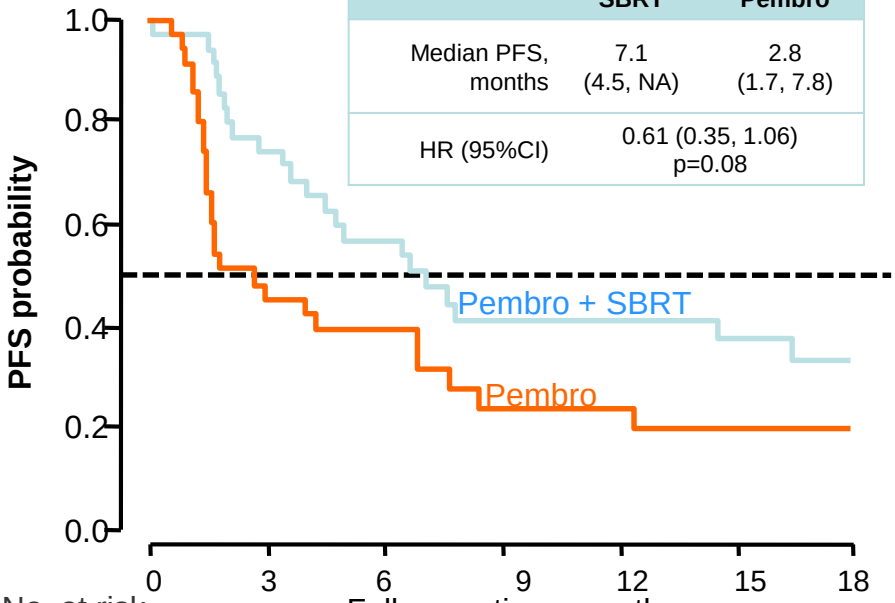
Pembrolizumab 200 mg q3w (n=40)

Primary endpoint
- ORR

Secondary endpoints
- PFS, OS, DCR, safety

PFS

	Pembro + SBRT	Pembro
Median PFS, months	7.1 (4.5, NA)	2.8 (1.7, 7.8)
HR (95%CI)	0.61 (0.35, 1.06) p=0.08	

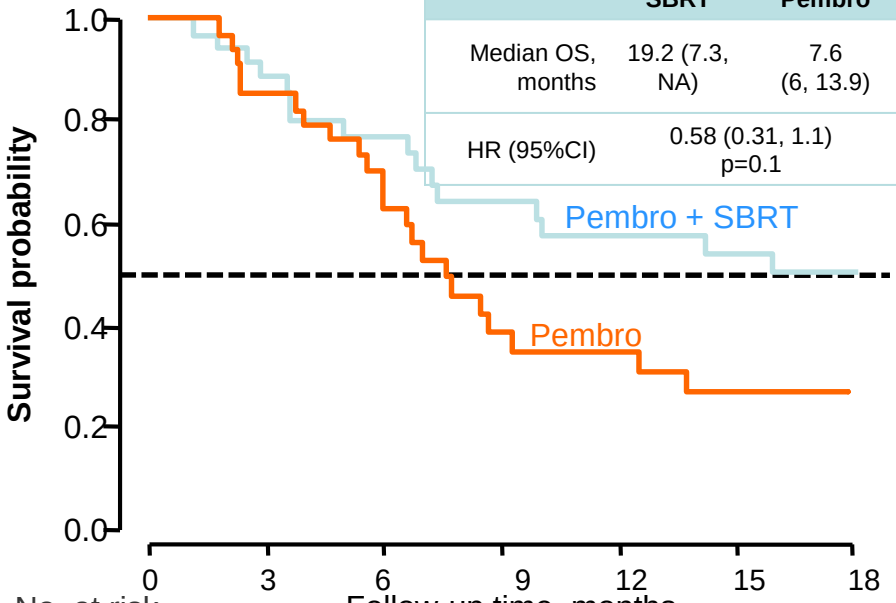


No. at risk

Pembro + SBRT	36	24	18	13	11	10	7
Pembro	35	16	10	6	6	6	3

OS

	Pembro + SBRT	Pembro
Median OS, months	19.2 (7.3, NA)	7.6 (6, 13.9)
HR (95%CI)	0.58 (0.31, 1.1) p=0.1	



No. at risk

	36	31	25	20	16	15	12
	39	29	20	10	9	7	5

	Pembrolizumab + SBRT (n=36)	Pembrolizumab (n=36)
Best overall response, n (%)		
Complete response	3 (12)	1 (3)
Partial response	14 (39)	7 (19)
Stable disease	9 (25)	9 (25)
Progressive disease	10 (28)	19 (53)
ORR at 12 weeks, % (n/N)		
Overall*	39 (13/36)	21 (7/34)
PD-L1 0%	22 (4/18)	5 (1/22)
PD-L1 1–49%	38 (3/8)	38 (3/8)
PD-L1 ≥50%	60 (6/10)	75 (3/4)
DCR at 12 weeks	64 (23/36)	42 (15/36)

*p=0.28

Conclusion: In patients with advanced NSCLC, SBRT given prior to pembrolizumab may improve outcomes predominantly in patients with PD-L1 negative tumours

Secondary analysis of KEYNOTE 001

- International, multicentre, phase 1 trial of single agent pembrolizumab in patients with progressive locally advanced or metastatic NSCLC
- Pembrolizumab IV at dose of 2mg/kg or 10mg/kg every 3 weeks or 10mg/kg every 2 weeks until disease progression/death/withdrawal of study
- Assessed patients treated on KEYNOTE-001 trial at a single institution
- Primary objective- to determine whether previous radiotherapy affected PFS, OS and pulmonary toxicity

Secondary analysis of KEYNOTE 001

- 98 patients were enrolled, one was lost to follow up
- 42 (43%) of 97 patients have previous RT for treatment of NSCLC before first cycle of pembroluzimab
- 38 (39%) received extracranial RT
- PFS with pembrolizumab was significantly longer in patients who received any RT than without; 4.4 months vs. 2.1 months (HR 0.56, p=0.019)
- OS was also significantly longer in previous RT arm 10.7 months vs. 5.3 months (HR 0.58, p=0.026)
- OS in patients who previously received extracranial RT compared to those without; 11.6 months vs 5.3 months (HR 0.59, p=0.034)

What is the optimal RT schedule to elicit an immune response?

Dose per fraction?

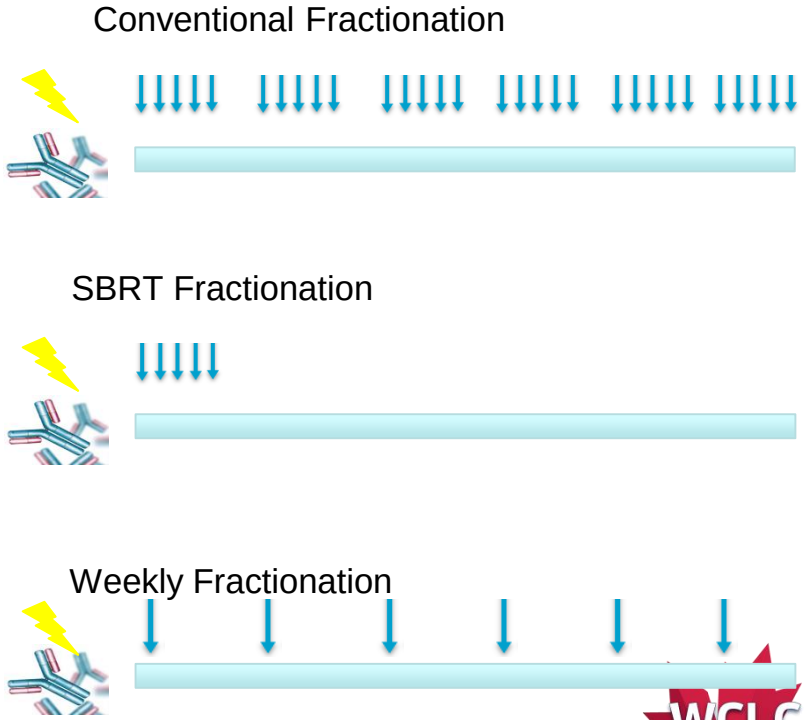
- Immunogenic cell death may be increased with dose higher than 2 Gy?
- Preclinical studies suggest 8-12 Gy may be optimal?

Number of fractions?

- Multiple may be better than single?
- Clinical abscopal effects mainly observed following 3-5 fractions
- Protracted RT courses may induce more lymphopenia?

Frequency of fractions?

- Is daily or alternate day or weekly fractionation optimal?



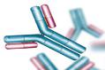
What is the optimal sequencing of RT & IO to elicit an immune response?

Preclinical evidence: concurrent (Dovedi et al Cancer Res 2014)

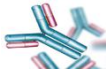
Sequential / Concurrent ?

- Abscopal responses occur when RT given concurrently with or following IO?
- RT with first IO cycle vs later IO cycle?

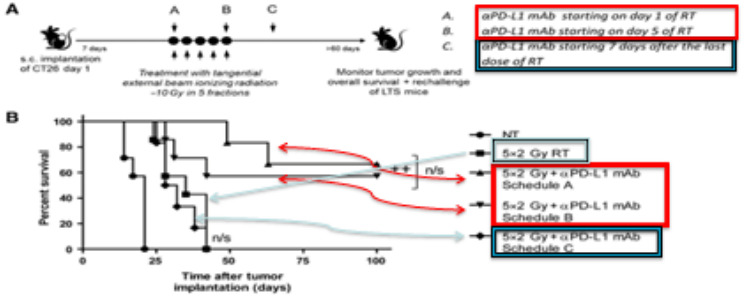
Concurrent



Sequential



Concurrent RT + anti-PD-L1 is superior to sequential therapy

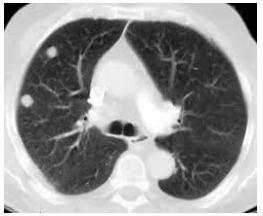


The Christie NHS

What is the optimal RT target to improve outcomes?

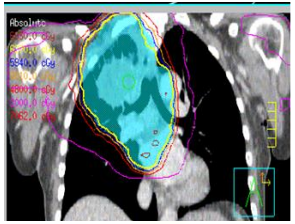
Radiotherapy target site?

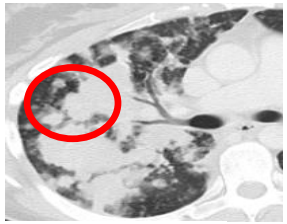
- Primary vs metastases – Clonal vs sub-clonal neo-antigens?
- Single vs multiple targets?



Radiotherapy target coverage?

