

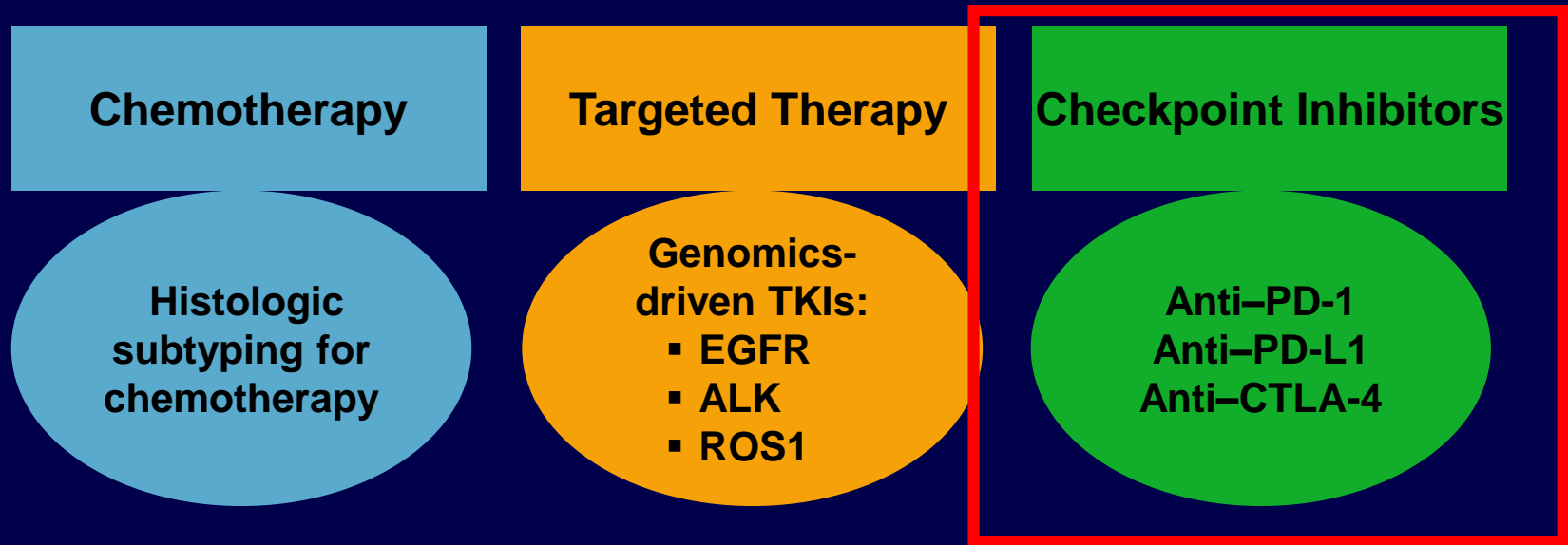
I° CONVEGNO REGIONALE SIFO "MEETING DI PRIMAVERA"
– "IL FARMACISTA CLINICO E I NUOVI MODELLI DI CURA"
Taormina, 11/12/13 maggio 2017



Stato dell'arte dell'immunoterapia. Il Paziente con NSCLC

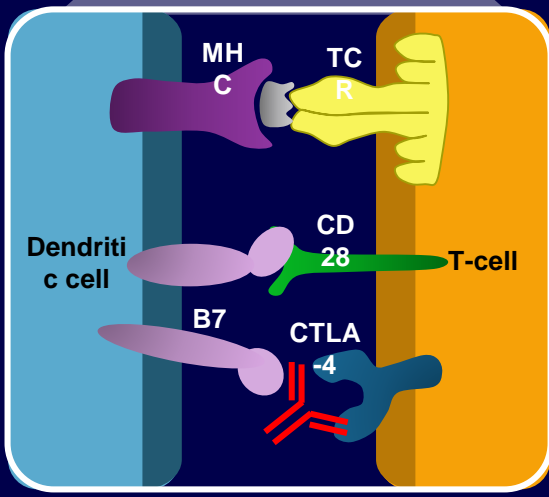
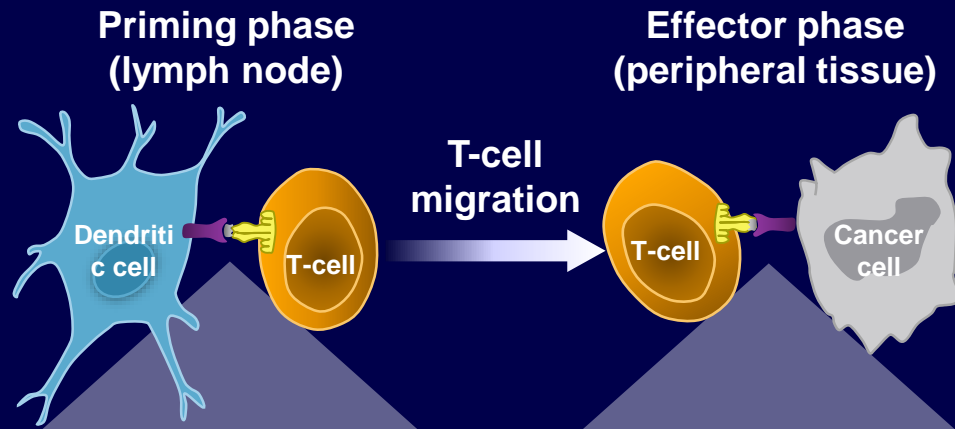
**Francesco Ferràù
Oncologia Medica
Ospedale "S.Vincenzo", Taormina**

