I° CONVEGNO REGIONALE SIFO

Meeting di primavera

"IL FARMACISTA CLINICO
E I NUOVI MODELLI DI CURA"

TAORMINA (ME),
11-12-13 MAGGIO 2017

ID ECM: 313-188877

IV SESSIONE - IMMUNONCOLOGIA

I biomarcatori nell'immunoncologia: L'importanza della selezione del paziente

Hector Soto Parra MD
Oncologia Medica

AZIENDA OSPEDALIERO-UNIVERSITARIA POLICLINICO-VITTORIO EMANUELE

I biomarcatori nell'immunoncologia: Perché è importante la selezione del paziente?

- **Migliorare il risultato terapeutico –Efficacia-**
  - **pochi pz/grandi benefici vs molti pz/pochi vantaggi**
- **Contenere i costi –Farmacoeconomia-**
- **Controllo adeguatezza prescrittiva -Ente regolatorio-**
- **Disegno di nuovi studi -Ricerca-**

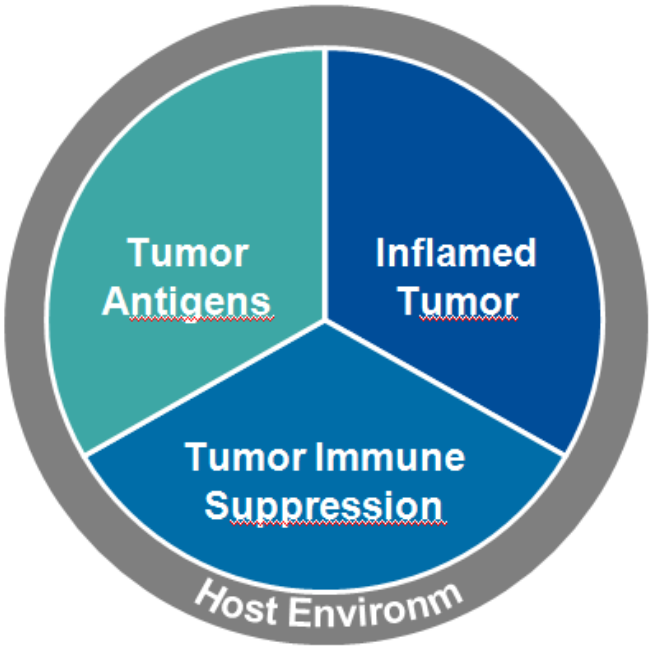
Tumor and Immune Biomarkers Being Evaluated to Predict Better Outcomes to Immuno-Oncology Therapy

Tumor Antigens

- Biomarkers indicative of hypermutation & neo-antigens may predict response to IO treatment

Examples:

– ***TMB, MSI-High, Neo-Antigens***



Inflamed Tumor Microenvironment

- Biomarkers (intra- or peri-tumoral) indicative of an inflamed phenotype may predict response to IO treatment

Examples:

– ***PD-L1, Inflammatory Signatures***

Tumor Immune Suppression

- Biomarkers that identify tumor immune system evasion beyond PD-1/CTLA-4 to inform new IO targets and rational combinations

Examples:

– ***Tregs, MDSCs, IDO, LAG-3***

Host Environment

- Biomarkers which characterize the host environment, beyond tumor microenvironment, may predict response to IO treatment

Examples:

– ***Microbiome, Germline Genetics***

IDO = indoleamine-2,3 dioxygenase; LAG-3 = lymphocyte activation gene-3; MDSCs = myeloid-derived suppressor cells; MSI-High = microsatellite instability high; TMB = tumor mutational burden. Adapted from Blank C.U. et al., *Science* 2016;352:658–660.

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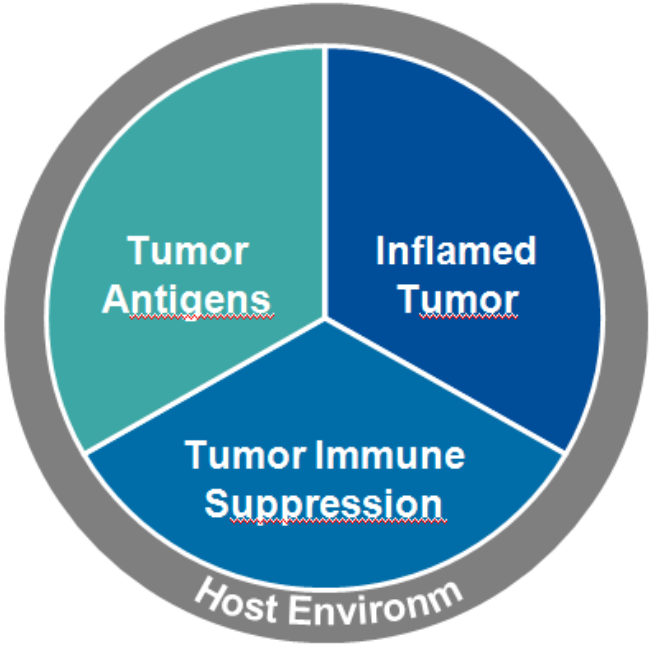

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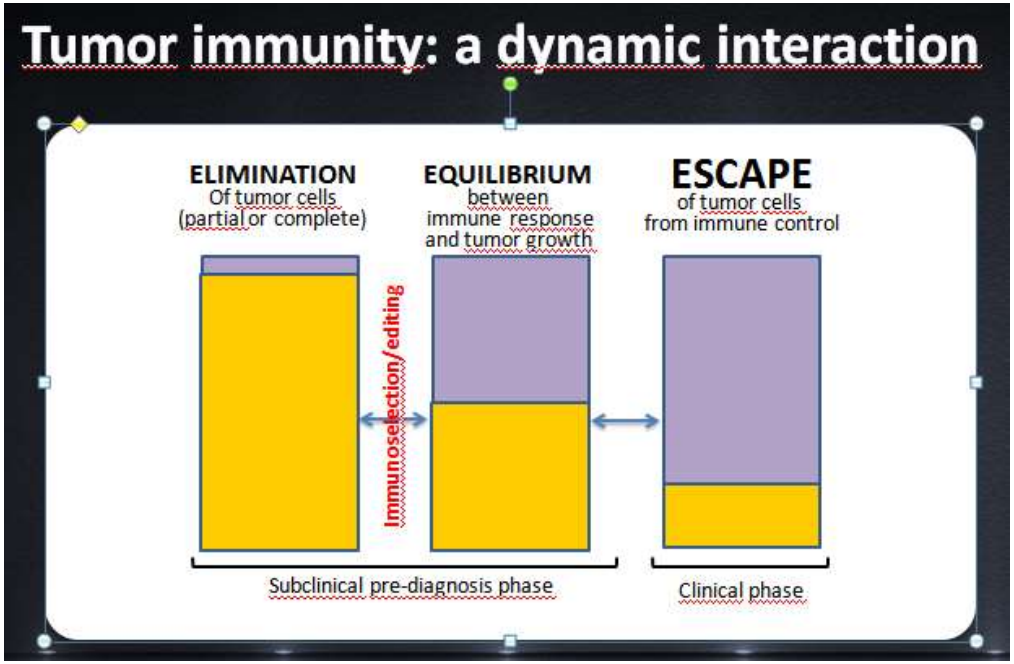
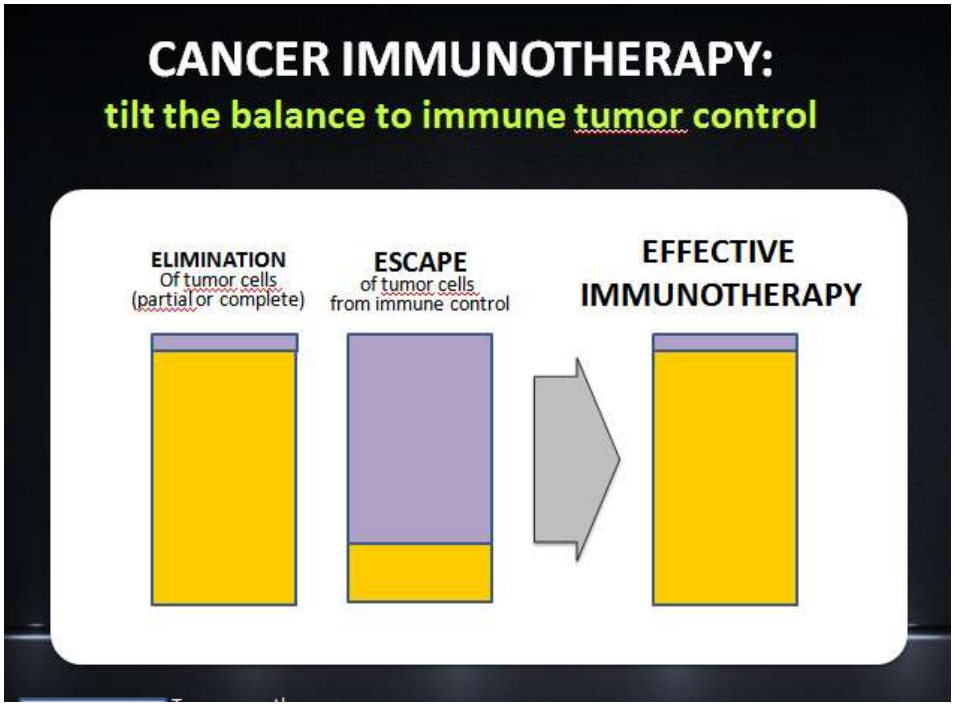
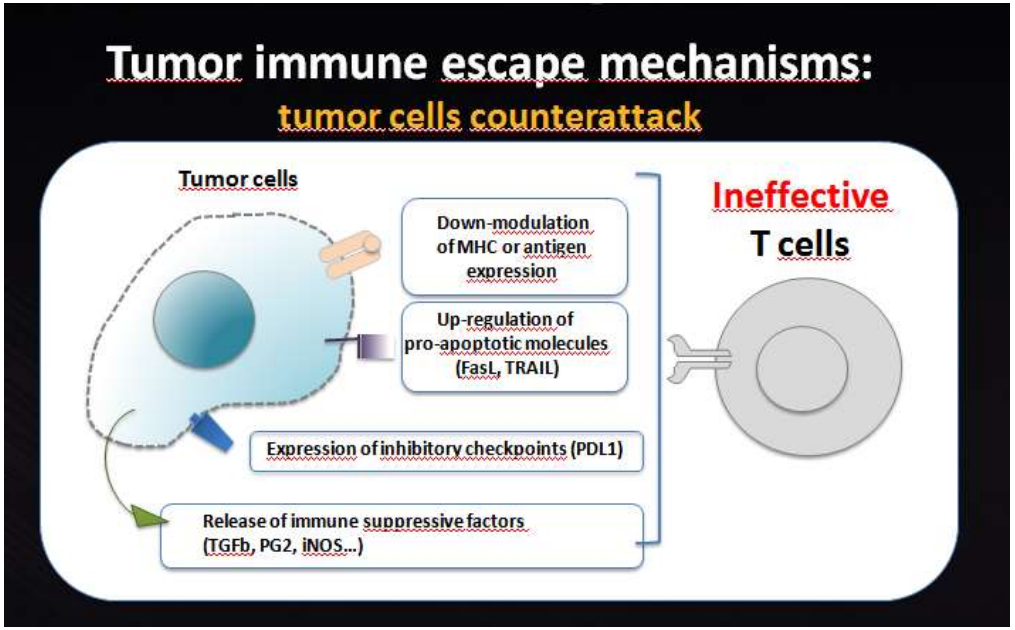
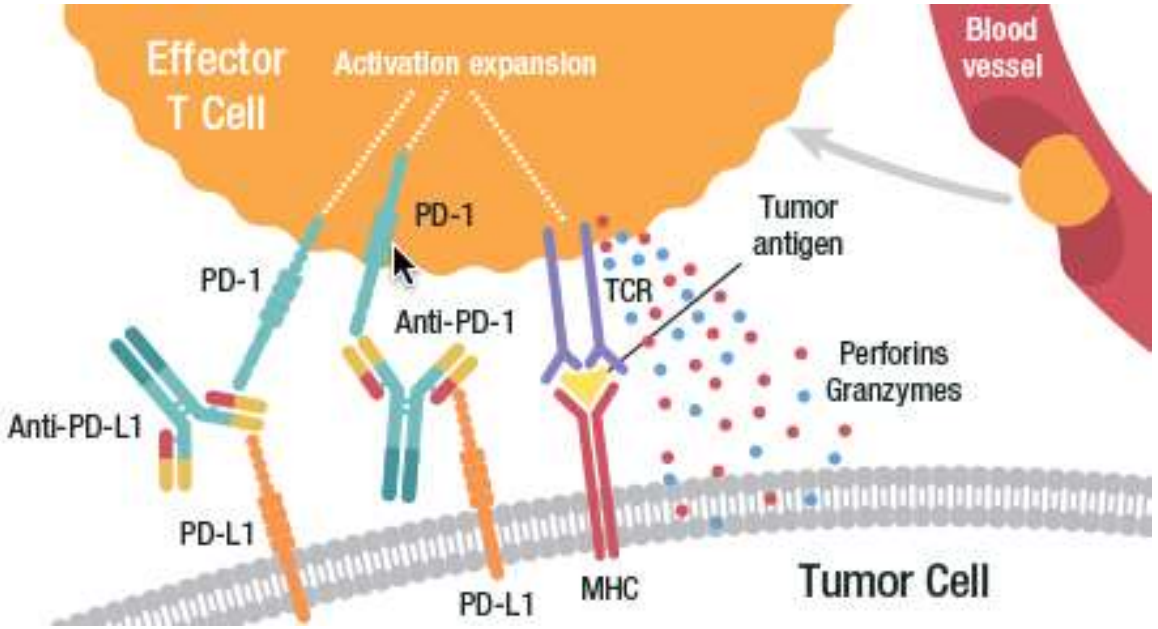

Tumor immunity: a dynamic interaction
ELIMINATION
Of tumor cells
(partial or complete)
EQUILIBRIUM
between
immune response
and tumor growth
ESCAPE
of tumor cells
from immune control
Immunoselection/editing
Subclinical pre-diagnosis phase
Clinical phase


CANCER IMMUNOTHERAPY:
tilt the balance to immune tumor control
ELIMINATION
Of tumor cells
(partial or complete)
ESCAPE
of tumor cells
from immune control
EFFECTIVE
IMMUNOTHERAPY



Anti-PD1
Nivolumab
Pembrolizumab

Anti-PDL1
Atezolizumab
Durvalumab
Avelumab



Solid Tumors
Anti-PD1/PDL1 FDA Approved

Anti-PD1

Nivolumab: Melanoma,NSCLC, Renal, Bladder, H&N

Pembrolizumab: Melanoma, **NSCLC***, H&N

Anti-PDL1

Avelumab: Merkel cell carcinoma

Atezolizumab: NSCLC, Urothelial

Durvalumab: Urothelial

*** non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test.**

Randomised Trials of Anti PD-1 / anti-PD-L1 Agents

Study	Line	Agents	PD-L1	Result	HR
CheckMate 026	1st	Nivo vs Chemo	≥1%	No difference in PFS, OS	1.15, 1.02
KEYNOTE-024	1st	Pembro vs Chemo	>50%	Improved OS	0.60
CheckMate 017	2nd	Nivo vs Docetaxel	Unselected	Improved OS	0.59
CheckMate 057	2nd*	Nivol vs Docetaxel	Unselected	Improved OS	0.73
KEYNOTE-010	2nd*	Pembro vs Docetaxel	>1%	Improved OS (2, 10 mg/kg)	0.61, 0.71
POPLAR	2nd or 3rd	Atezo vs Docetaxel	Unselected	Improved OS	0.73
OAK	2nd or 3rd	Atezo vs Docetaxel	Unselected	Improved OS	0.73

*3rd line for EGFR or ALK +ve tumours

Borghaei et al. N Engl J Med 2015; 373: 1627-39. Brahmer et al. N Engl J Med 2015; 373: 123 – 35.
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Barlesi et al. ESMO 2016 LBA44. Socinski et al. ESMO 2016
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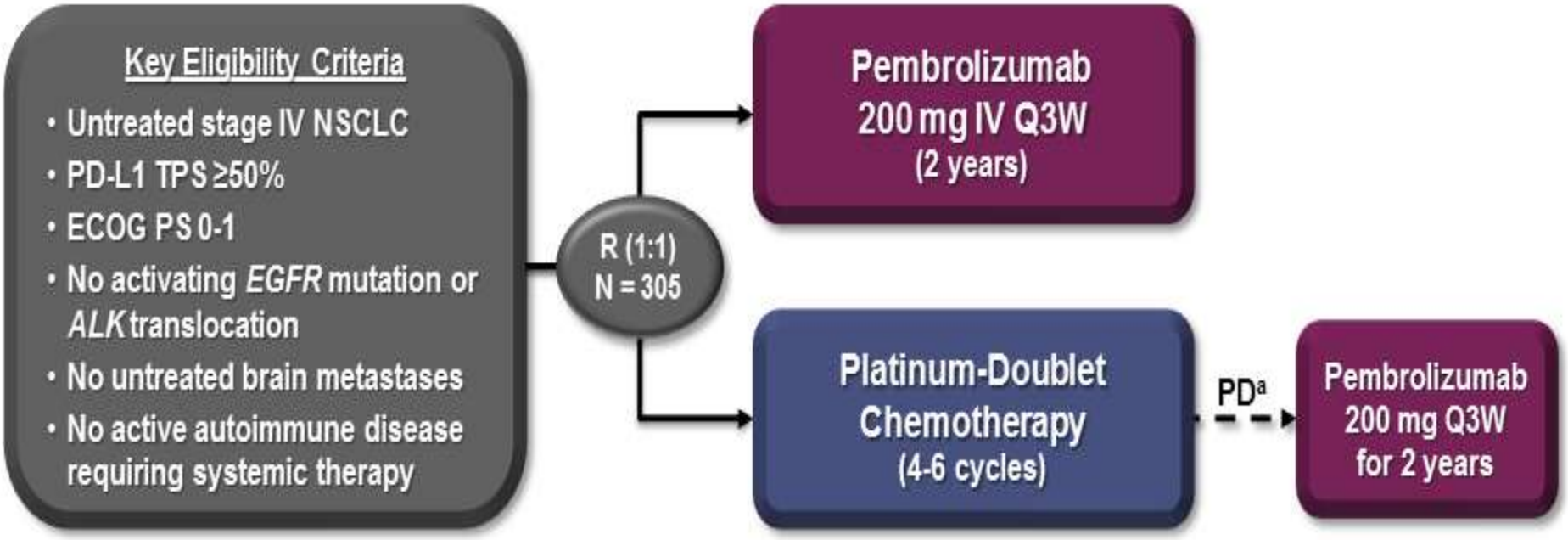
KEYNOTE-024 Study Design (NCT02142738)



