



Associazione Italiana di Oncologia Medica
SEZIONE REGIONE LAZIO

The Best of the Year 2018

ROMA - 19 dicembre 2018

NH Collection Vittorio Veneto

TUMORI DEL POLMONE IMMUNOTERAPIA

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Dove è

KEYNOTE 024 study design



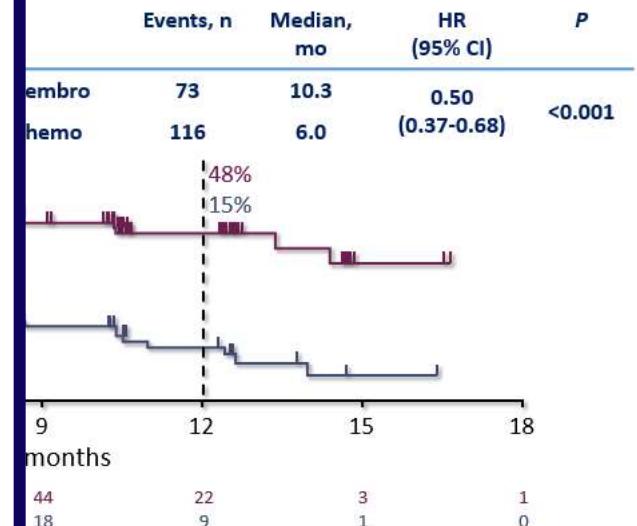
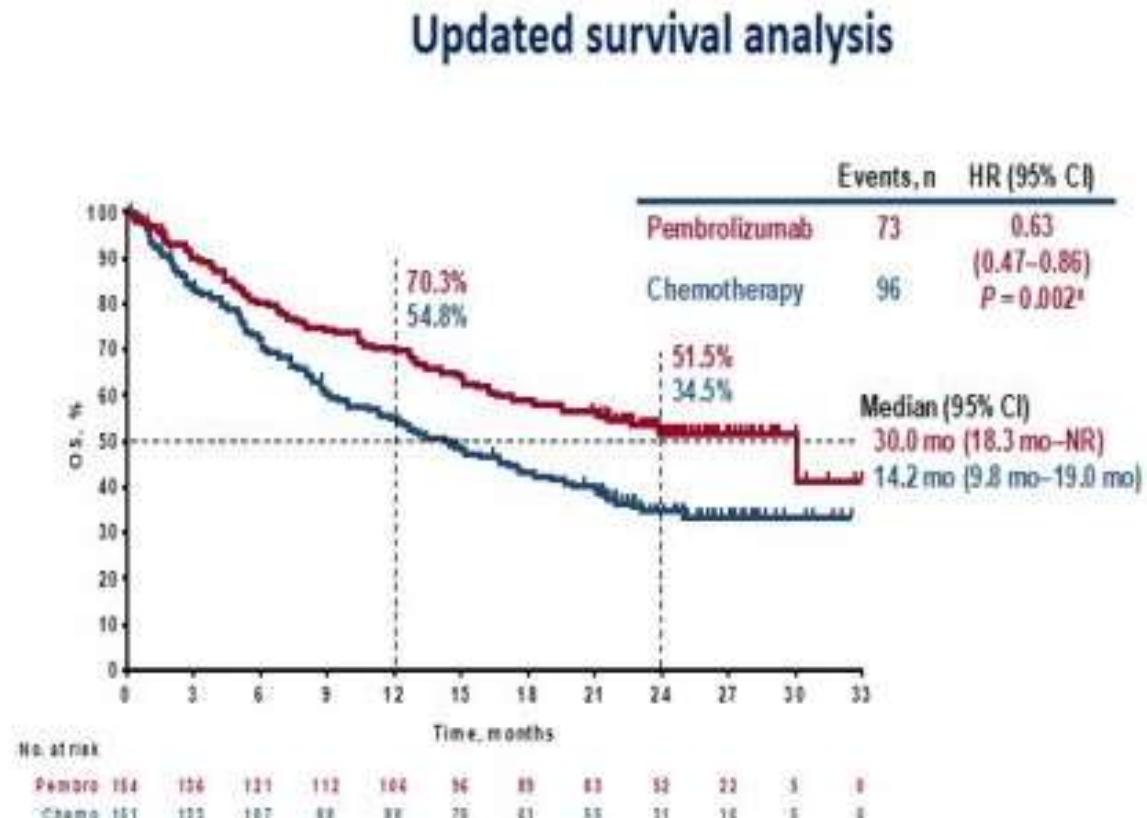
Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent review)

Secondary: OS, ORR, safety

Exploratory: DOR

Eligible for crossover; progressive disease (PD) had to be confirmed by blinded, independent review; all safety criteria had to be met.



E NEI PAZ PD-L1 < 50 % ???

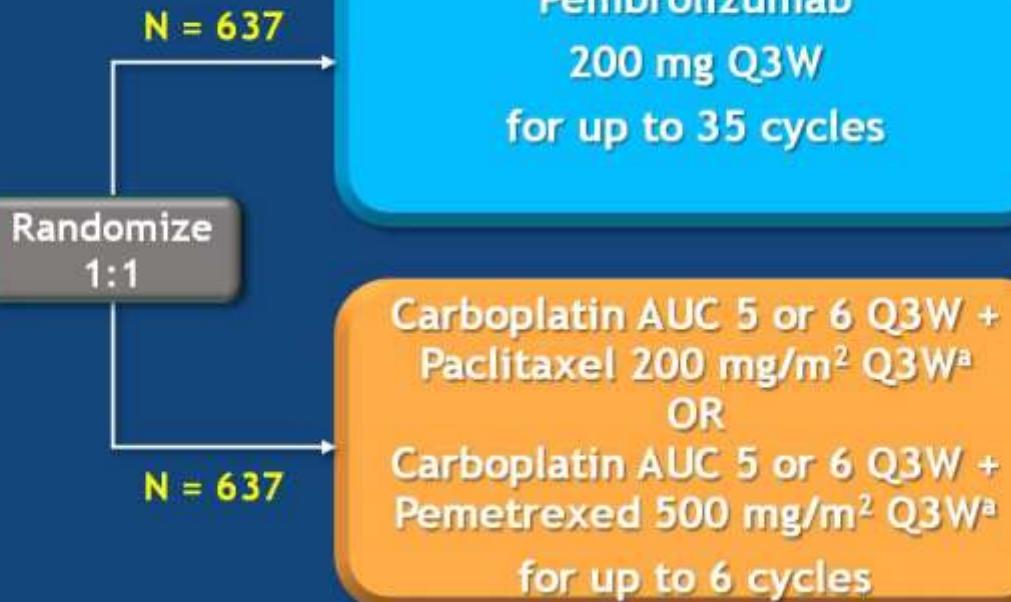
KEYNOTE-042 Study Design

Key Eligibility Criteria

- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS $\geq 1\%$
- No sensitizing EGFR or ALK alterations
- ECOG PS 0 or 1
- No untreated or unstable CNS metastases
- No history of pneumonitis that required systemic corticosteroids

Stratification Factors

- Region (east Asia vs rest of the world)
- ECOG PS (0 vs 1)
- Histology (squamous vs nonsquamous)
- PD-L1 TPS ($\geq 50\%$ vs 1-49%)



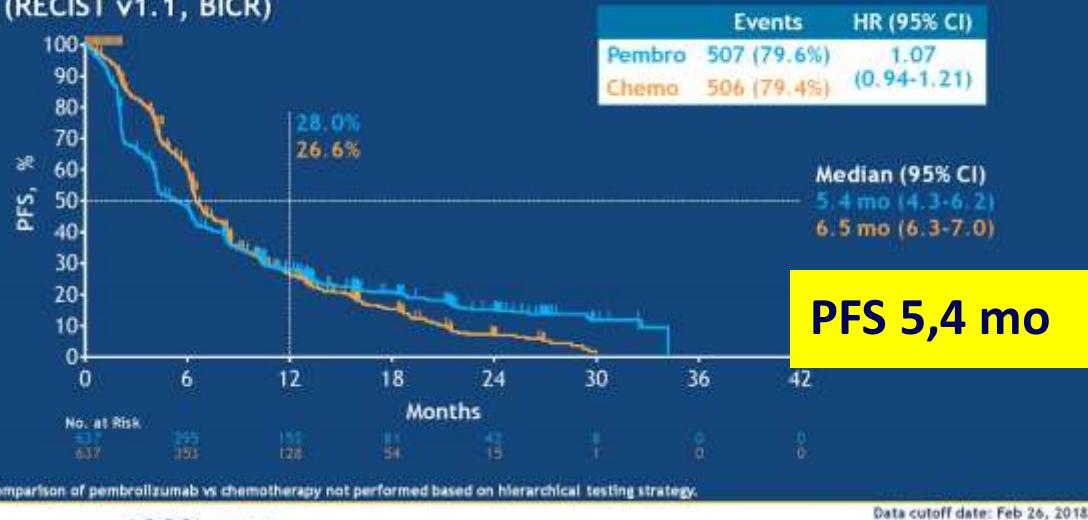
End points

- Primary: OS in PD-L1 TPS $\geq 50\%$, $\geq 20\%$, and $\geq 1\%$
- Secondary: PFS and ORR in TPS $\geq 50\%$, $\geq 20\%$, and $\geq 1\%$; safety in TPS $\geq 1\%$

^aPemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology.

Progression-Free Survival: TPS \geq 1%

(RECIST v1.1, BICR)

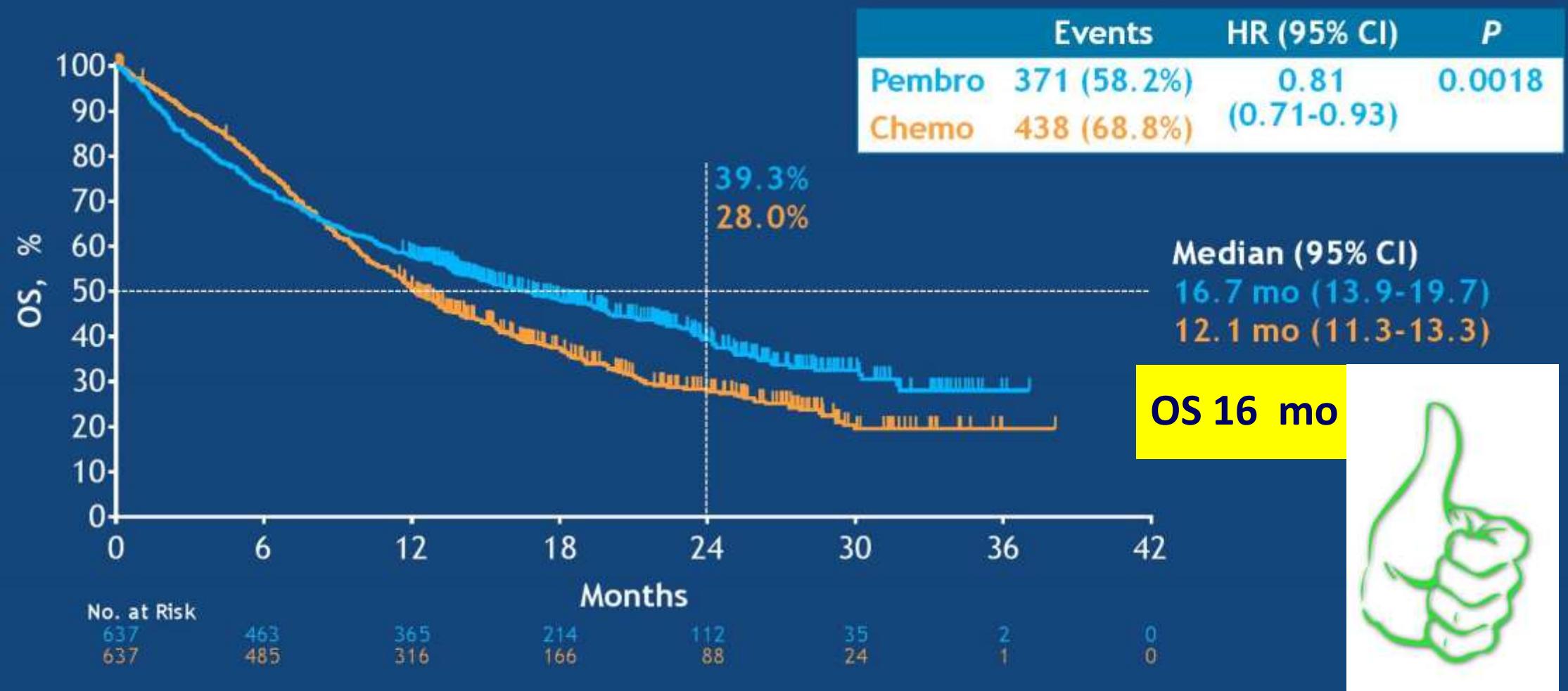


Progression-Free Survival: TPS \geq 50%

(RECIST v1.1, BICR)



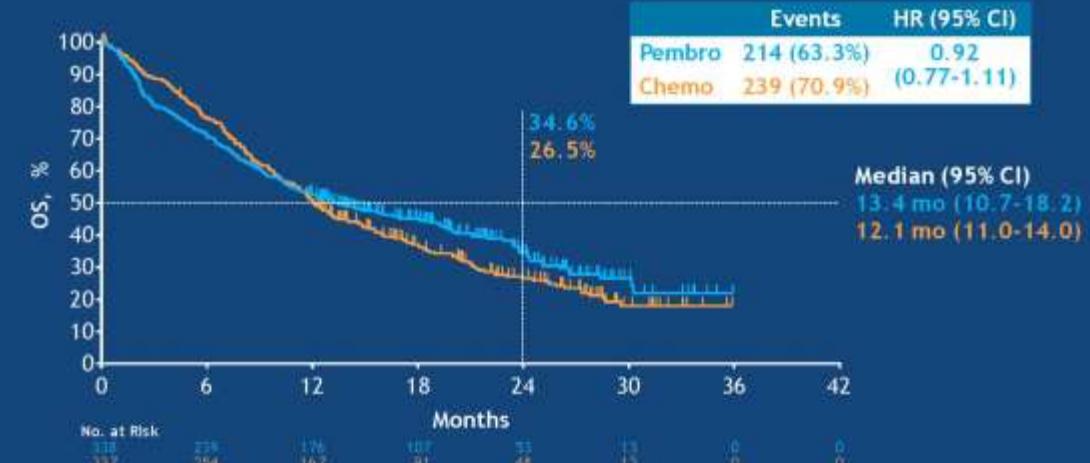
Overall Survival: TPS \geq 1%



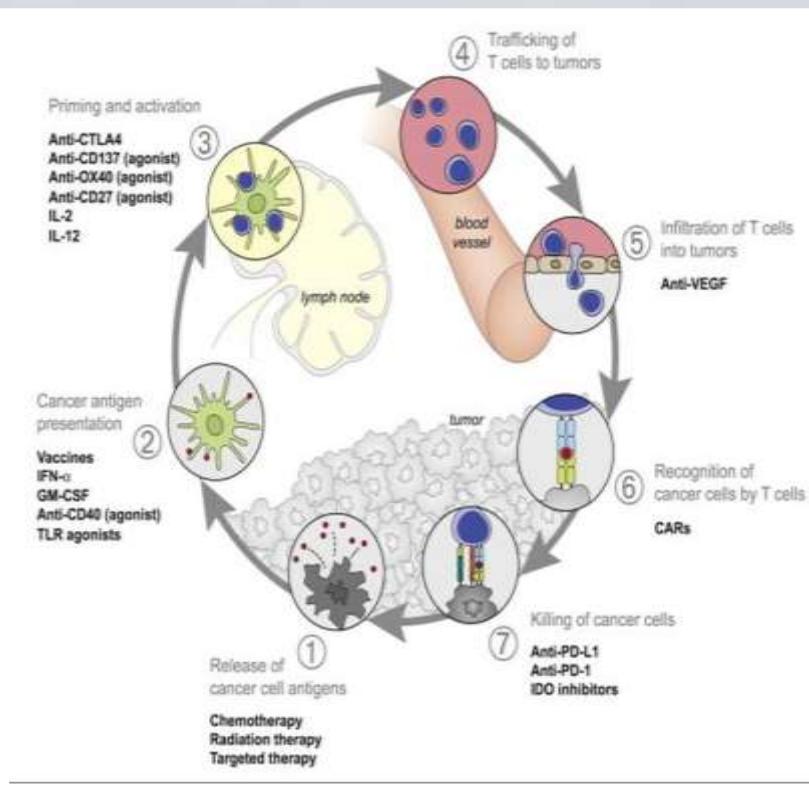
Overall Survival: TPS ≥50%



Overall Survival: TPS ≥1-49% (Exploratory Analysis^a)



COME MIGLIORARE LA RISPOSTA ALL'IMMUNOTERAPIA ?