Possibilità terapeutiche per personalizzare la terapia nel Paziente con NSCLC

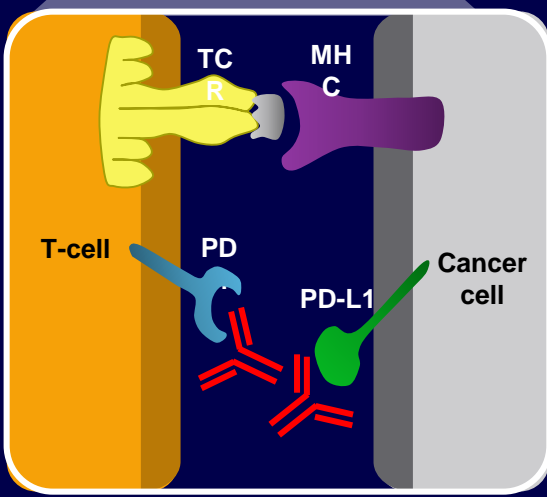


- Qual'è il setting ottimale per il “giusto” trattamento nel “giusto” Paziente (prima linea, seconda linea, linee successive) ?

CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment



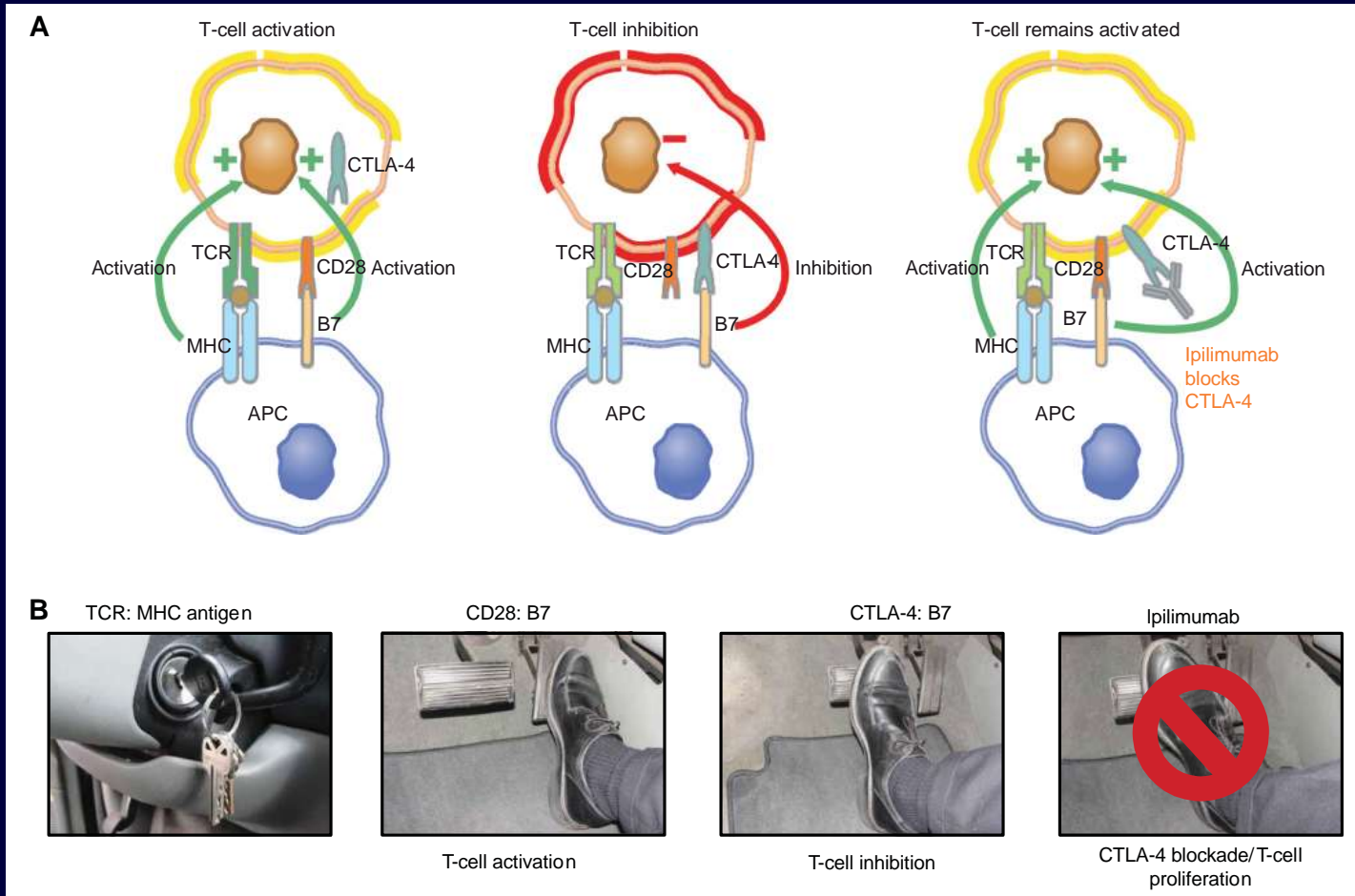
CTLA-4 mAbs:
Ipilimumab
Tremelimumab



PD-1 mAbs:
Nivolumab
Pembrolizumab