Key End Points

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

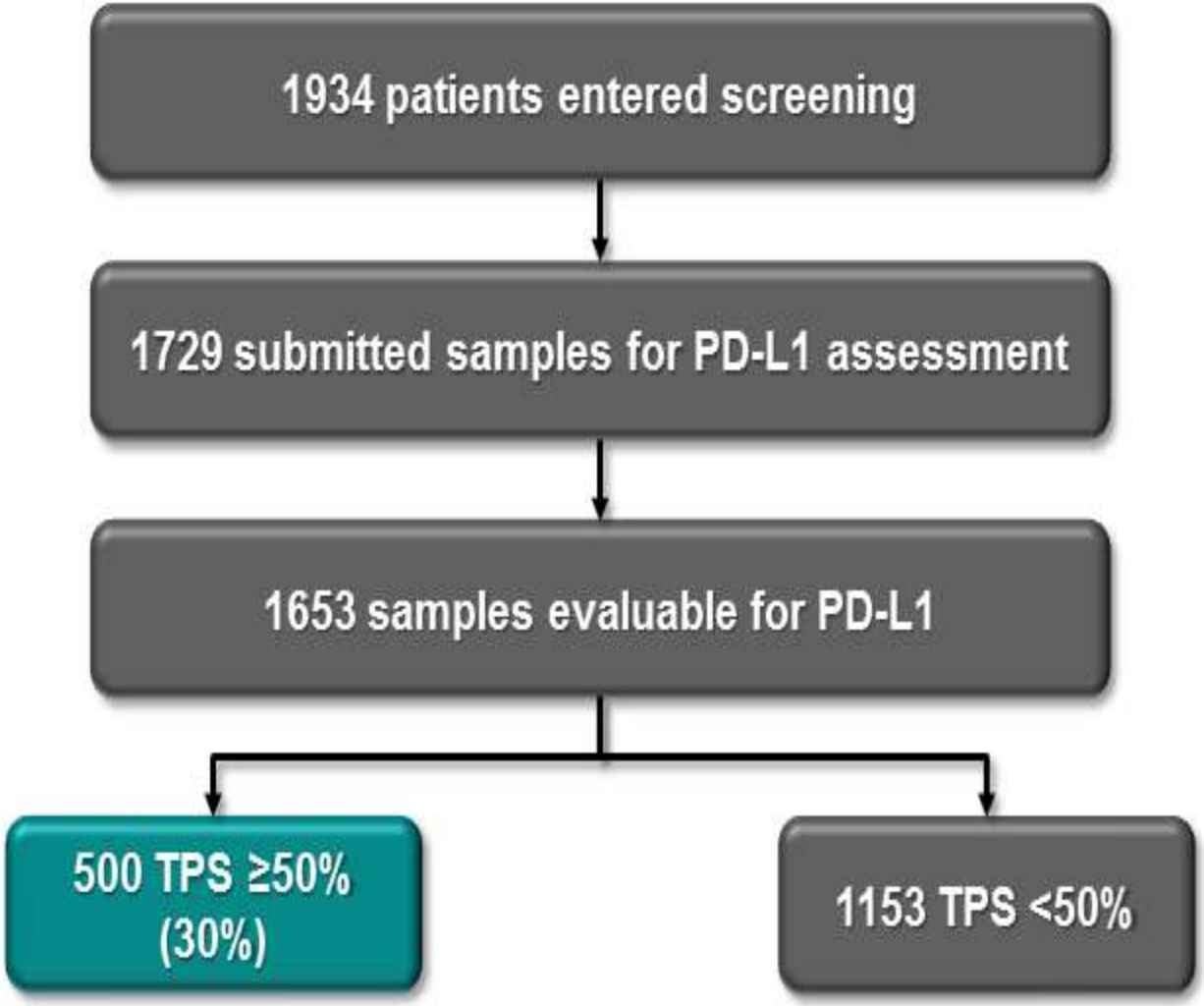
Secondary: OS, ORR, safety

Exploratory: DOR

Median duration follow up: 11.2 months

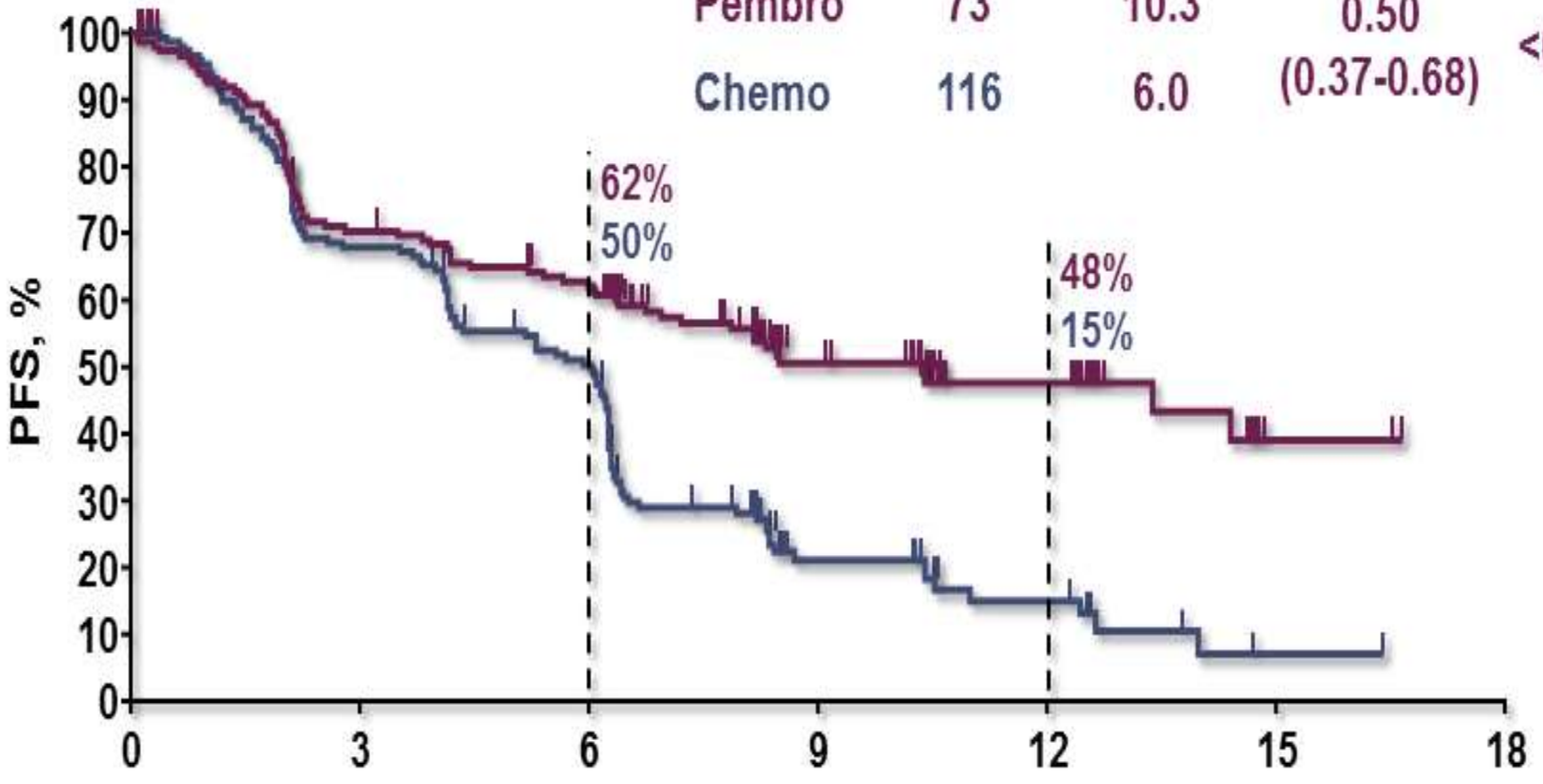
[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

PD-L1 Screening



Progression-Free Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	73	10.3	0.50 (0.37-0.68)	<0.001
Chemo	116	6.0		



No. at risk

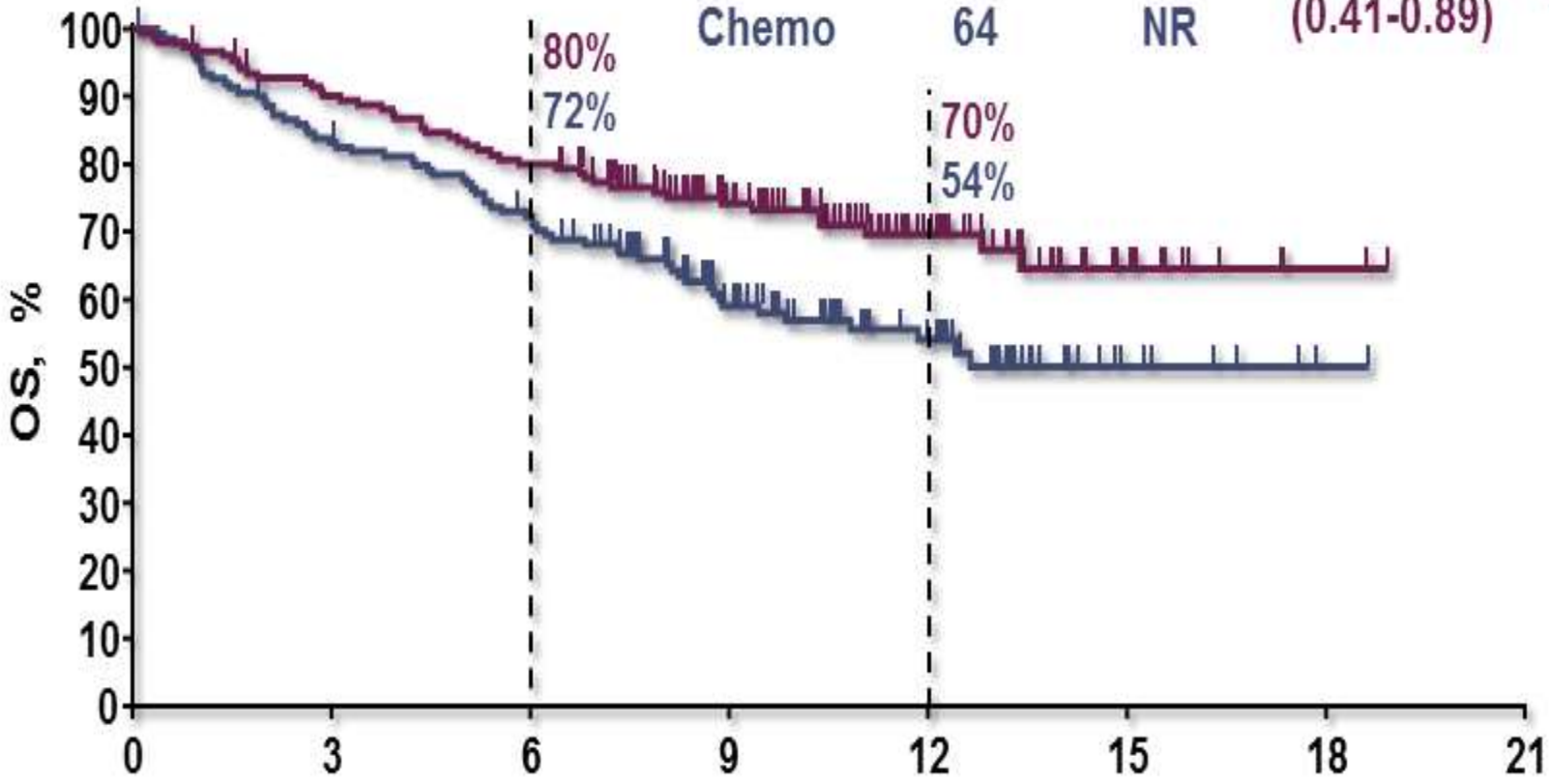
154	104	89	44	22	3	1
151	99	70	18	9	1	0

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

M Reck. ESMO 2016.

Overall Survival

	Events, n	Median, mo	HR (95% CI)	P
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		

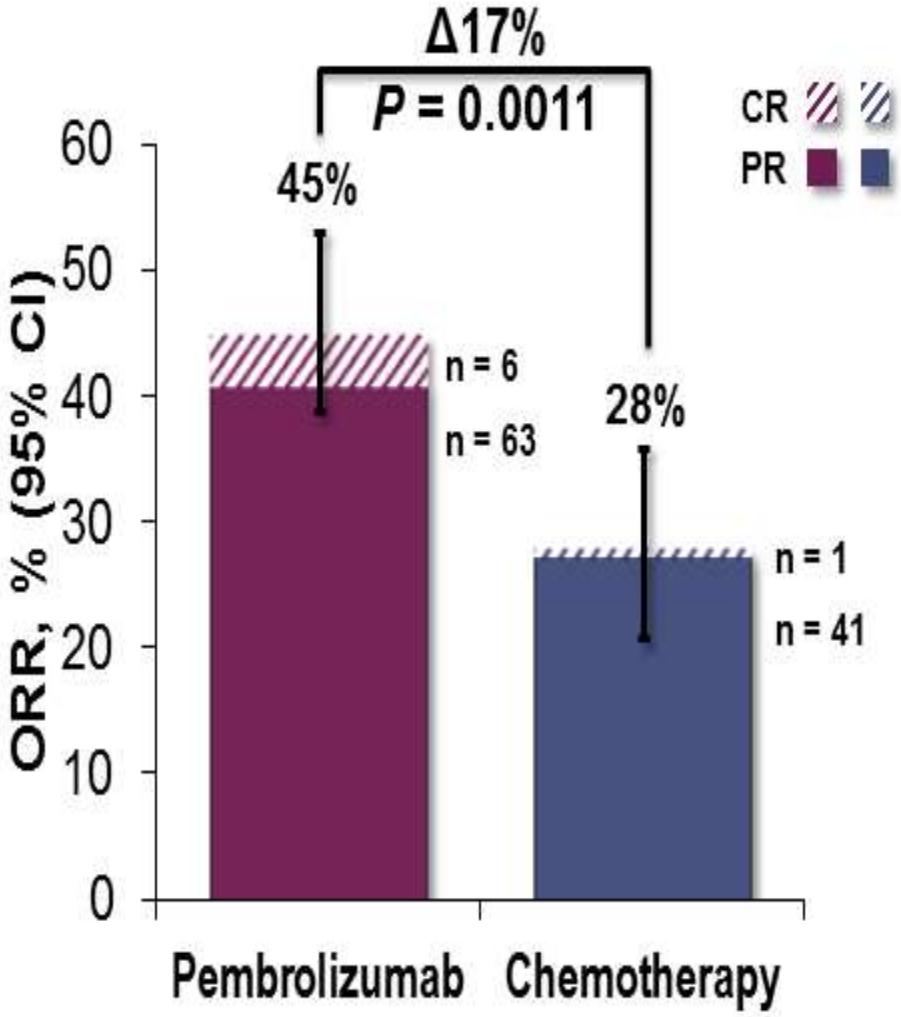


No. at risk

154	136	121	82	39	11	2	0
151	123	106	64	34	7	1	0

Data cut-off: May 9, 2016.

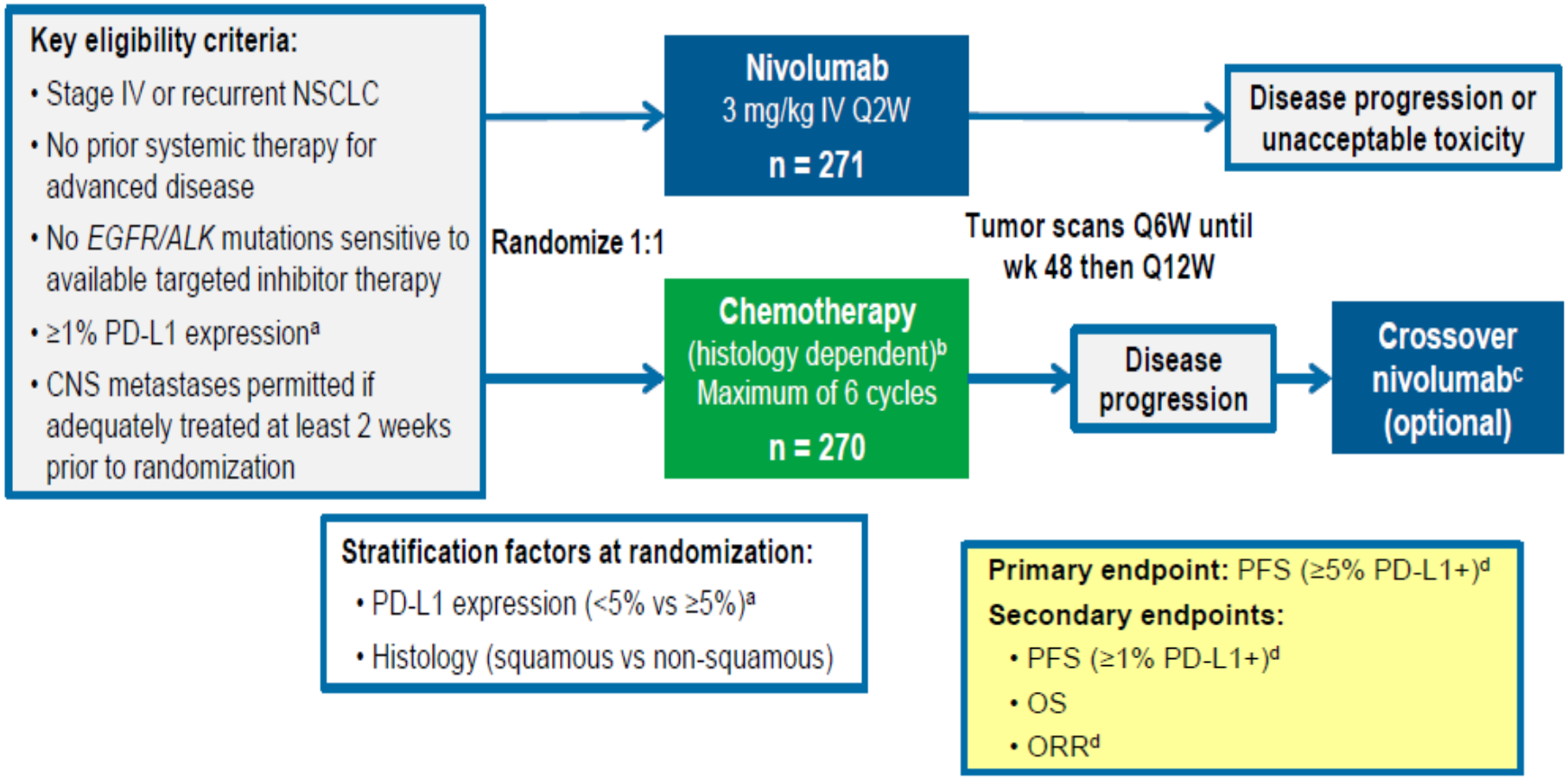
Confirmed Objective Response Rate



	Pembro Responders n = 69	Chemo Responders n = 42
TTR, mo median (range)	2.2 (1.4-8.2)	2.2 (1.8-12.2)
DOR, mo median (range)	NR (1.9+ to 14.5+)	6.3 (2.1+ to 12.6+)

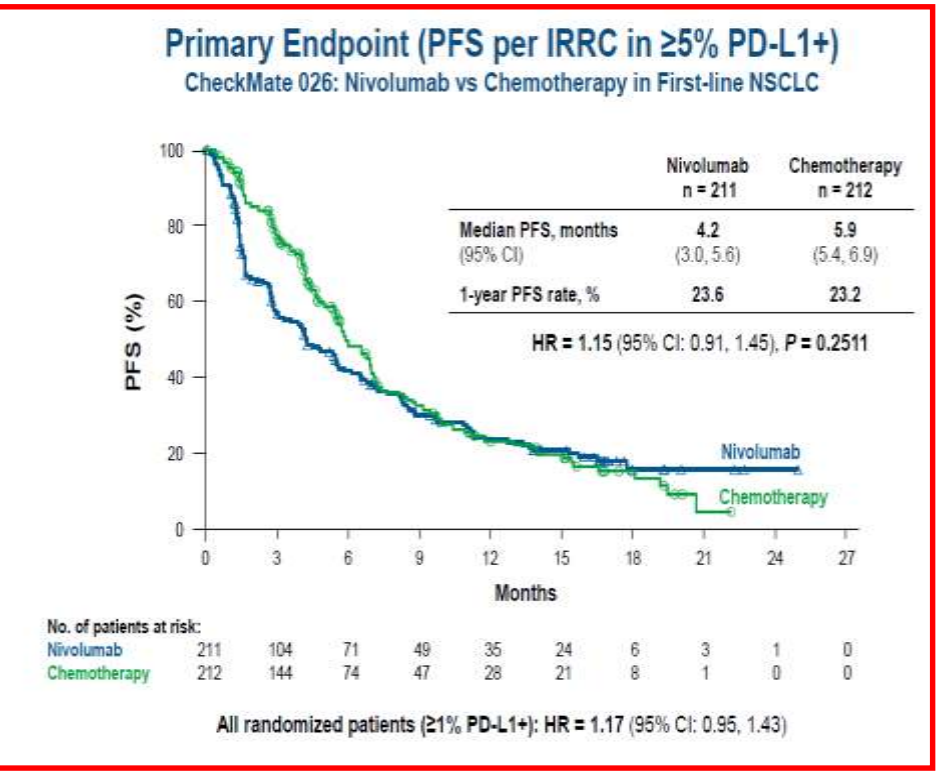
Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

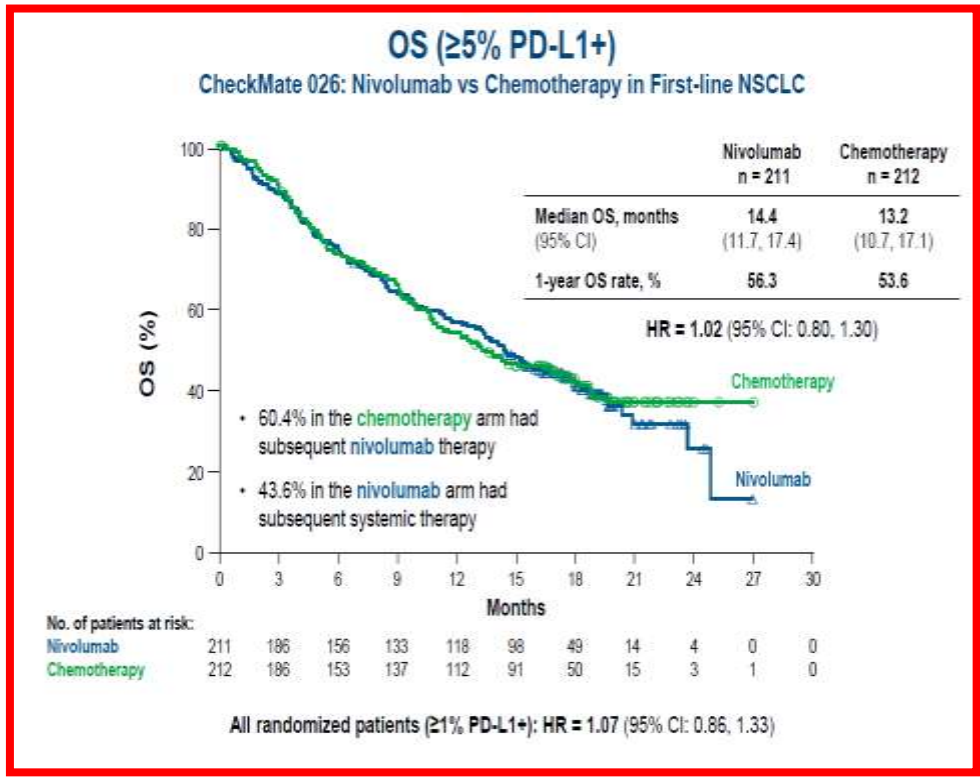
Phase 3 CheckMate 026 Study Design: Nivolumab vs Chemotherapy in First-line NSCLC



[a]Dako 28-8 validated; archival tumor samples obtained ≤6 months before enrollment were permitted; PD-L1 testing was centralized
[b]Squamous: gemcitabine 1250 mg/m^2 + cisplatin 75 mg/m^2; gemcitabine 1000 mg/m^2 + carboplatin AUC 5; paclitaxel 200 mg/m^2 + carboplatin AUC 6; Non-squamous: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2; pemetrexed 500 mg/m^2 + carboplatin AUC 6; option for pemetrexed maintenance therapy
[c]Permitted if crossover eligibility criteria met, including progression confirmed by independent radiology review