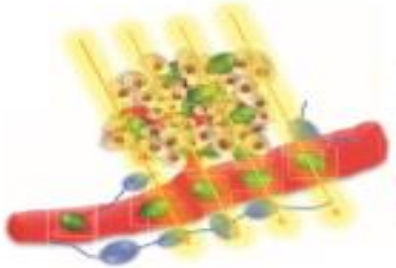
- Is it necessary to treat the whole of a lesion?





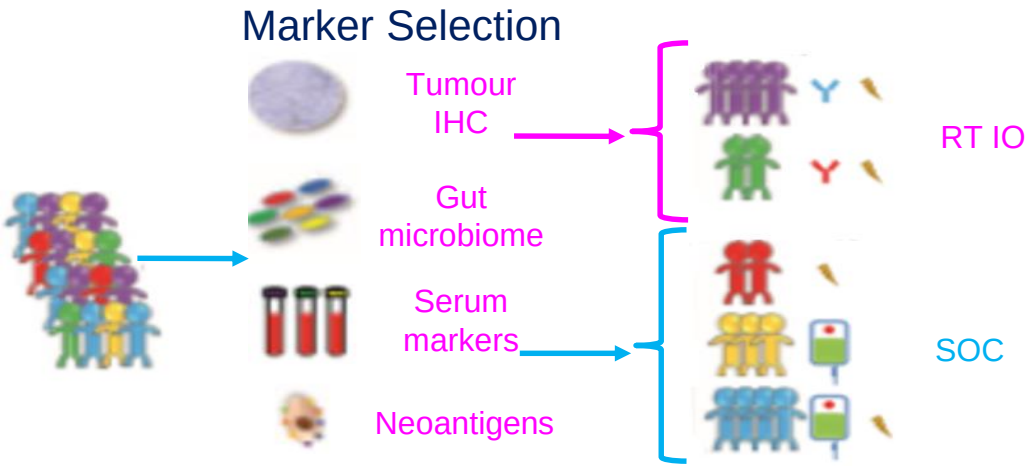
Radiotherapy field size?

- Large RT volumes may cover more lymphoid tissue & induce more lymphopenia
- Circulating lymphocytes highly sensitive to RT (D90 = 0.5 Gy)



How do we select the patients who will benefit from addition of RT to IO?

- Overall tumour burden?
- Prior treatment?
- Initial response to IO alone?
- Imaging biomarkers?
- Gut biomarkers e.g. Microbiome?
- Blood biomarkers e.g. Myelosuppression / neutrophil to lymphocyte ratio?
- Tissue biomarkers e.g. PDL1 / Mutational burden / Neoantigen load / TILs?



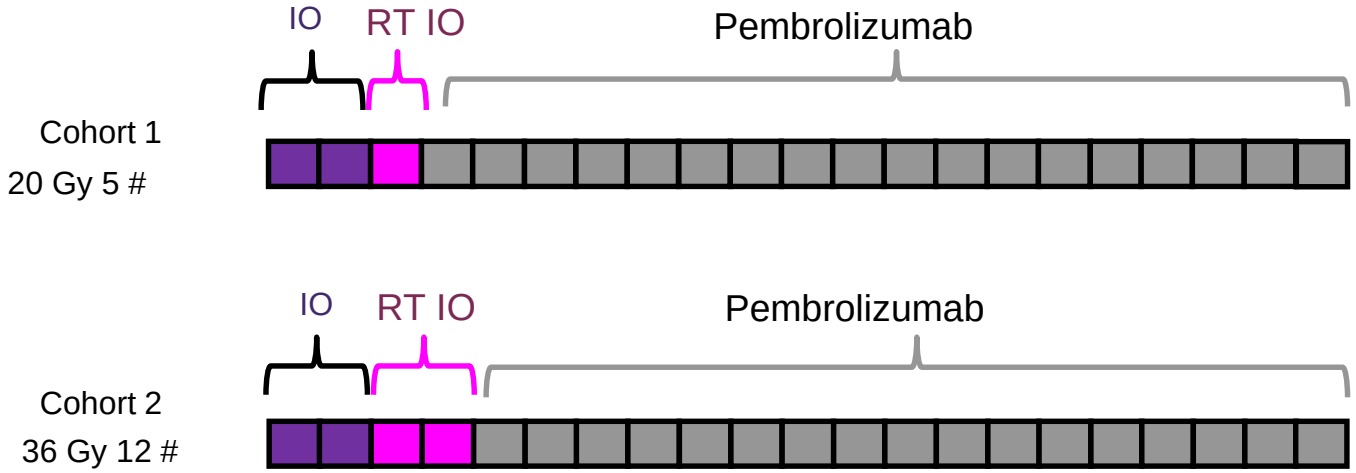
Ongoing clinical trials

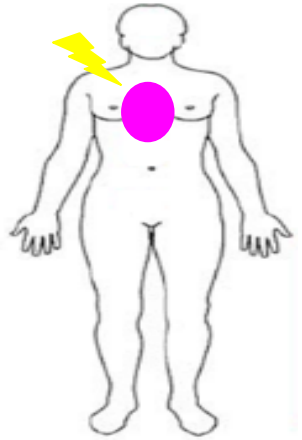
Palliative thoracic RT with IO

PEAR: Pembrolizumab and Palliative RT for Advanced NSCLC

Primary endpoint: Toxicity
Target 21 patients

Royal Marsden
NCT03245177





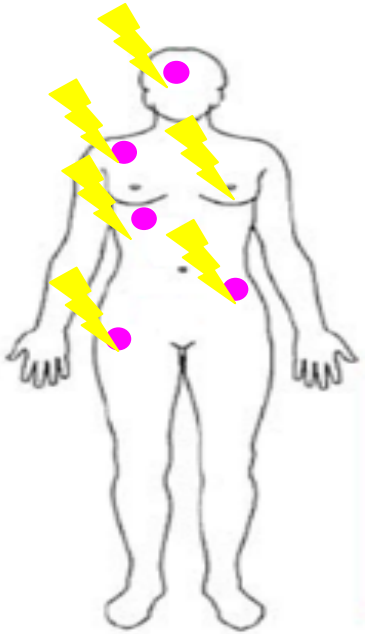
IO RT in Oligo-Metastatic Disease

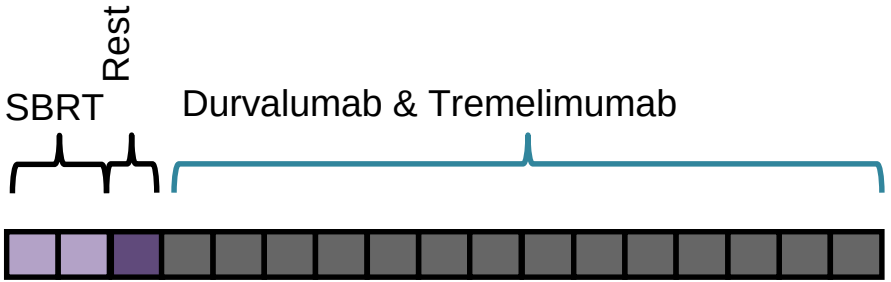
NCT03275597

Wisconsin

Phase Ib
Primary endpoint: Toxicity
Target 21 patients

30-50 Gy in 5# over 2w
up to 6 sites of disease





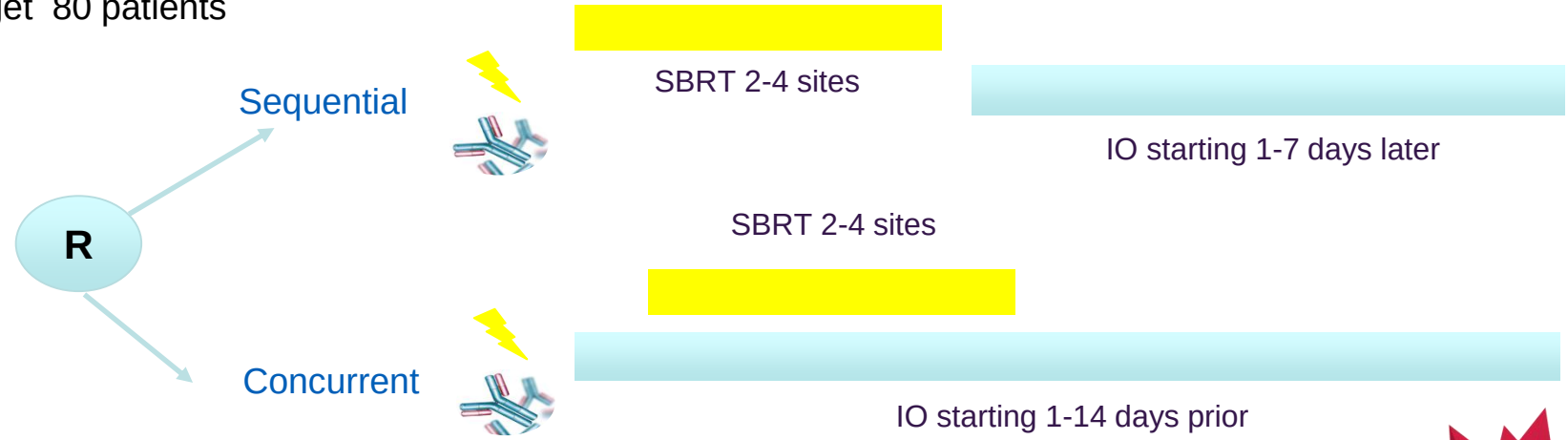
SBRT with IO in Poly-Metastatic Disease

Strategy: To achieve 'in-situ vaccine' for minimal toxicity & immune suppression?