PD-L1 mAbs:
Atezolizumab
Avelumab
Durvalumab

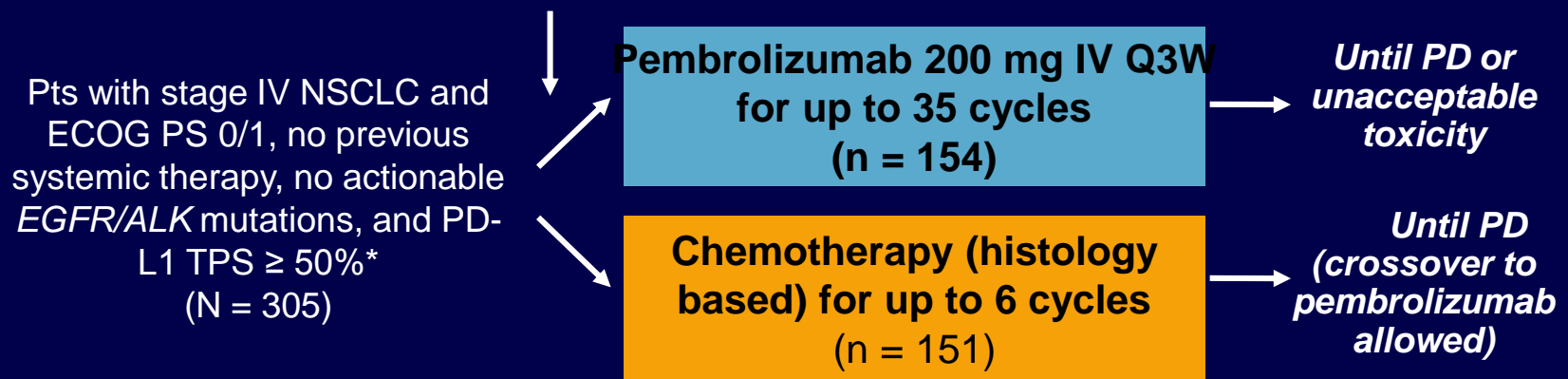
Check point inhibitors augments T-Cell activation



KEYNOTE-024: Pembrolizumab vs CT as First-line Therapy for Advanced NSCLC

- Open-label phase III trial

Stratified by ECOG PS (0 vs 1), histology (squamous vs nonsquamous), and enrollment region



- Primary endpoint: PFS
- Secondary and exploratory endpoints: ORR, OS, DoR, and safety