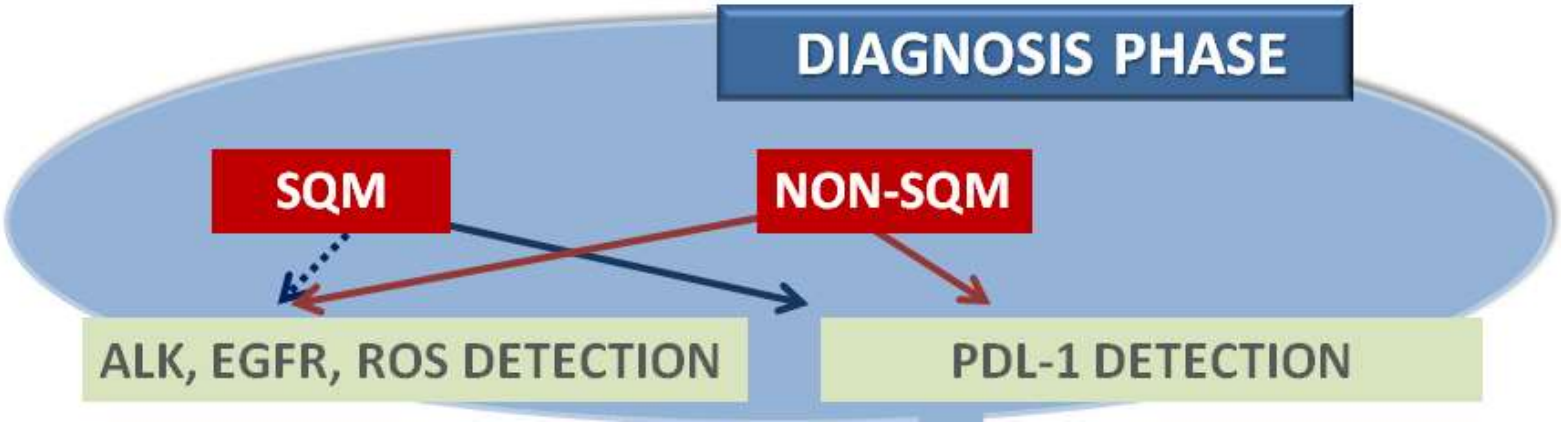
PFS, OS & ORR



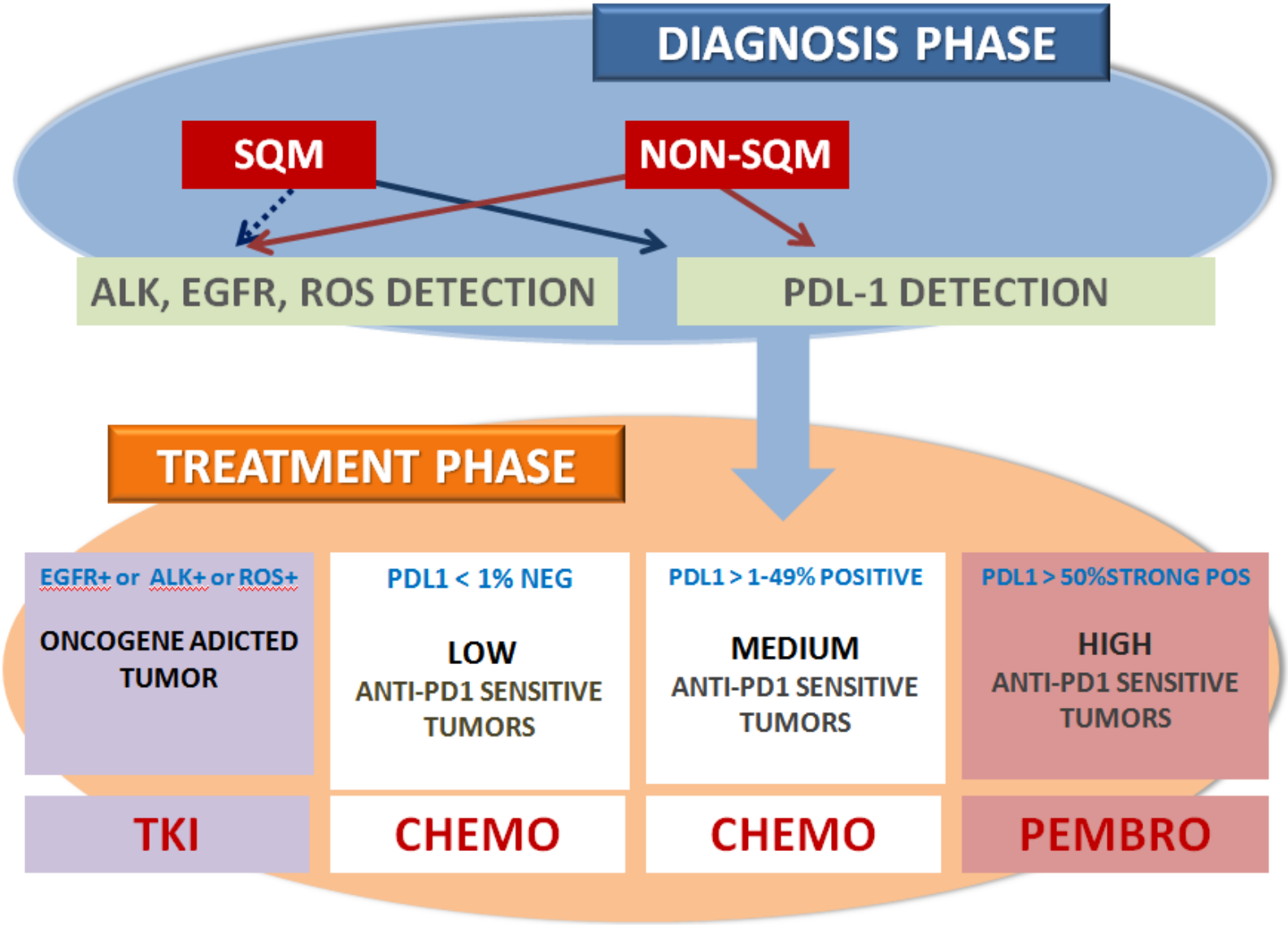


	Nivolumab (n = 211)	Chemotherapy (n = 212)
ORR, % (95% CI)	26.1 (20.3, 32.5)	33.5 (27.2, 40.3)

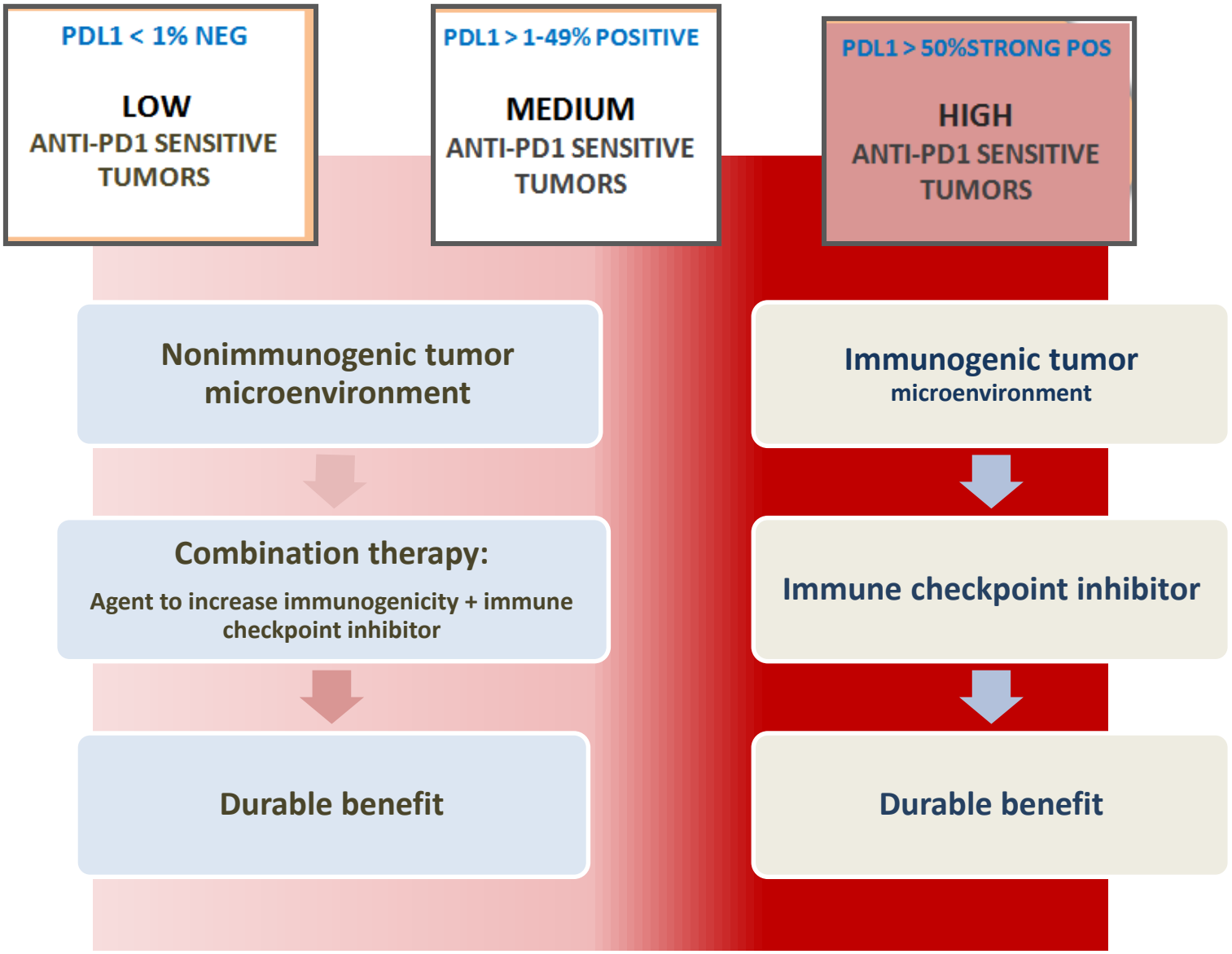
1° line NSCLC DX/TX Algorithm



1° line NSCLC DX/TX Algorithm



1° line NSCLC IO CLINICAL RESEARCH



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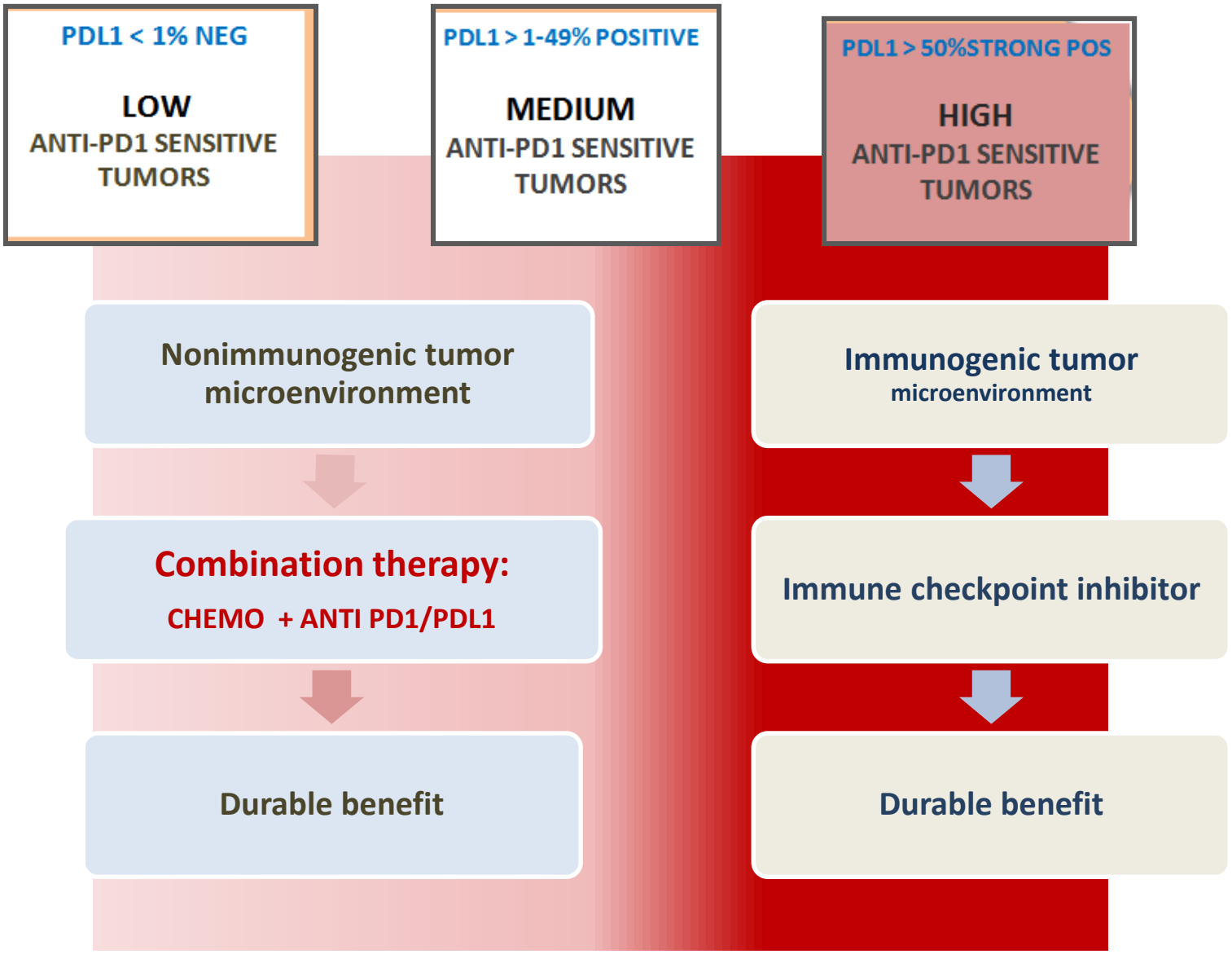
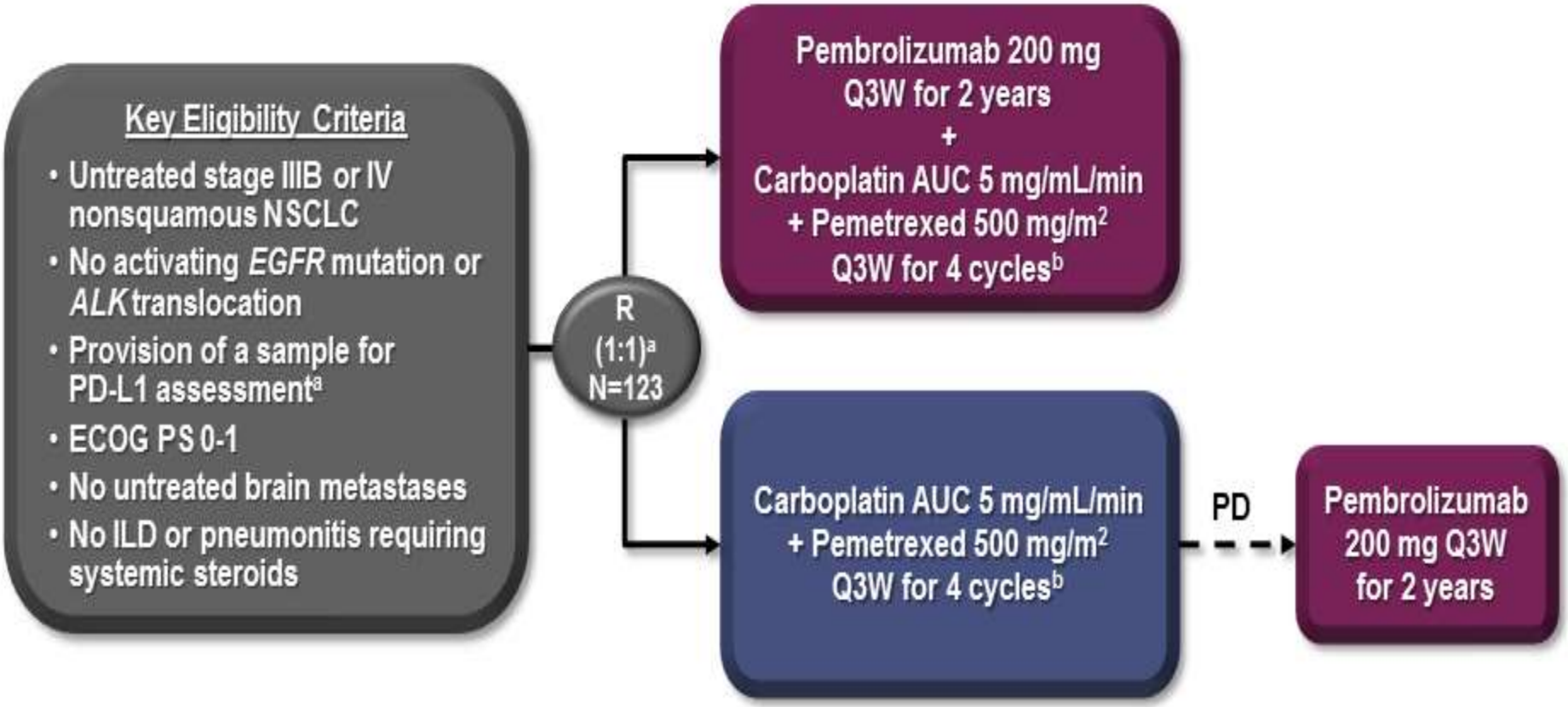


KEYNOTE-021 Cohort G



End Points

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

Key secondary: PFS

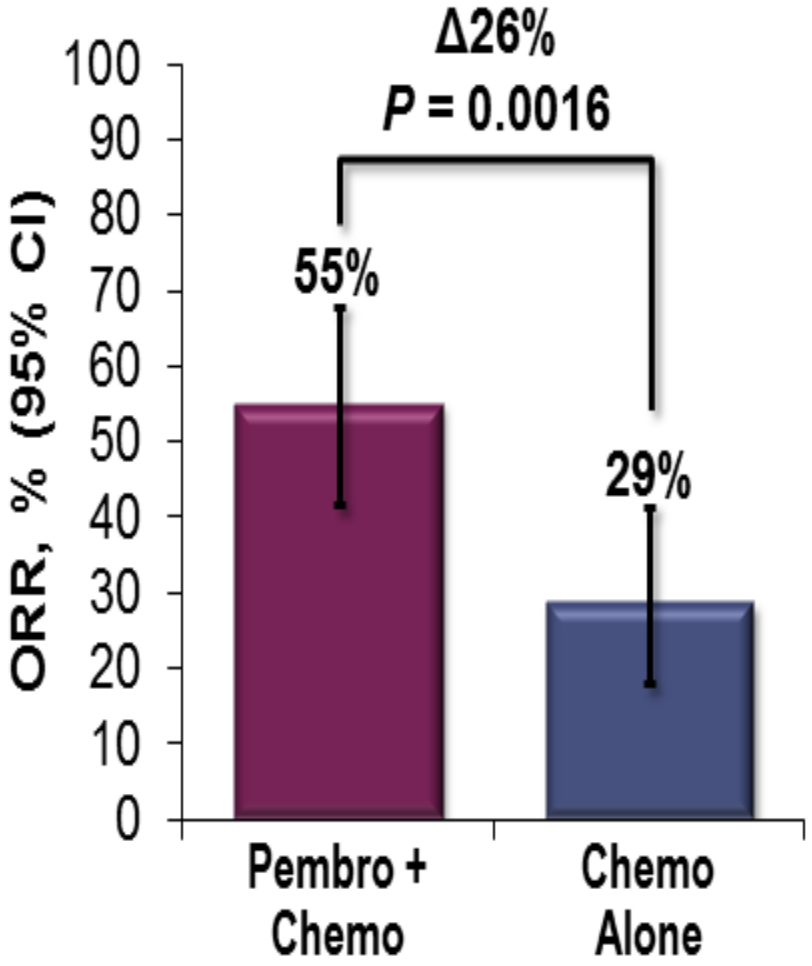
Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

PD=progressive disease.

[a]Randomization was stratified by PD-L1 TPS <1% vs ≥1%.

[b]Indefinite maintenance therapy with pemetrexed 500 mg/m^2 Q3W permitted.

Confirmed Objective Response Rate
(RECIST v1.1 by Blinded, Independent Central Review)

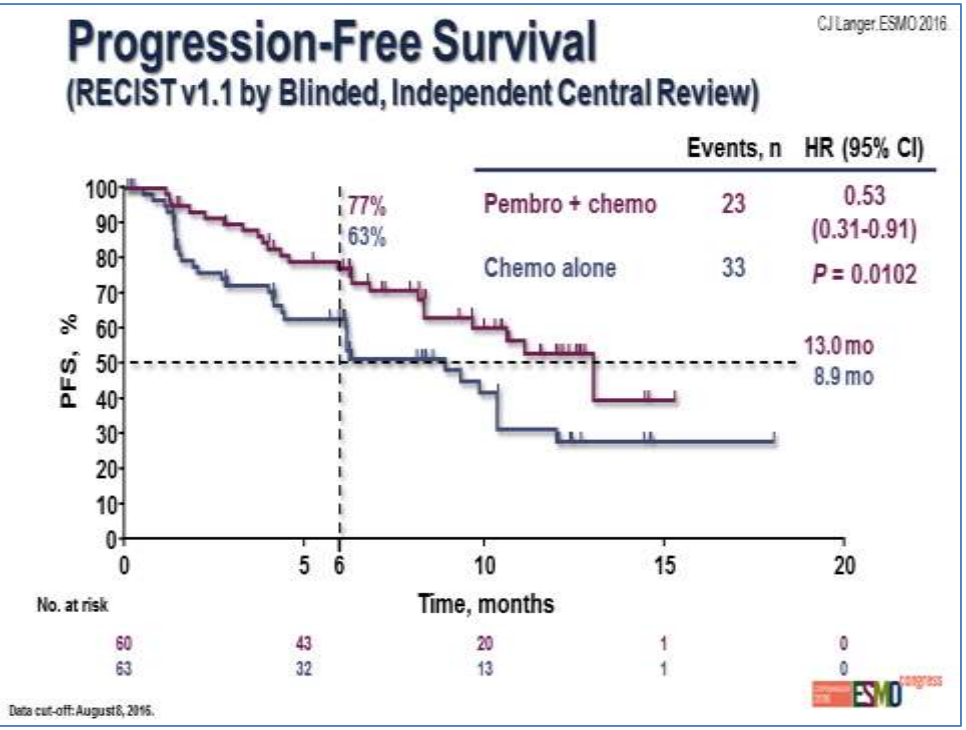


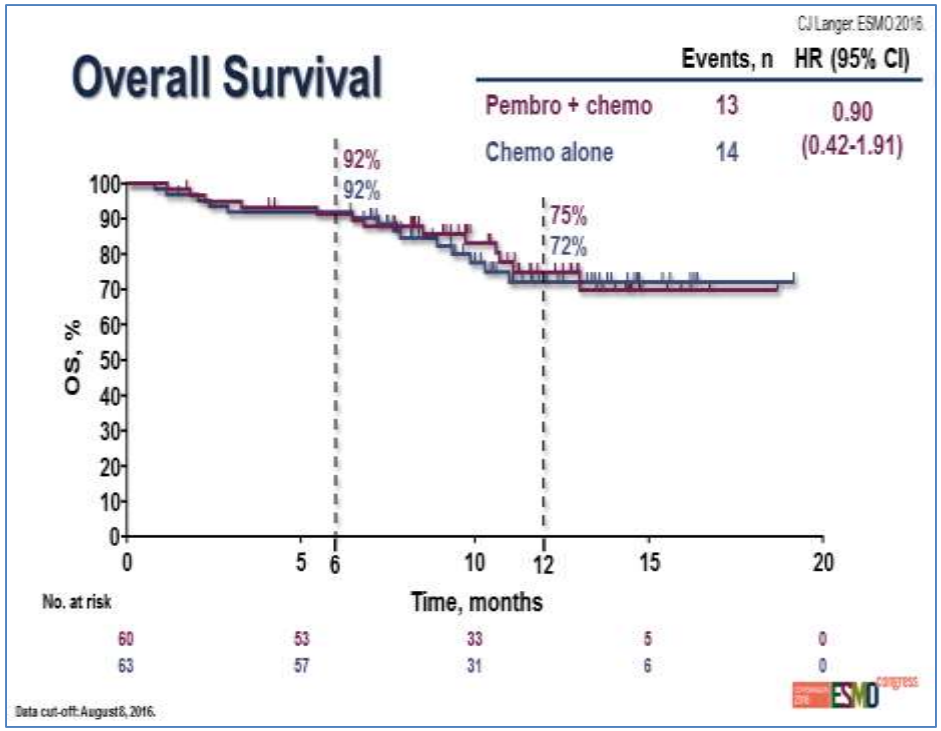
	Pembro + Chemo Responders n = 33	Chemo Alone Responders n = 18
TTR, mo median (range)	1.5 (1.2-12.3)	2.7 (1.1-4.7)
DOR, mo median (range)	NR (1.4+-13.0+)	NR (1.4+-15.2+)
Ongoing response,[a] n (%)	29 (88)	14 (78)

DOR = duration of response; TTR = time to response.
[a]Alive without subsequent disease progression.