IMMUNO + TARGET

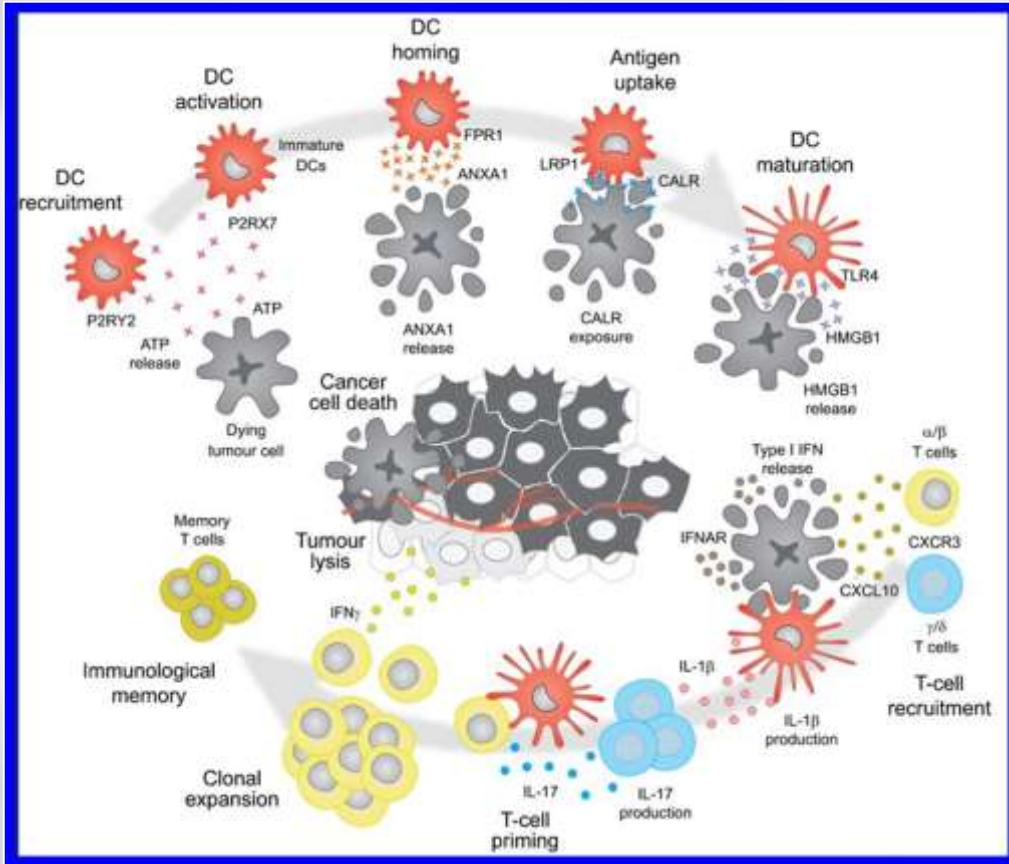
IMP 150

IMMUNO + CHT

KN 189, 407
IMP 132,131

COMBO IMMUNO

CK 227

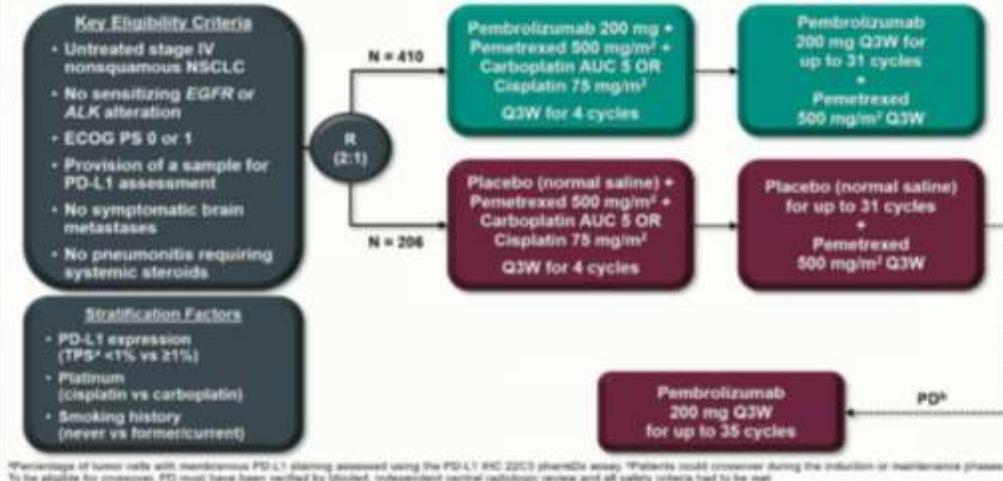


IMMUNO + CHT

KN 189, 407
IMP 132,131

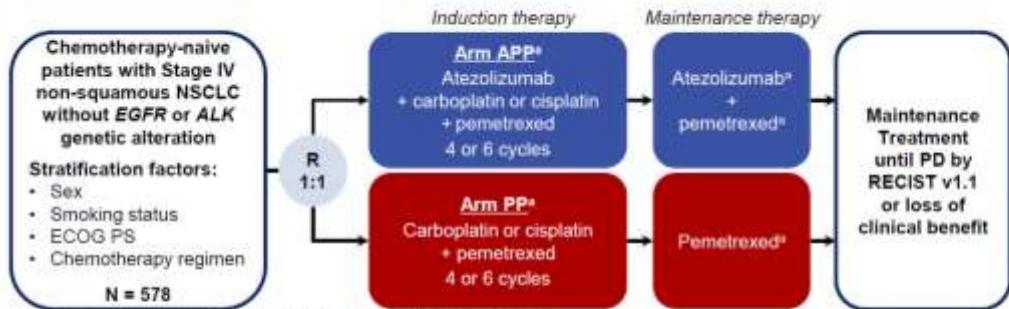
CHT + IMMUNO

KEYNOTE-189 Study Design (NCT02578680)



ADK

IMpower132 Study Design

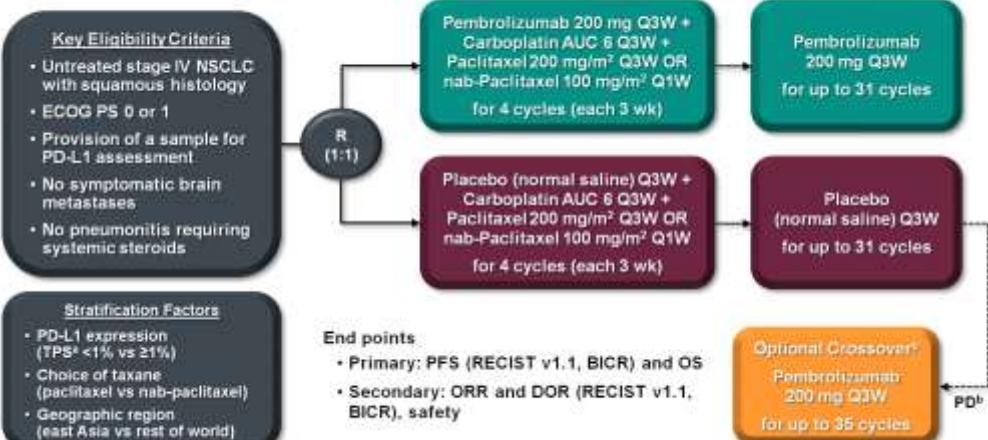


- Co-primary endpoints: INV-assessed PFS and OS
- Secondary endpoints: INV-assessed ORR and DOR, PRO and safety measures
- Exploratory analyses: clinical and biomarker subgroup analyses

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. *Atezolizumab: 1200 mg IV q3w; Carboplatin: AUC 6 mg·min/L/min IV q3w; Cisplatin: 75 mg/m² IV q3w; Pemetrexed: 500 mg/m² IV q3w. NCT02657434. Data cutoff: May 22, 2018.

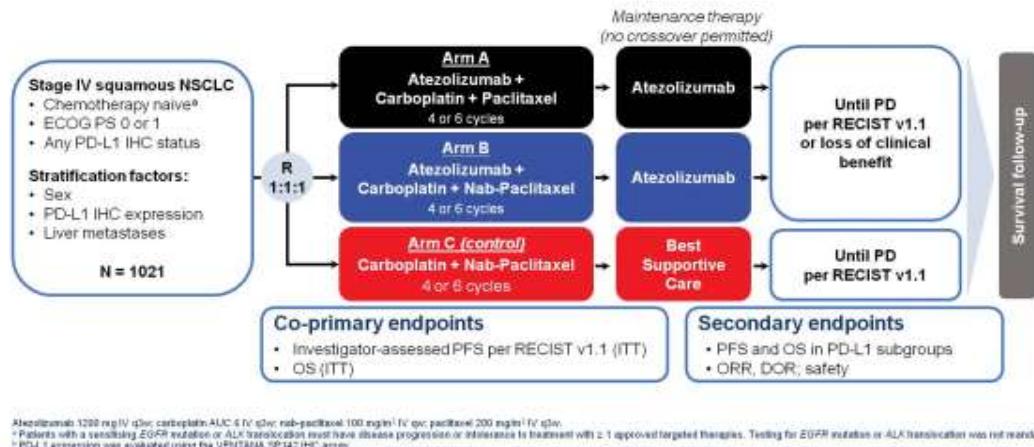
Survival follow-up

KEYNOTE-407 Study Design (NCT02775435)



SQ

IMpower131: Study Design

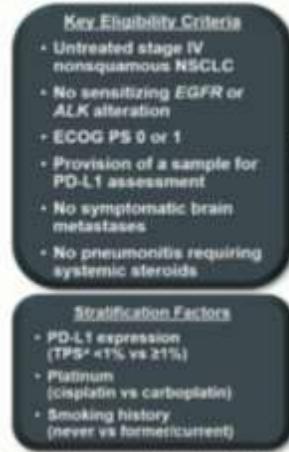


Survival follow-up

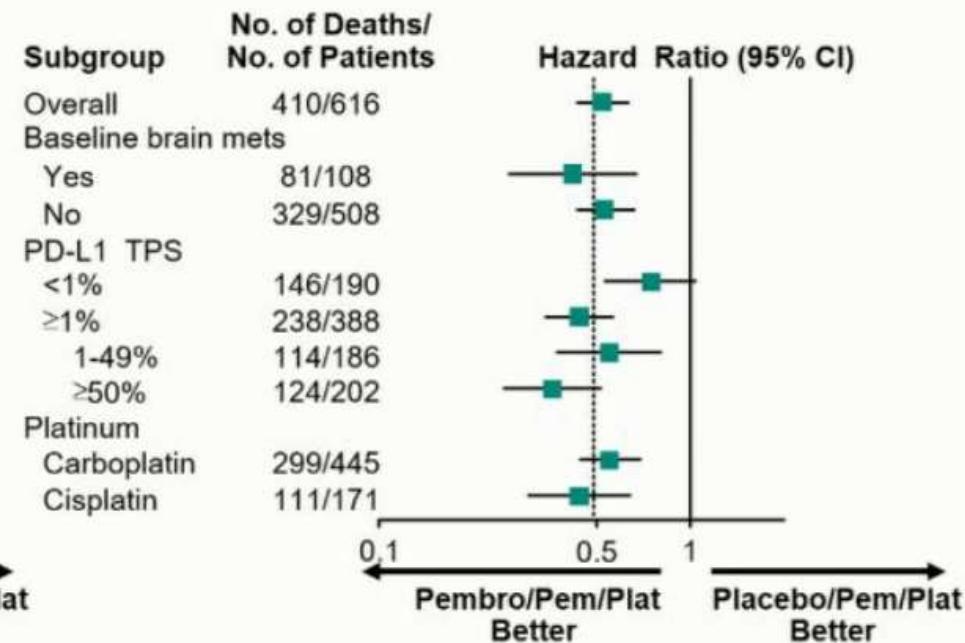
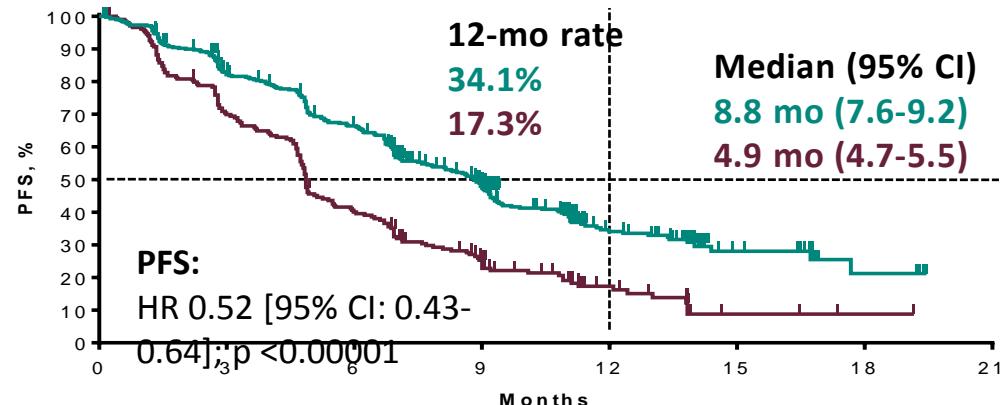
ADK

PFS

KEYNOTE-189 Study Design (NCT02578680)



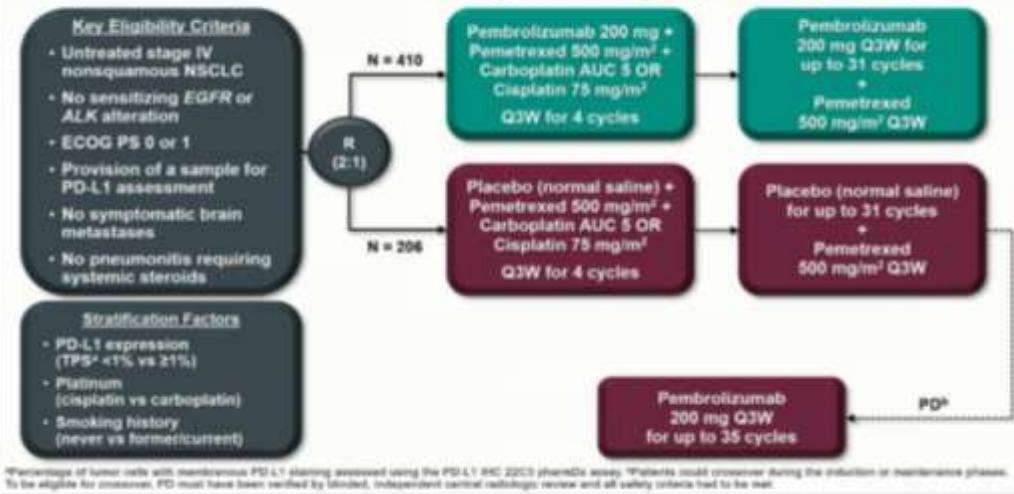
*Percentage of tumor cells with membranous PD-L1 staining assessed using the IHC 22C3 pharmDx assay. *Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria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



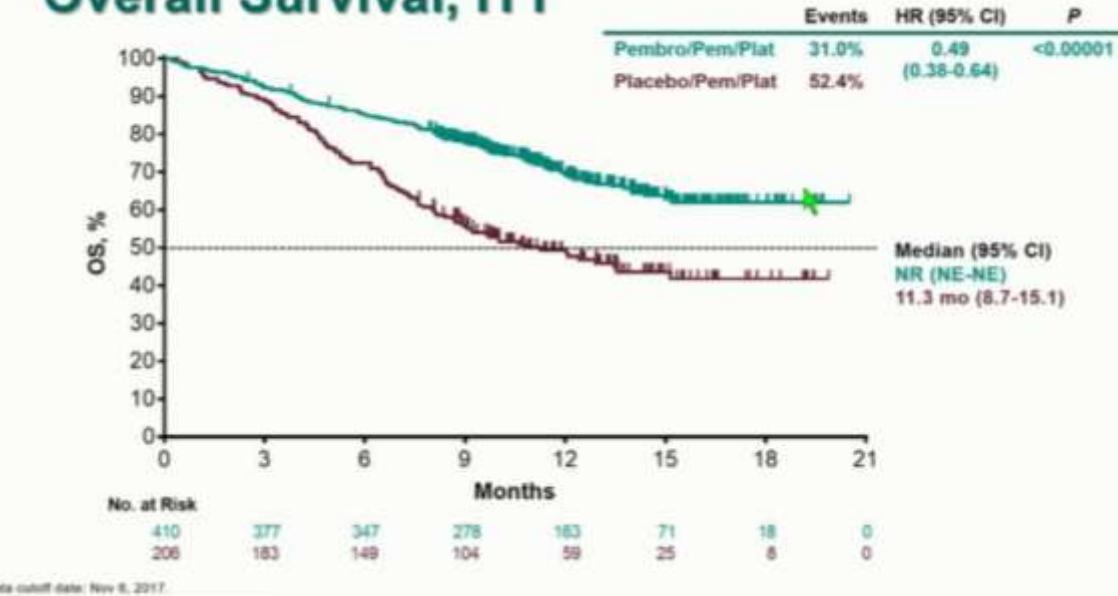
ADK

OS

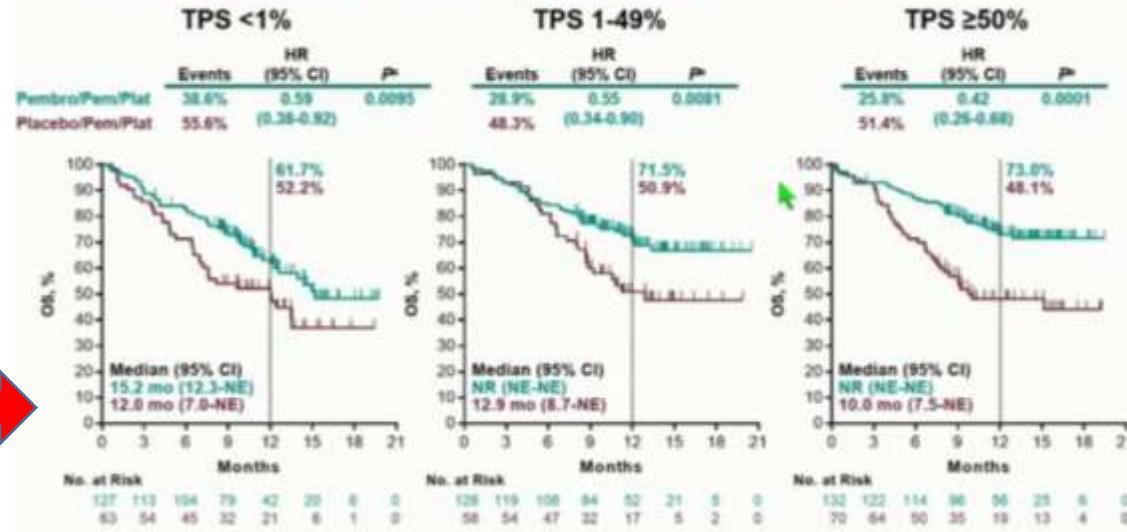
KEYNOTE-189 Study Design (NCT02578680)