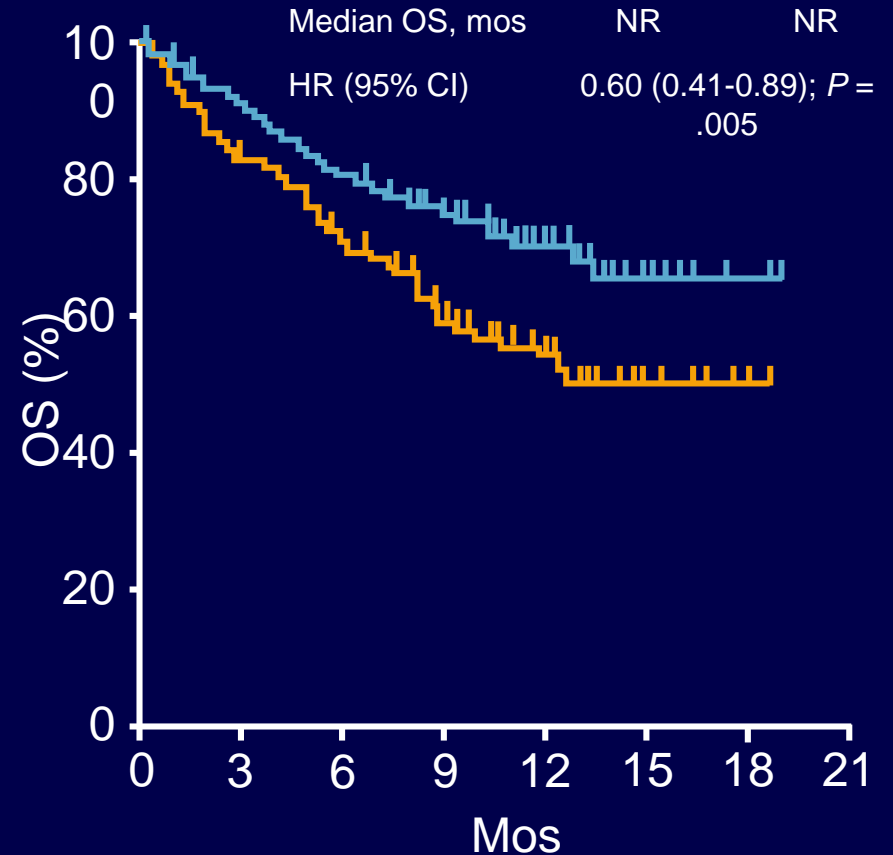
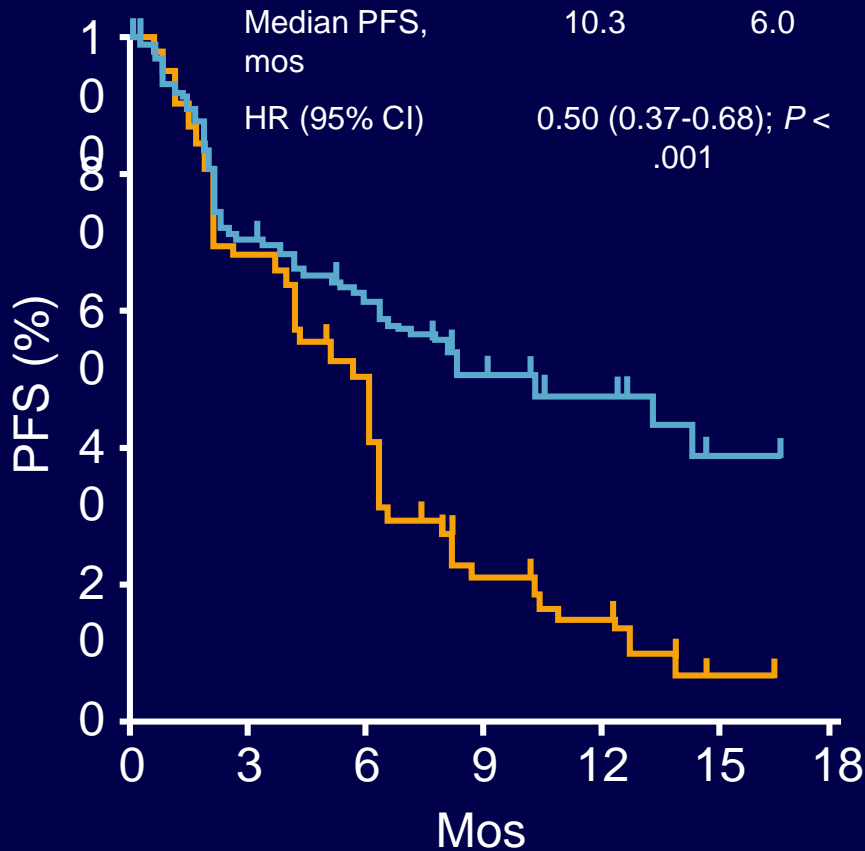
KEYNOTE-024: Survival Outcomes