Data cut-off: August 8, 2016.

PFS&OS





CJ Langer. ESMO 2016.

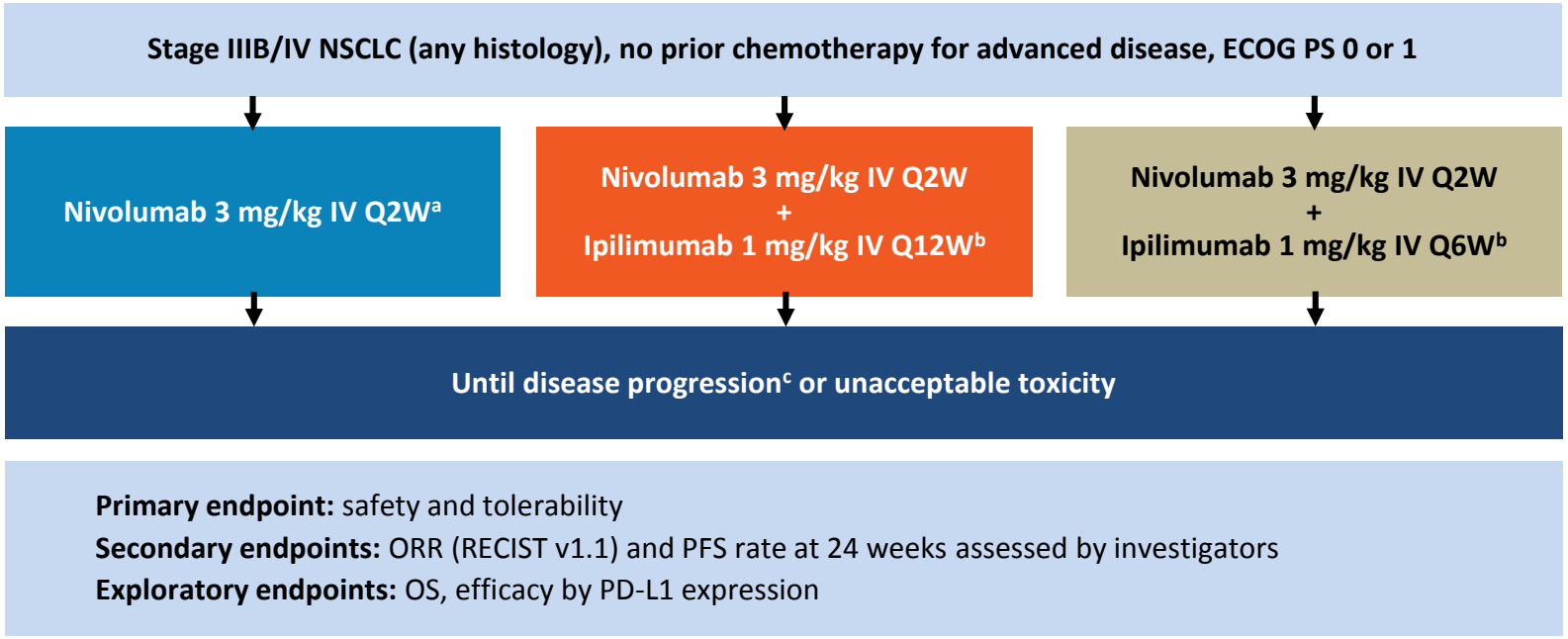
IASLC
International Association for the Study of Lung Cancer
IASLC 17TH WORLD CONFERENCE ON LUNG CANCER
WWW.IASLC.ORG DECEMBER 4–7, 2016 VIENNA, AUSTRIA

First-Line Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Patients With Advanced NSCLC: Long-Term Outcomes From CheckMate 012

Scott N. Gettinger,[1] Naiyer Rizvi,[2] Laura Q. Chow,[3] Hossein Borghaei,[4] Julie Brahmer,[5] Frances A. Shepherd,[6] Neal E. Ready,[7] David E. Gerber,[8] Scott J. Antonia,[9] Jonathan W. Goldman,[10] Rosalyn Juergens,[11] William J. Geese,[12] Tina C. Young,[12] Xuemei Li,[12] Matthew D. Hellmann[2]

[1]Yale Cancer Center, New Haven, CT, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]University of Washington, Seattle, WA, USA; [4]Fox Chase Cancer Center, Philadelphia, PA, USA; [5]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [6]Princess Margaret Cancer Centre, Toronto, Canada; [7]Duke University Medical Center, Durham, NC, USA; [8]University of Texas Southwestern Medical Center, Dallas, TX, USA; [9]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [10]University of California, Los Angeles, Los Angeles, CA, USA; [11]Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; [12]Bristol-Myers Squibb, Princeton, NJ, USA

Phase 1 CheckMate 012 Study Design: First-Line Nivolumab ± Ipilimumab in NSCLC

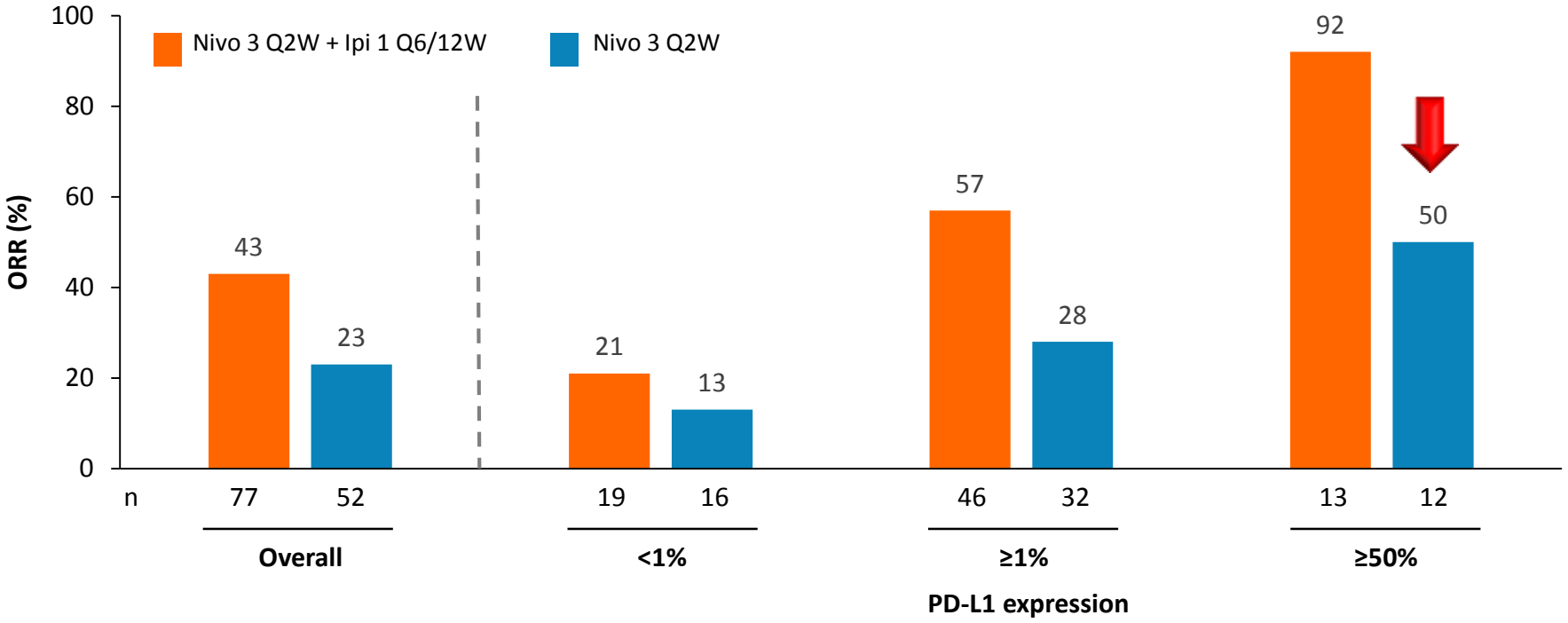


- Updated data[d] presented here are based on median follow-up durations of 22 months (monotherapy) and 16 months (combination cohorts)
  - Overall additional follow-up relative to previous reports: monotherapy, +~18 months;[1] combination cohorts, +6 months[2]

ClinicalTrials.gov number NCT01454102; [a]Treatment allocation not randomized; [b]Treatment allocation randomized; earlier cohorts evaluated other dosing schedules/regimens[2] [c]Patients tolerating study treatment permitted to continue treatment beyond RECIST v1.1-defined progression if considered to be deriving clinical benefit
[d]Based on a September 2016 database lock
1. Gettinger S, et al. *J Clin Oncol* 2016;34:2980–2987; 2. Hellmann MD, et al. *Lancet Oncol* 2016 Dec 5. [Epub ahead of print].

Nivolumab ± Ipilimumab ORR by Tumor PD-L1 Expression

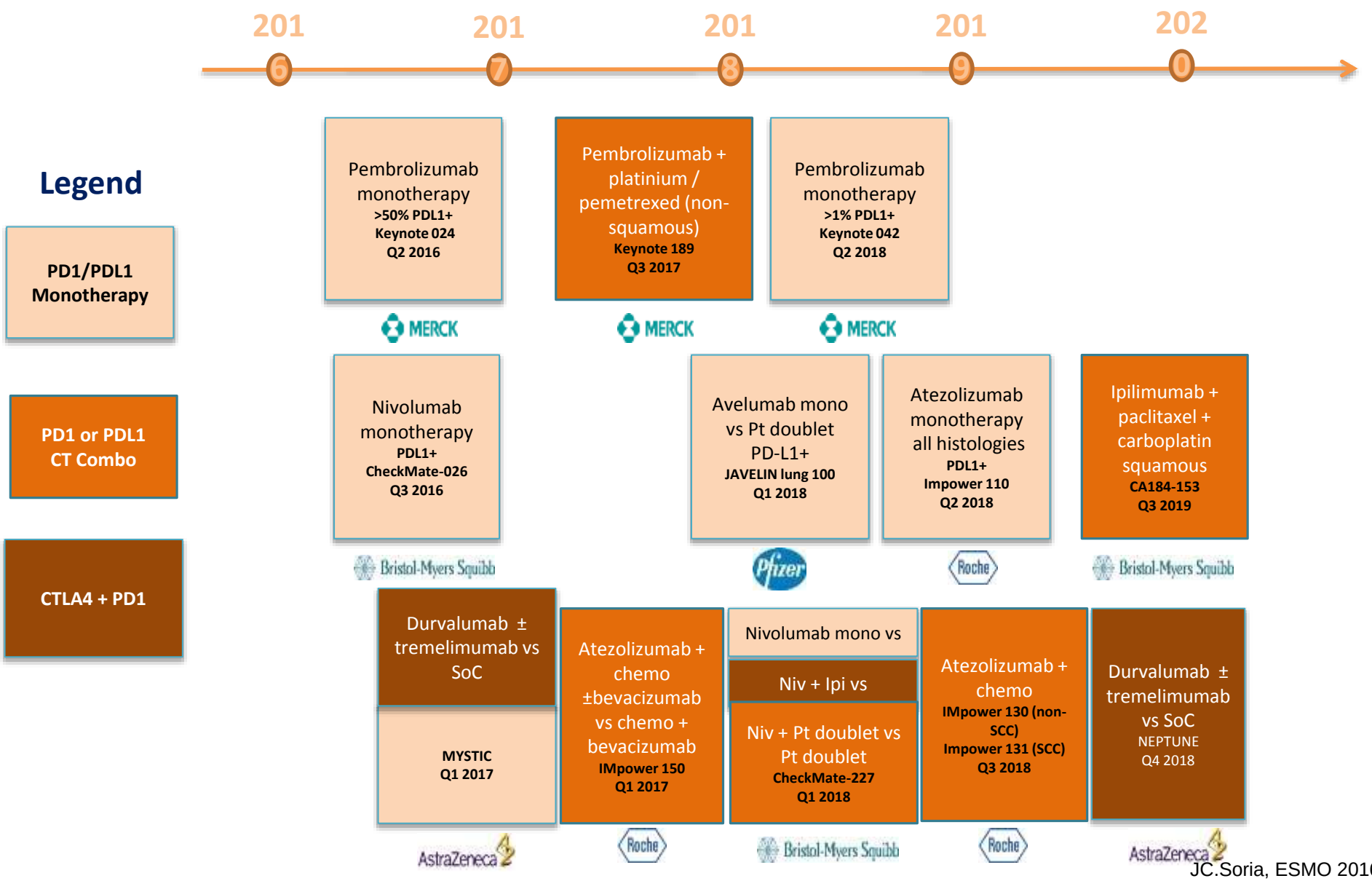
CheckMate 012: First-Line Nivolumab ± Ipilimumab in NSCLC



- 5 CRs (10%) were achieved in the nivolumab monotherapy cohort (1 in a patient with tumor PD-L1 expression <1%)
- 6 CRs (8%) were achieved in the nivolumab + ipilimumab cohorts[a] (3 in patients with tumor PD-L1 expression <1%)

Based on a September 2016 database lock; [a]3 determined radiographically per RECIST v1.1 and 3 identified by pathologic evaluation

Upcoming randomized immunotherapy trials in 1st line NSCLC and projected read-out timelines



JC.Soria, ESMO 2016

Come cambia l'algoritmo di trattamento nella pratica clinica del NSCLC

Immunoterapia: Cosa si ha fato imparare?

1° LINEA

2° LINEA

Randomised Trials of Anti PD-1 / anti-PD-L1 Agents

Study	Line	Agents	PD-L1	Result	HR
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Barlesi et al. ESMO 2016 LBA44. Socinski et al. ESMO 2016
Reck et al. N Engl J Med 2016; 375: 1823 - 33

Summary of phase III studies of immunotherapy in previously treated patients

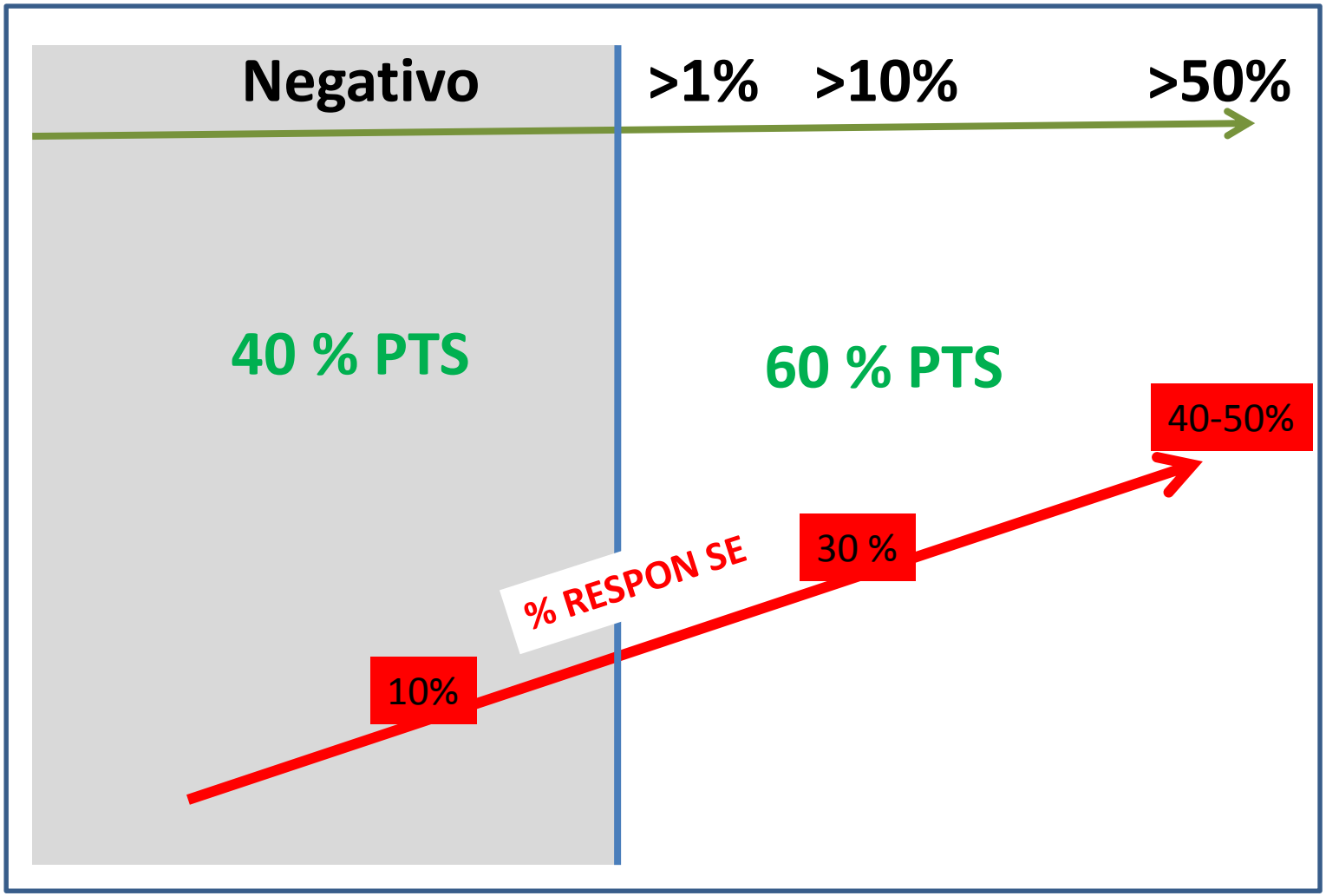
	CheckMate 017[1] Nivolumab vs docetaxel	CheckMate 057[1] Nivolumab vs docetaxel	KEYNOTE-010[2] Pembrolizumab (2mg/kg or 10mg/kg) vs docetaxel	OAK[3] Atezolizumab vs docetaxel
Phase of study	**III**	**III**	**II/III**	**III**
PD-L1 selected	**No**	**No**	**Yes (TPS* ≥1%)**	**No**
Study size, n	**272 (135 vs 137)**	**582 (292 vs 290)**	**1,033 (344 vs 346 vs 343)**	**1,225 (425 vs 425)***
Histology	**Squamous**	**Non-squamous**	**All-comers**	**All-comers**
Line of therapy, %				
2L	**100**	**88**	**69**	**75**
3L	**0**	**11**	**20**	**25**
>3L	**0**	**<1**	**9**	**0**
Other/unknown	**0**	**0**	**<1**	**0**
Subsequent CIT (immunotherapy arm vs chemo arm), %	**<1 vs 2**	**1 vs 2**	**0.6 vs 1.7 vs 13.1**	**4.5 vs 17.2**
Crossover from chemo arm to study immunotherapy, %	**4**	**6**	**Not permitted**	**Not permitted**
Median OS, months HR vs docetaxel (p value)	**9.2 vs 6.0 0.62 (p=0.0004)**	**12.2 vs 9.5 0.75 (p<0.001)**	**10.4 vs 12.7 vs 8.5 2mg/kg: 0.71 (p=0.0008) 10mg/kg: 0.61 (p<0.0001)**	**13.8 vs 9.6 0.73 (p=0.0003)**

*850 in primary population
NR = not reached

1. Borghaei, et al. ASCO 2016
2. Herbst, et al. Lancet 2015; 3. Barlesi, et al. ESMO 2016

2°-Line NSCLC

Anti PD-1 / anti-PD-L1 Agents , PD-L1 expression



Second line – Nivolumab
Checkmate 017 (SQM)

CheckMate 017 (NCT01642004) - Study Design

- Stage IIIb/IV SQ NSCLC
- 1 prior platinum doublet-based chemotherapy
- ECOG PS 0–1
- Pre-treatment (archival or fresh) tumor samples required for PD-L1 analysis

N = 272

Randomize 1:1

Nivolumab
3 mg/kg IV Q2W until PD or unacceptable toxicity
n = 135

Docetaxel
75 mg/m² IV Q3W until PD or unacceptable toxicity
n = 137

Patients stratified by region and prior paclitaxel use

- **Primary Endpoint:**
  - OS
- **Additional Endpoints:**
  - Investigator-assessed ORR
  - Investigator-assessed PFS
  - Correlation between PD-L1 expression and efficacy
  - Safety
  - Quality of life (LCSS)

- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was $P < 0.03$

LCSS = Lung cancer symptom scale

ASCO Annual Meeting

IASLC

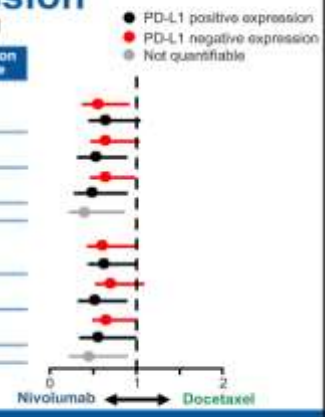
16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 DENVER, COLORADO, USA