COSINR: Metastatic NSCLC
Primary endpoint: Safety
Target 80 patients

NCT03223155

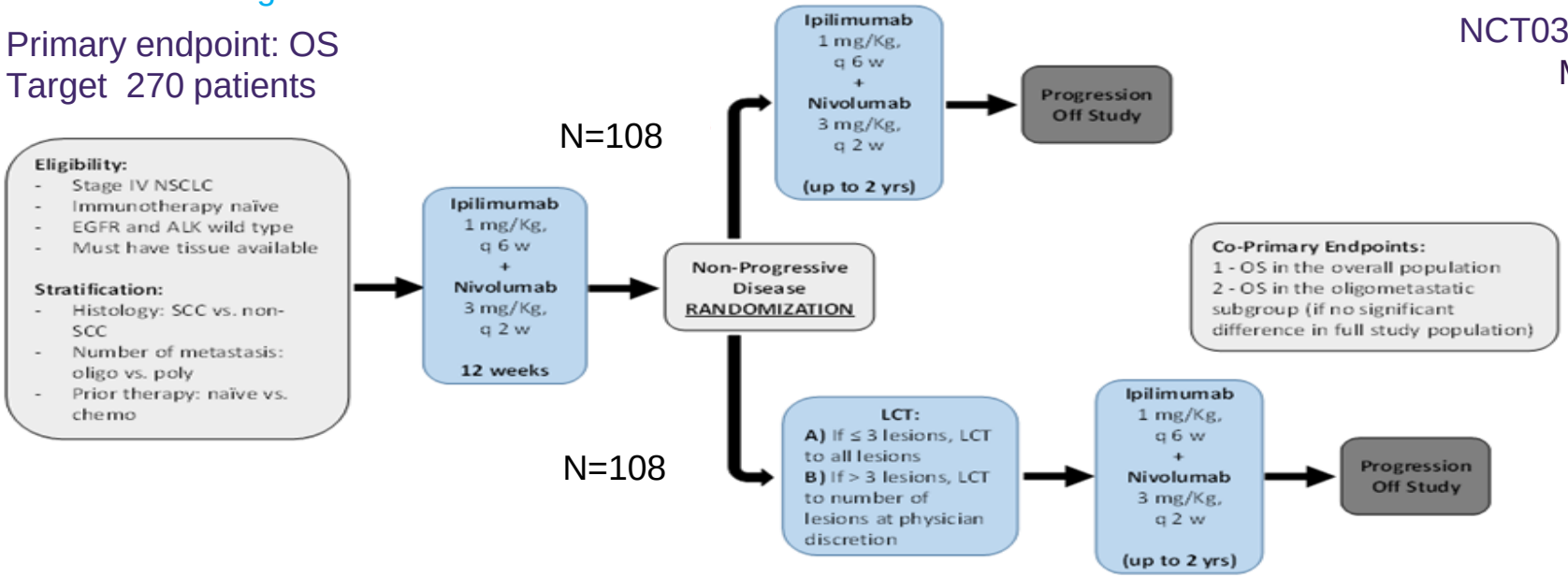
Chicago



LONESTAR: Oligo-metastatic & Metastatic NSCLC

Primary endpoint: OS
Target 270 patients

NCT03391869
MDACC

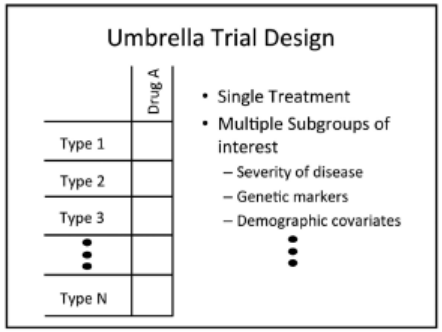


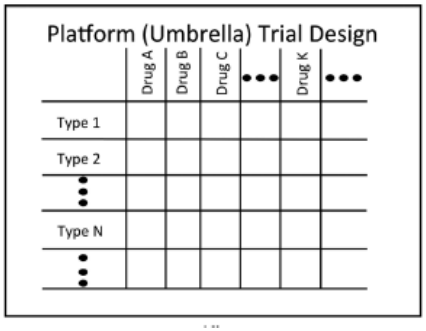
Trials of immune checkpoint inhibitors & SBRT in advanced NSCLC

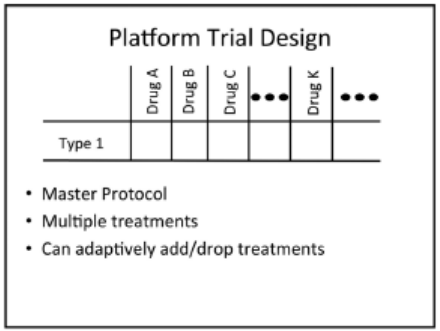
NCT	IO	Radiotherapy	Trial phase	Institution
NCT02239900	Ipilumumab	SBRT 50 Gy 4# 1-4 lesions cycle 1 vs 3	Phase I/II	MDACC
NCT02608385	Pembrolizumab	SBRT 3-5# varied total dose depending on site	Phase I	Chicago
NCT02400814	Atezolizumab	SBRT 50 Gy 5# pre vs cycle 1 vs cycle 3	Phase I	California
NCT02444741	Pembrolizumab	SBRT 50 Gy 4# vs wide field RT 45 Gy 15# cycle 1 vs 3	Phase I/II	MDACC
NCT02407171	Pembrolizumab	SBRT 1-5# (8 Gy 1#, 30 Gy 5#, 30 Gy 3#)	Phase I/II	Yale
NCT02492568	Pembrolizumab	SBRT 24 Gy 3# pre vs Pembrolizumab alone	Phase II	NKI

Ko et al. Clinical Ca Res 2018

Can we be more efficient with trial design?





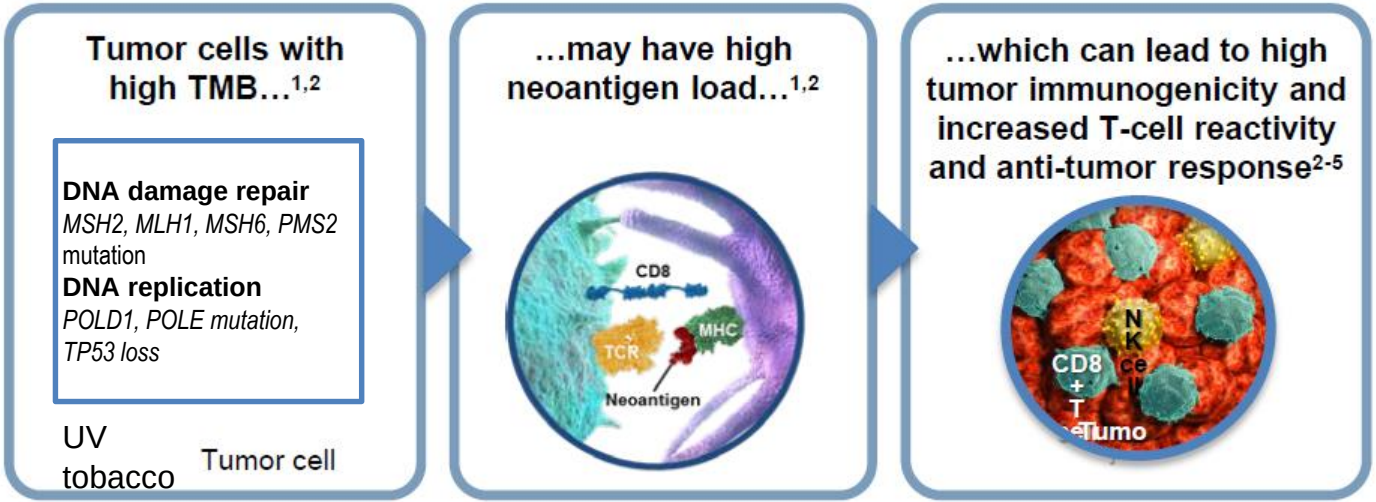


Saville. Clinical trials 2016

TAKE HOME MESSAGES

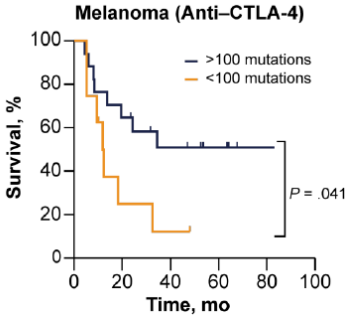
- RT in combination with IO is a promising strategy in cancer treatment
- Number of RT-IO clinical trials is rapidly increasing
- However optimal partnering with IOs to maximise this effect is unclear
- Questions remains to be answered:
  - Optimal dose and fractionation to ensure adequate priming for IO
  - Sequencing of therapies
  - The extent of tumour that should be irradiated while minimizing local toxicity
  - Best trial endpoints to use (e.g. ?iRECIST and duration of repsonse vs. PFS/RECIST criteria)

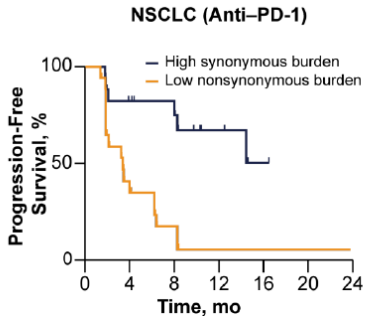
Tumors with High Mutation Burden are Rational Target for IO Therapy

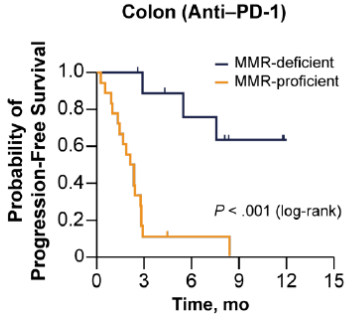


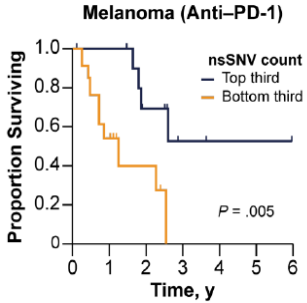
Schumacher TN et al Science 2015;348:69-74
Kim JM et al Ann Oncol 2016:1492-1504
Liontos M et al Ann Tran L/ med 2016:264
Sharma P et al Science 2015:56-61
Giannakis M et al Cell Rep 2016:857-865

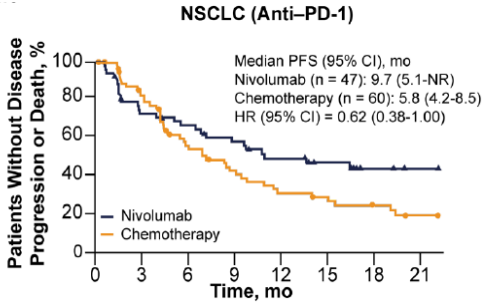
High Tumor Mutation Burden
as Predictive biomarker for IO Therapy