PFS

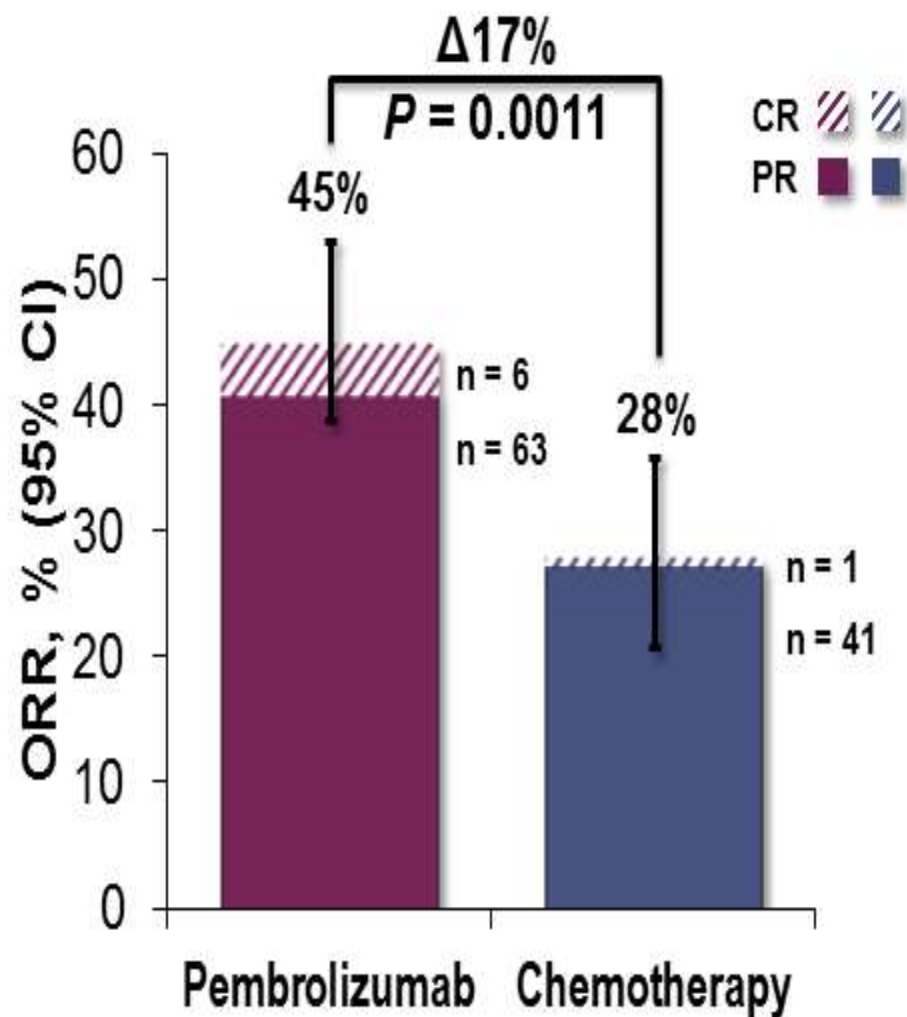
OS

Pembro
(n = 154) **CT**
(n = 151)

Pembro
(n = 154) **CT**
(n = 151)