Efficacy by PD-L1 Expression

- Survival benefit with nivolumab was independent of PD-L1expression level

PD-L1 Expression	Patients, n Nivolumab	Patients, n Docetaxel	Unstratified HR (95% CI)	Interaction P-value
OS				
<1%	54	52	0.58 (0.37, 0.92)	0.56
≥1%	63	56	0.69 (0.45, 1.05)	
<5%	75	69	0.70 (0.47, 1.02)	0.47
≥5%	42	39	0.53 (0.31, 0.89)	
<10%	81	75	0.70 (0.48, 1.01)	0.41
≥10%	36	33	0.50 (0.28, 0.89)	
Not quantifiable	18	29	0.39 (0.19, 0.82)	
PFS				
<1%	54	52	0.66 (0.43, 1.00)	0.70
≥1%	63	56	0.67 (0.44, 1.01)	
<5%	75	69	0.75 (0.52, 1.08)	0.16
≥5%	42	39	0.54 (0.32, 0.90)	
<10%	81	75	0.70 (0.49, 0.99)	0.35
≥10%	36	33	0.58 (0.33, 1.02)	
Not quantifiable	18	29	0.45 (0.23, 0.89)	

- 83% of patients (225/272) had quantifiable PD-L1 expression

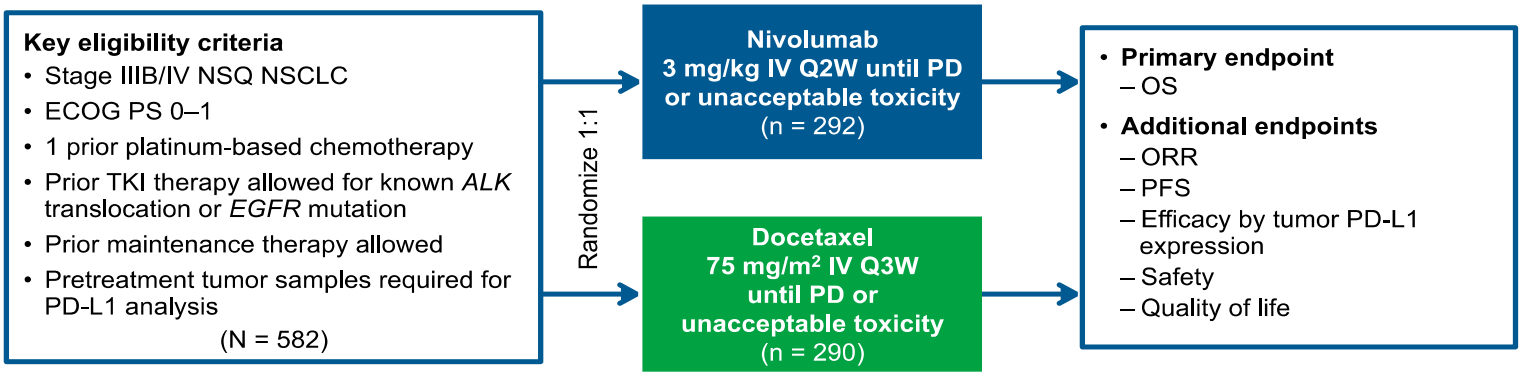


Based on December 2014 DBL

13

Second line – Nivolumab
Checkmate 057

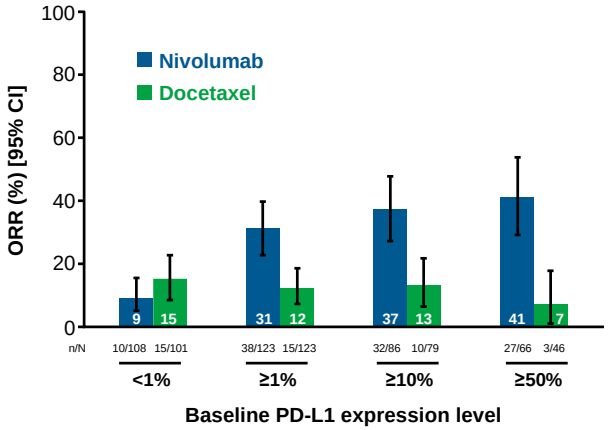
Phase 3 CheckMate 057 Study Design: Nivolumab vs Docetaxel in Previously Treated NSQ NSCLC

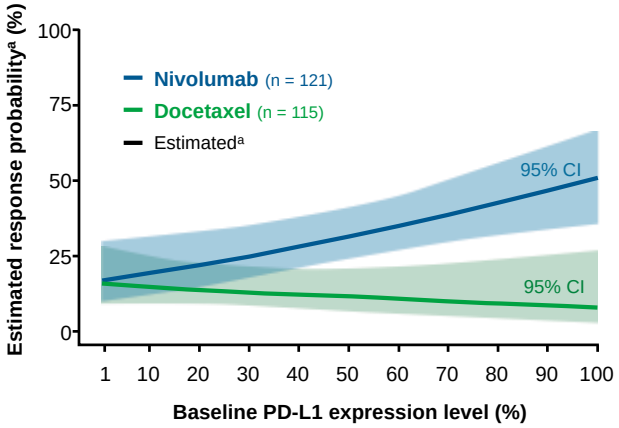


Randomization stratified by prior maintenance therapy and line of therapy (second-line vs third-line)

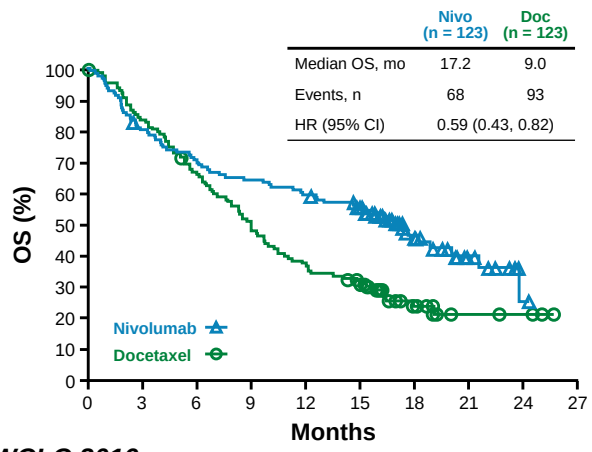
Second line – Nivolumab
Checkmate 057

PD-L1 Expression Continuum and Response Probability
CheckMate 057: Nivolumab vs Docetaxel in Previously Treated NSQ NSCLC

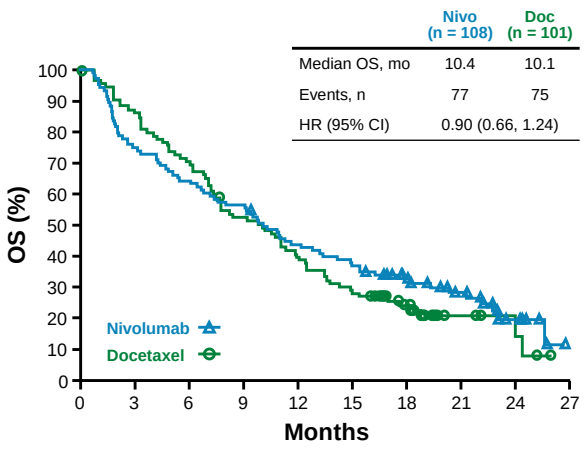




≥1% PD-L1 Expression



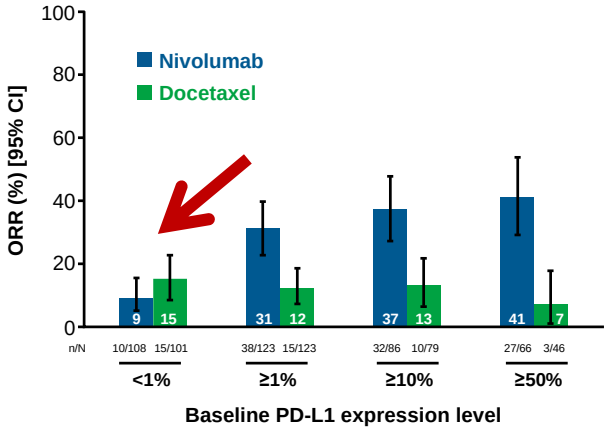
<1% PD-L1 Expression

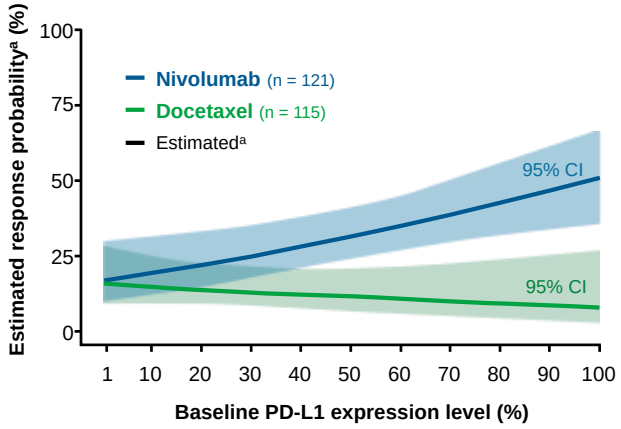


Solange Peters et al. WCLC 2016

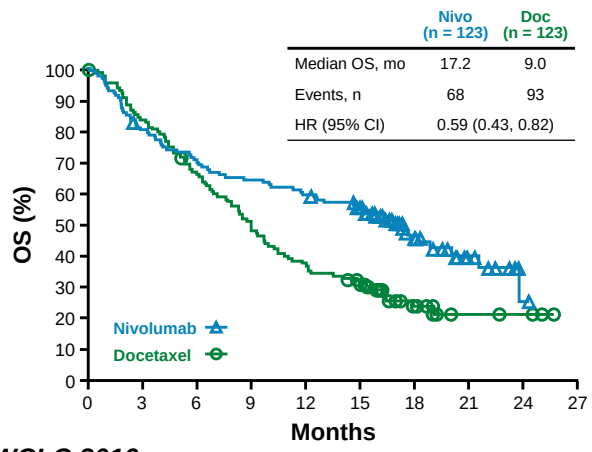
Second line – Nivolumab
Checkmate 057

PD-L1 Expression Continuum and Response Probability
CheckMate 057: Nivolumab vs Docetaxel in Previously Treated NSQ NSCLC

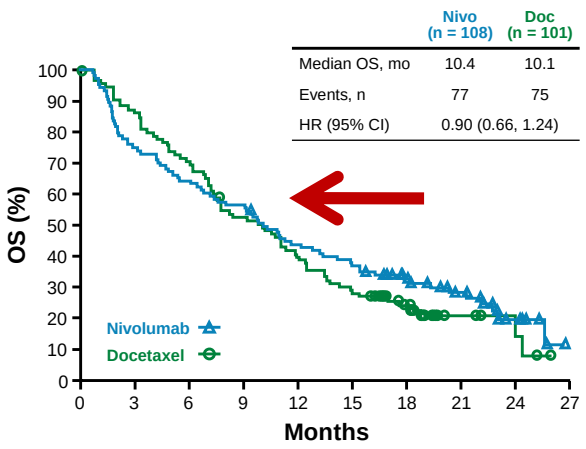




≥1% PD-L1 Expression



<1% PD-L1 Expression



Solange Peters et al. WCLC 2016

KEYNOTE-010 Study Design

Patients

- Advanced NSCLC
- Confirmed PD after ≥1 line of chemotherapy[a]
- No active brain metastases
- ECOG PS 0-1
- PD-L1 TPS ≥1%
- No serious autoimmune disease
- No ILD or pneumonitis requiring systemic steroids

R
1:1:1

- Pembrolizumab 2 mg/kg IV Q3W for 24 months
- Pembrolizumab 10 mg/kg IV Q3W for 24 months
- Docetaxel 75 mg/m^2 Q3W per local guidelines[c]

Stratification factors:

- ECOG PS (0 vs 1)
- Region (East Asia vs non-East Asia)
- PD-L1 status[b] (TPS ≥50% vs 1%-49%)

End points in the TPS ≥50% stratum and TPS ≥1% population

- Primary: PFS and OS
- Secondary: ORR, duration of response, safety

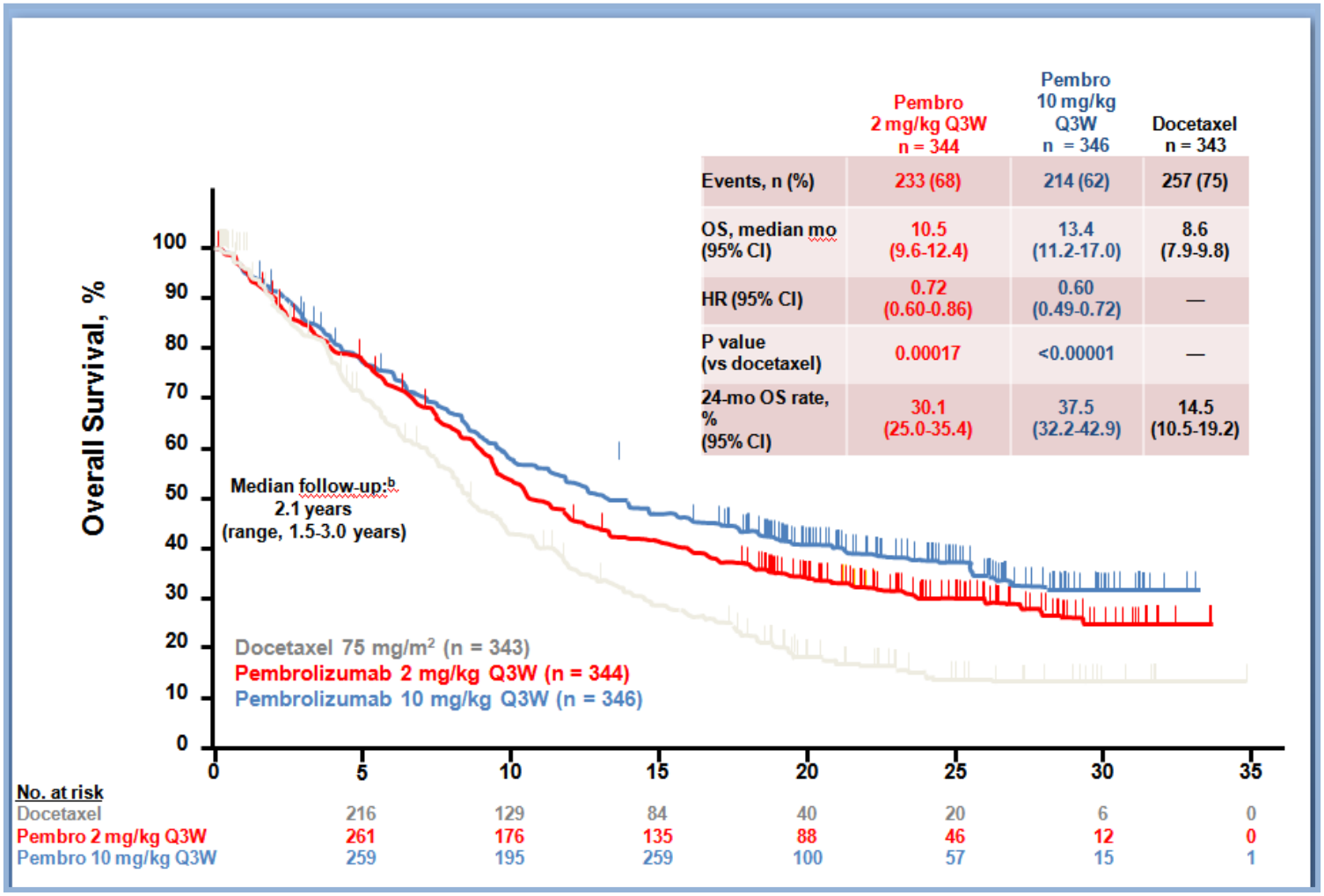
ClinicalTrials.gov, NCT01905657.

[a]Prior therapy must have included ≥2 cycles of platinum-doublet chemotherapy. An appropriate tyrosine kinase inhibitor was required for patients whose tumors had an *EGFR* sensitizing mutation or an *ALK* translocation.

[b]Added after 441 patients enrolled based on results from KEYNOTE-001 (Garon EB et al. *N Engl J Med*. 2015;372:2018-28).

[c]Patients received the maximum number of cycles permitted by the local regulatory authority.

OS KEYNOTE-010 STUDY

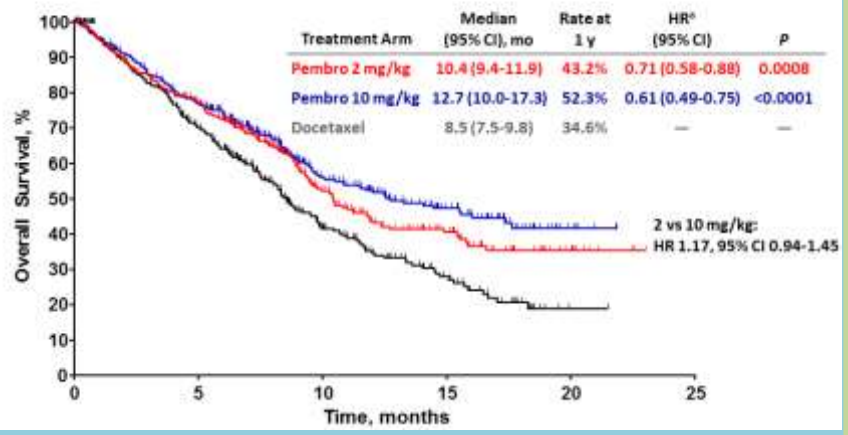


6769 Herbst WCLC 2016

Efficacy to PEMBROLIZUMAB according to PDL1 expresion (KN-010)

RS Herbst. Presented December 20, 2015

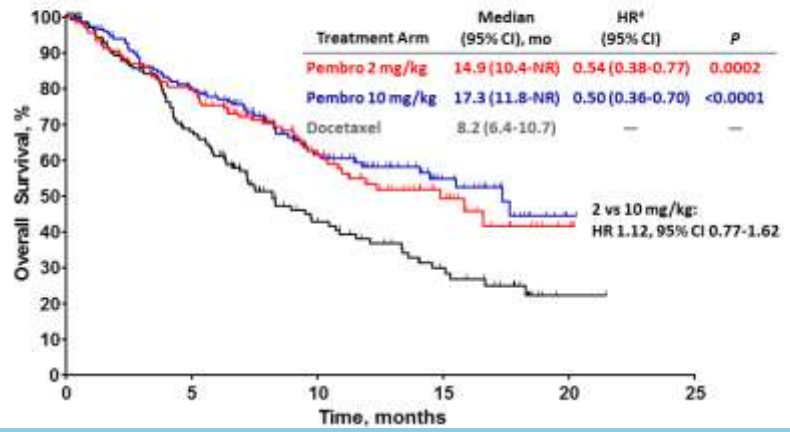
OS, PD-L1 TPS ≥1% (Total Population)



PD-L1 TPS ≥1%	Pembro 2 mg/kg n = 344	Pembro 10 mg/kg n = 346	Docetaxel n = 343
ORR, % (95% CI)	18 (14-22) $P = 0.0005^a$	18 (14-23) $P = 0.0002^a$	9 (6-13)

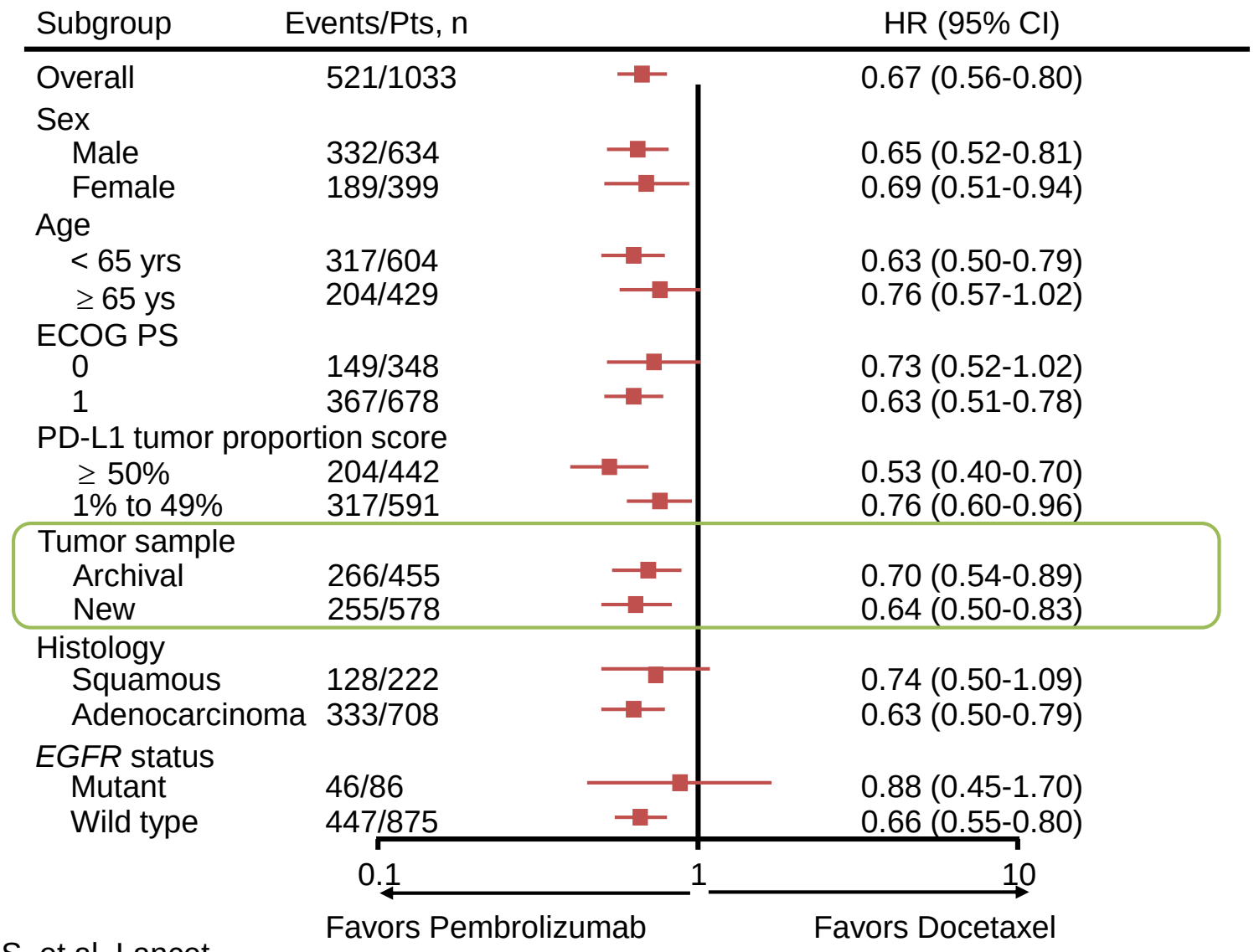
RS Herbst. Presented December 20, 2015

OS, PD-L1 TPS ≥50% Stratum



PD-L1 TPS ≥50%	Pembro 2 mg/kg n = 139	Pembro 10 mg/kg n = 151	Docetaxel n = 152
ORR, % (95% CI)	30 (23-39) $P < 0.0001^a$	29 (22-37) $P < 0.0001^a$	8 (4-13)

KEYNOTE-010: OS by Pt Subgroup



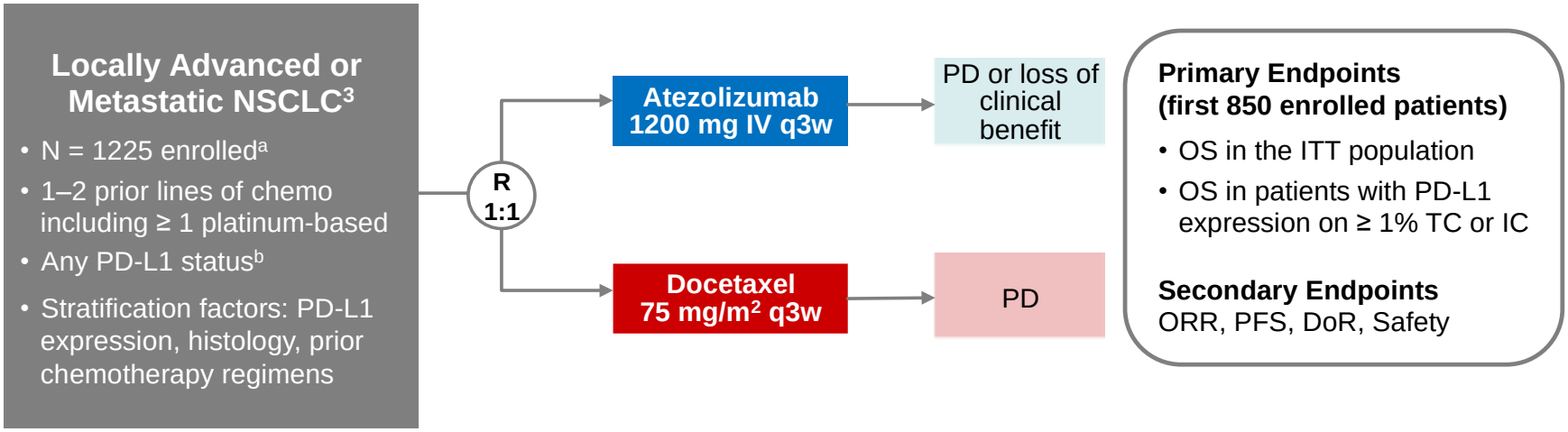
Herbst RS, et al. Lancet. 2016;387:1540-1550.