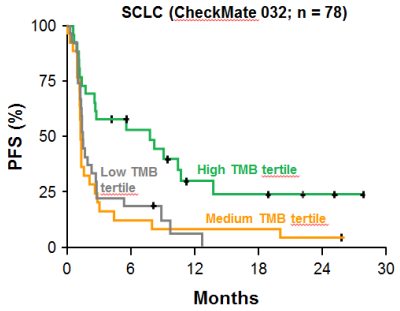








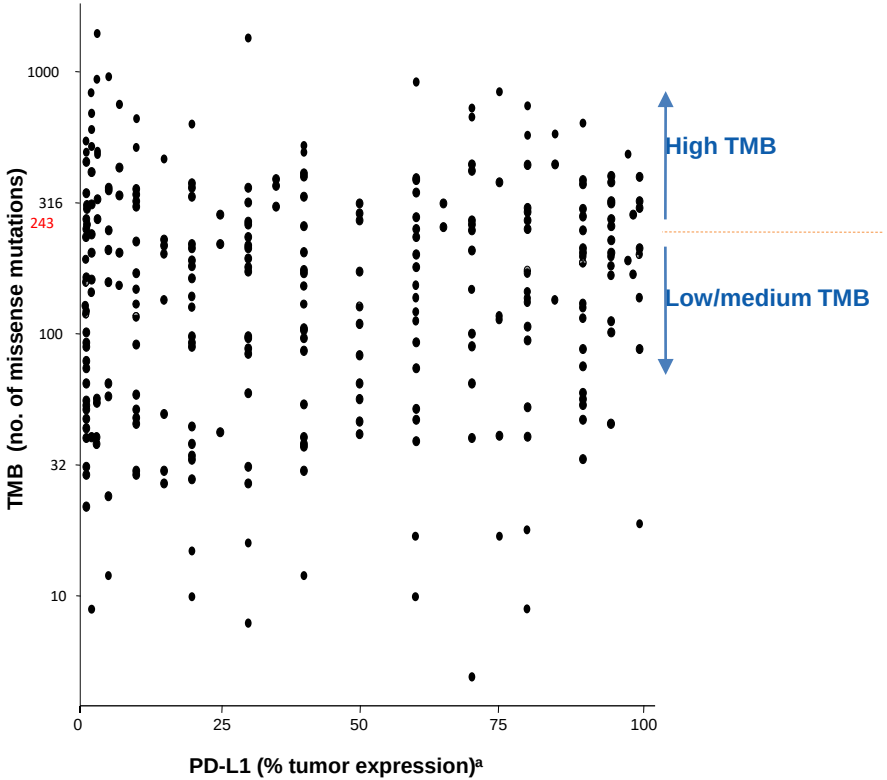




Snyder A et al NEJM 2014;371:2189-99
Rizvi NA et al Science 2015;348:124-8
Let DT et al NEJM 2015;372:2509-20
Van Allen EM et al Science 2015;350:207-211
Hugo W et al Cell 2016;165:35-44
Carbone DP et al NEJM 2017;376:2415-26
Hellman et al Cancer Cell 2018

No association between TMB and PDL1 expression

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC



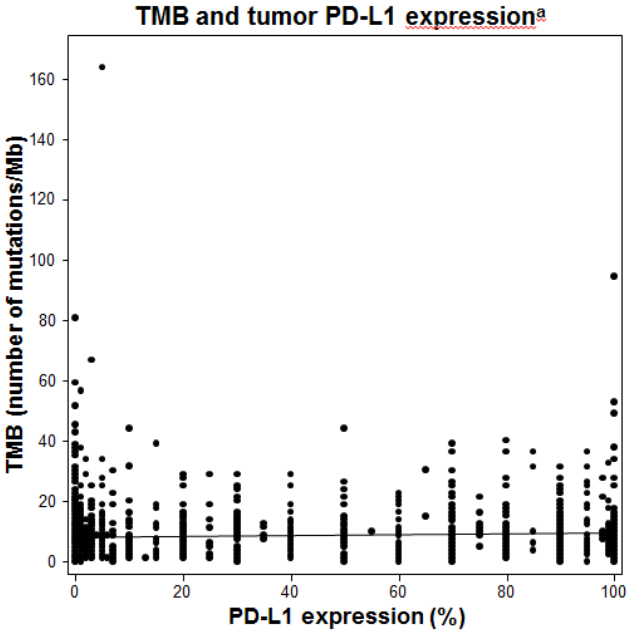
- There was no association between TMB and PD-L1 expression in patients with ≥1% PD-L1 tumor expression

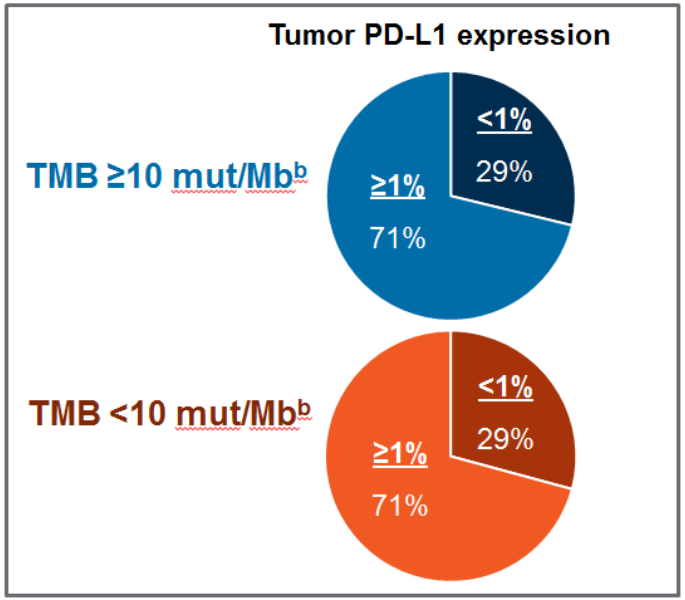
[a]All patients had ≥1% PD-L1 tumor expression

Carbone DP et al NEJM 2017;376:2415-26

TMB and PDL1 Expression Identify Distinct and Independent Populations of NSCLC

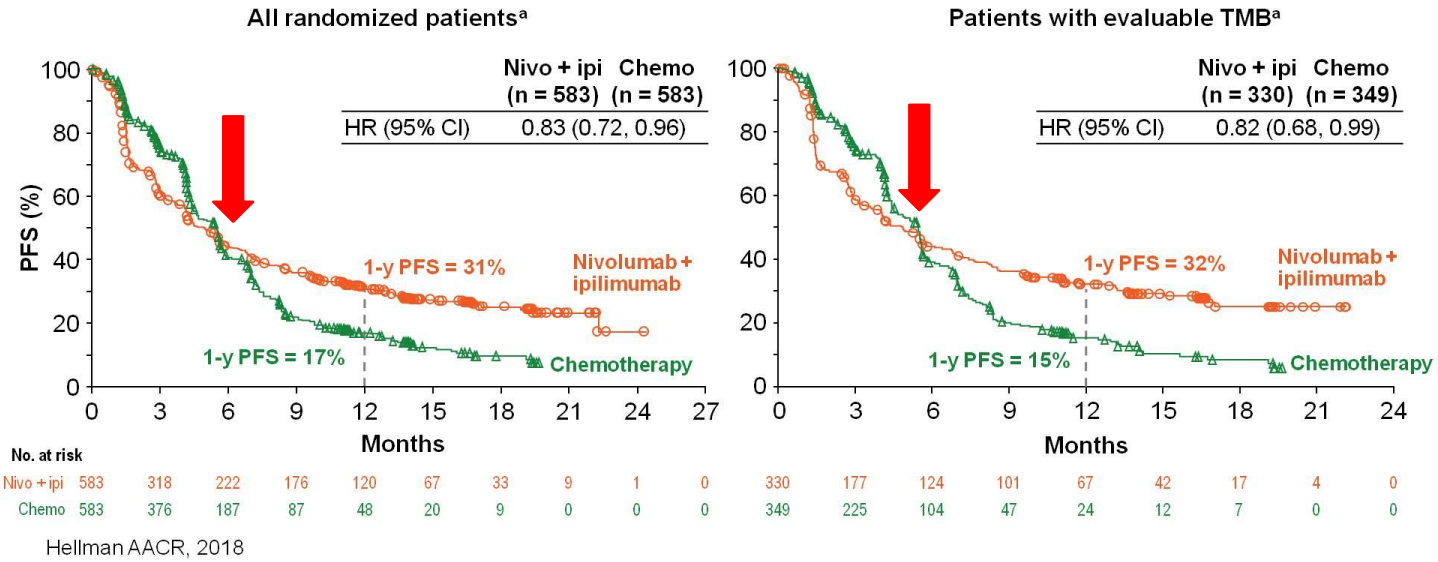
- 58% all randomized patients (n=1004) had TMB-evaluable samples
- Among them, 44% of patients have ≥ 10 mut/Mb





[a]Symbols (dots) in the scatterplot may represent multiple data points, especially for patients with <1% tumor PD-L1 expression. The black line shows the relationship between TMB and PD-L1 expression as described by a linear regression model; [b]Among patients in the nivolumab +ipilimumab and chemotherapy arms; TMB ≥10 mut/Mb, n = 299; TMB <10 mut/Mb, n = 380

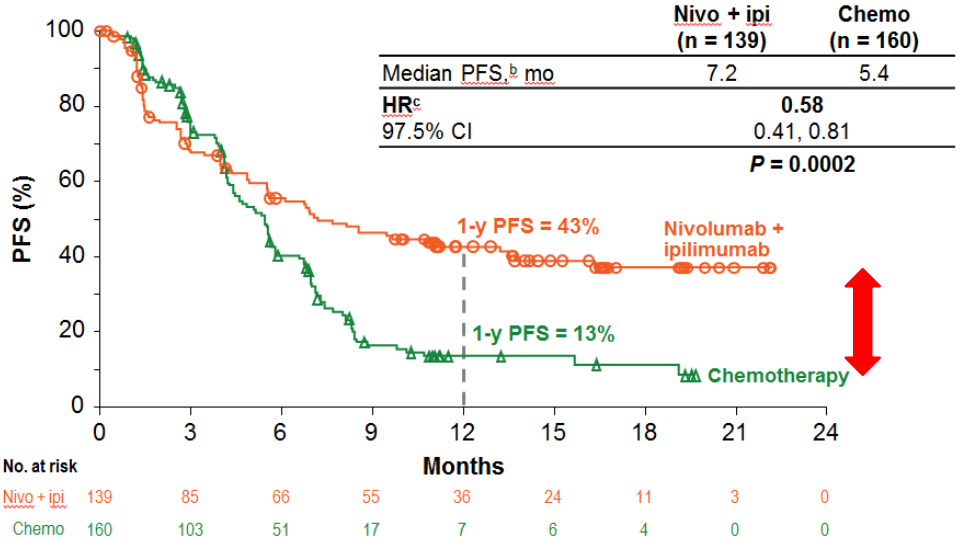
PFS in All Randomized vs TMB-Evaluable Patients



Hellman AACR, 2018

[a]Patients who did not progress or die were censored on the date of their last evaluable tumor assessment; those who did not have any study tumor assessments and did not die were censored on their date of randomization