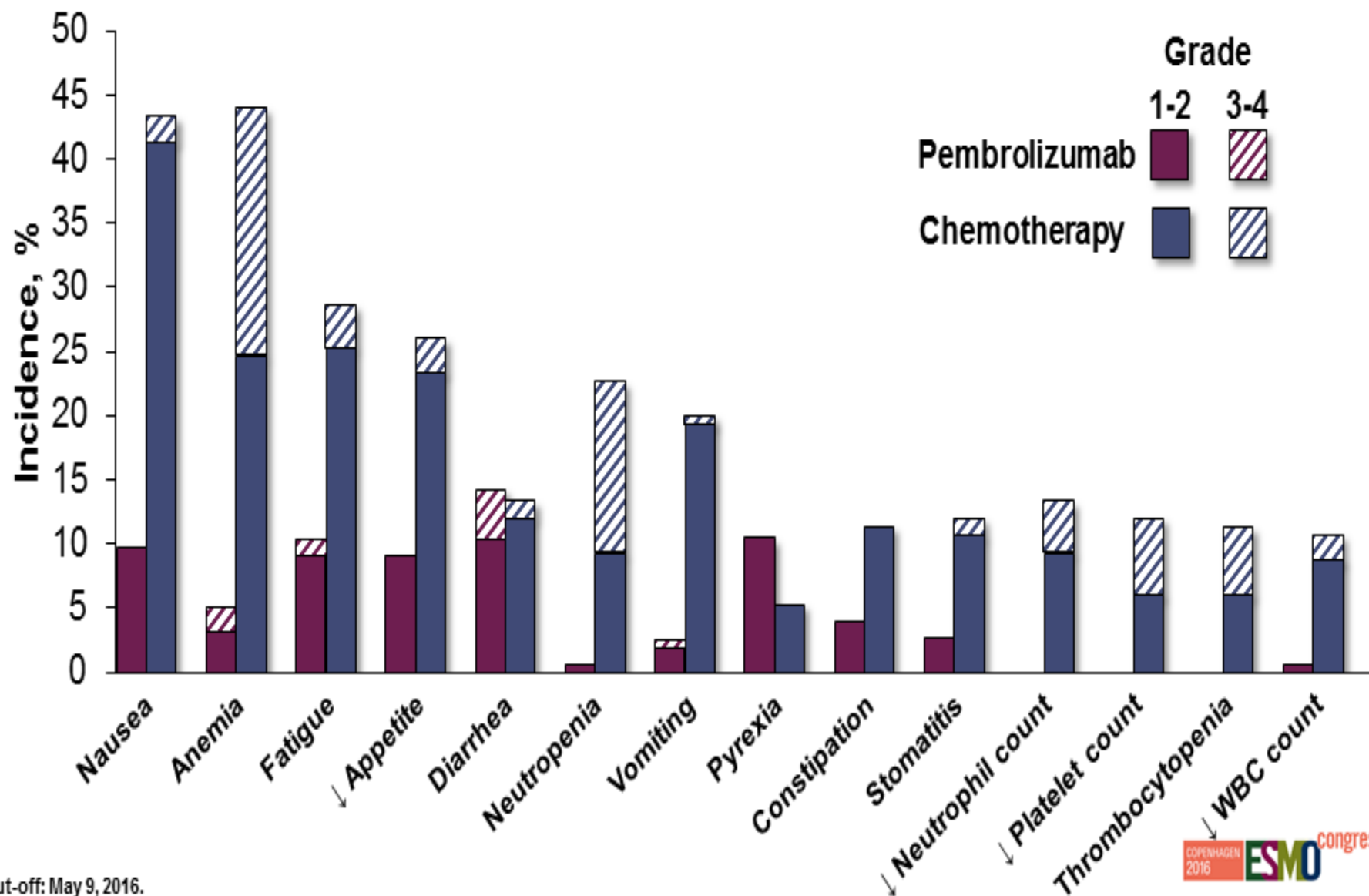


Confirmed Objective Response Rate

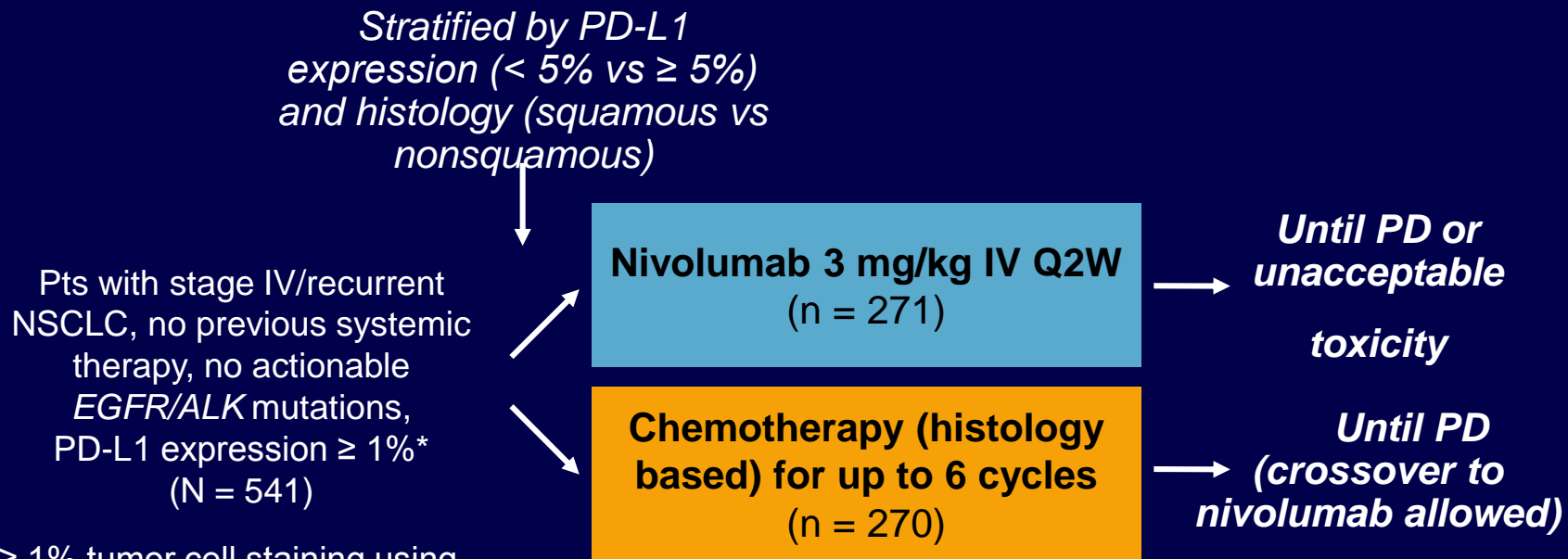


	Pembro Responders n = 69	Chemo Responders n = 42
TTR, mo median (range)	2.2 (1.4-8.2)	2.2 (1.8-12.2)
DOR, mo median (range)	NR (1.9+ to 14.5+)	6.3 (2.1+ to 12.6+)