Second line – Atezo Subgroups OAK PhIII

Phase III OAK study design

Atezolizumab (anti–PD-L1) is an engineered mAb that inhibits the PD-L1/PD-1 and PD-L1/B7.1 interactions to restore anti-tumor T-cell activity and enhance T-cell priming[1,2]

OAK study design



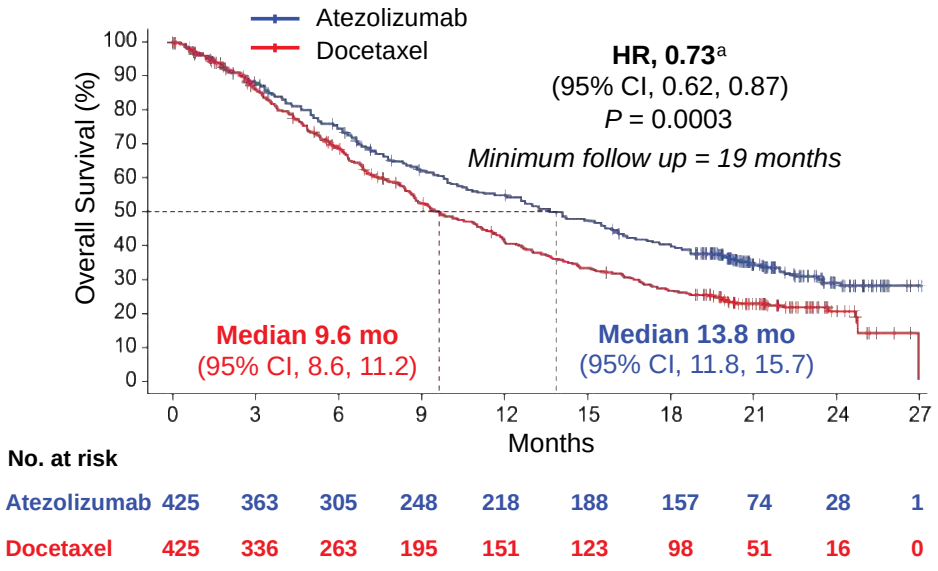
[a]A prespecified analysis of the first 850 patients provided sufficient power to test the co-primary endpoints of OS in the ITT and TC1/2/3 or IC1/2/3 subgroup (≥ 1% PD-L1 expression).
[b]PD-L1 expression assessed with VENTANA SP142 IHC assay

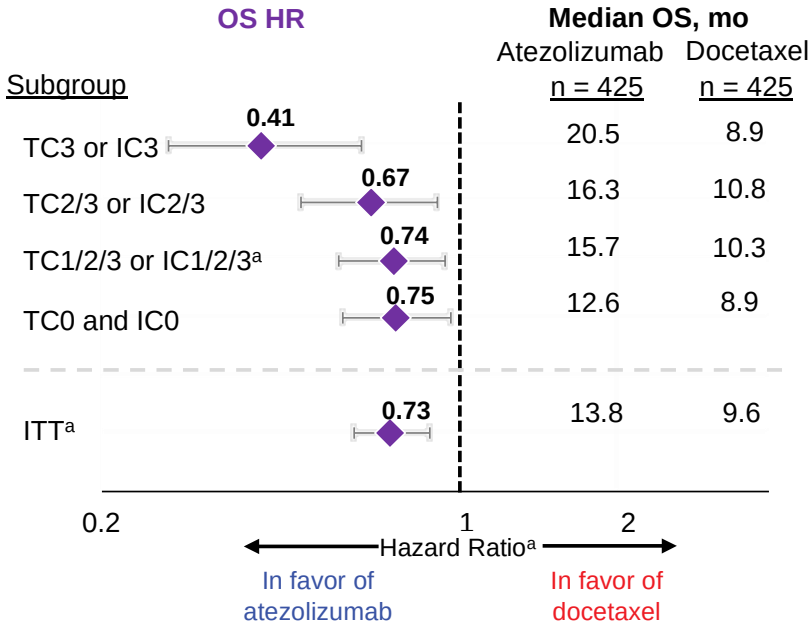
1. Herbst *Nature* 2014. 2. Chen *Immunity* 2013. 3. Barlesi et al. ESMO 2016 LBA44

Gadgeel et al., WCLC 2016

Second line – Atezo Subgroups OAK PhIII

Overall survival, ITT (n = 850) and PD-L1 subgroups



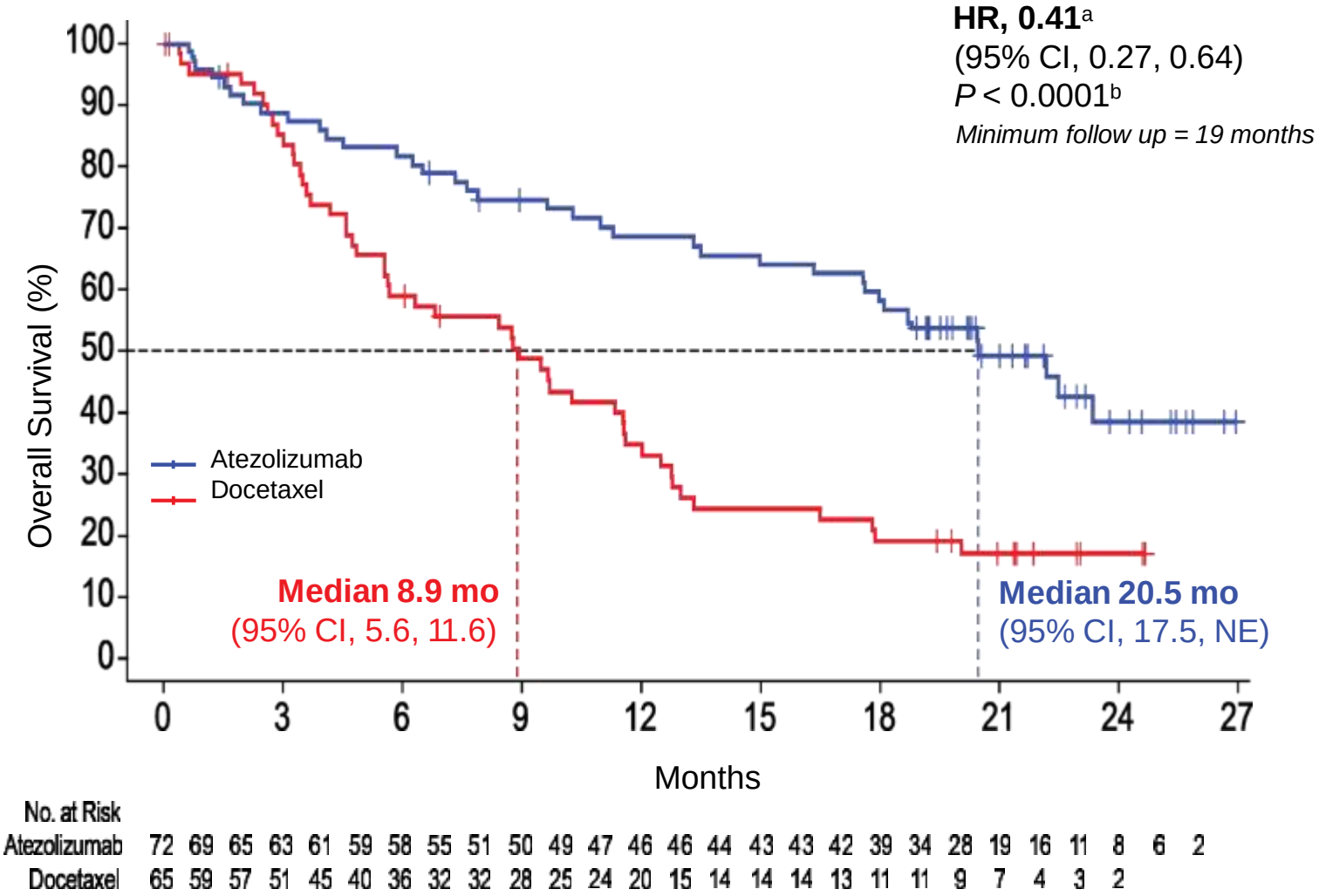


[a]Stratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for other subgroups.
TC, tumor cells; IC, tumor-infiltrating immune cells; OS, overall survival.
Barlesi et al. ESMO 2016 LBA44

Gadgeel et al., WCLC 2016

OS, PD-L1 EXPRESSION ON ≥ 50% TC OR ≥ 10% IC

TC3 OR IC3; 16% OF PATIENTS

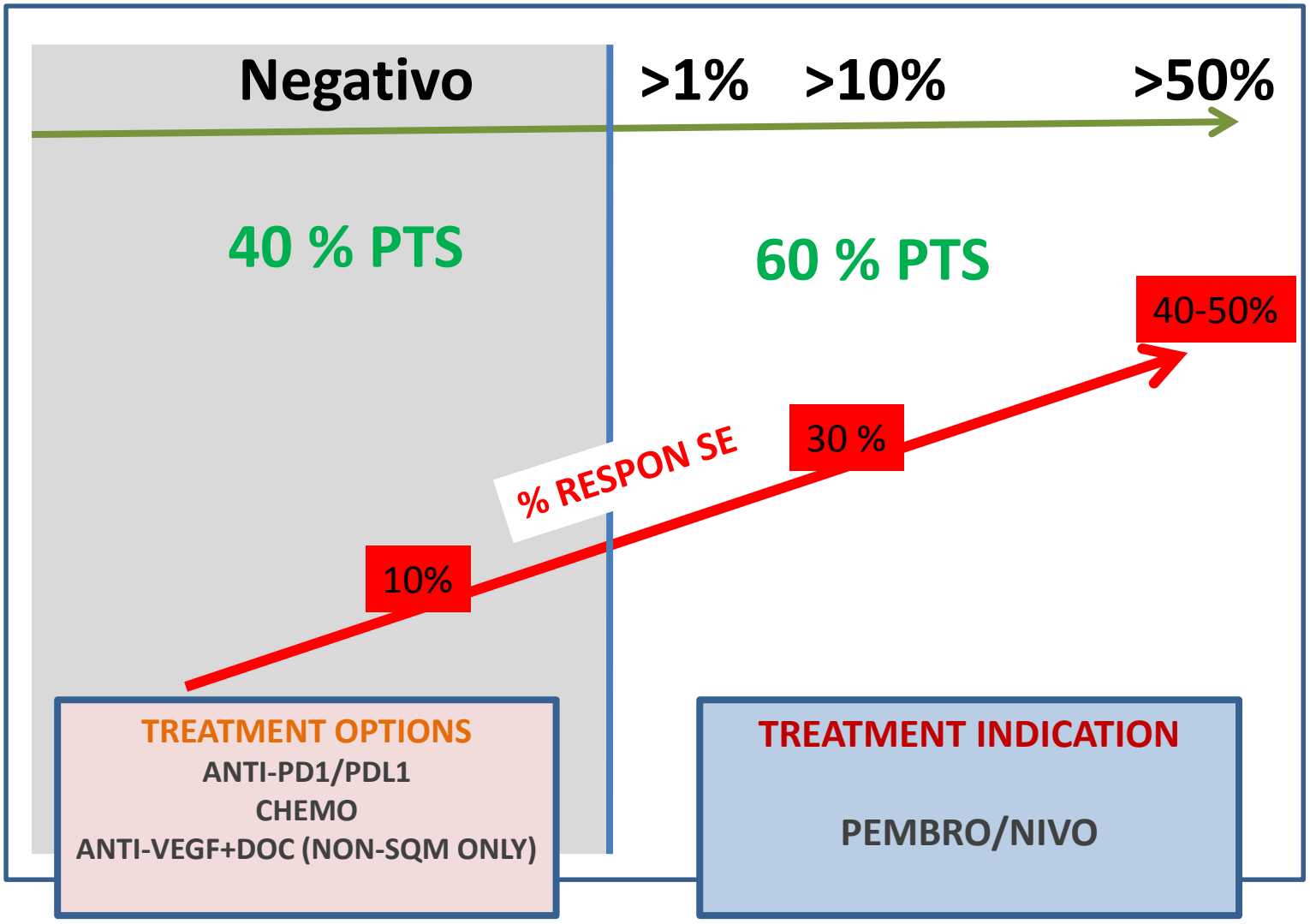


[a]Unstratified HR.
[b]*P* values for descriptive purpose only.
TC, tumor cells; IC, tumor-infiltrating immune cells; OS, overall survival.

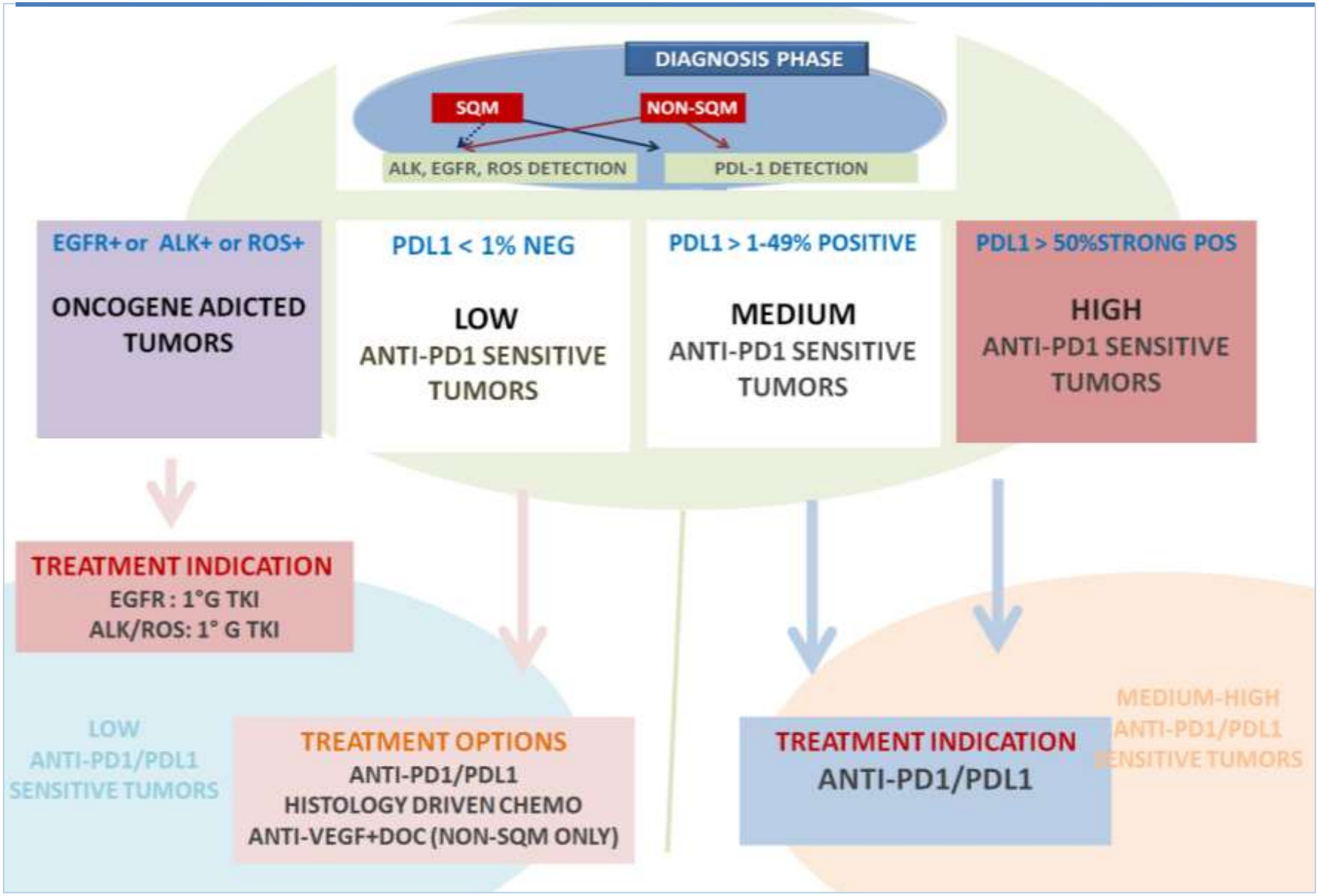
Barlesi et al, Atezolizumab Phase III OAK Study. http://tago.ca/9Hh

2°-Line NSCLC (Non-Sqm)

Anti PD-1 / anti-PD-L1 Agents , PD-L1 expression



2°-line NSCLC DX/TX algorithm: "1° Schenario" Non-SQM



I biomarcatori nell'immunoncologia: L'importanza della selezione del paziente

Melanoma

Rene

Vescica

Testa e collo

PDL1 ?

I biomarcatori nell'immunoncologia: L'importanza della selezione del paziente

Melanoma

Rene

Vescica

Testa e collo

PD-L1 ?