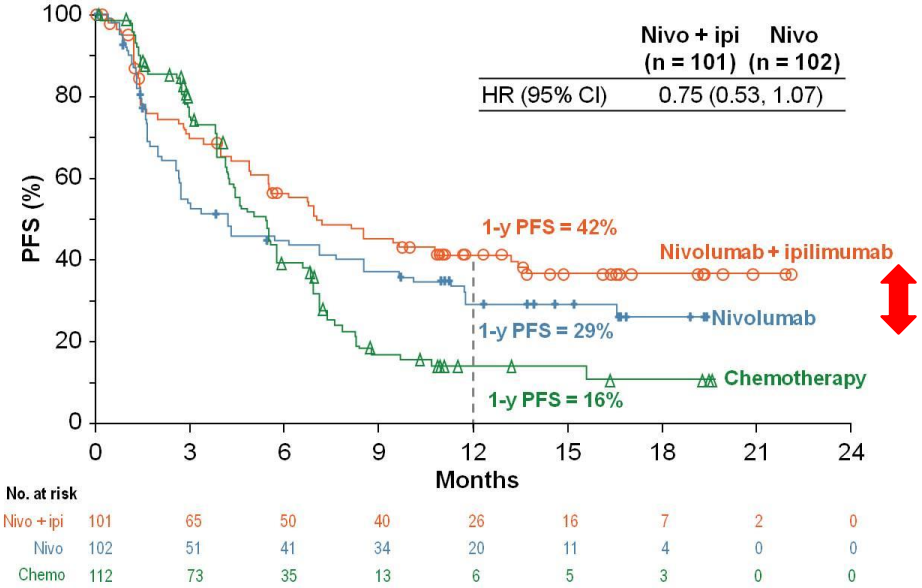
Co-primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)[a]



- In patients with TMB <10 mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)[d]

[a]Per blinded independent central review (BICR); median (range) of follow-up in the co-primary analysis population was 13.6 mo (0.4, 25.1) for nivo + ipi and 13.2 mo (0.2, 26.0) for chemo; [b]95% CI: nivo + ipi (5.5, 13.2 mo), chemo (4.4, 5.8 mo); [c]95% CI: 0.43, 0.77 mo; [d]The *P*-value for the treatment interaction was 0.0018

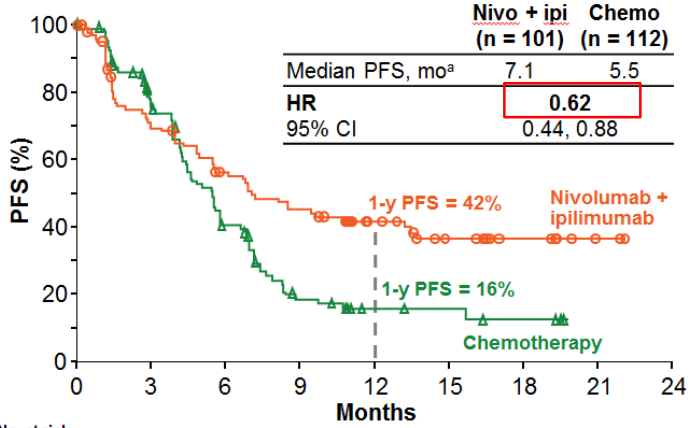
PFS: Nivolumab + Ipilimumab vs Nivolumab in Patients With High TMB (≥10 mut/Mb) and ≥1% PD-L1 Expression



Hellman AACR, 2018

PFS in Patients With High TMB (≥10 mut/Mb) by Tumor PD-L1 Expression

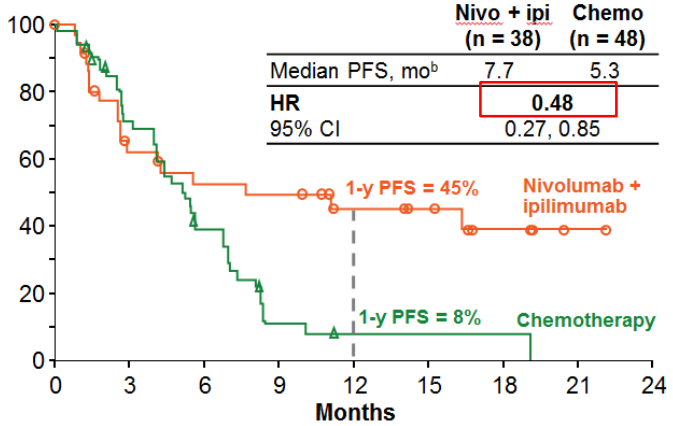
≥1% PD-L1 expression



No. at risk

Nivo + ipi	101	65	50	40	26	16	7	2	0
Chemo	112	73	35	13	6	5	3	0	0

<1% PD-L1 expression



Nivo + ipi	38	20	16	15	10	8	4	1	0
Chemo	48	30	16	4	1	1	1	0	0

[a]95% CI: nivo + ipi (5.5, 13.5 mo), chemo (4.3, 6.6 mo); [b]95% CI: nivo + ipi (2.7 mo, NR), chemo (4.0, 6.8 mo)

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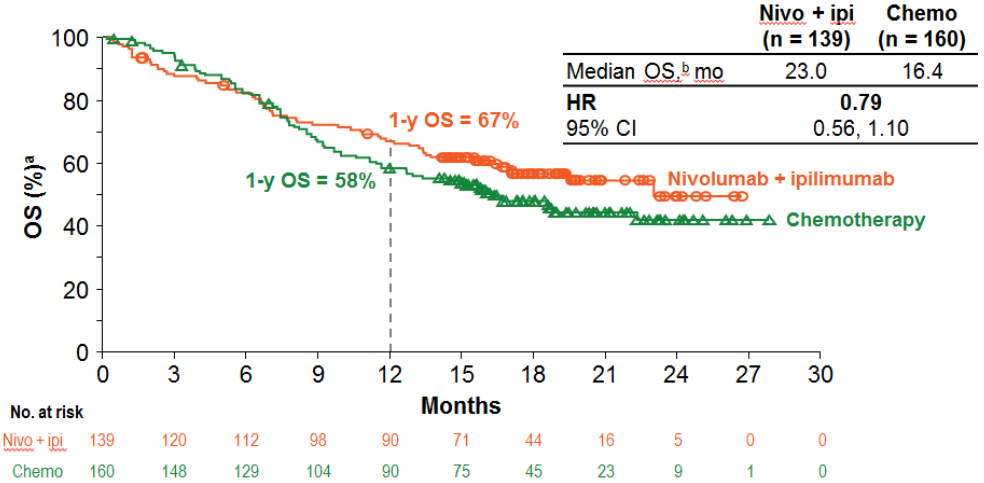
Preliminary Overall Survival With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)



	Nivo + ipi (n = 139)	Chemo (n = 160)
Median OS,[b] mo	23.0	16.4
HR	**0.79**	
95% CI	0.56, 1.10	

- Database lock: March 15, 2018; minimum follow-up: 14.2 months; 53% of patients were censored
- In the chemotherapy arm, 31.3% received subsequent immunotherapy (38.3% among those with disease progression[c])

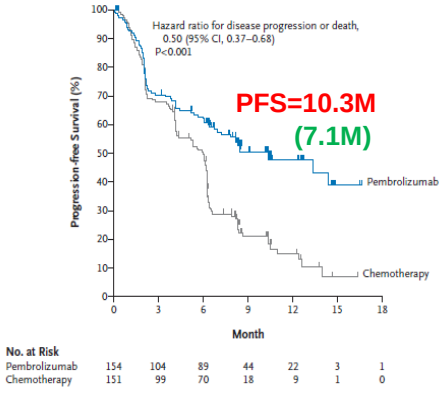
[a]In the first 1.5 months, 8 deaths occurred in the nivo + ipi arm (4 due to disease progression; 1 patient never treated [respiratory sepsis]; 2 due to AEs unrelated to study drug per investigator [thromboembolism, septic shock]; 1 due to myocarditis related to study drug), and 2 deaths occurred in the chemo arm (1 due to disease progression; 1 due to multiple brain infarctions related to carboplatin); [b]95% CI: nivo + ipi (16.5 mo, NR), chemo (12.6 mo, NR); [c]Per investigator

IO Mon *vs* IO/Chemotherapy *vs* IO/IO Combo

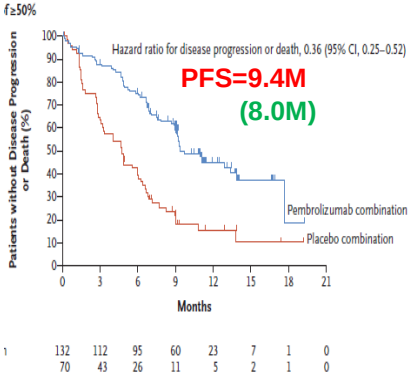
Study	Patients	Regimen	PFS (mons)	1yr OS (%)
KEYNOTE 024	NSCLC	Pembrolizumab (TPS ≥ 50%)	10.3	70%
KEYNOTE 042	NSCLC	Pembrolizumab (TPS ≥ 50%)	7.1	66%
KEYNOTE189	ADC	Carbo/Pem/Pembrolizumab	8.8	69.2%
IMpower 150	ADC	Carbo/Pacli/Beva/Atezolizumab	8.3	67%
KEYNOTE 407	SCC	Carbo/Pacli/Pembrolizumab	6.4	63%
IMpower 131	SCC	Carbo/nab-pacli/Atezolizumab	6.3	56.9%
IMpower132	ADC	Carbo/pem/Atezolizumab	7.6	59.6%
CheckMate 227	NSCLC	Ipilimumab/Nivolumab(TMB≥10)	7.2	67%

Which Regimen in High PDL1 expression ?

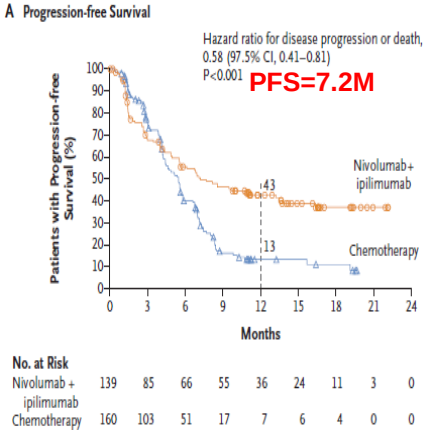
KEYNOTE 024 (042)
(PDL1 ≥ 50%) Pembro

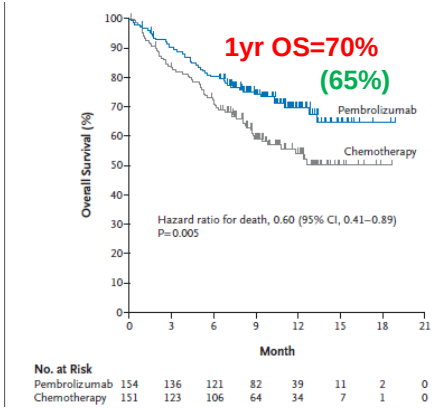


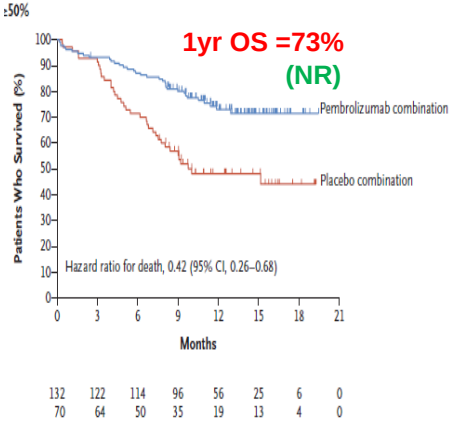
KEYNOTE 189 (407)
(PDL1 ≥ 50%) Pembro+chemo

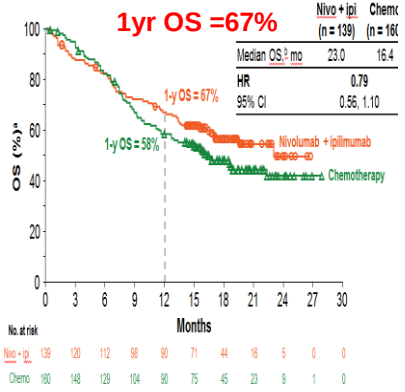


CheckMate 227
(TMB≥10mut/Mb) Ipi/Nivo







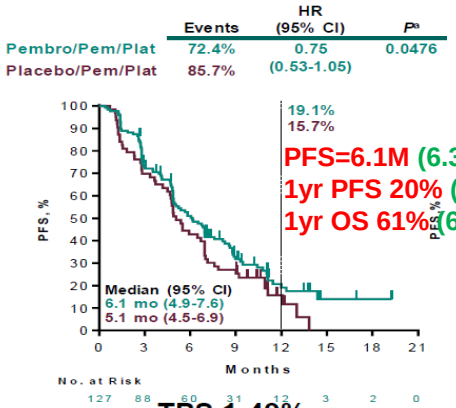


Which Regimen in Low PDL1 expression ?