Treatment-Related AEs With Incidence >10%



CheckMate-026: Nivolumab vs CT in First-line Therapy for Advanced NSCLC

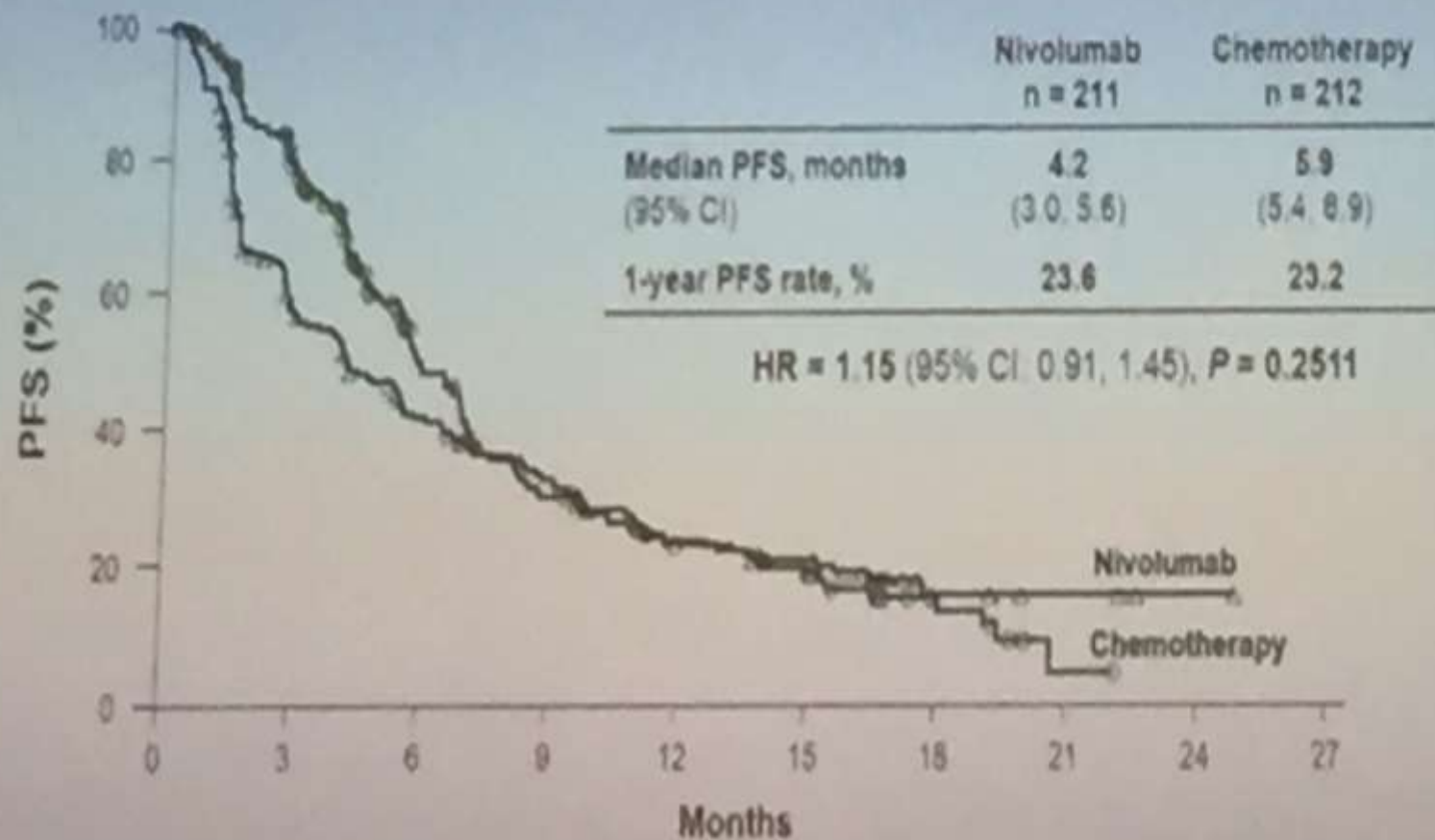


*≥ 1% tumor cell staining using 28-8 complementary diagnostic IHC assay.