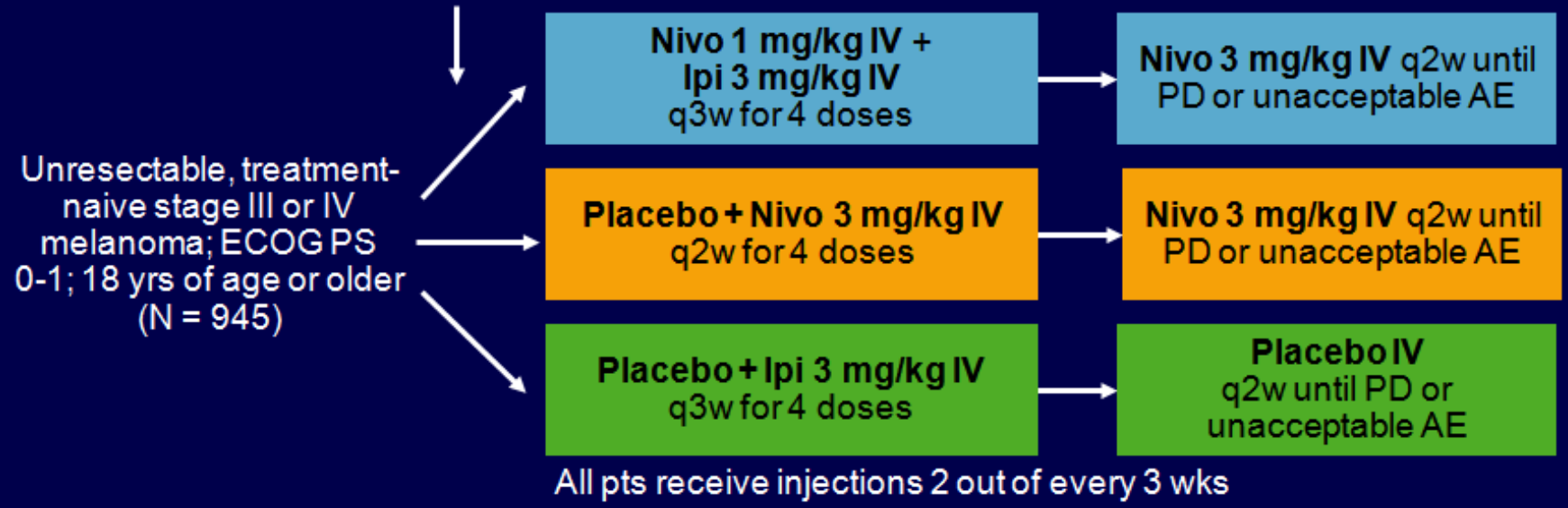
PD-1 Inhibitors: Approved Indications in Advanced Melanoma

- **Nivolumab**
  - Single agent (3 mg/kg q2w) for **unresectable or metastatic** melanoma with or without a *BRAF* V600 mutation
  - In combination with ipilimumab for **unresectable or metastatic** melanoma
    - Nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3w x 4 then nivolumab 3 mg/kg q2w
- **Pembrolizumab**
  - Single agent (2 mg/kg q3w) for **unresectable or metastatic** melanoma

Nivo + Ipi vs Nivo vs Ipi for First-line Treatment of Melanoma (Checkmate 067)

A randomized, double-blind phase III study

Stratified by tumor PD-L1 status (positive vs negative/indeterminate), BRAF mutation status (V600 mutation positive vs wild type), and AJCC metastasis stage (M0, M1a, or M1b vs M1c)

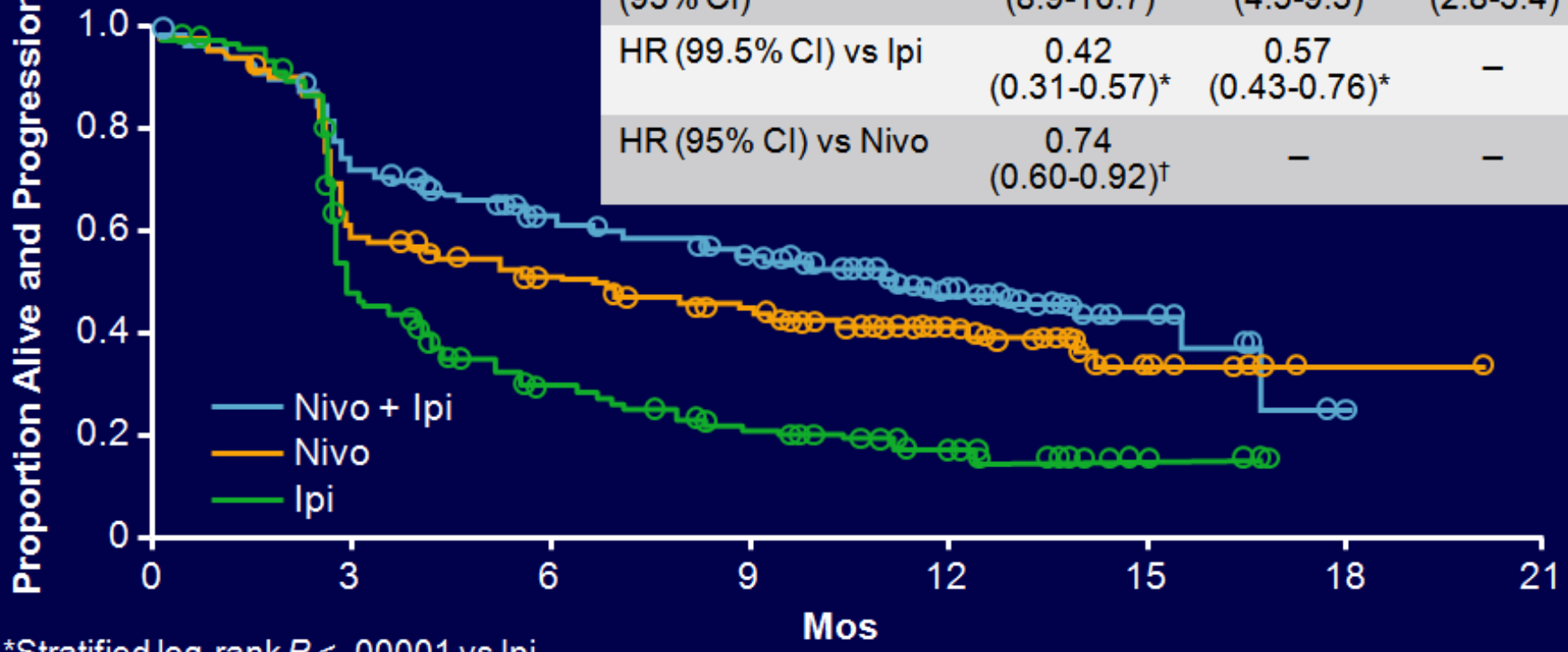


- **Primary endpoint: OS, PFS**
- **Secondary endpoint: ORR, OS by PD-L1, safety**

Larkin J, et al. N Engl J Med. 2015;373:23-34.

CheckMate 067: Improved PFS With Nivo + Ipi or Nivo Alone vs Ipi Alone

	Nivo + Ipi (n = 314)	Nivo (n = 316)	Ipi (n = 315)
Median PFS, mos (95% CI)	11.5 (8.9-16.7)	6.9 (4.3-9.5)	2.9 (2.8-3.4)
HR (99.5% CI) vs Ipi	0.42 (0.31-0.57)*	0.57 (0.43-0.76)*	–
HR (95% CI) vs Nivo	0.74 (0.60-0.92)†	–	–

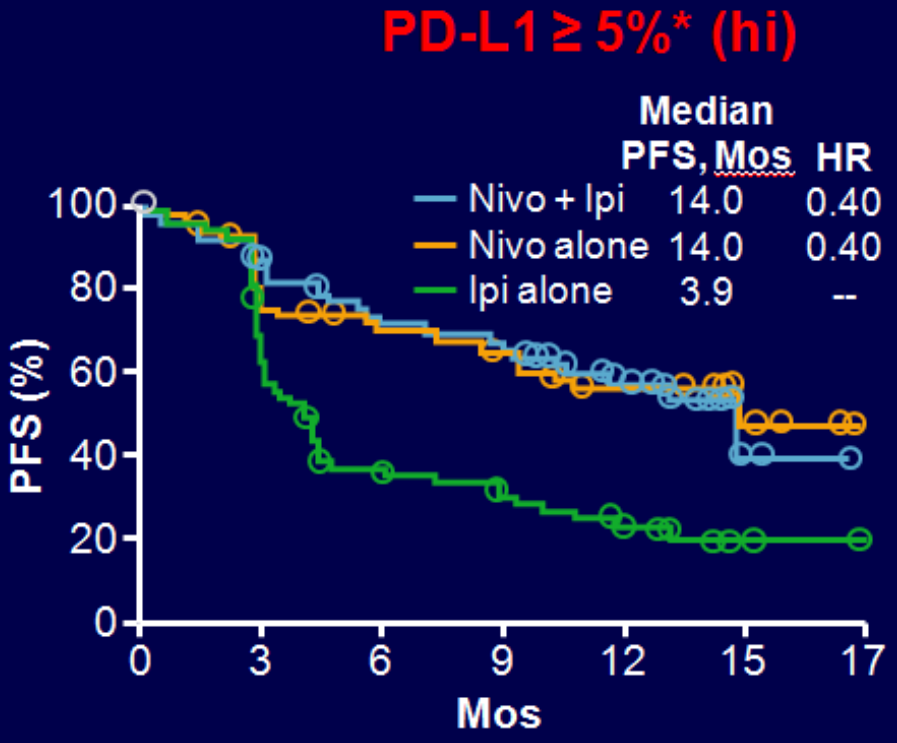


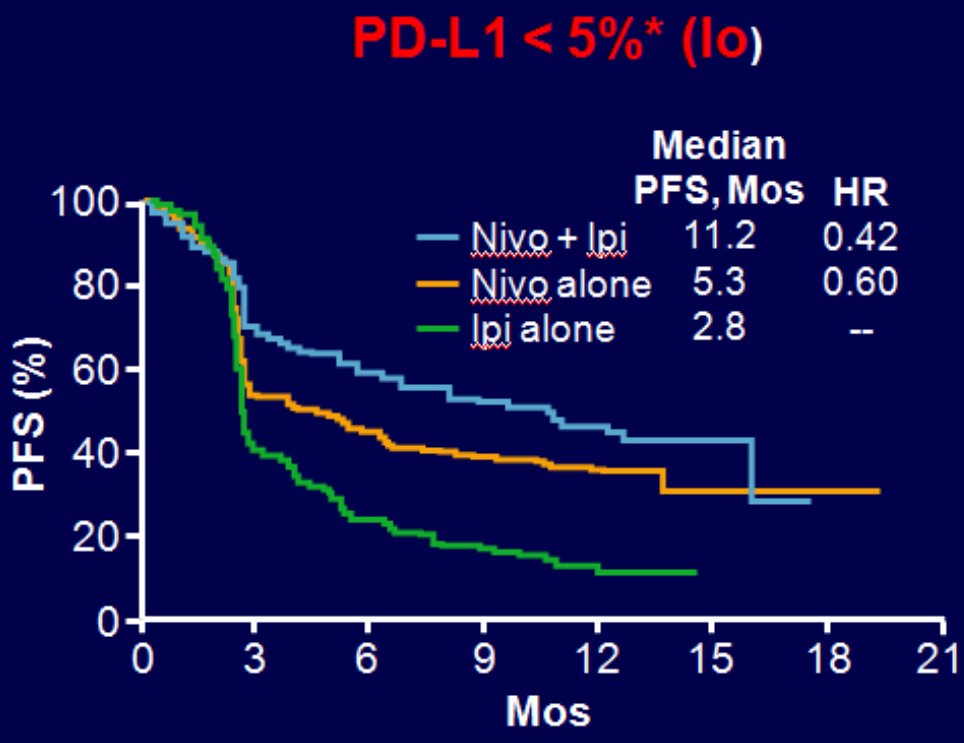
*Stratified log-rank $P < .00001$ vs Ipi.

†Exploratory endpoint. Study not powered to detect a statistical difference between Nivo + Ipi and Nivo.

Larkin J, et al. N Engl J Med. 2015;373:23-34.

CheckMate 067: Nivo + Ipi Provides Most Benefit for PD-L1lo, Similar to Nivo for PD-L1hi

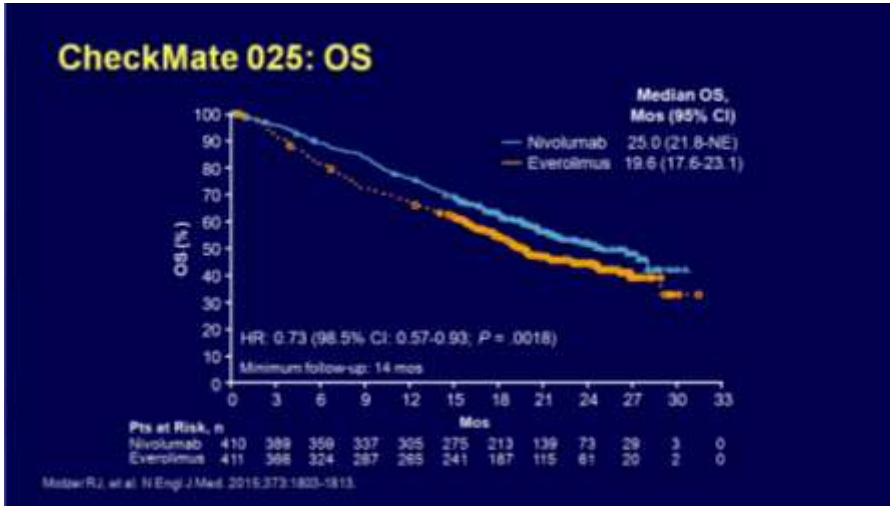




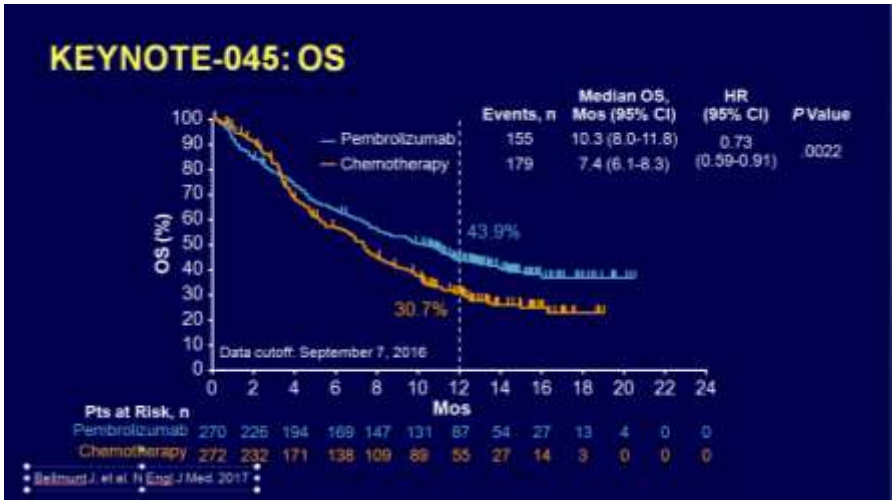
*Per validated PD-L1 IHC assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

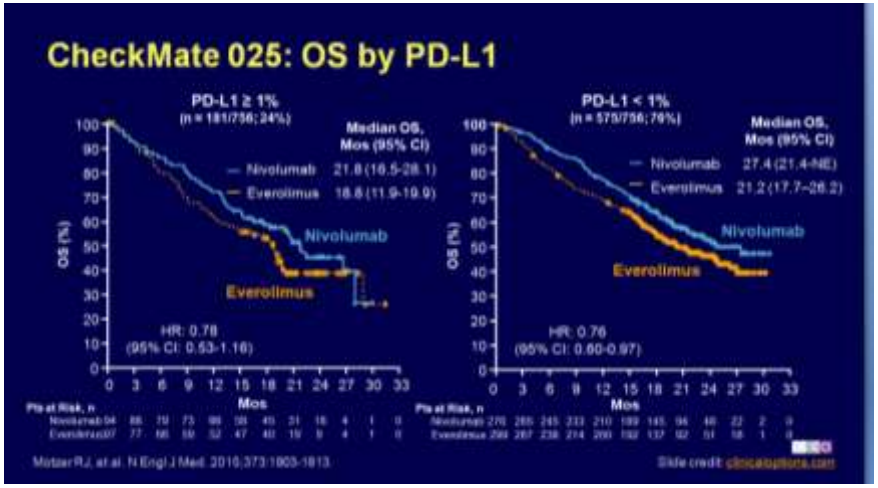
Larkin J, et al. N Engl J Med. 2015;373:23-34.

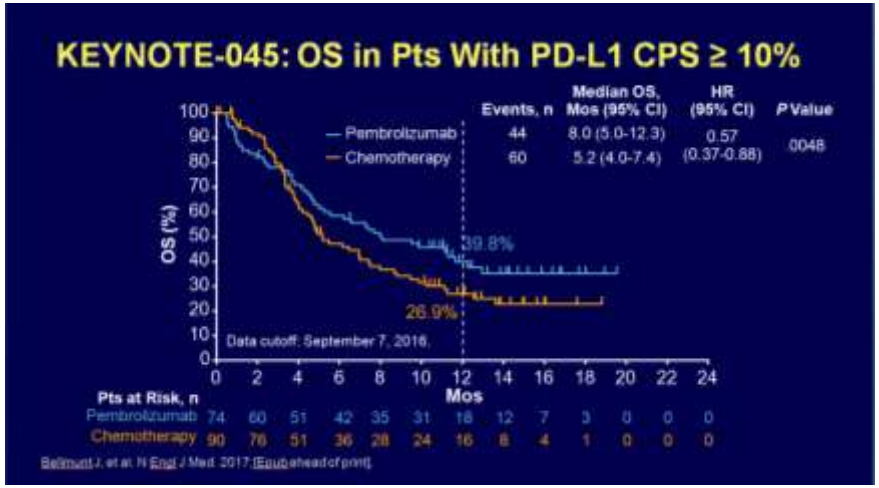
RENE – 2° linea



VESCICA – 2° linea







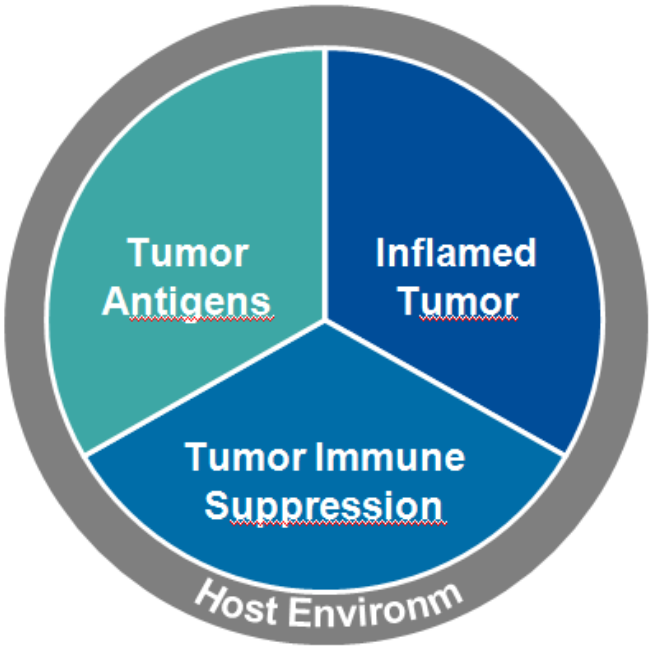
Tumor and Immune Biomarkers Being Evaluated to Predict Better Outcomes to Immuno-Oncology Therapy

Tumor Antigens

- Biomarkers indicative of hypermutation & neo-antigens may predict response to IO treatment

Examples:

– ***TMB, MSI-High, Neo-Antigens***



Inflamed Tumor Microenvironment

- Biomarkers (intra- or peri-tumoral) indicative of an inflamed phenotype may predict response to IO treatment

Examples:

– ***PD-L1, Inflammatory Signatures***

IDO = indoleamine-2,3 dioxygenase; LAG-3 = lymphocyte activation gene-3; MDSCs = myeloid-derived suppressor cells; MSI-High = microsatellite instability high; TMB = tumor mutational burden. Adapted from Blank C.U. et al., *Science* 2016;352:658–660.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

ABSTRACT

BACKGROUND

Somatic mutations have the potential to encode "non-self" immunogenic antigens. We hypothesized that tumors with a large number of somatic mutations due to mismatch-repair defects may be susceptible to immune checkpoint blockade.

METHODS

We conducted a phase 2 study to evaluate the clinical activity of pembrolizumab, an anti–programmed death 1 immune checkpoint inhibitor, in 41 patients with progressive metastatic carcinoma with or without mismatch-repair deficiency. Pembrolizumab was administered intravenously at a dose of 10 mg per kilogram of body weight every 14 days in patients with mismatch repair–deficient colorectal cancers, patients with mismatch repair–proficient colorectal cancers, and patients with mismatch repair–deficient cancers that were not colorectal. The coprimary end points were the immune-related objective response rate and the 20-week immune-related progression-free survival rate.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Diaz at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, 1650 Orleans St., Rm. 590, Baltimore, MD 21287, or at ldiaz1@jhmi.edu.

This article was published on May 30, 2015, at NEJM.org.

N Engl J Med 2015;372:2509-20.
DOI: 10.1056/NEJMoa1500596

Pembrolizumab in Mismatch Repair–Deficient CRC: Overview

- **Mismatch repair defects lead to MSI-H**
  - **MSI-H** associated with hereditary nonpolyposis colorectal carcinoma and present in 15% of CRCs across all stages
  - **MSI-H** tumors harbor genetic mutations that are potentially recognizable by immune system; **abundant expression of neoantigens on tumor cells creates inflamed microenvironment with high expression of immune checkpoints, such as PD-1**
- **PD-1 blockade has antitumor effects in MSI-H tumors**
- Pembrolizumab, an immune checkpoint inhibitor of PD-1, evaluated in pts with treatment-refractory, progressive, metastatic cancer by mismatch repair status[1]
  - Received breakthrough therapy designation in 11/2015 for tx of MSI-H CRC
- Current report summarizes phase I data on PD-1 blockade with pembrolizumab in pts with mismatch repair–deficient CRC[2]

1. Le DT, et al. N Engl J Med. 2015;372:2509-2520.
2. Le DT, et al. ASCO 2016. Abstract 103.

Pembrolizumab in Mismatch Repair–Deficient CRC: Study Design

- Eligibility for cohorts A and B:
  - Histologically confirmed metastatic or locally advanced CRC, with or without mismatch repair deficiency
  - Mismatch repair deficiency defined as: deficiency in MLH1, MSH2, MSH6 or PMS2 by IHC, or microsatellite instability in ≥ 2 loci by PCR
  - Measurable disease
  - ≥ 2 previous cancer therapy regimens
  - ECOG PS ≤ 1
  - No previous anti–PD-1/PD-L1/PD-L2, anti-CD137, anti–OX-40, anti–CTLA-4
- Pembrolizumab 10 mg/kg every 2 wks
- Current report: updated data from cohort A

Cohort A (n = 28)
MMRD CRC

Cohort B (n = 25)
MMRP CRC

Cohort C (n = 30)
MMRD non-CRC

Le DT, et al. ASCO 2016. Abstract 103.

Pembrolizumab in Mismatch Repair–Deficient CRC: Pt Population

Characteristics	MMRD CRC (n = 28)	MMRP CRC (n = 25)
Median age, yrs (range)	49 (26-75)	62 (32-79)
Male, n (%)	15 (54)	16 (64)
ECOG PS, n (%)		
▪ 0	5 (18)	7 (28)
▪ 1	23 (82)	18 (72)
No. of previous treatments, median	3	4
Liver metastases, n (%)	14 (50)	15 (60)
Lynch syndrome, n (%)		
▪ Yes	15 (54)	0 (0)
▪ No	2 (7)	25 (100)
▪ Unknown	11 (39)	0 (0)

Le DT, et al. ASCO 2016. Abstract 103.

Pembrolizumab in Mismatch Repair–Deficient CRC: Efficacy

Outcome	MMRD CRC (n = 28)	MMRP CRC (n = 25)
Median follow-up, mos	9.3	6
ORR, % (95% CI)	**57 (39-73)**	**0 (0-13)**
Response, %		
▪ CR	11	0
▪ PR	46	0
▪ SD (Wk 12)	32	16
▪ PD	4	44
▪ NE (no 12-wk scan)	7	40
Disease control rate, % (95% CI)	89 (73-96)	16 (6-35)
Median PFS, mos	NR	2.3
Median OS, mos	NR	5.98

Le DT, et al. ASCO 2016. Abstract 103.

Tumor Mutation Burden As a Predictive Biomarker for Immuno-Oncology Therapies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elipenahli, B.S., Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D., Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and Timothy A. Chan, M.D., Ph.D.