KEYNOTE 189 (407)

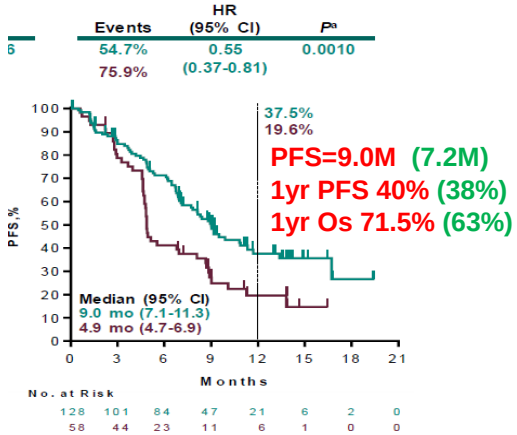
Pembro+chemo

TPS <1%



PFS=6.1M (6.3M)
1yr PFS 20% (25%)
1yr OS 61% (63%)

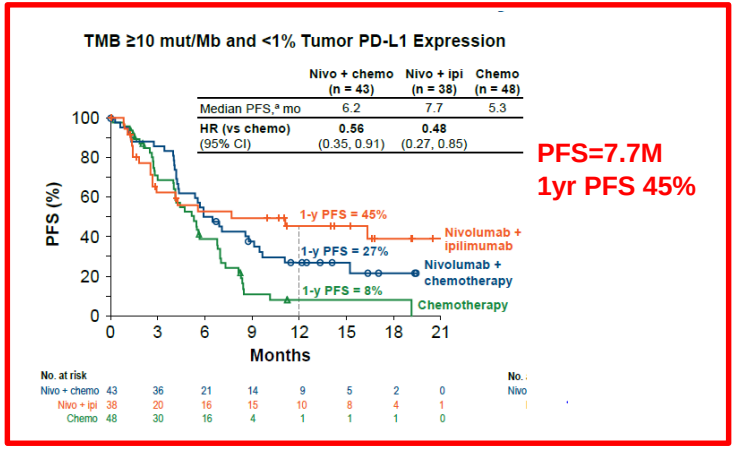
TPS 1-49%



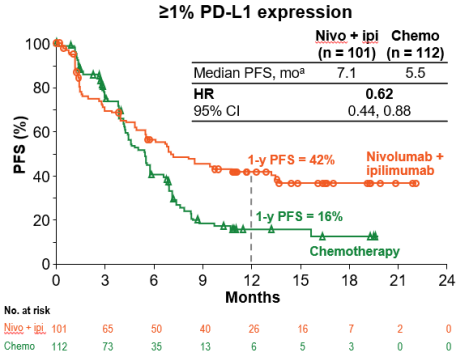
PFS=9.0M (7.2M)
1yr PFS 40% (38%)
1yr Os 71.5% (63%)

CheckMate 227

(TMB≥10mut/Mb) Ipi/Nivo



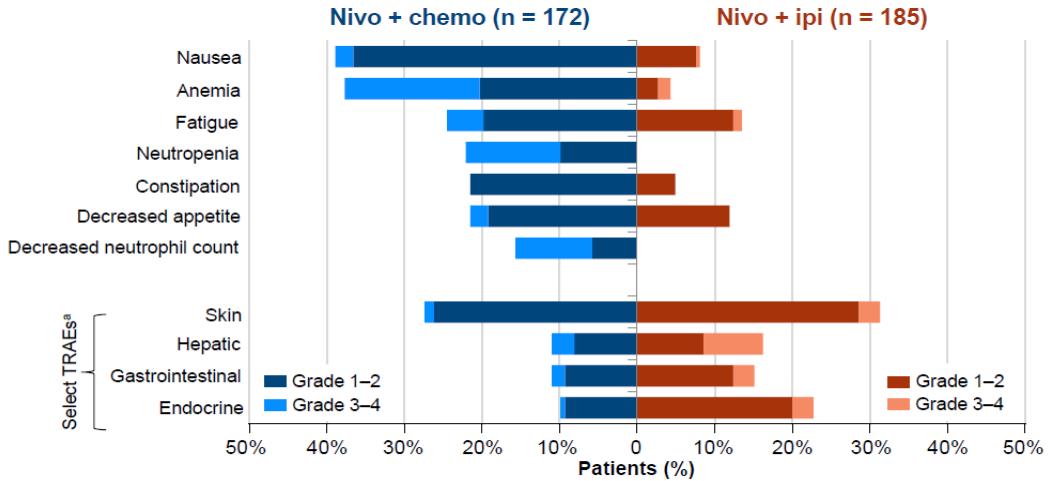
PFS=7.7M
1yr PFS 45%



PFS=7.1M
1yr PFS 42%

Safety Summary of Treatment-Related AEs

	Nivolumab + chemotherapy (n = 172)		Nivolumab + ipilimumab (n = 185)		Chemotherapy (n = 183)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE,[a] %	92	52	74	25	77	35
TRAE leading to discontinuation,[b] %	13	8	16	10	14	9
Median number of doses received, n	8.5 for nivolumab (Q3W) 4–7 for chemo (Q3W)		8.0 for nivolumab (Q2W) 3.0 for ipilimumab (Q6W)		4–7 for chemo (Q3W)	



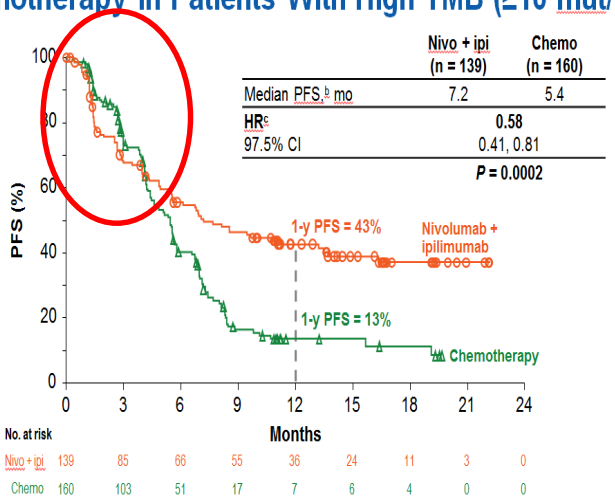
- TRAEs in the chemo arm were consistent with prior reports[1,2]

Challenges of TMB for "Patient Selection" for IO

- **TMB is not ideal predictive biomarker, either**
- **TMB is not ready yet in clinical practice**

CheckMate 227: Nivo + Ipi in 1L NSCLC With High TMB (≥10 mut/Mb)

Co-primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)[a]



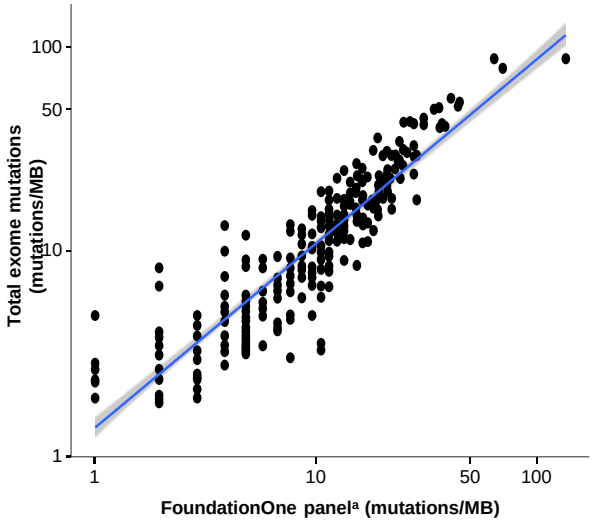
	Nivo + ipi (n = 139)	Chemo (n = 160)
Median PFS,[b] mo	7.2	5.4
HR[c]	0.58	
97.5% CI	0.41, 0.81	
	P = 0.0002	

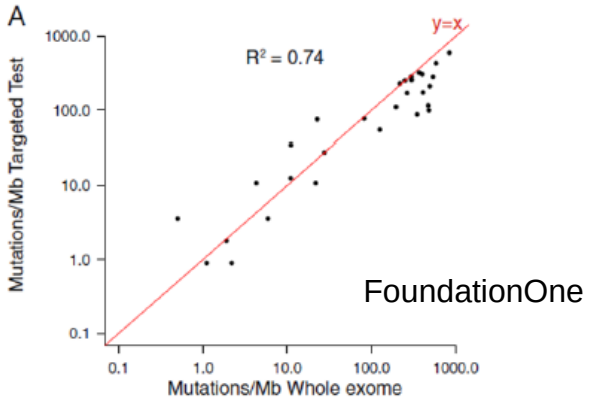
- In patients with TMB <10 mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)[d]

[a]Per blinded independent central review (BICR); median (range) of follow-up in the co-primary analysis population was 13.6 mo (0.4, 25.1) for nivo + ipi and 13.2 mo (0.2, 26.0) for chemo; [b]95% CI: nivo + ipi (5.5, 13.2 mo), chemo (4.4, 5.8 mo); [c]95% CI: 0.43, 0.77 mo; [d]The *P*-value for the treatment interaction was 0.0018