Overall Survival, ITT



Overall Survival by PD-L1 TPS

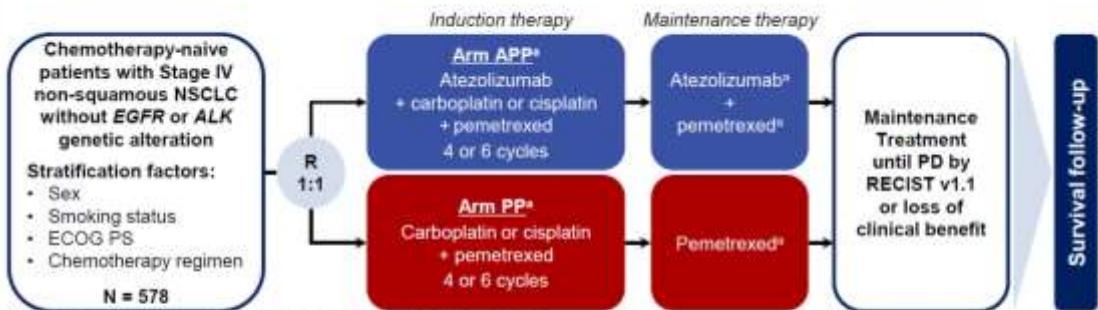


ADK

PFS

Final Investigator-Assessed PFS, ORR and DOR

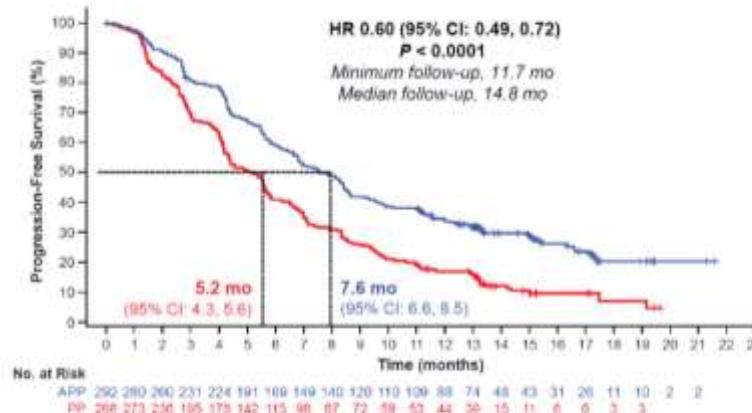
IMpower132 Study Design



- 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

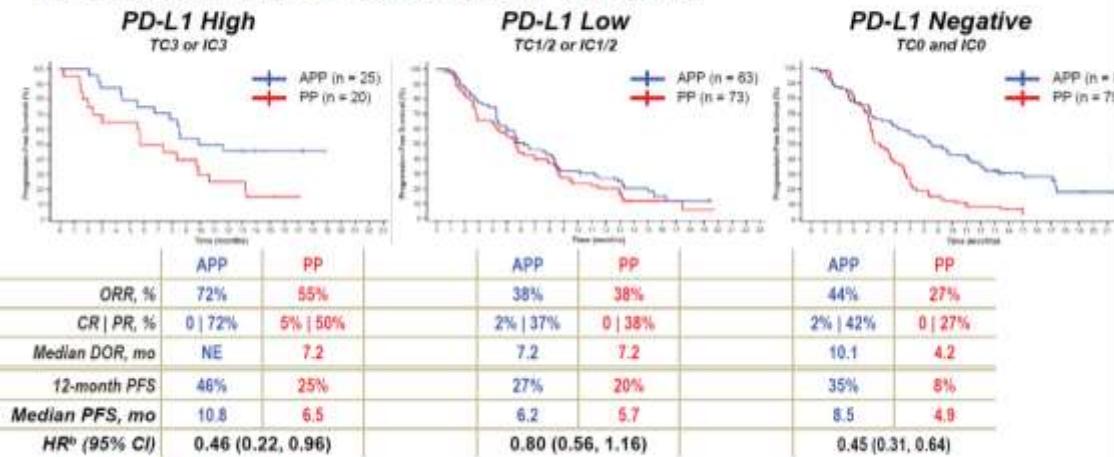
Biomarker-evaluable tissue not mandatory for enrolment (was available from 60% of patients)

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·min/L/min IV q3w; Cisplatin: 75 mg/m² IV q3w; Pembrolizumab: 2 mg/kg IV q3w. NCT02657434. Data cutoff: May 22, 2018.



MUNICH 2018 ESMO congress
a Unstratified median PFS was 7.2 mo with APP and 6.6 mo with PP (stratified HR: 0.758 [95% CI: 0.623, 0.923] P = 0.055)

Exploratory Analysis: PFS by PD-L1 Status in Biomarker-Evaluable Patients^a

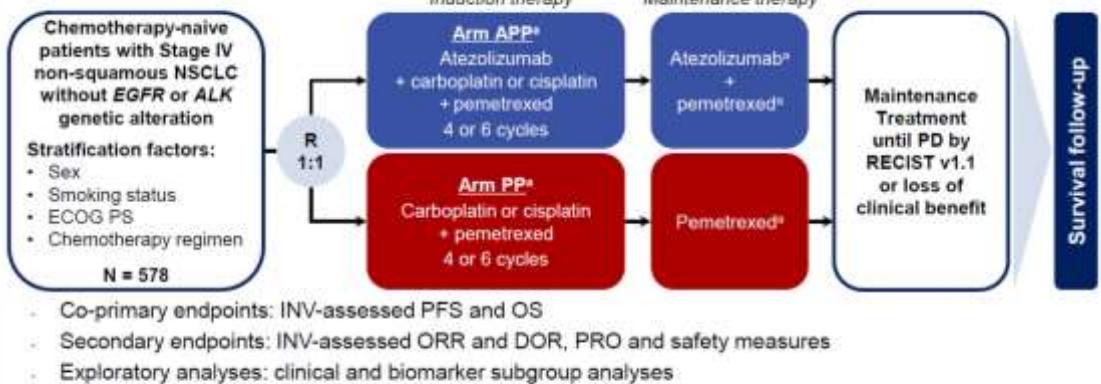


© 2018 ESMO congress
a Unstratified HR. Data cutoff: May 22, 2018.
b Unstratified HR. Data cutoff: May 22, 2018.

PFS 10.8 !!!

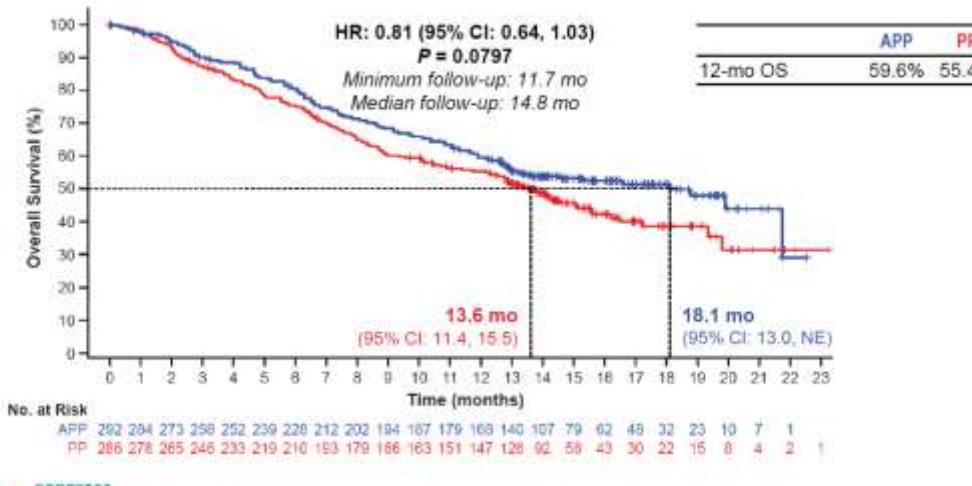
ADK OS

IMpower132 Study Design



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. * Atezolizumab: 1200 mg IV q3w; Carboplatin: AUC 6 mg·min/Lmin IV q3w; Cisplatin: 75 mg/m² IV q3w.
Platinum-based chemotherapy was allowed in both arms. NCT02657434. Data cutoff: May 22, 2018.

Interim OS Analysis



OS analysis at 14.8 months. HR: 0.81 (95% CI: 0.64, 1.03). P = 0.0797. Minimum follow-up: 11.7 mo. Median follow-up: 14.8 mo.

Overall Survival (%)

Time (months)

No. at Risk

APP 292 284 273 258 252 239 228 212 202 194 187 179 168 140 107 79 62 49 32 23 10 7 1
PP 286 278 265 246 233 219 210 193 179 166 163 151 147 128 92 58 43 30 22 15 8 4 2 1

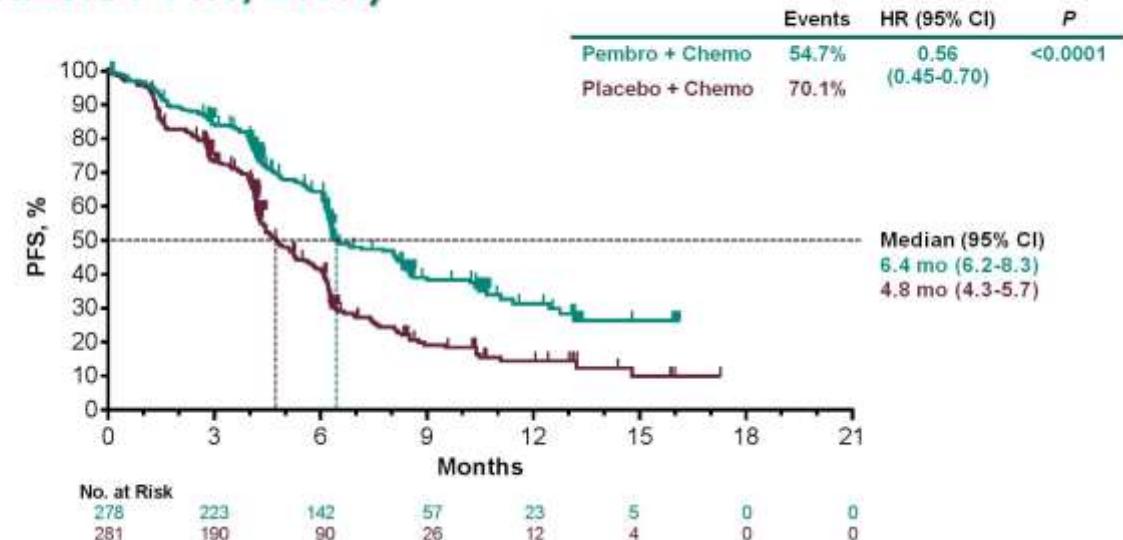


Frequency of OS events: 44% and 49% in arms APP and PP respectively.

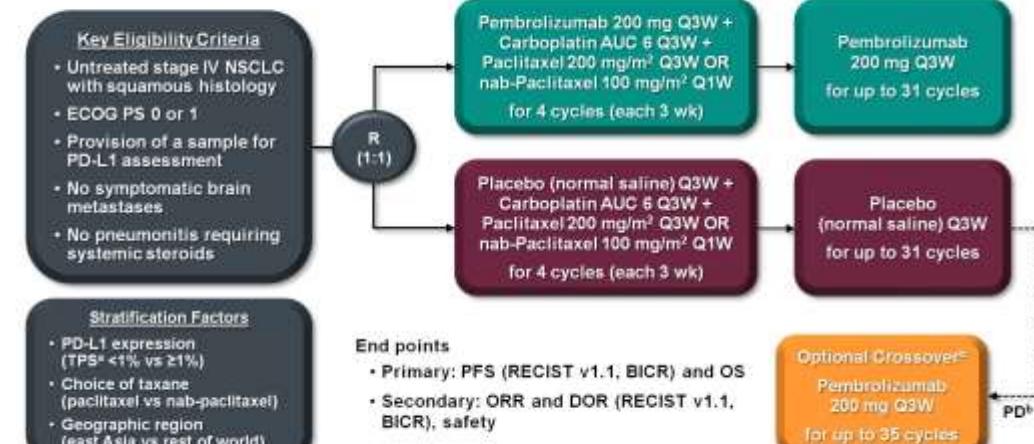
SQ

PFS

Progression-Free Survival at IA2, ITT (RECIST v1.1, BICR)



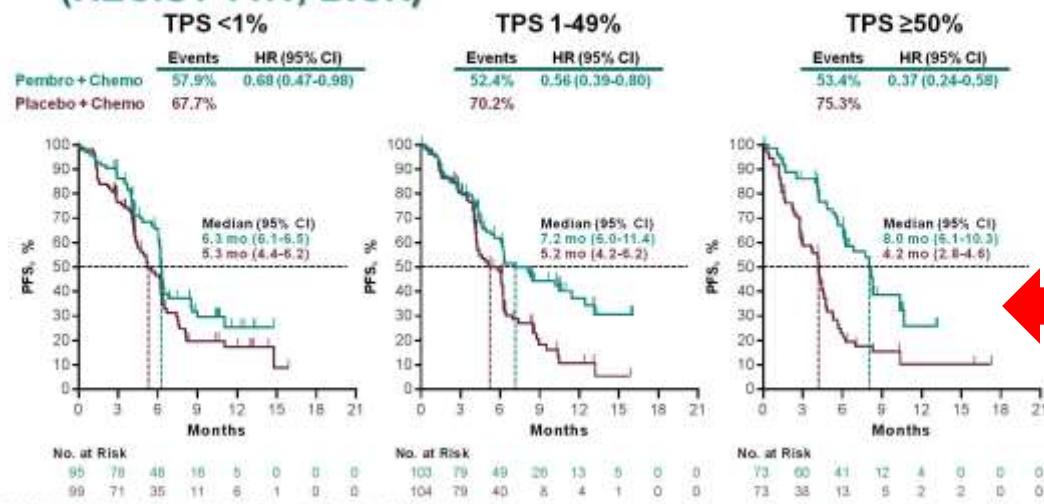
KEYNOTE-407 Study Design (NCT02775435)



BICR, blinded independent central radiologic review. *Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay.

^aPatients 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.

Progression-Free Survival by PD-L1 TPS (RECIST v1.1, BICR)

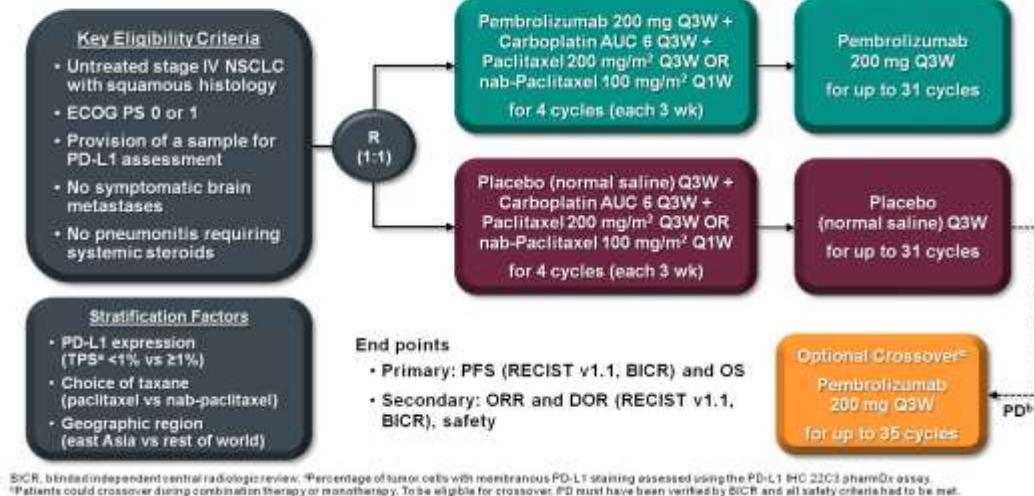


BICR, blinded independent central review. Data cutoff date: Apr 3, 2018.

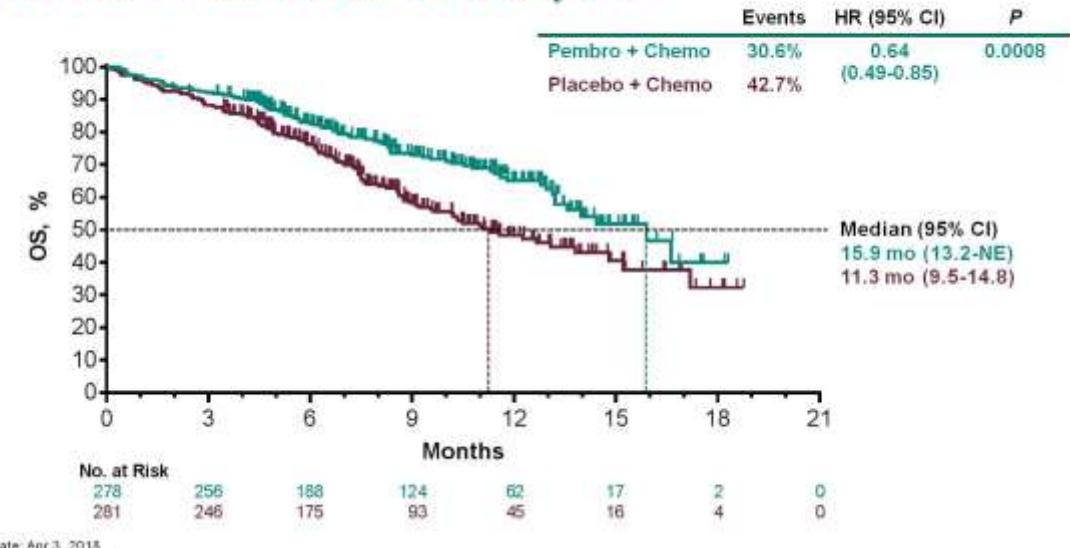
SQ

OS

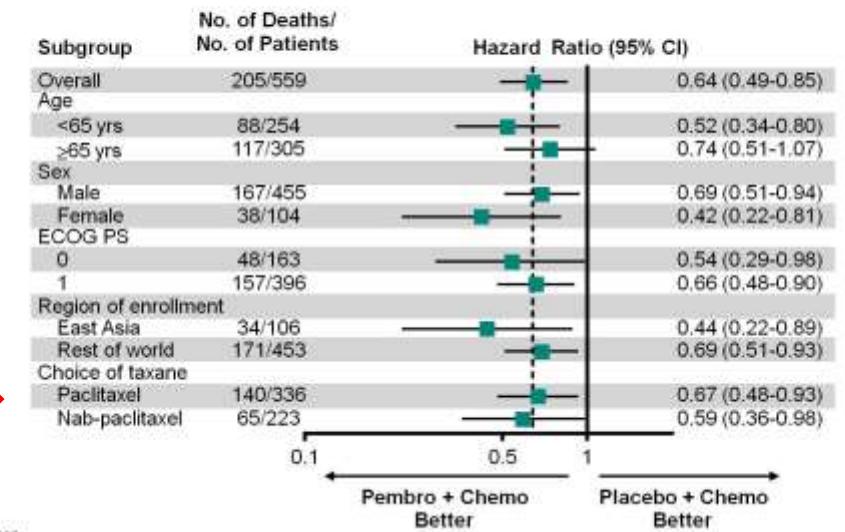
KEYNOTE-407 Study Design (NCT02775435)



Overall Survival at IA2, ITT



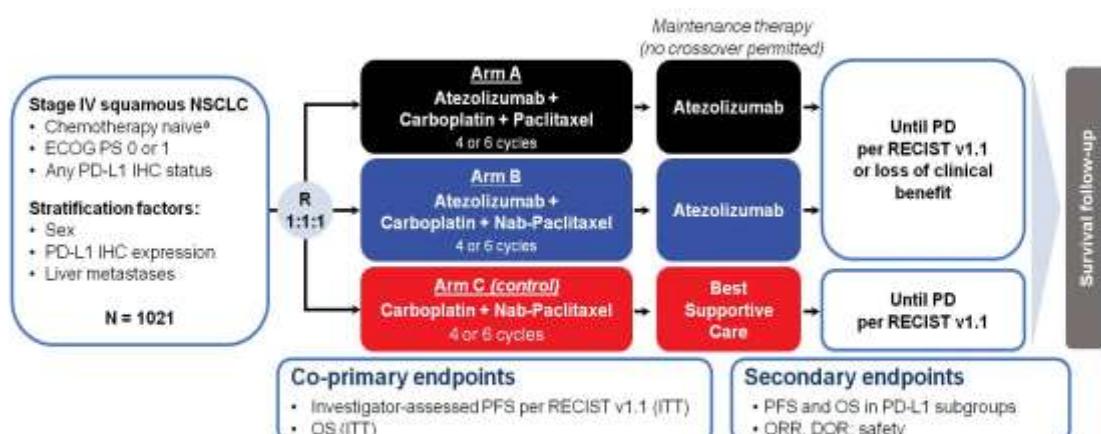
Overall Survival at IA2 in Key Subgroups



SQ

PFS

IMpower131: Study Design



Abscisulimab 1200 mg IV q3w; carboplatin AUC 4 IV q3w; nab-paclitaxel 100 mg/m² IV q3w; paclitaxel 200 mg/m² IV q3w.