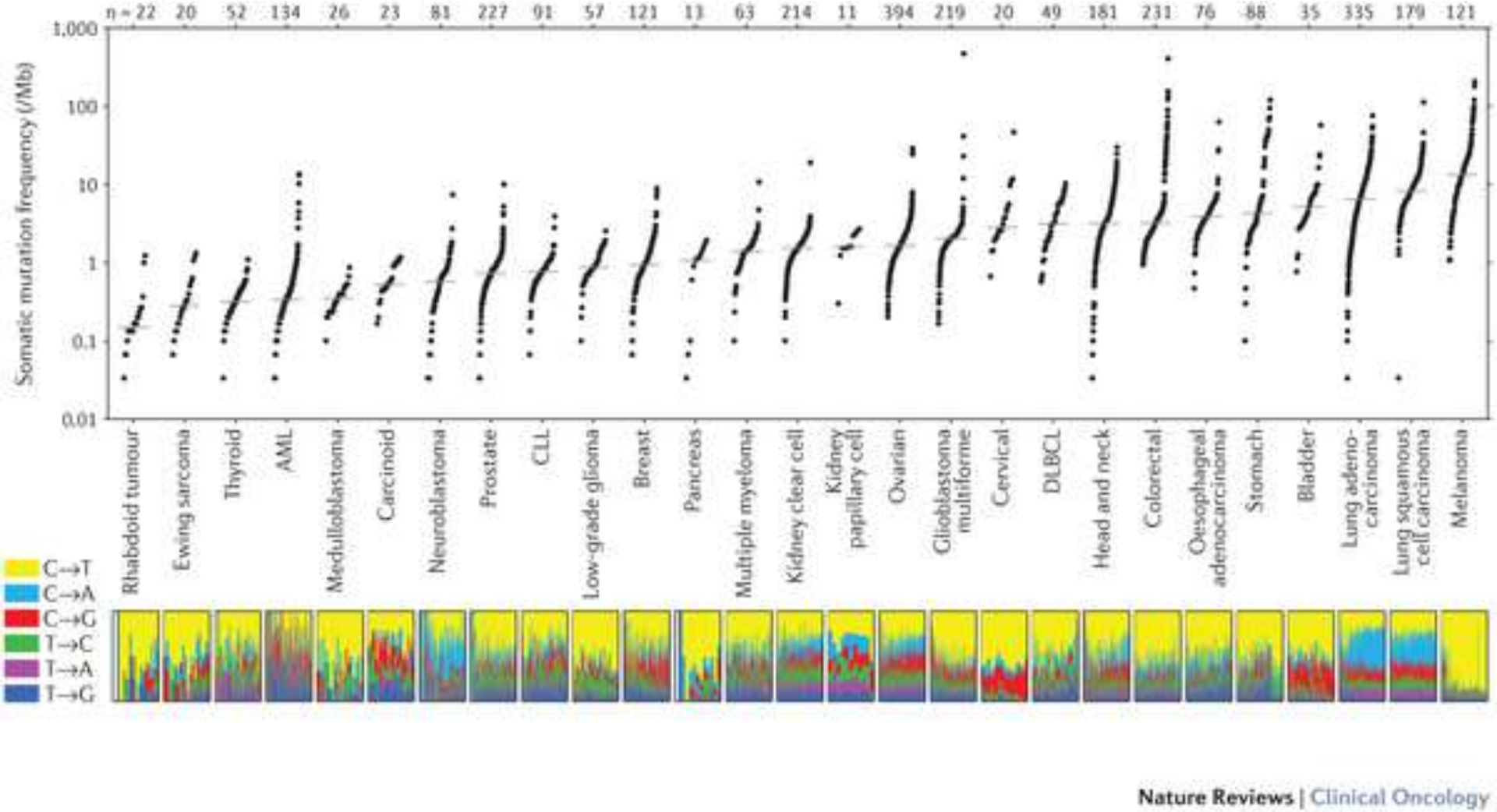
RESEARCH | *REPORTS*

CANCER IMMUNOLOGY

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

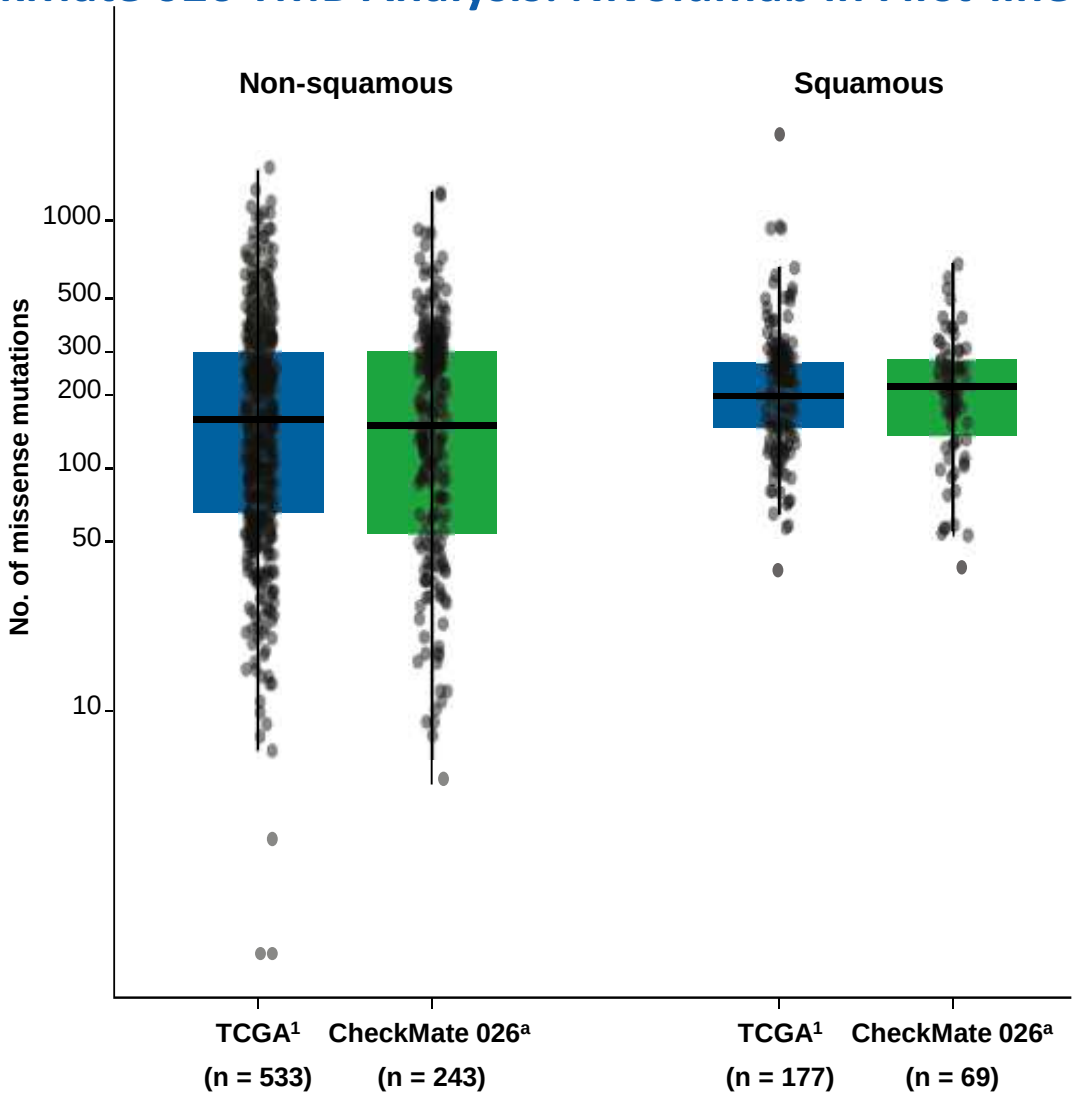
Naiyer A. Rizvi,[1,2*†] Matthew D. Hellmann,[1,2*] Alexandra Snyder,[1,2,3*] Pia Kvistborg,[4] Vladimir Makarov,[3] Jonathan J. Havel,[3] William Lee,[5] Jianda Yuan,[6] Phillip Wong,[6] Teresa S. Ho,[6] Martin L. Miller,[7] Natasha Rekhtman,[8] Andre L. Moreira,[8] Fawzia Ibrahim,[1] Cameron Bruggeman,[9] Billel Gasmi,[10] Roberta Zappasodi,[10] Yuka Maeda,[10] Chris Sander,[7] Edward B. Garon,[11] Taha Merghoub,[1,10] Jedd D. Wolchok,[1,2,10] Ton N. Schumacher,[4] Timothy A. Chan[2,3,5†]

1. Snyder A, et al. *N Engl J Med* 2014;371:2189–2199
2. Rizvi NA, et al. *Science* 2015;348:124–128
3. Van Allen EM, et al. *Science* 2015;350:207–211
4. Rosenberg JE, et al. *Lancet* 2016;387:1909–1920
5. Hugo W, et al. *Cell* 2016;165:35–44
6. Hellmann M. Presented at the 14th International Congress on Targeted Anticancer Therapies; March 21–23, 2016; Washington, DC, USA. Oral O2.2
7. Kowanetz M, et al. Presented at the 2016 IASLC 17th World Conference; December 4–7, 2016; Vienna, Austria. Oral OA20.01


n = 22 20 52 134 26 23 81 227 91 57 121 13 63 214 11 394 219 20 49 181 231 76 88 35 335 179 121
Somatic mutation frequency (/Mb)
1,000
100
10
1
0.1
0.01
Rhabdoid tumour
Ewing sarcoma
Thyroid
AML
Medulloblastoma
Carcinoid
Neuroblastoma
Prostate
CLL
Low-grade glioma
Breast
Pancreas
Multiple myeloma
Kidney clear cell
Kidney papillary cell
Ovarian
Glioblastoma multiforme
Cervical
DLBCL
Head and neck
Colorectal
Oesophageal adenocarcinoma
Stomach
Bladder
Lung adeno-carcinoma
Lung squamous cell carcinoma
Melanoma
C→T
C→A
C→G
T→C
T→A
T→G

TMB in The Cancer Genome Atlas[1] and CheckMate 026 Samples[a]

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

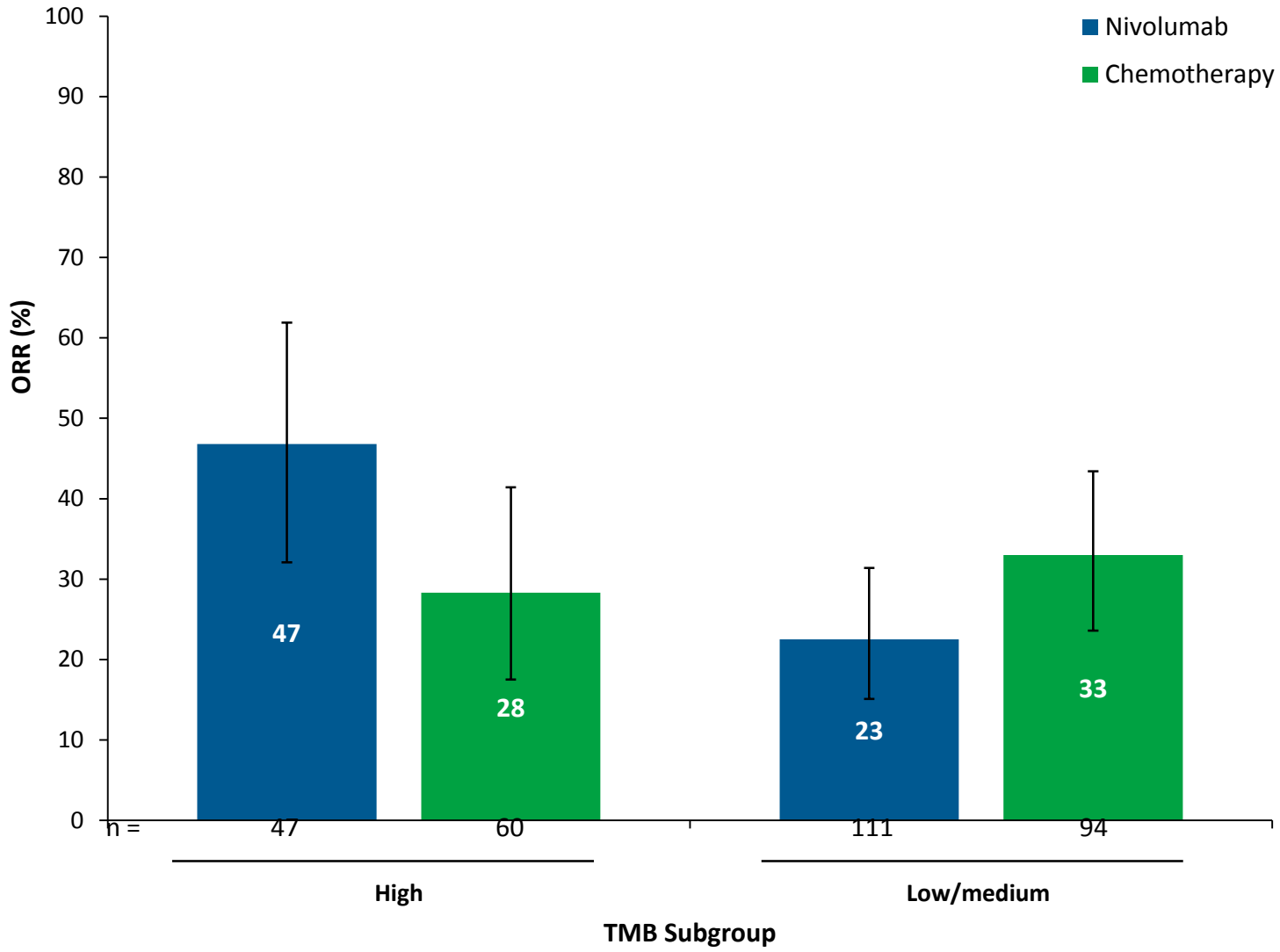


[a]Samples were from whole exome sequencing

1. Broad Institute TCGA Genome Data Analysis Center (2015): Firehose stddata__2015_02_04 run. Broad Institute of MIT and Harvard. doi:10.7908/C19P30S6

ORR by Tumor Mutation Burden Subgroup

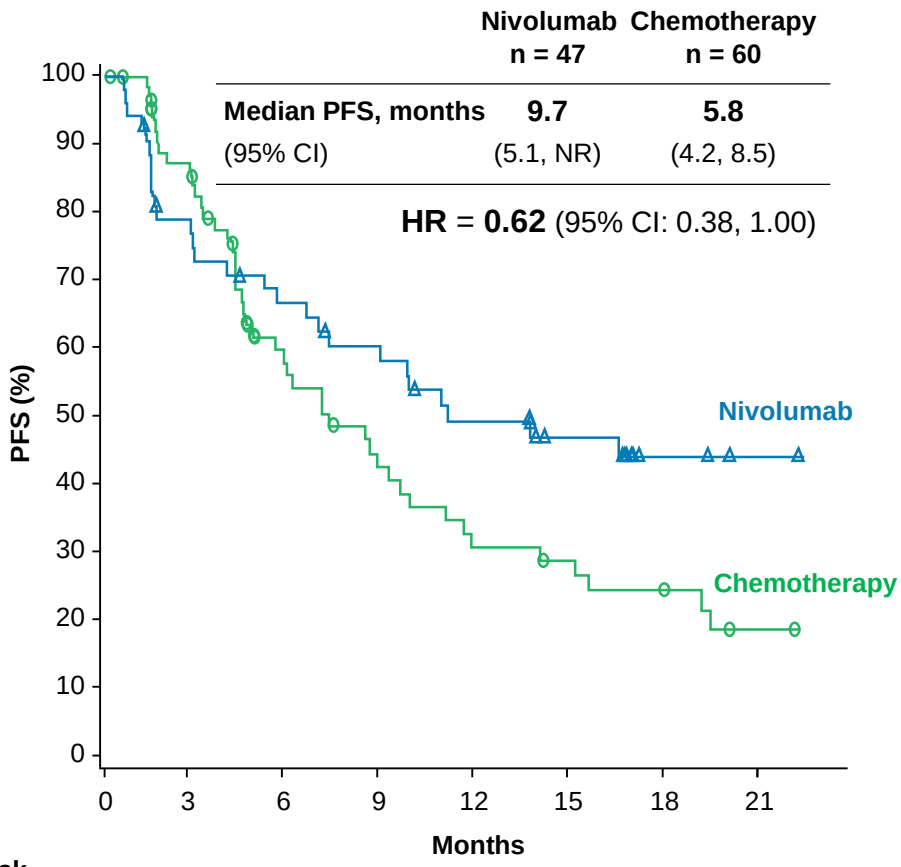
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC



PFS by Tumor Mutation Burden Subgroup

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

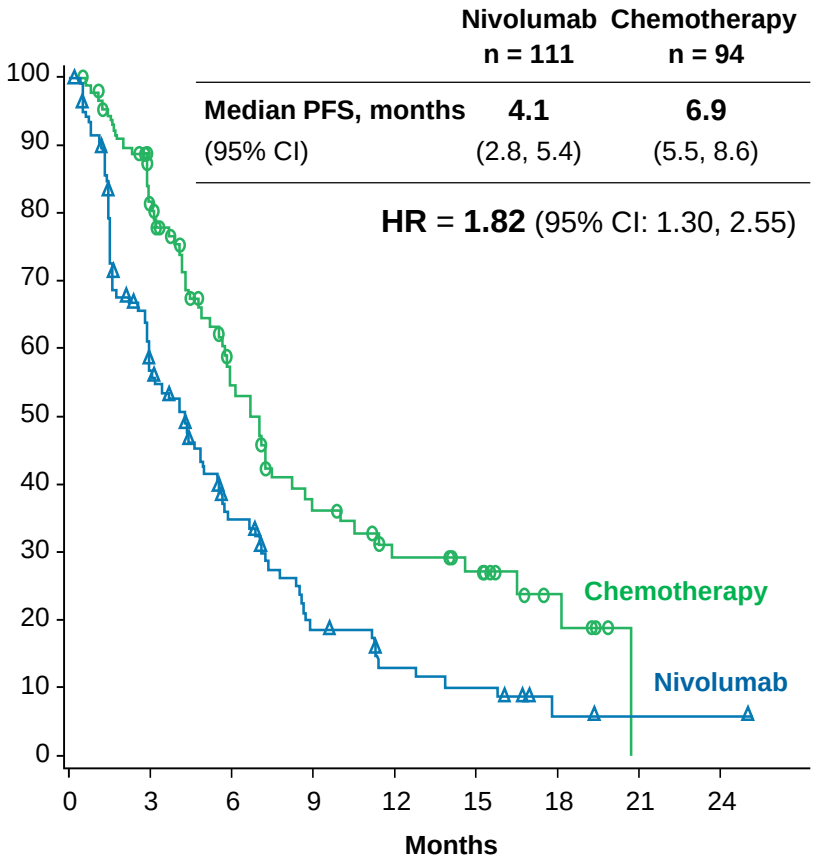
High TMB



No. at Risk

Nivolumab	47	30	26	21	16	12	4	1
Chemotherapy	60	42	22	15	9	7	4	1

Low/medium TMB



Nivolumab	111	54	30	15	9	7	2	1	1
Chemotherapy	94	65	37	23	15	12	5	0	0

A.O.U. Policlinico – Vittorio Emanuele

The Role of ERCC-1 Polymorphisms as Predictive Biomarker of Response to Nivolumab in Advanced NSCLC

Abstract ID: 6154

Medical Oncology Unit
A.O.U. Policlinico Vittorio Emanuele Catania, Italy

Vienna, 4 – 7 December 2016

Methods: Study design

- Stage IIIB/IV NSCLCs
- Previous platinum-based therapy
- ≥ 18 years
- PS (ECOG) 0 – 1
- Archival tissue availability
- No autoimmune diseases

Evaluation of single nucleotide polymorphisms (SNPs) by pyrosequencing analysis on tumor DNA:

- **rs11615**
- **rs3212986**
- **rs2298881**

Nivolumab 3 mg/kg q2w

- Until PD or unacceptable toxicity
- Treatment beyond progression was allowed in presence of clinical benefit

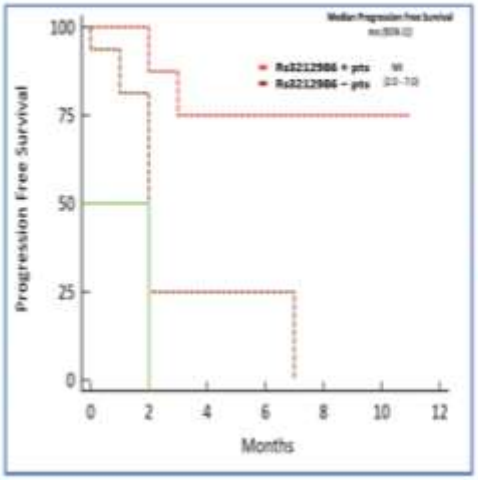
- Responses were assessed according to RECIST 1.1 criteria → Radiological assessments were performed every 6 weeks.
- PFS was calculated from the beginning of the treatment until PD or patient's death.

Results: Objective Response Rate

	All patients	Rs3212986 + patients	Rs3212986 – patients
Type of response	(N = 24	N= 8	N= 16
Complete Response — no. (%)	1 (4)	1 (12.5)	0
Partial Response — no. (%)	5 (21)	4 (50)	1 (6)
Stable Disease — no. (%)	5 (21)	2 (25)	3 (19)
Progressive Disease — no. (%)	13 (54)	1 (12.5)	12 (75)
ORR (95% CI) — %	25 (10-47)	62.5 (25-92)	6 (0-30)
Disease control rate (95% CI) — %	46 (25-67)	87.5 (47-100)	25 (7-52)

ORR is higer in Rs3212986 + pts than Rs3212986 – pts
(62,5% VS. 6% p= 0.006)

Results: Progression Free Survival



PFS is higher in Rs3212986 + pts than Rs3212986 – pts
NR vs. 2.0 months
(HR = 0.21, 95% CI, 0.07 to 0.58; P = 0.004)

Conclusioni

- La determinazione del PDL1 ha un valore limitato per la selezione dei pazienti nei tumori solidi
- Nella ricerca biomedica e prioritario individuare nuovi biomarkers per questa tipologia di faramci
- E’ necessaria una maggiore conoscenza dei meccanismi di risposta ai farmaci immunoterapici

I° CONVEGNO REGIONALE SIFO

Meeting di primavera

"IL FARMACISTA CLINICO
E I NUOVI MODELLI DI CURA"

TAORMINA (ME),
11-12-13 MAGGIO 2017

ID ECM: 313-188877

IV SESSIONE - IMMUNONCOLOGIA

I biomarcatori nell'immunoncologia: L'importanza della selezione del paziente

Hector Soto Parra MD
Oncologia Medica

AZIENDA OSPEDALIERO-UNIVERSITARIA POLICLINICO-VITTORIO EMANUELE