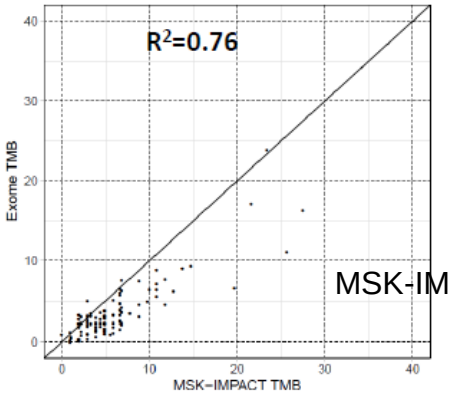
15

High Concordance rate between Whole Exome Sequencing *vs* Targeted gene panel





FoundationOne



MSK-IMPACT

Frampton GM, et al. Nat Biotechnol 2013;31:1023–1031
Chalmerss wt al Gen Medicine 2017
Zehir Nat Med 2017

Challenges of TMB for “Patient Selection” for IO

- TMB is not perfect predictive biomarker
- **TMB is not ready yet in clinical practice**
  - **Cost**
  - **Tissue availability**
  - **Turn around time (TAT)**
  - **No standard platform for NGS**
    - **Variable cut off value for TMB**
    - **Different gene numbers**

Ongoing Clinical Trials of anti-CTLA-4 + anti PD/PDL1

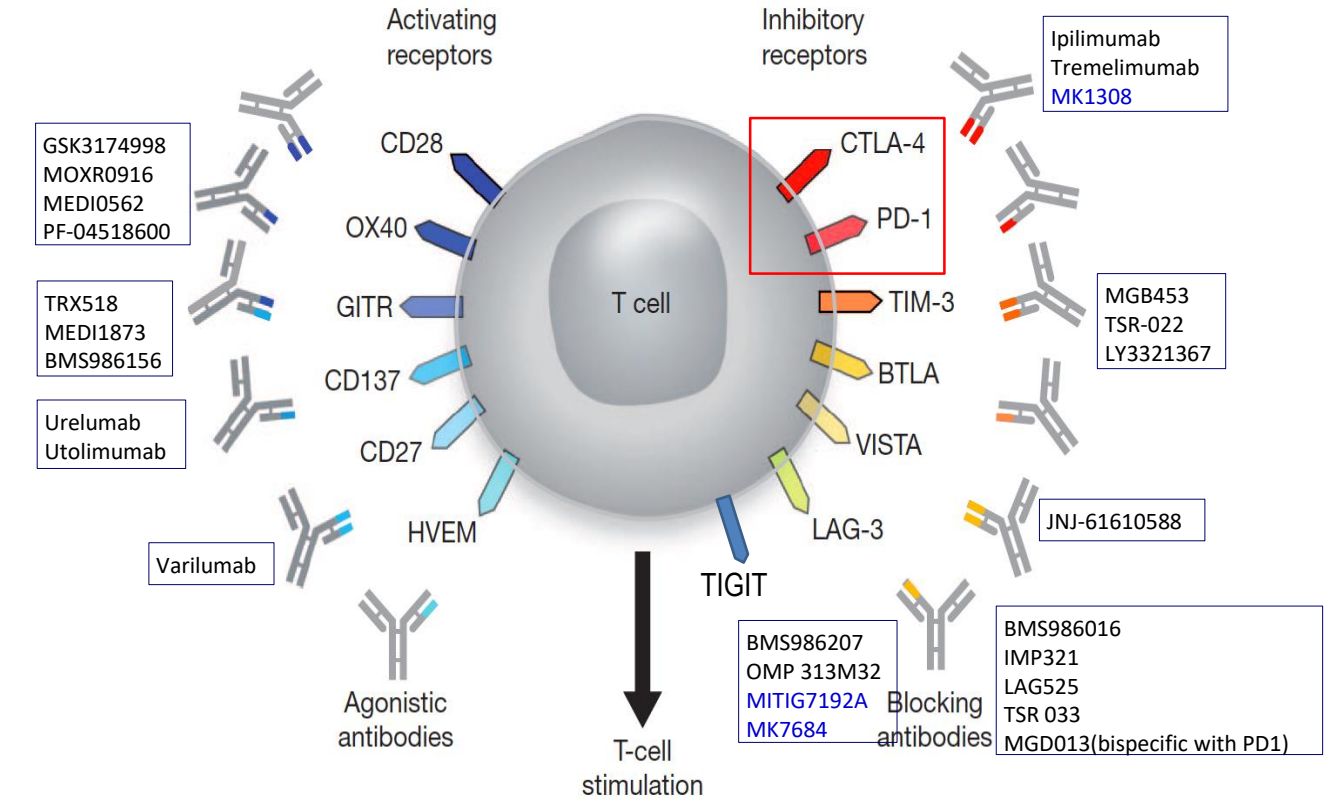
Study	N	Design	Primary end point
MYSTIC*	675	Durvalumab + Tremelimumab Durvalumab Platinum doublets	PFS
NEPTUNE	800	Durvalumab +Tremelimumab Platinum doublets	OS

* Mystic did not meet the primary end point

Other IO + IO Combinations

Costimulatory receptors

Coinhibitory receptors

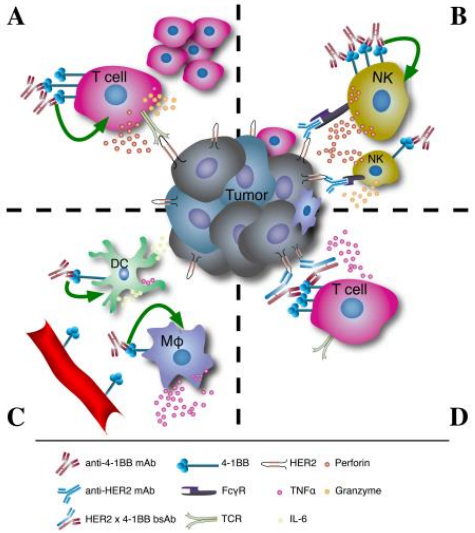


Mellman et al. Nature 2011

Phase 1/2 Trial of Urelumab (Anti 4-1BB) + Nivolumab

- 4-1 BB (CD1367) is an inducible costimulatory receptor expressed on activated T cell, NK cells, DC

- Previous high dose : severe hepatotoxicity
- Urelumab 3 or 8mg q 4 weeks + nivolumab 3mg/kg or 240mg iv q 2 weeks
- 46 malignant melanoma **ORR 50% (50% for PDL1 + 47% PDL1 –)**
- One NSCLC, one HN has response
- No significant added toxicity

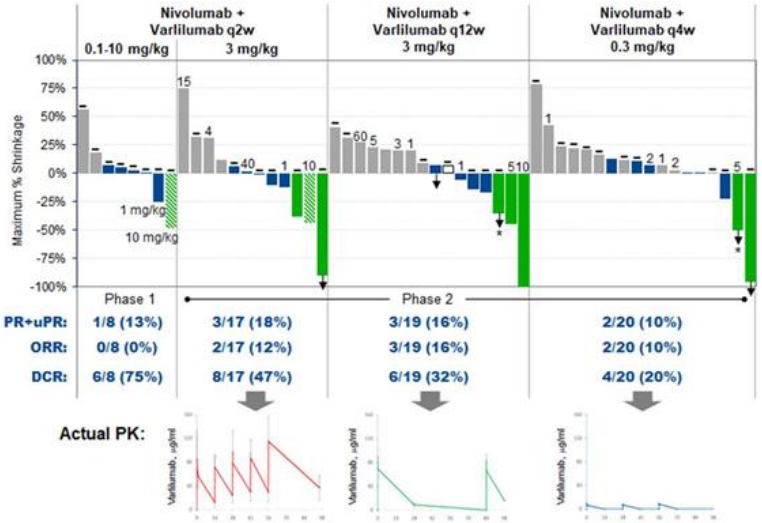


Massarellin et al SITC 2016

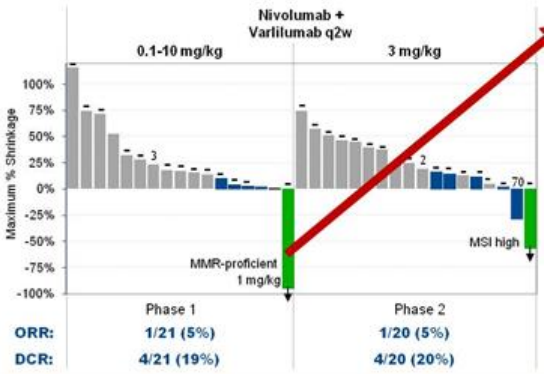
Phase I/2 Trial of Varlilumab (Anti-CD27) + Nivolumab

- CD27 is a member of TNF receptor superfamily expressed on most T cells/B/NK
- CD27 activation leads cell survival, activation and proliferation
- Varlilumab is fully human IgG1 CD 27 agonist mAb
- Varlilumab 3mg/kg q 2 weeks + nivolumab 240mg q 2 weeks
- Expansion cohort with ovarian cancer and colon cancer was presented
- Well tolerable and no additive toxicity

Ovarian cancer



Colon cancer

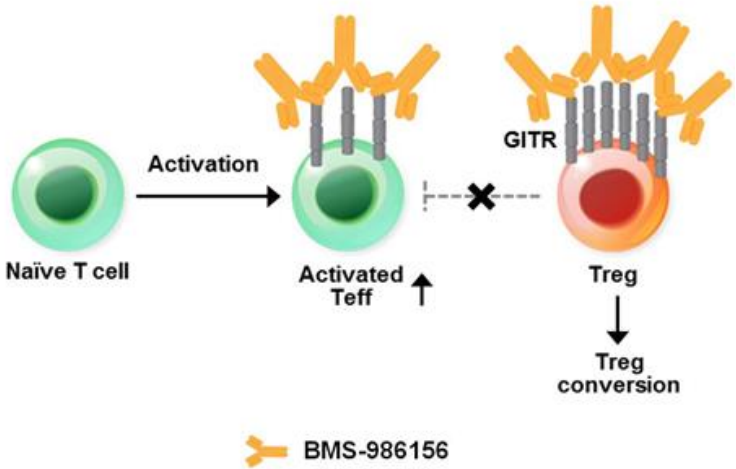


Sanborn et al ASCO 2018

Phase I Trial of BMS-986156 (Anti-GITR) + nivolumab

- GITR is a costimulatory receptor upregulated on T cell activation
- Intratumoral Treg express higher levels of GITR than Teffs
- BMS 986156 is a fully human IgG1 agnosit mAb that binds to GITR
  - Incresing Teff survival and function
  - Reducing Tre-medicated supression of Teffs
  - Promoting Treg reduction through conversion to other immune cells (eg, Teffs)

- Adverse events: fever (30%), chills (16%), fatigue (14%)



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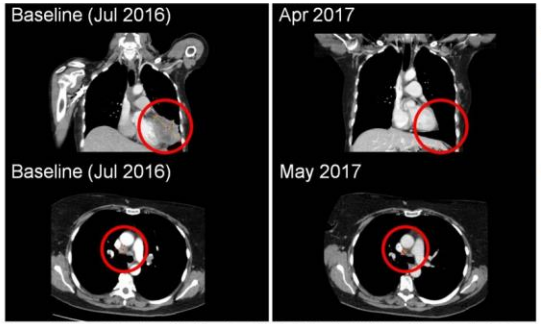
Tumor Type Known to Have High GITR Expression: Response to BMS-986156 + Nivolumab in a Patient With Cervical Cancer

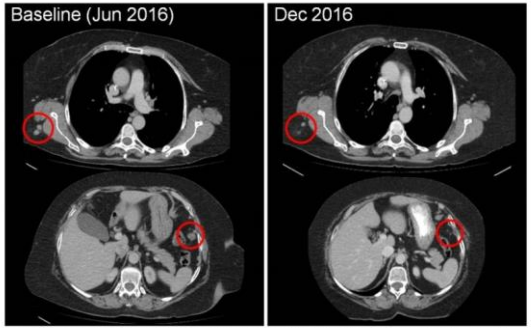


- Cervical cancer has been associated with high GITR expression[1-3]
- Patient (44 years old) with metastatic cervical cancer had 3+ prior lines of therapy (chemotherapy ± VEGF inhibitor)
- Partial response with BMS-986156 240 mg + nivolumab 240 mg
  - Best change in tumor burden was −62%
  - Response is ong

Images provided by Tarek Meniawy, Linear Clinical Research and Sir Charles Gairdner Hospital, University of Western Australia, Australia.