*Patients with a sensibilizing EGFR mutation or ALKB transcription must have disease progression or intolerance to treatment with 2 approved targeted therapies. Testing for EGFR mutation or ALKB transcription was not mandatory.

PD-L1 expression was evaluated using the VENTANA SP142 IHC assay.

PRESENTED AT: 2018 ASCO ANNUAL MEETING
#ASCO18

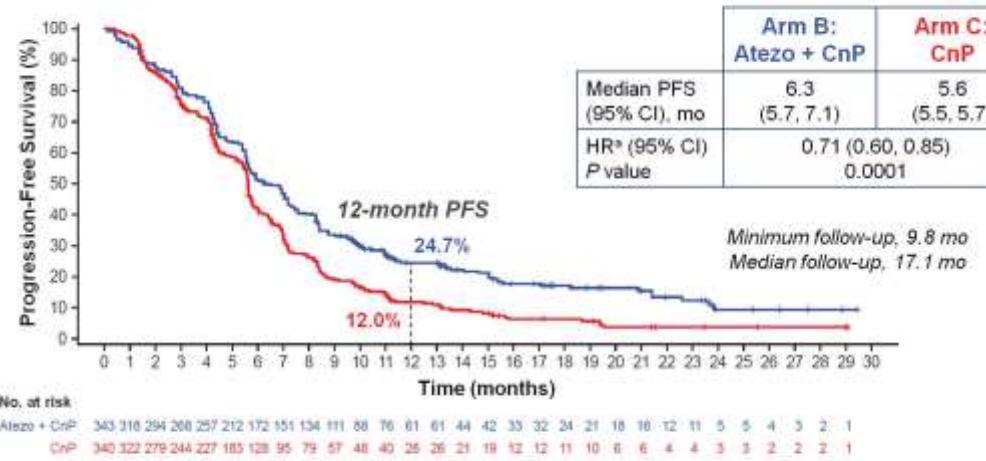
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PRESENTED BY: Jotte R, et al. IMpower131 PFS Analysis.

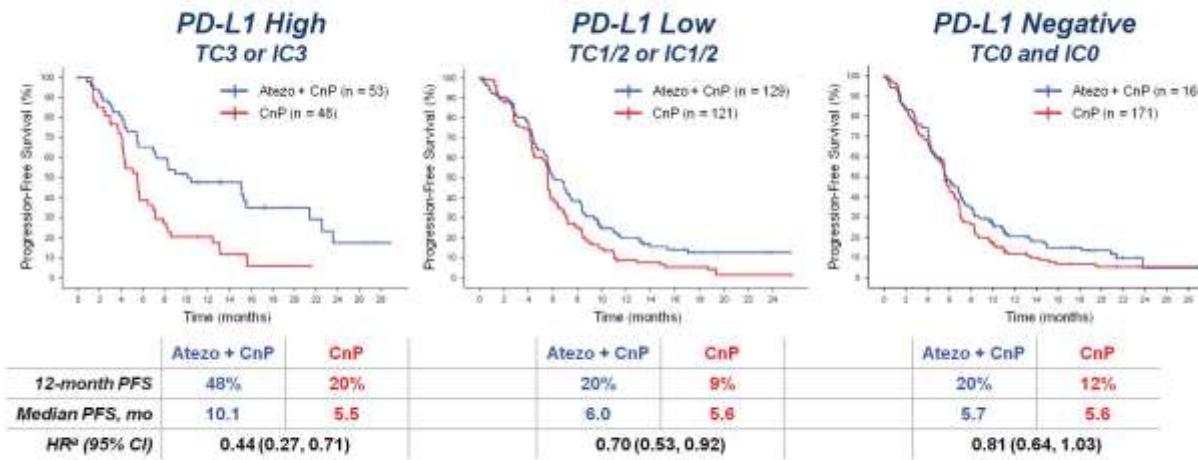
<https://bit.ly/2snPEzb>

PFS 10.1 !!!

INV-Assessed PFS in the ITT Population (Arm B vs Arm C)

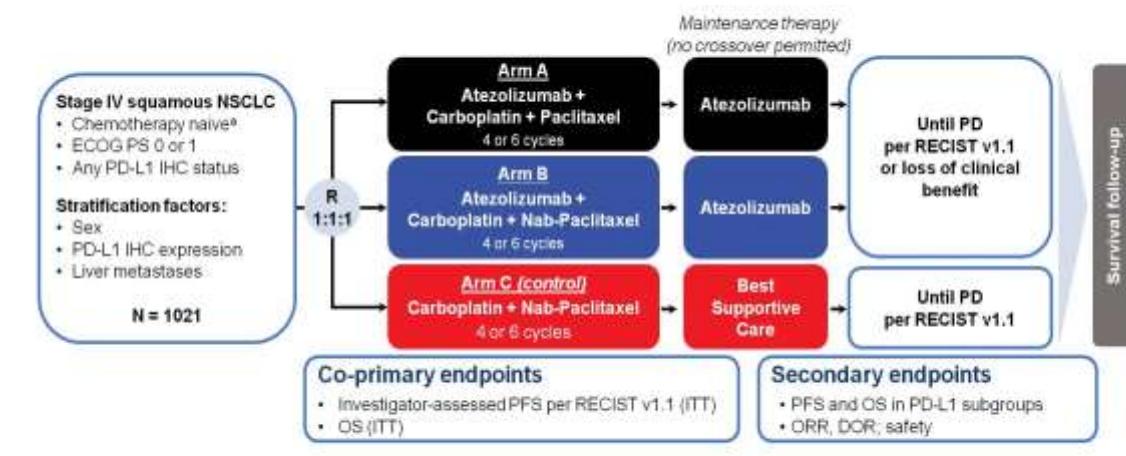


INV-Assessed PFS in PD-L1 Subgroups (Arm B vs Arm C)



SQ OS

IMpower131: Study Design



*Atezolizumab 1200 mg IV q3w; carboplatin: AUC 6 IV q3w; nab-paclitaxel: 100 mg/m² IV q3w; paclitaxel: 200 mg/m² IV q3w.

*Patients with a sensitizing EGFR mutation or ALKB translocation must have disease progression or intolerance to treatment with ≥ 1 approved targeted therapies. Testing for EGFR mutation or ALKB translocation was not mandatory.

†PD-L1 expression was evaluated using the VENTANA SP142 IHC assay.

PRESENTED AT:
2018 ASCO
ANNUAL MEETING

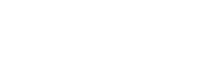
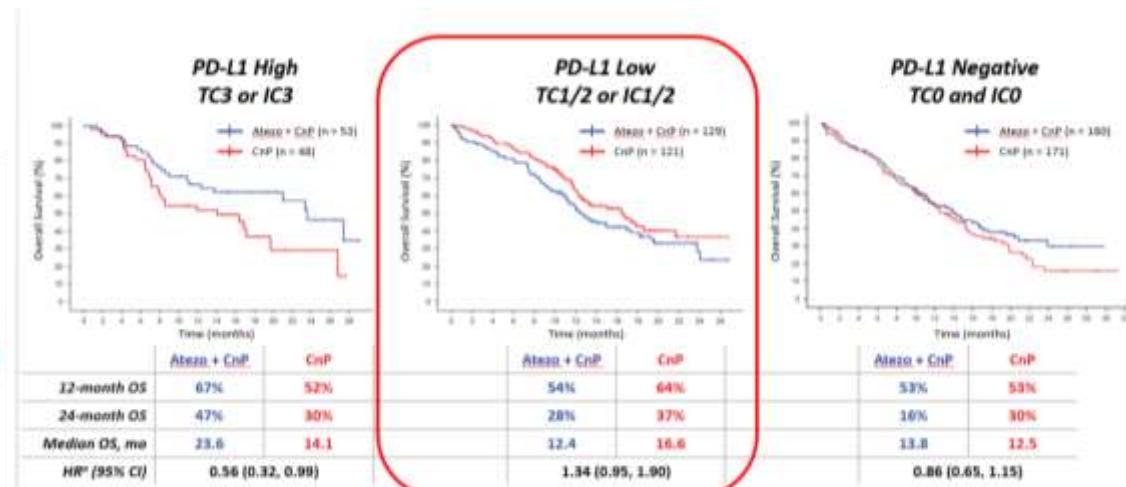
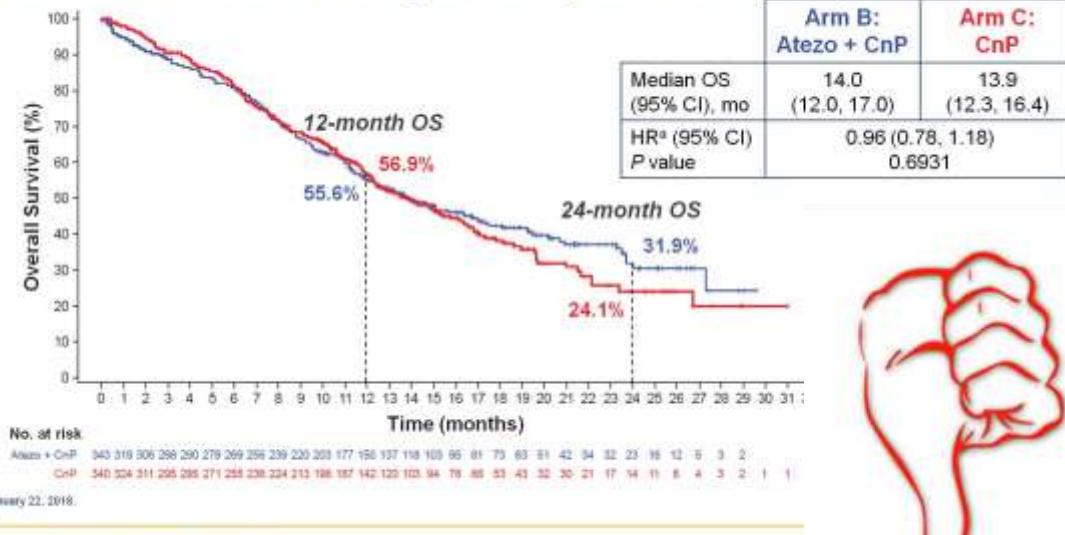
IASCO18
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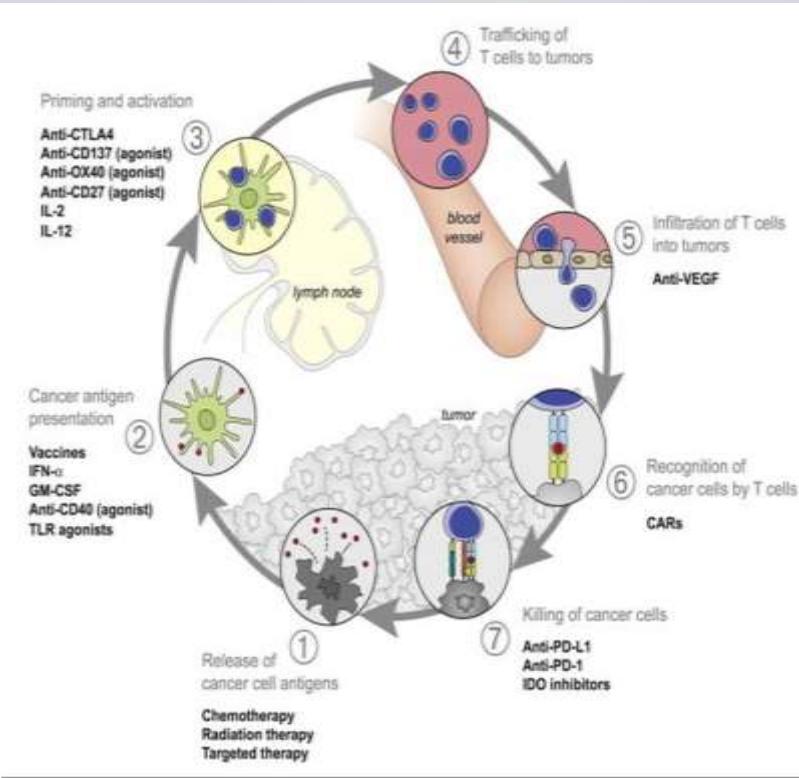
PRESENTED BY: Jotte R, et al. IMpower131 PFS Analysis.

<https://tinyurl.com/2snP>



First Interim OS in the ITT Population (Arm B vs Arm C)





IMP 150

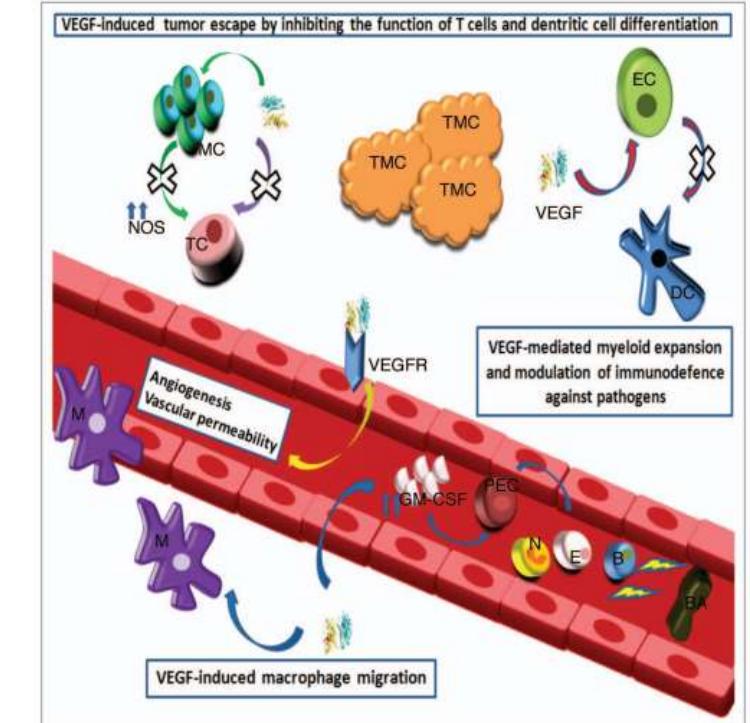
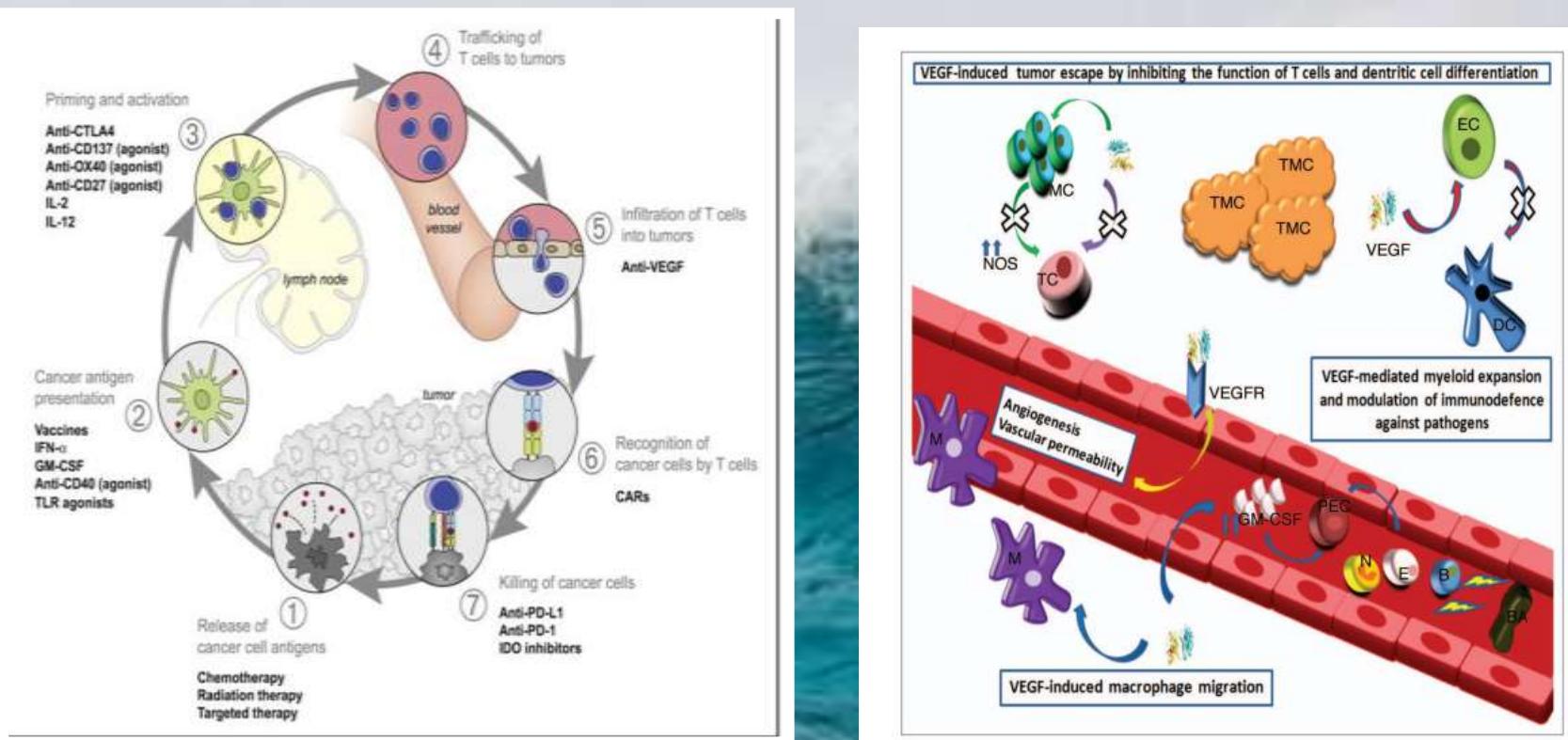
IMMUNO +
TARGET

KN 189, 407
IMP 132,131

IMMUNO + CHT

COMBO IMMUNO

CK 227



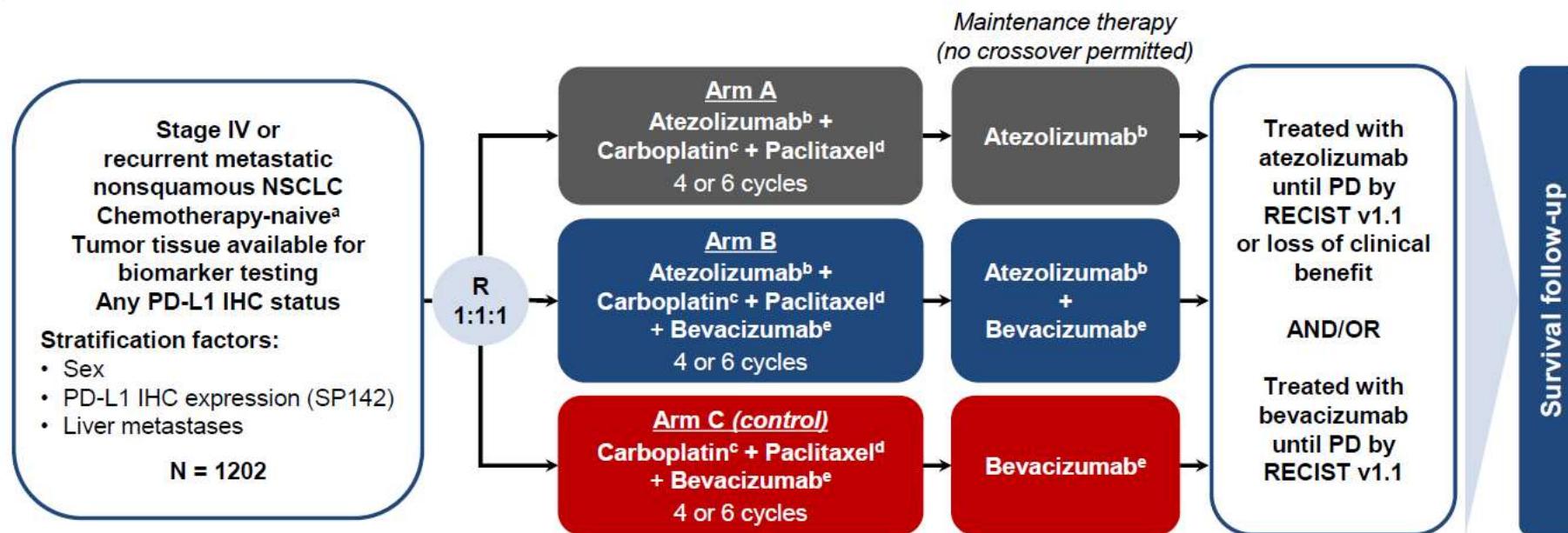
IMP 150

IMMUNO +
TARGET

CHT + IMMUNO + TARGET

5

IMpower150 Study Design



The primary PFS analysis of IMpower150 assessed whether the addition of atezolizumab to Arm C provided clinical benefit

- This analysis will focus on whether this combination provides clinical benefit in key biomarker and special interest subgroups

^a Patients with a sensitizing EGFR mutation or ALK translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.

^b Atezolizumab: 1200 mg IV q3w. ^c Carboplatin: AUC 6 IV q3w. ^d Paclitaxel: 200 mg/m² IV q3w. ^e Bevacizumab: 15 mg/kg IV q3w.

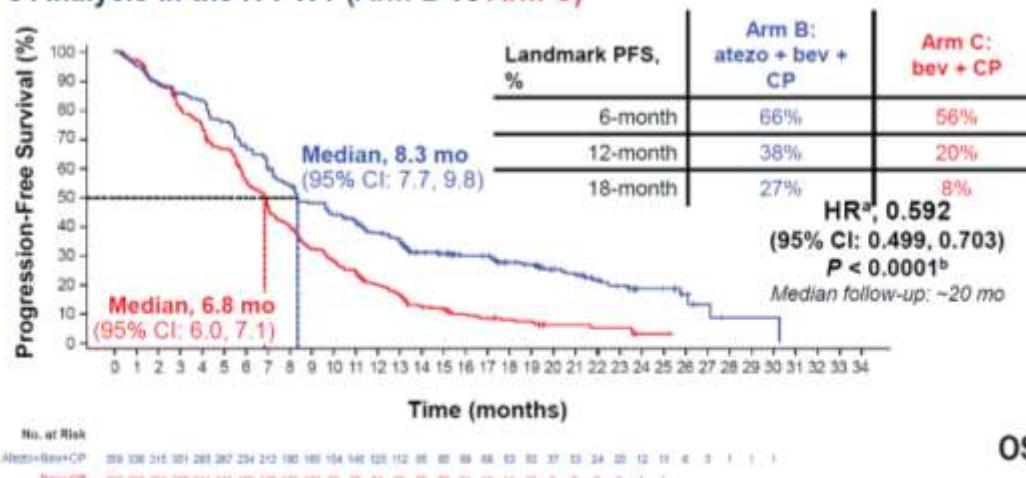
Kowanetz M, Socinski M, et al. AACR 2018

IMpower150: Efficacy Across Subgroups

CHT + IMMUNO + TARGET vs CHT + TARGET

PFS

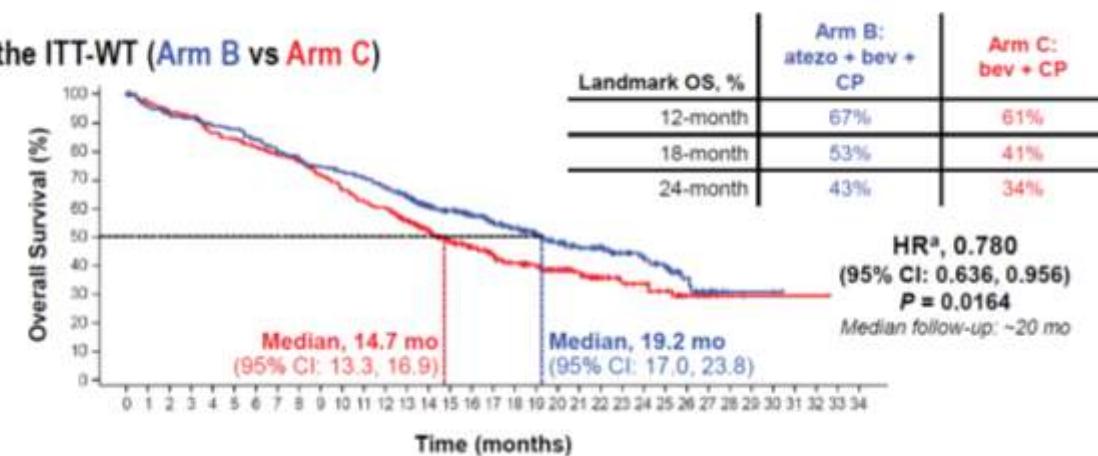
Updated PFS Analysis in the ITT-WT (Arm B vs Arm C)



- Statistically significant and clinically meaningful PFS benefit with atezolizumab + bevacizumab + chemotherapy was previously observed¹ and continued to improve with additional follow-up

OS

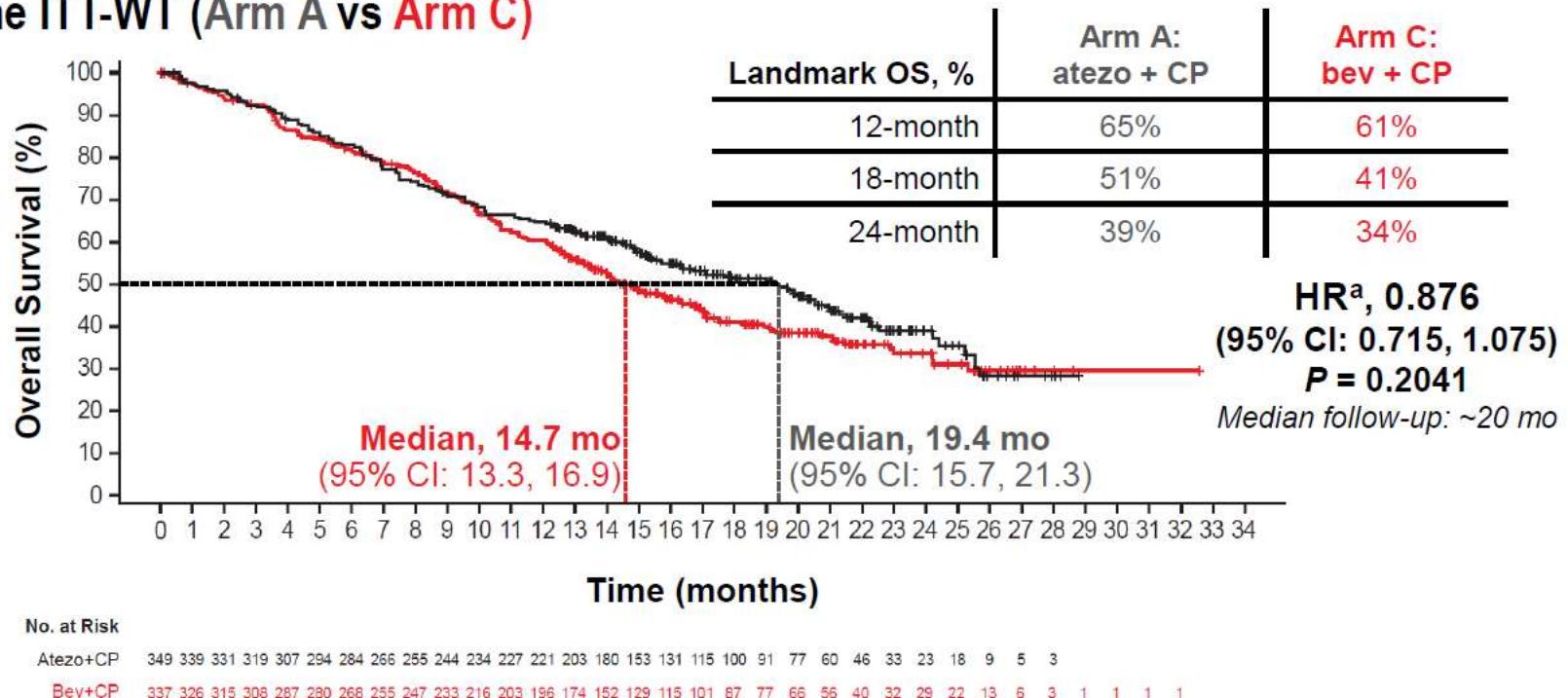
OS in the ITT-WT (Arm B vs Arm C)



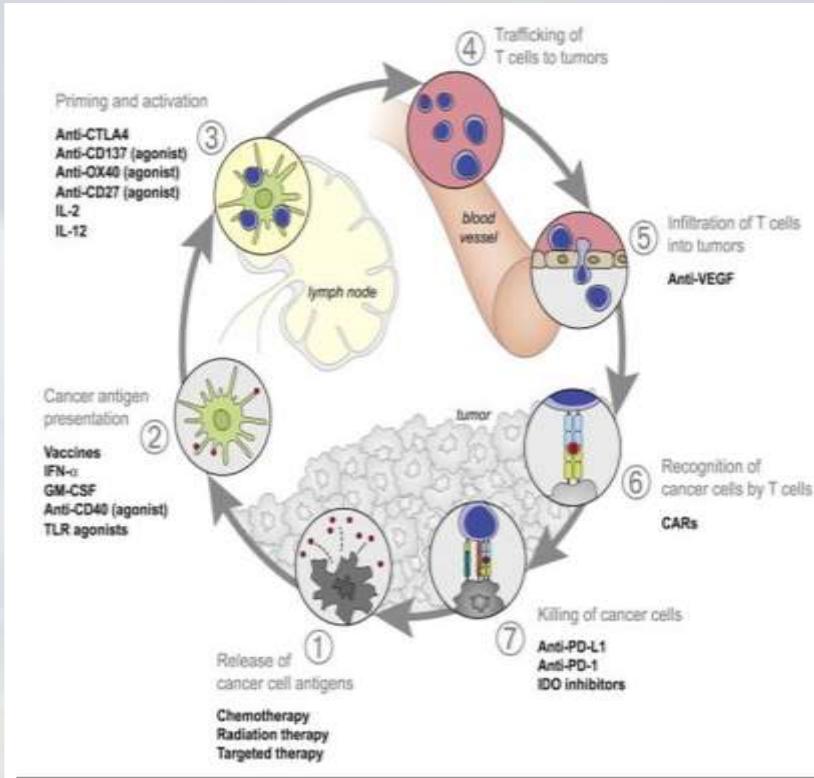
- Statistically significant and clinically meaningful OS benefit with atezolizumab + bevacizumab + chemotherapy vs bevacizumab + chemotherapy was observed

CHT + IMMUNO vs CHT + TARGET

OS in the ITT-WT (Arm A vs Arm C)



- A trend toward OS benefit was observed with atezolizumab + chemotherapy vs bevacizumab + chemotherapy, but the efficacy boundary has not yet been crossed and will be tested again at the time of the final analysis



IMP 150

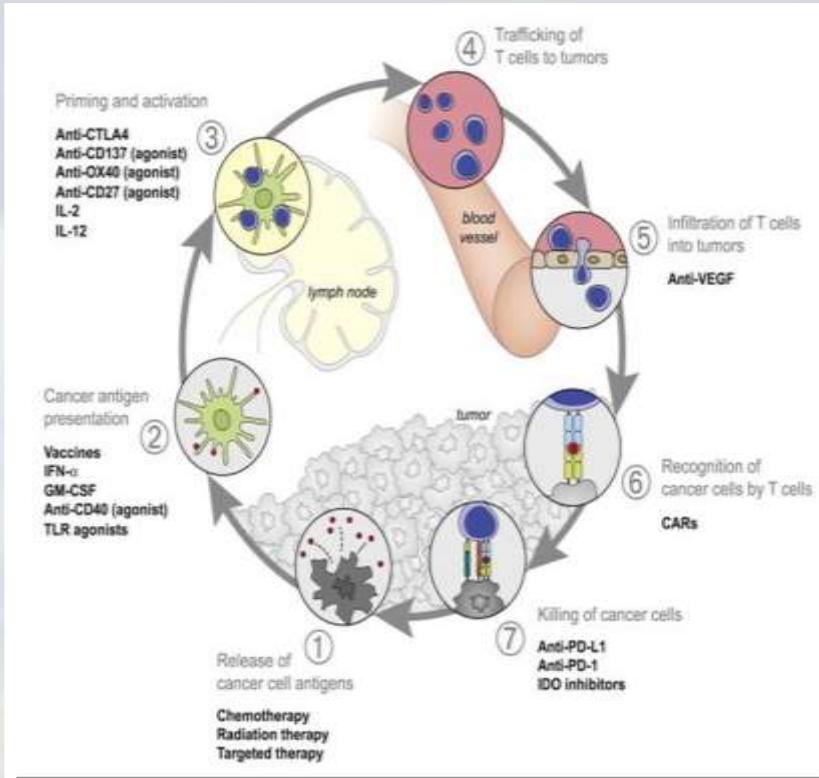
IMMUNO +
TARGET

KN 189, 407
IMP 132,131

IMMUNO + CHT

CK 227

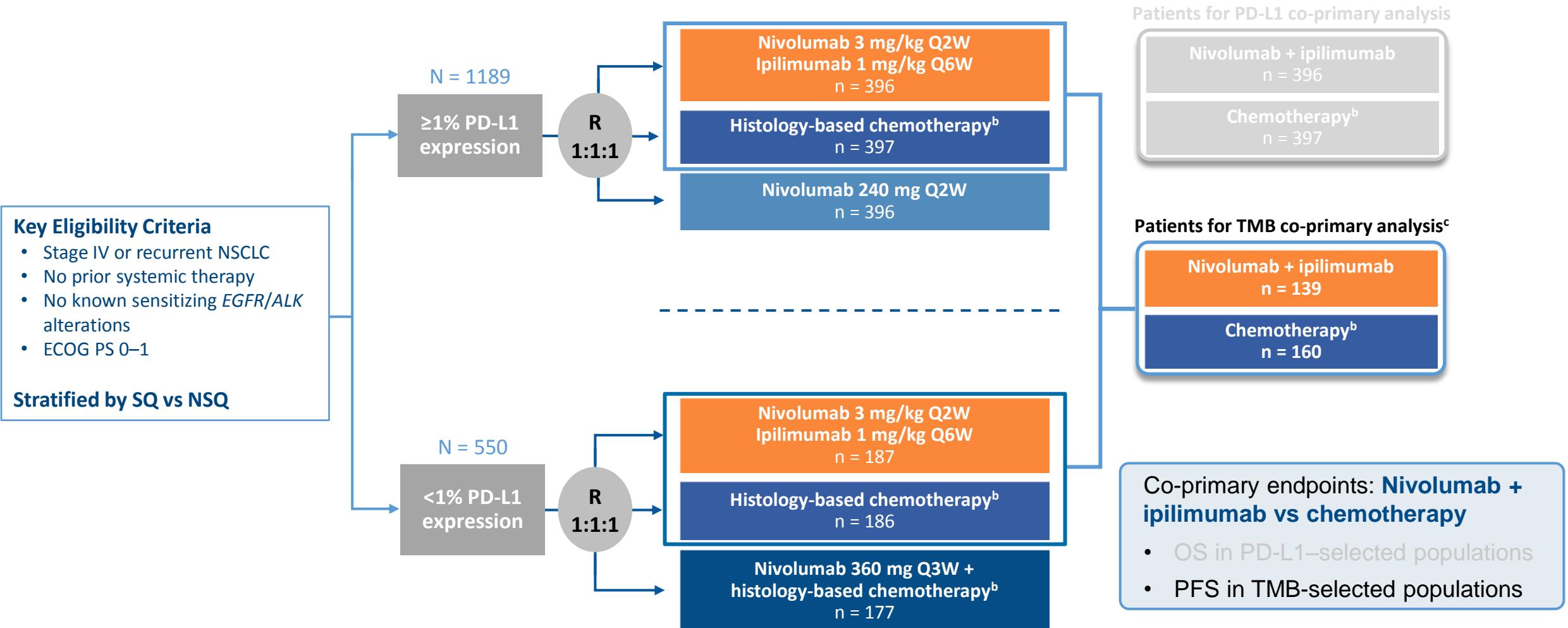
COMBO IMMUNO



COMBO IMMUNO

CK 227

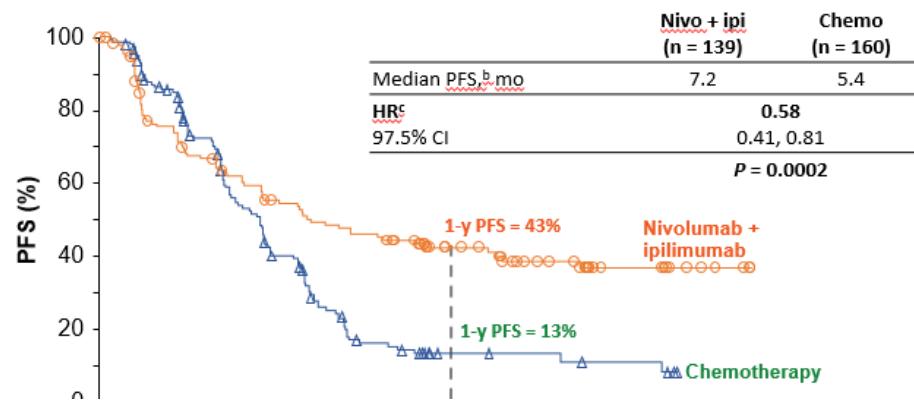
CHECKMATE 227



Database lock: January 24, 2018; minimum follow-up: 11.2 months

^aNCT02477826 ^bNSQ: pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; ^cSQ: gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles; ^cThe TMB co-primary analysis was conducted in the subset of patients randomized to nivolumab + ipilimumab or chemotherapy who had evaluable TMB ≥10 mut/Mb

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



Press release TMB checkmate 227

- In patients with NSCLC and high tumor mutational burden (TMB) (≥ 10 mutations/megabase).