1. Padovani CT et al. *Rev Soc Bras Med Trop.* 2013;46:288–292; 2. Visser J et al. *Clin Exp Immunol.* 2007;150:199–209; 3. Bristol-Myers Squibb. Data on file.

Response After Progression on Anti–PD-1 Therapy: BMS-986156 + Nivolumab in a Patient With Melanoma



- Patient (59 years old) with metastatic melanoma had 3 prior lines of therapy
  - BRAF inhibitor
  - PD-1 inhibitor (pembrolizumab [Feb to May 2014]; best response was progressive disease)
  - BRAF + MEK inhibitor
- Partial response with BMS-986156 100 mg + nivolumab 240 mg
  - Best change in tumor burden was −41%
  - Duration of response at data cutoff was 24 weeks; response is still ongoing

Images provided by Matteo S. Carlino, Crown Princess Mary Cancer Centre, Westmead Hospital and The University of Sydney, Australia.

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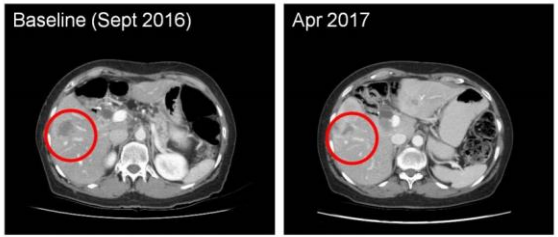
Tumor Type Not Typically IO Responsive: Response to BMS-986156 + Nivolumab in a Patient With Adenocarcinoma of the Ampulla of Vater



Images provided by Jennifer L. Spratlin, Cross Cancer Institute, University of Alberta, Canada.

- Patient (69 years old) with adenocarcinoma of the ampulla of Vater had 3 prior lines of chemotherapy
- Partial response with BMS-986156 240 mg + nivolumab 240 mg; best change in tumor burden was −38%
  - Duration of response at data cutoff was 16 weeks; response is still ongoing

IO, immuno-oncology.

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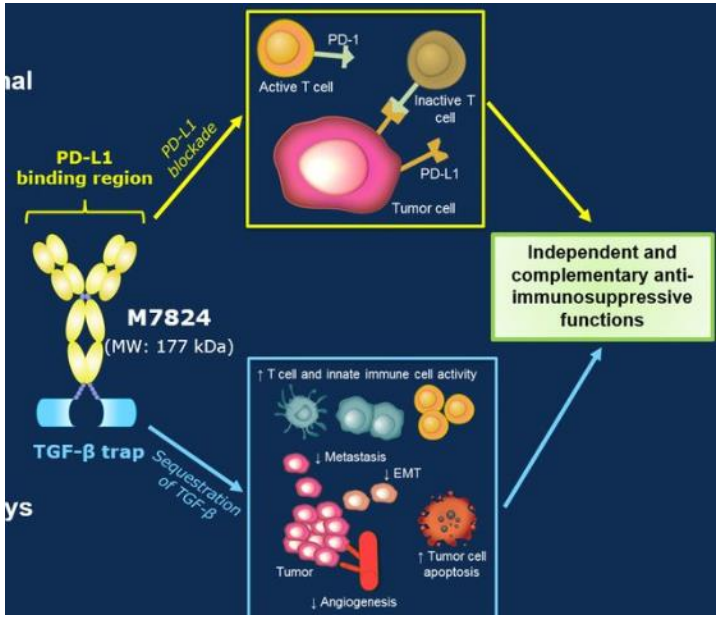
M7824, Bifunctional fusion protein targeting PD-L1 and TGFβ

- TGF-β plays a role in tumor immune escape and promotes tumor progression and metastasis via immune and non-immune related processes
- M7824 is a bifunctional targeting of the TGFβ and PDL1 pathway
  - TGFβ neutralizing trap component: extracellular domain of human TGF-BR2, binds TGFβ1, β2, β3
  - Antibody component: fully human IgG1 mAb against human PDL1



Strauss et al ASCO 2018

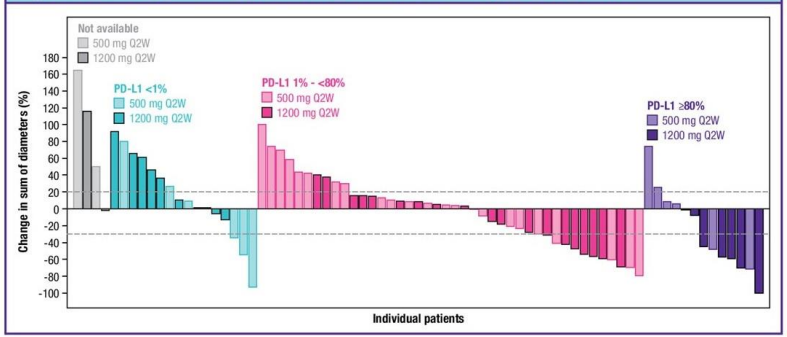
M7824 in NSCLC in phase I study

Table 2. Investigator-assessed efficacy

	500-mg Q2W n=40	1200-mg Q2W n=40	Overall N=80
Best overall response[a], n (%)			
Complete response	0 (0)	1 (2.5)	1 (1.3)
Partial response	8 (20.0)	10 (25.0)	18 (22.5)
Stable disease	3 (7.5)	7 (17.5)	10 (12.5)
Progressive disease	22 (55.5)	21 (52.5)	43 (53.8)
Not evaluable	7 (17.5)	1 (2.5)	8 (10.0)
ORR, n/N (%)			
All[a]	8/40 (20.0)	11/40 (27.5)	19/80 (23.8)
PD-L1+ (≥1%)	6/31 (19.4)	11/27 (40.7)	17/58 (29.3)
PD-L1–high (≥80%)	2/6 (33.3)	5/7 (71.4)	7/13 (53.8)
Disease control rate (DCR), n/N (%)			
All[a]	11/40 (27.5)	18/40 (45.0)	29/80 (36.3)
PD-L1+ (≥1%)	9/31 (29.0)	15/27 (55.6)	24/58 (41.4)
PD-L1–high (≥80%)	2/6 (33.3)	5/7 (71.4)	7/13 (53.8)
Median PFS[a], months (95% CI)			
All	1.4 (1.3–2.7)	2.7 (1.3–8.1)	2.1 (1.4–2.9)
PD-L1+ (≥1%)	1.6 (1.3–3.3)	6.8 (2.6–NR)	2.7 (1.6–6.8)
PD-L1–high (≥80%)	1.5 (0.2–NR)	NR (2.7–NR)	8.1 (1.4–NR)
Median OS, months (95% CI)			
All	10.9 (4.6–NR)	NR (11.8–NR)	12.2 (10.5–NR)
PD-L1+ (≥1%)	10.3 (4.5–NR)	NR (12.2–NR)	NR (10.3–NR)
PD-L1–high (≥80%)	NR (1.0–NR)	NR (9.5–NR)	NR (9.5–NR)

[a]Efficacy according to RECIST v1.1

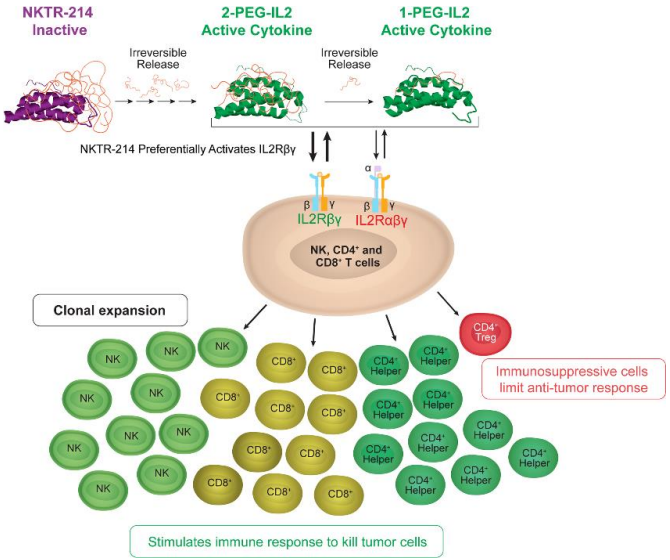
Figure 3. Change in target lesions from baseline by PD-L1 status



Paz-Arest al ASCO 2018

Phase I/2 NKTR-214 (CD122 biased agonist) plus nivolumab

- NKTR-214 is a prodrug of conjugated IL-2 designed with sustained signaling
- Mitigation of rapid immune stimulation to achieve safe, outpatient regimen every 3 week IV dosing
- Biased signaling preferentially activates and expands effector T cells and NK cells over Tregs in the tumor microenvironment
- RP2 dose 0.006mg/kg q 3 week + nivolumab 360mg q 3 week



Diab et al ASCO 2018

Conclusions

- **Ipi + Nivo Combination is tolerable and more effective in pts with high TBM**
- **TMB is a potential predictive genomic biomarker for IO/IO combination, independent of PDL1 expression**
- **Further improvement for test of TMB and long-term follow-up for overall survival are needed for incorporation into clinical practice**
- **Many combination trials with co-stimulatory or co-inhibitory receptor are ongoing with promising in early clinical trials.**
- **Development of biomarker for selection of patients and investigating cancer immunology by “reverse translating” to the lab from clinical studies is needed**