^aPer blinded independent central review. ^bPer blinded independent central review. ^c97.5% confidence interval.

	TMB ≥ 10 mut/Mb		TMB <10 mut/Mb	
	Nivo + Ipi	Chemo	Nivo + Ipi	Chemo
			Co-primary endpoint	Exploratory analysis
Median PFS, months²	7.2	5.4	3.2	5.5
Hazard ratio (CI)	0.58 (97.5% CI: 0.41–0.81) $P=0.0002$		1.07 (95% CI: 0.84–1.35)	
		Secondary endpoint*	Exploratory analysis	
Median OS, months¹	23.03	16.72	16.20	12.42
Hazard ratio (CI)	0.77 (95% CI: 0.56–1.06)		0.78 (95% CI: 0.61–1.00)	

*Descriptive analysis.

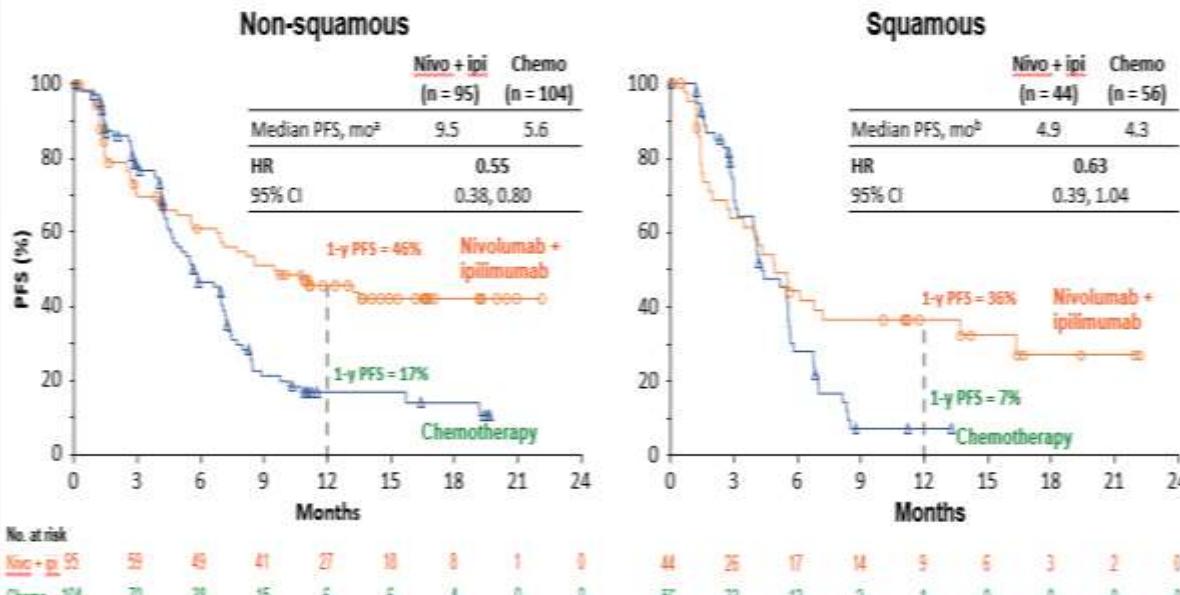
Chemo=chemotherapy; CI=confidence interval; ipi=ipilimumab; Mb=megabase; mos=months; mut=mutations; nivo=nivolumab; NSCLC= non-small cell lung cancer; OS=overall survival; TMB=tumor mutational burden.

1. Bristol-Myers Squibb. [press release]. October 19, 2018. 2. Hellmann MD et al. *N Engl J Med*. 2018;378(22):2093–2104. October 19, 2018.

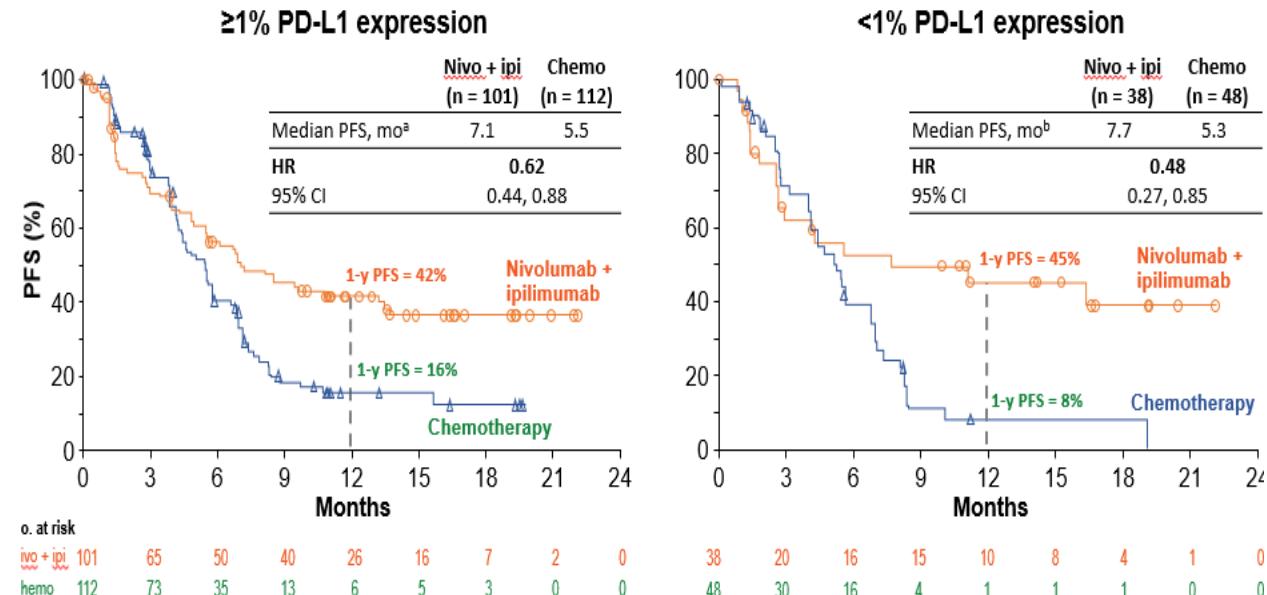
QUANDO TMB ALTO COMBO-IMMUNO !!

INDIP DA :

PFS in Patients With High TMB (≥ 10 mut/Mb) by Tumor Histology



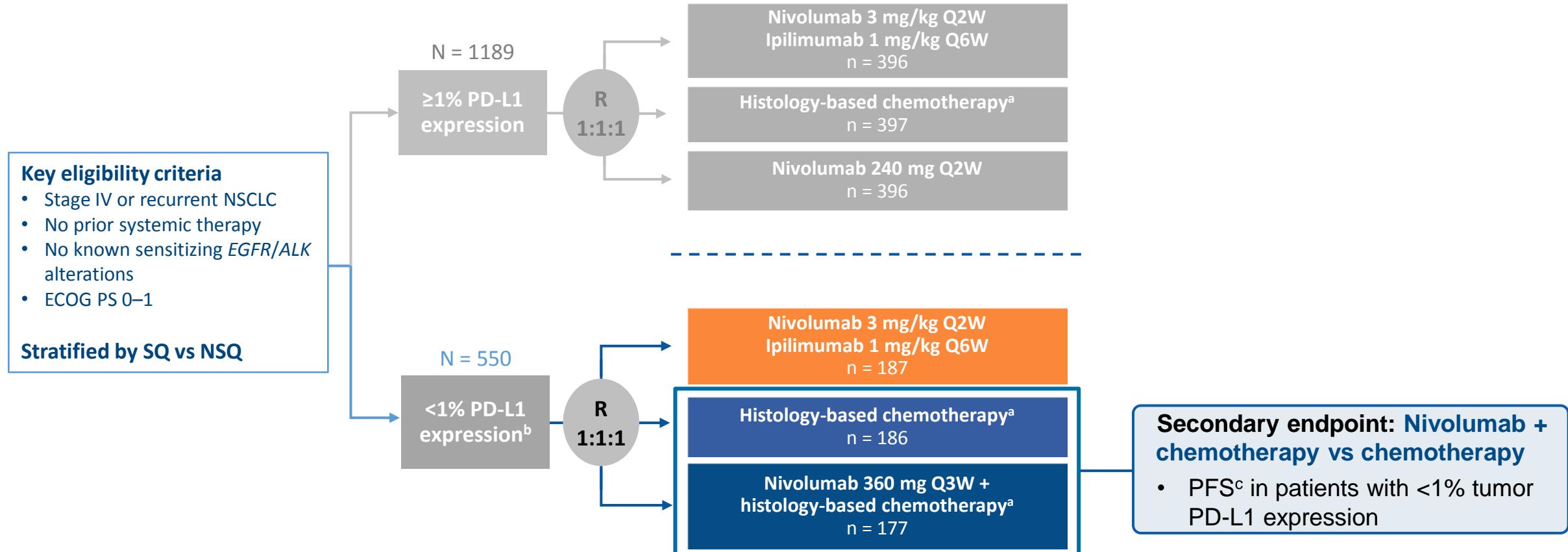
PFS in Patients With High TMB (≥ 10 mut/Mb) by Tumor PD-L1 Expression



^a95% CI: nivo + ipi (5.5 mo, NR), chemo (4.5, 7.0 mo); ^b95% CI: nivo + ipi (2.7, 13.7 mo), chemo (3.2, 5.6 mo)

95% CI: nivo + ipi (5.5, 13.5 mo), chemo (4.3, 6.6 mo); ^b95% CI: nivo + ipi (2.7 mo, NR), chemo (4.0, 6.8 mo)

CHECKMATE 227 PART 1 STUDY DESIGN



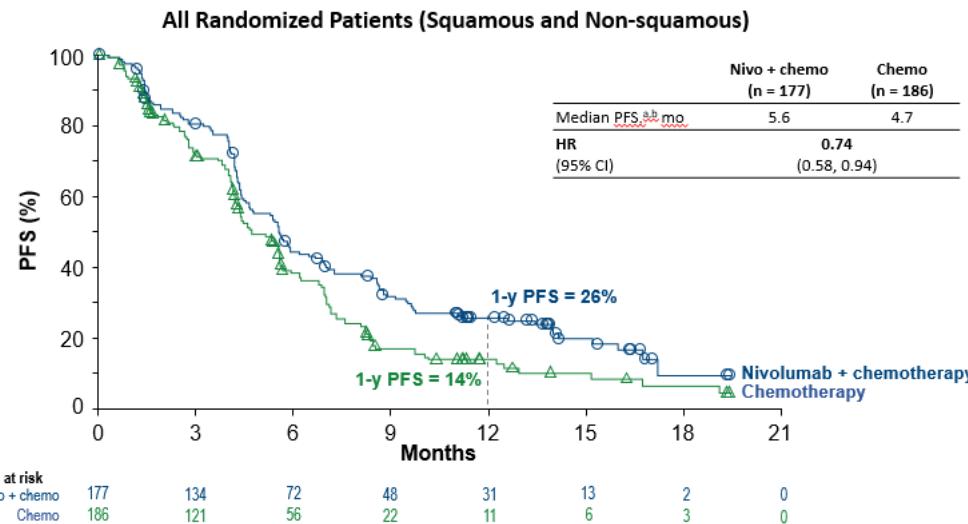
- Co-primary endpoints: OS in PD-L1-selected populations and PFS^c in TMB-selected populations treated with nivolumab + ipilimumab vs chemotherapy

Database lock: January 24, 2018; minimum follow-up: 11.2 months

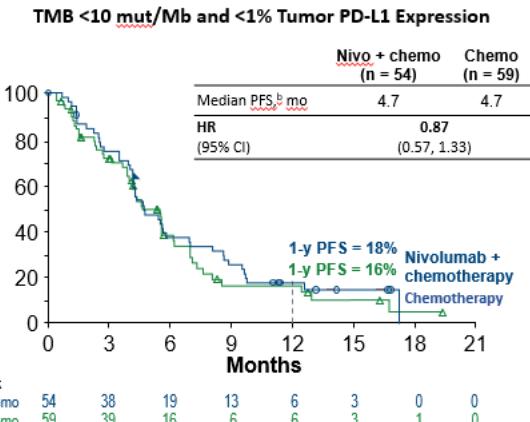
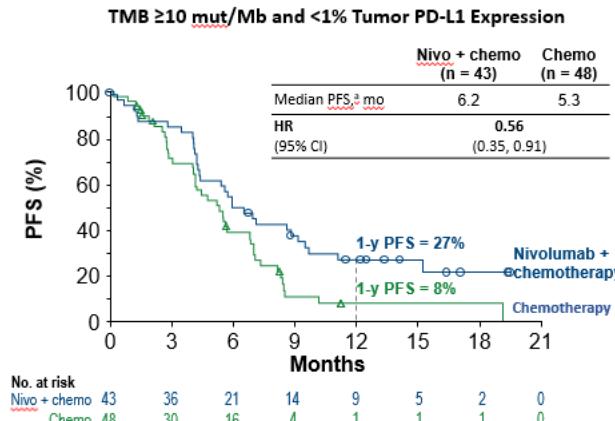
^aNSQ: pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy;
 SQ: gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles; ^bOne patient was randomized with <1% tumor PD-L1 expression in IVRS, but was subsequently found to have ≥1% tumor PD-L1 expression; ^cPer BICR

PFS: Nivolumab + Chemotherapy vs Chemotherapy in Patients With <1% Tumor PD-L1 Expression

NIVO + CHT



PFS: Nivolumab + Chemotherapy vs Chemotherapy By TMB

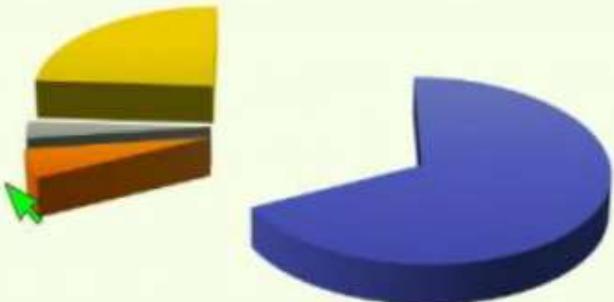


- TMB ≥10 mut/Mb: ORR was 60.5% with nivo + chemo and 20.8% with chemo
- TMB <10 mut/Mb: ORR was 27.8% with nivo + chemo and 22.0% with chemo

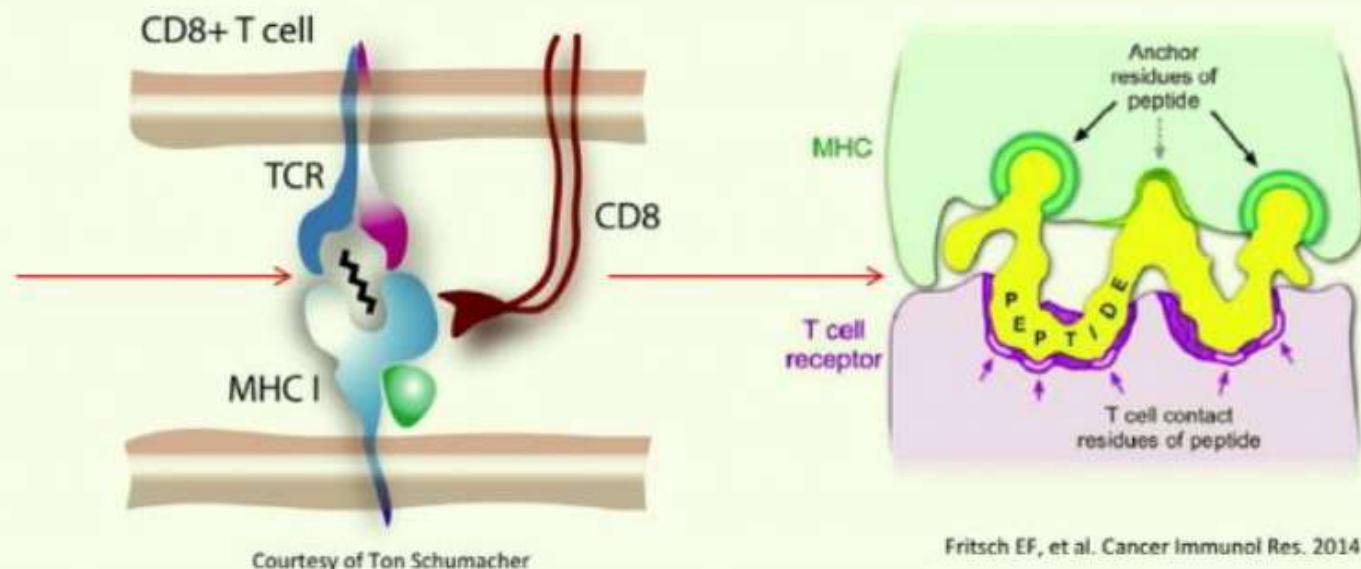
^a95% CI: nivo + chemo (4.3, 9.1 mo), chemo (4.0, 6.8 mo); ^b95% CI: nivo + chemo (4.2, 6.9 mo), chemo (3.9, 6.2 mo)

SOLO NEL TMB ALTO !!!

TMB is a surrogate for (predicted) neoantigens

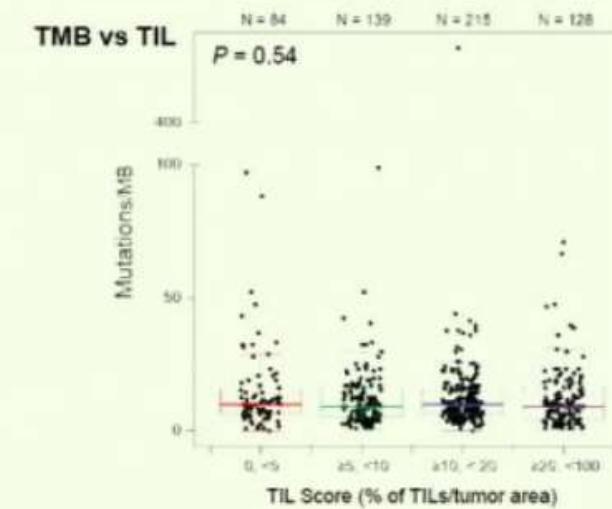
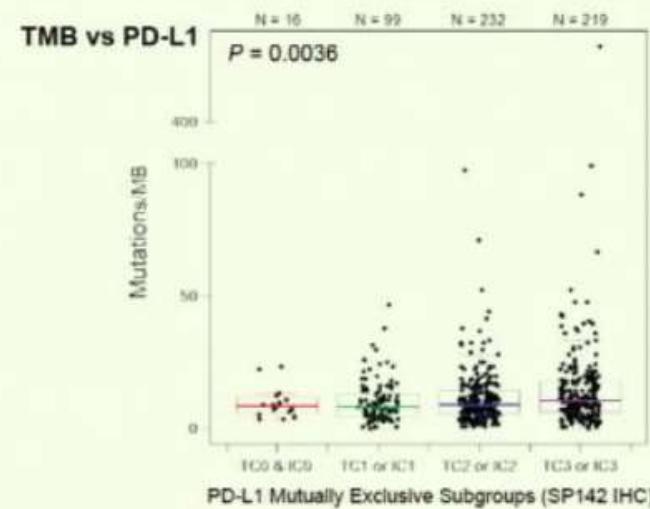
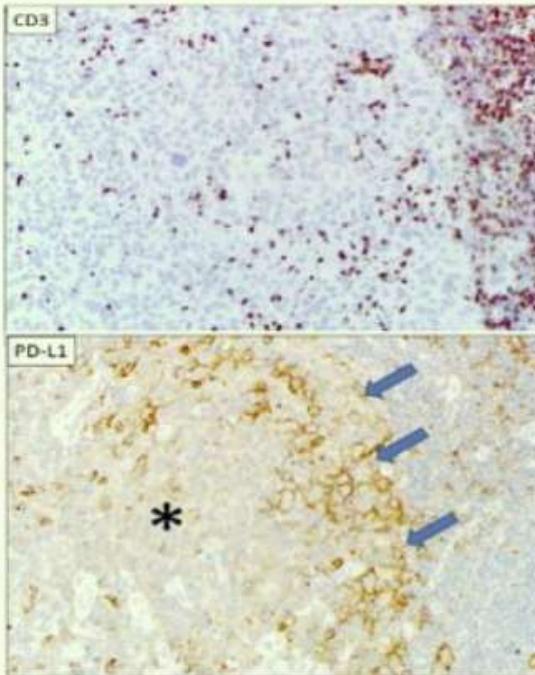


- Missense (65%) ■ Nonsense (5%)
- Indels (3%) ■ Silent (21%)



TMB and PD-L1

TMB independent of immune phenotype
(BIRCH, FIR, POPLAR trial data)



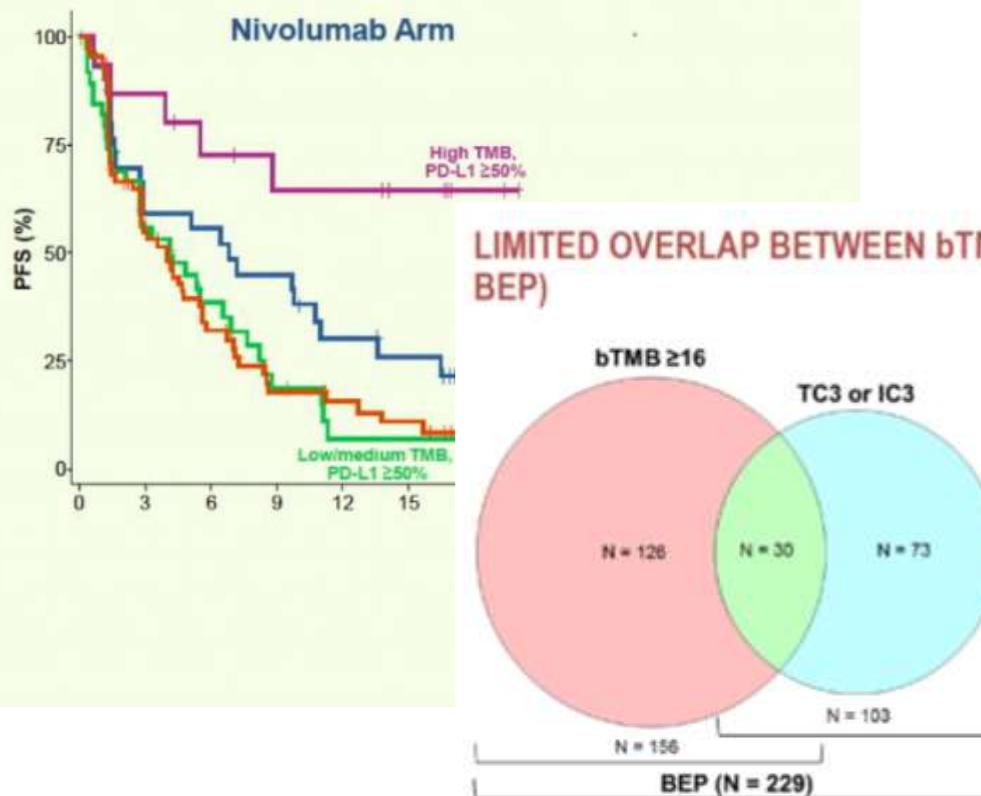
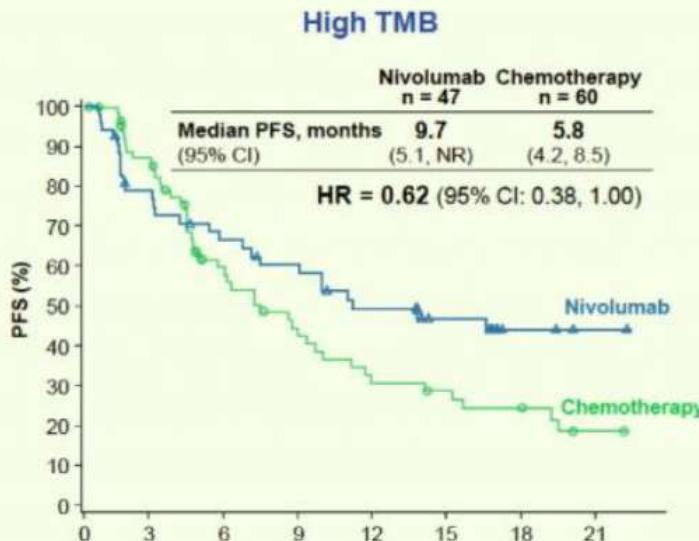
Kowanetz et al, WCLC 2016

Courtesy Janice Taube

TMB indipendente da PD-L1

CM 026:

Discordant outcomes in TMB high / PD-L1 high vs TMB high / PD-L1 low



- Non-significant overlap between the bTMB ≥16 and TC3 or IC3 subgroups (Fisher exact test, $P = 0.62$)
 - 19.2% of tumors with bTMB ≥16 were also TC3 or IC3
 - 29.1% of tumors with TC3 or IC3 also had bTMB ≥16

	PFS HR (95% CI)	OS HR (95% CI)
bTMB ≥16	0.64 (0.46, 0.91)	0.64 (0.44, 0.93)
TC3 or IC3	0.62 (0.41, 0.93)	0.44 (0.27, 0.71)
bTMB ≥16 and TC3 or IC3	0.38 (0.17, 0.85)	0.23 (0.09, 0.58)

^aPD-L1 expression was evaluated by immunohistochemistry (IHC) using the VENTANA SP142 assay. TC3 or IC3, ≥10% of TC or ≥10% of IC express PD-L1. BEP, bevacizumab-evaluable population; IC, tumor-infiltrating immune cell; TC, tumor cell.

LIMITI DEL TMB :

Targeted panel TMB validation and IO threshold definition

1. WES

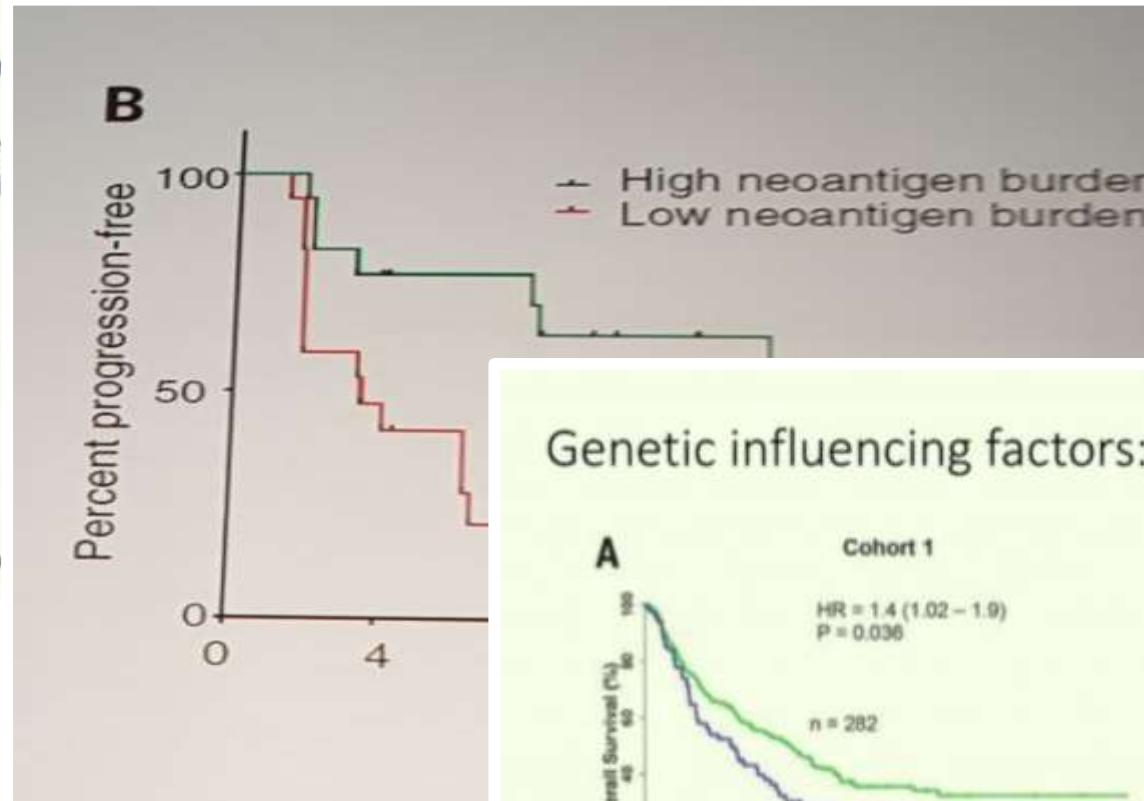
- Coding regions of 21,522 genes
- TMB defined as the number of missense mutations per tumor genome examined

2. FoundationOne®

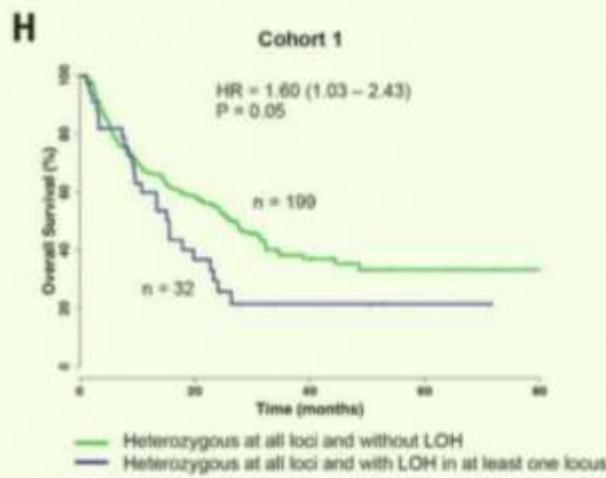
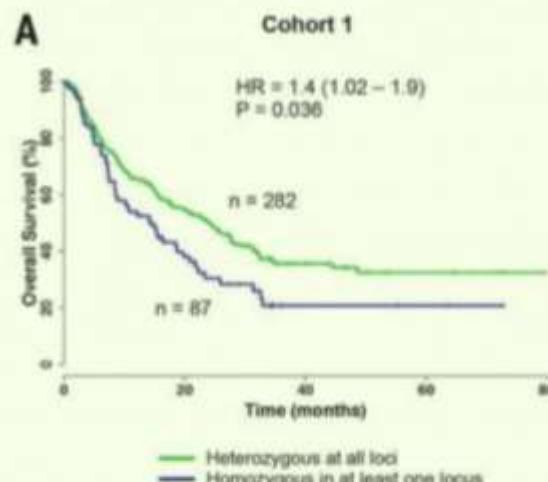
- A targeted gene panel of 324 cancer-related genes
- TMB defined as the number of somatic mutations per tumor genome examined



1. Szustakowski J et al. SITC 2017. 3. Szustakowski et al.



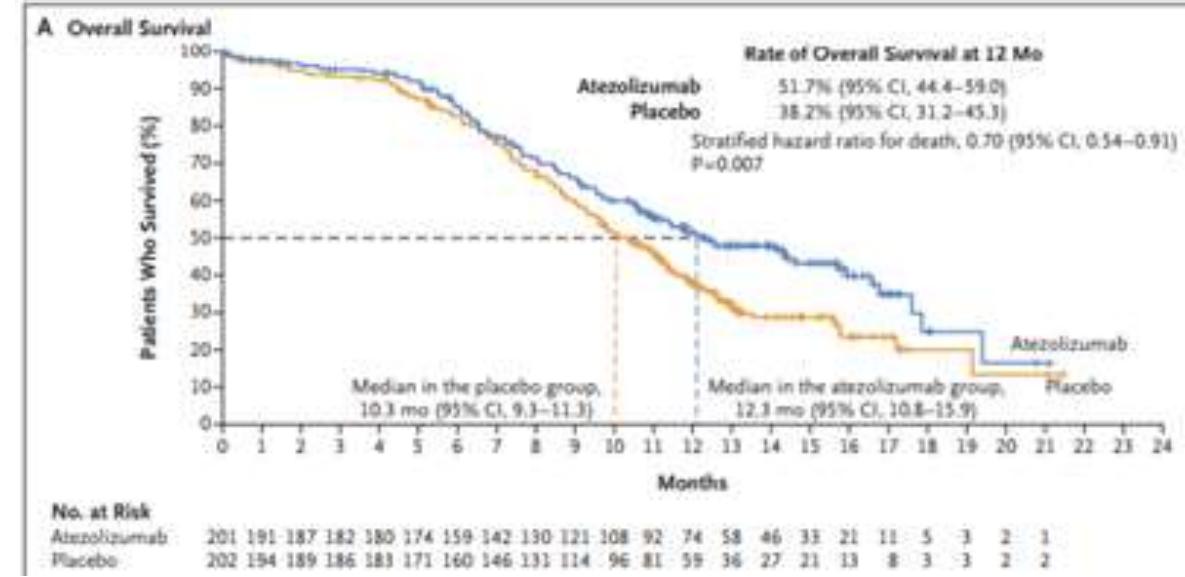
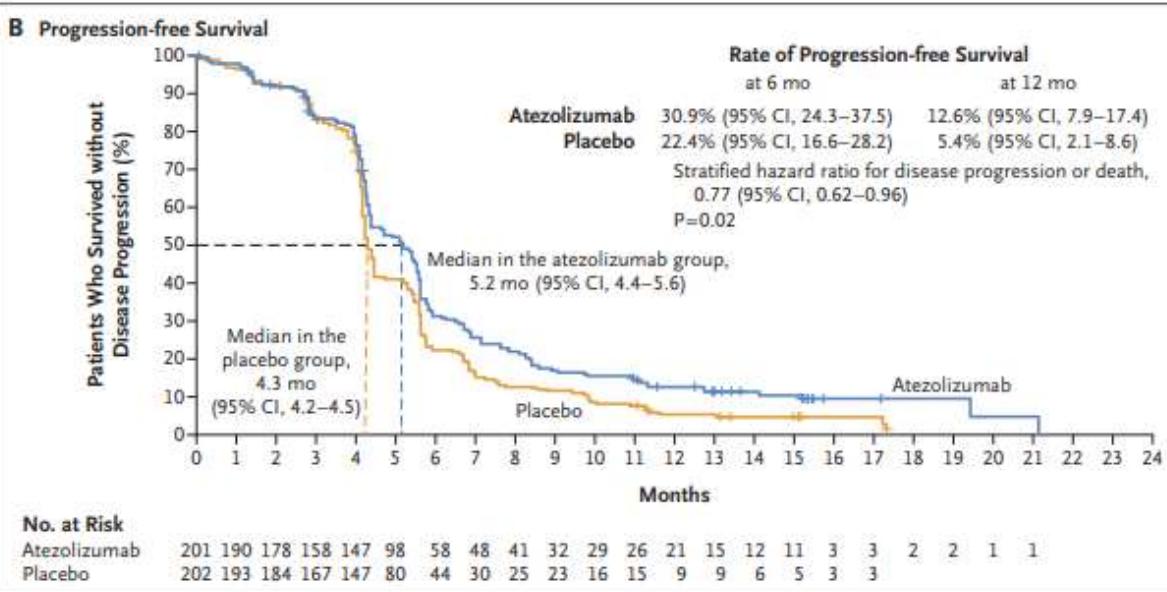
Genetic influencing factors: HLA Class I zygosity and LOH



First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

L. Horn, A.S. Mansfield, A. Szczesna, L. Havel, M. Krzakowski, M.J. Hochmair, F. Huemer, G. Losonczy, M.L. Johnson, M. Nishio, M. Reck, T. Mok, S. Lam, D.S. Shames, J. Liu, R. Dino, A. Lopez-Chavez, F. Kabbiravar, W. Lin, A. Sandler
and

The NEW ENGLAND JOURNAL of MEDICINE



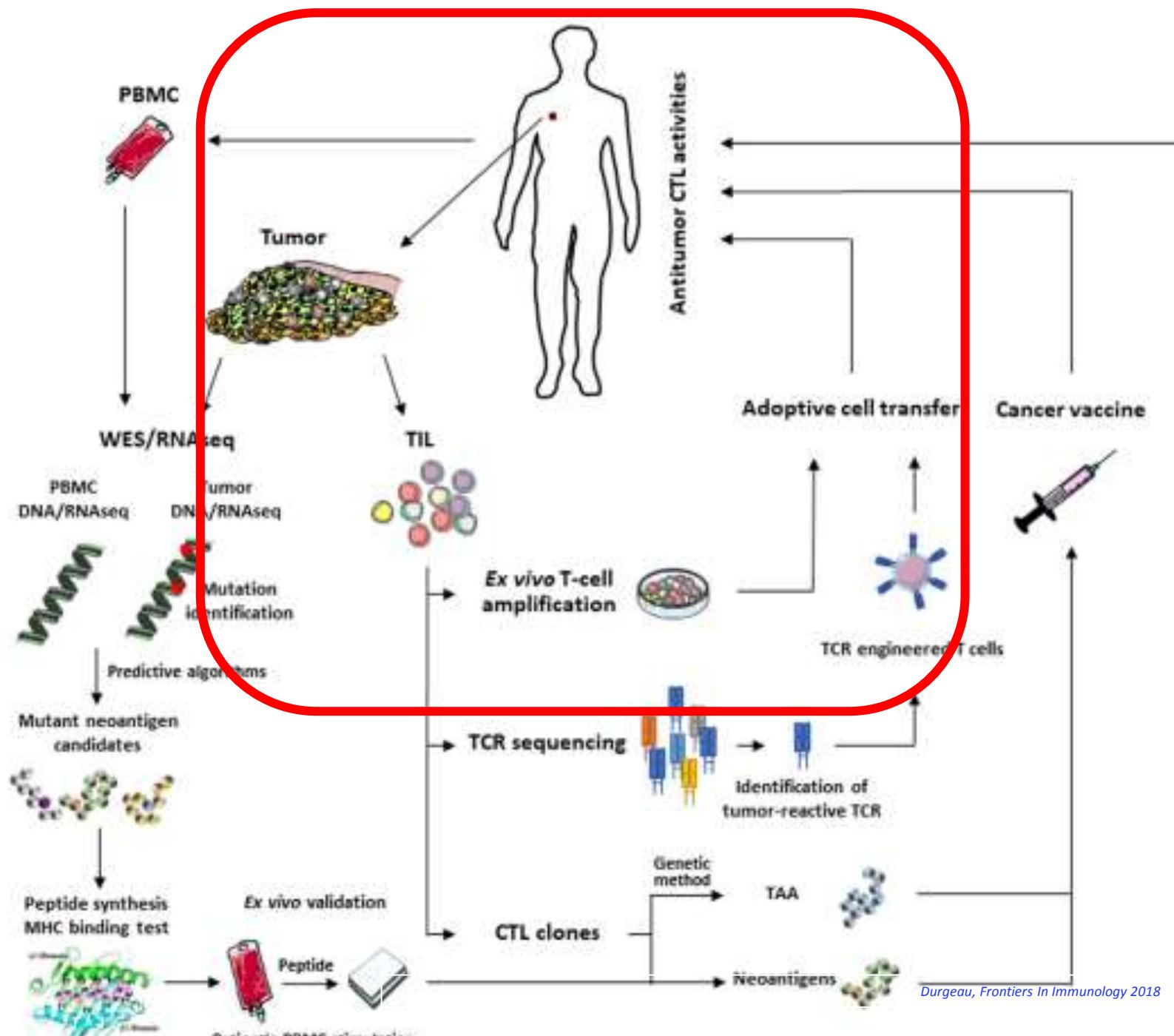


NUOVI ORIZZONTI

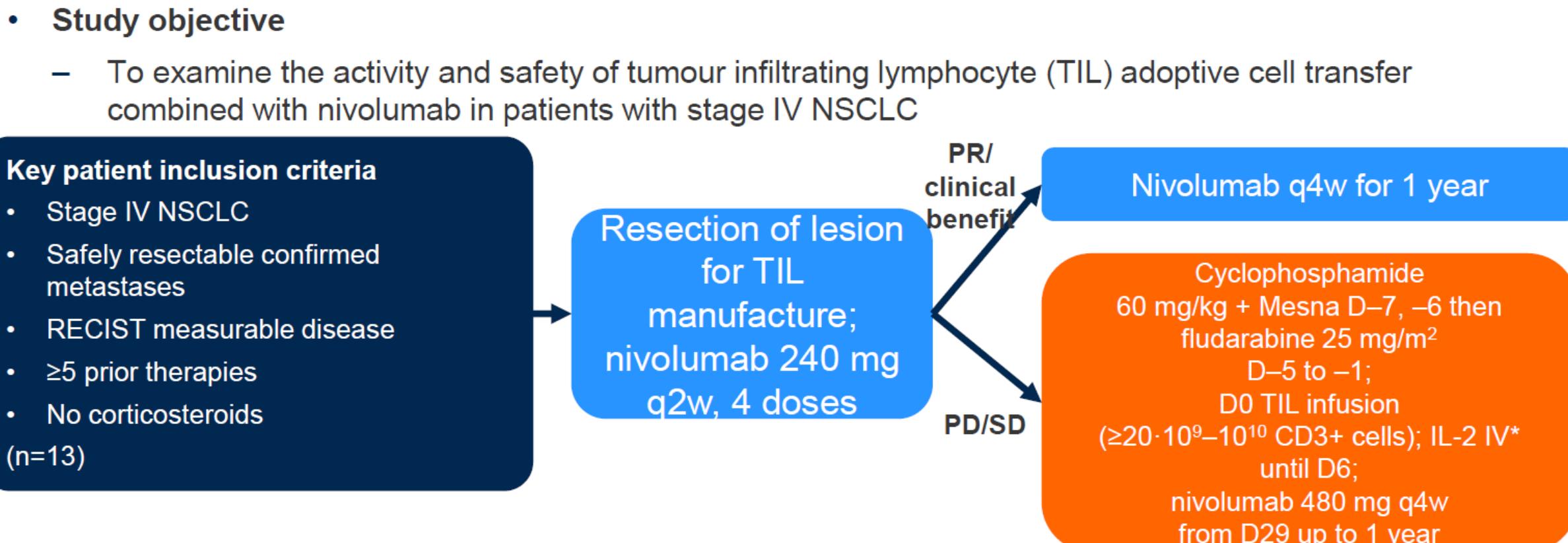
TRATTAMENTO

BIOMARCATORI

TERAPIA ADOTTIVA



Safety and Clinical Activity of Adoptive Cell Transfer Using Tumor Infiltrating Lymphocytes (TIL) Combined with Nivolumab in NSCLC



Primary endpoint

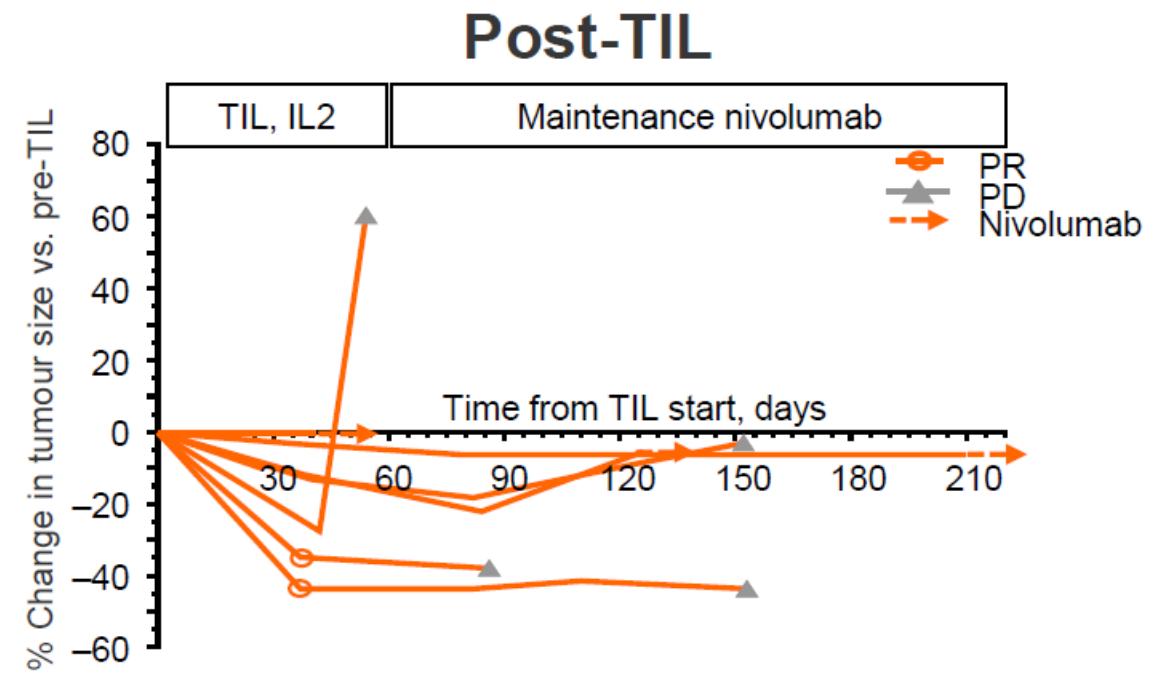
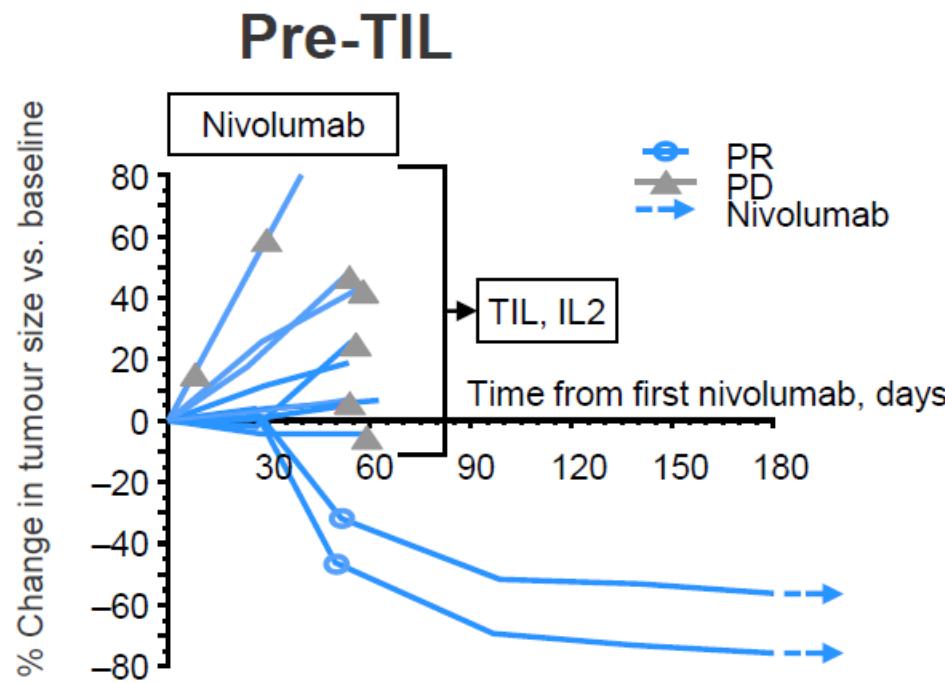
- Safety/tolerability

Secondary endpoints

- Efficacy, PK, PD, tumour proteomics, whole exome sequencing, transcriptomics

*IL-2 intermediate dose: 18 miU/m² over 6, 12 and 24 hours then 4.5 miU/m² over 24 hours x 3) on D1–6

Depth and Duration of Response



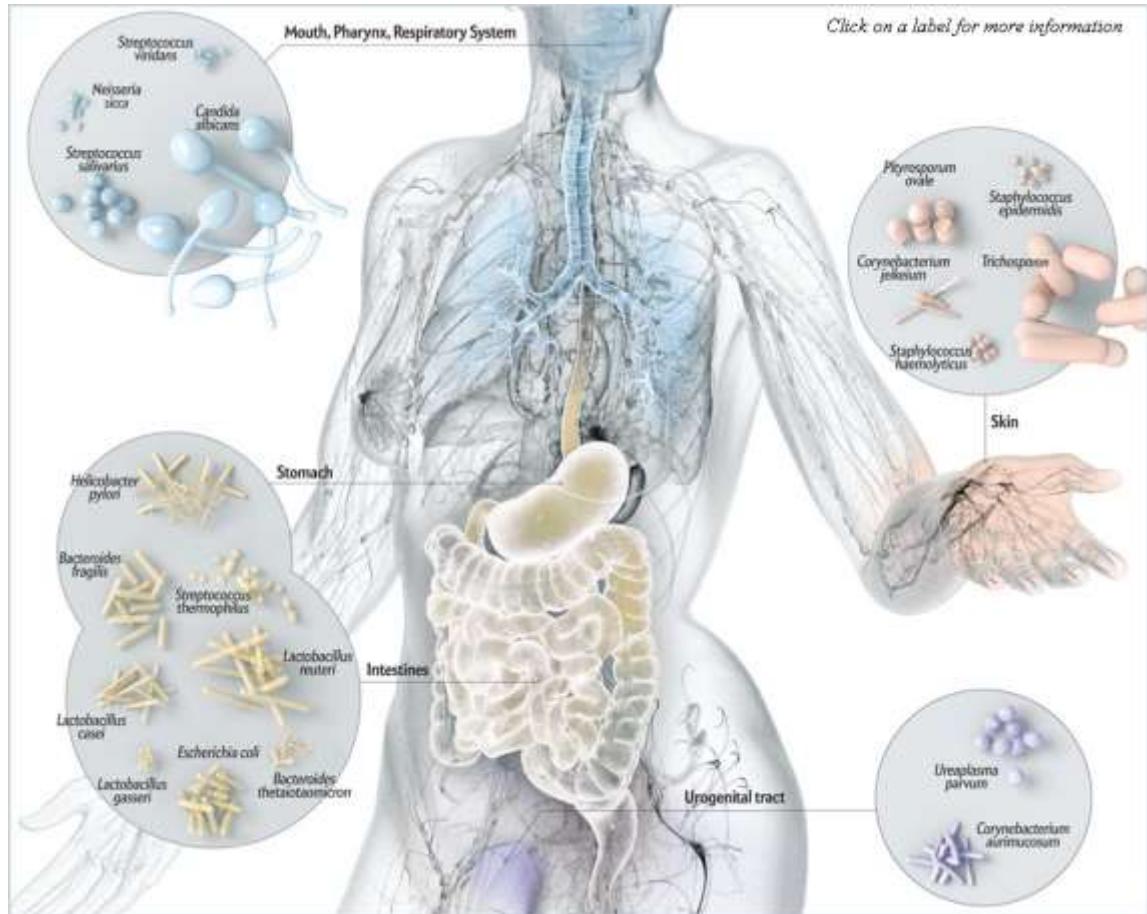
Creelan BC et al. J Thorac Oncol 2018;13(suppl):Abstr OA05.03



NUOVI ORIZZONTI

BIOMARCATORI

CHI È IL MICROBIOTA ?



Insieme di batteri e altri microorganismi
(funghi, protozoi, virus)

All'interno del corpo umano, si stima che ci siano **10 volte più cellule** microbiche delle cellule umane. (**10^{14}**)

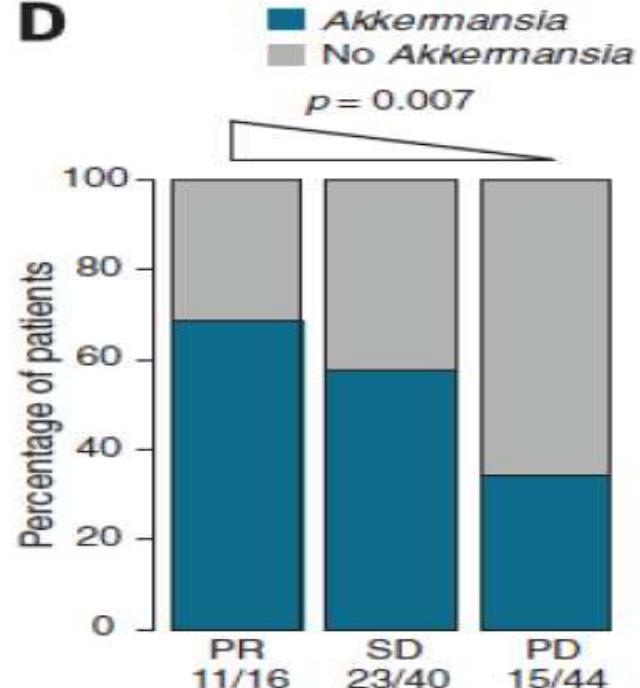
300-500 specie (main phyla: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria)

CANCER IMMUNOTHERAPY

Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors



D



nature
genetics

LETTERS

<https://doi.org/10.1038/s41588-018-0135-7>

The fecal metabolome as a functional readout of the gut microbiome

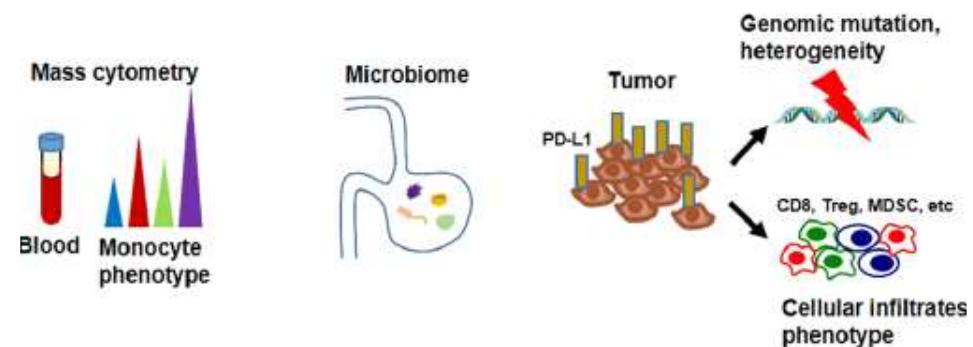
COME MIGLIORARE LA RISPOSTA ALL'IMMUNOTERAPIA ?

TRATTAMENTO



- ✓ NUOVE COMBINAZIONI/SEQUENZE : EFFETTO IMMUNOLOGICO-IMMUNOPROFILO
- ✓ NUOVE STRATEGIE

BIOMARCATORI



Thanks for your attention