- Primary endpoint: PFS (≥ 5% PD-L1 positive)
- Secondary endpoints: PFS (≥ 1% PD-L1 positive), ORR, OS

Primary Endpoint (PFS per IRRC in $\geq 5\%$ PD-L1+)

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC



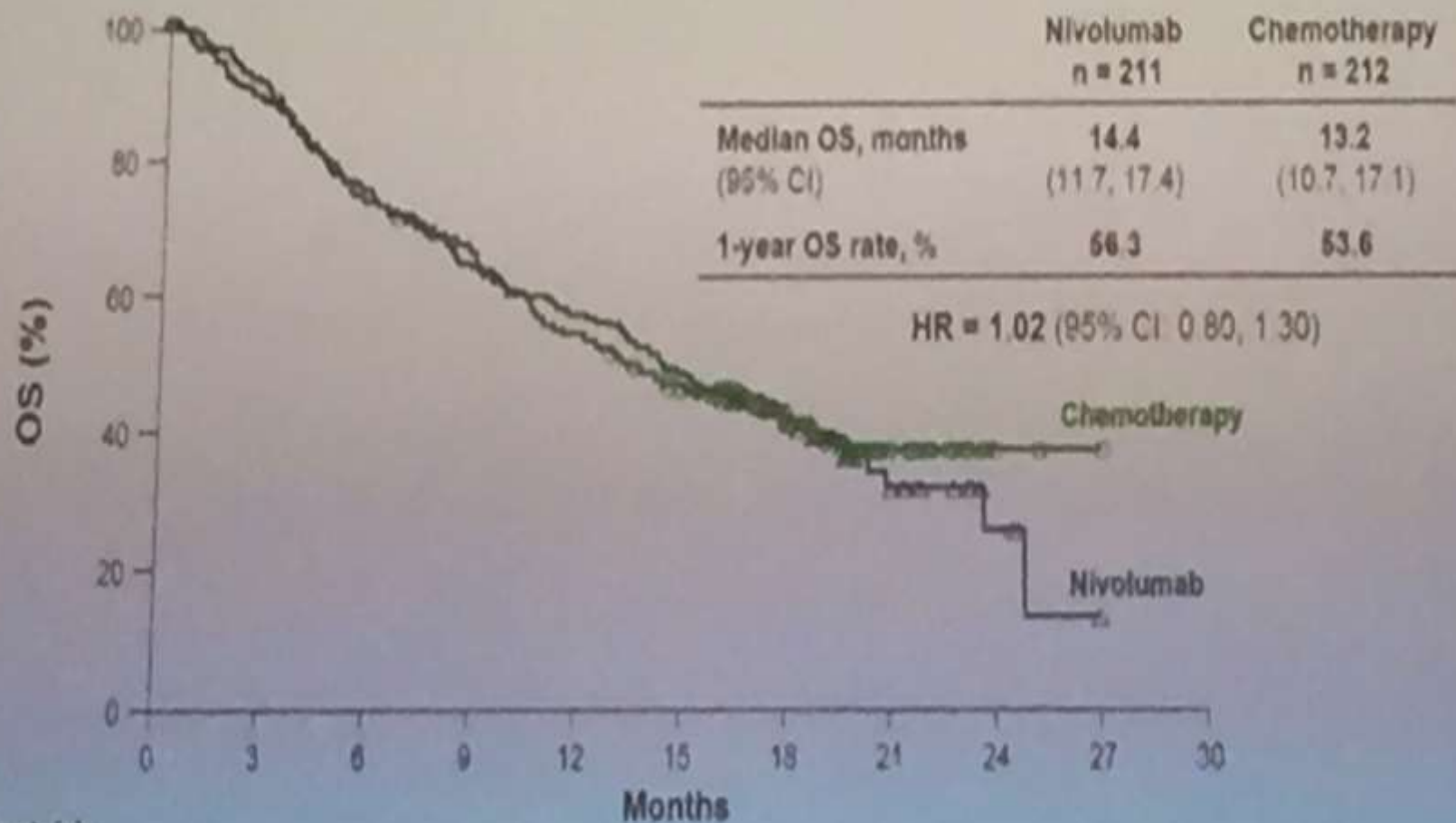
No. of patients at risk:

Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

All randomized patients ($\geq 1\%$ PD-L1+): HR = 1.17 (95% CI 0.95, 1.43)

OS ($\geq 5\%$ PD-L1+)

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC



No. of patients at risk:

Nivolumab	211	186	166	133	118	98	49	14	4	0	0
Chemotherapy	212	186	163	137	112	91	50	15	3	1	0

All randomized patients ($\geq 1\%$ PD-L1+): HR = 1.07 (95% CI: 0.88, 1.33)

IMMUNOTERAPIA DI PRIMA LINEA NEL NSCLC

**NEL TUMORE POLMONARE NON MICROCITOMA
LE EVIDENZE DI LETTERATURA INDICANO CHE**

- PEMBROLIZUMAB E' SUPERIORE ALLA CHEMIOTERAPIA**
- NIVOLUMAB NON E' SUPERIORE ALLA CHEMIOTERAPIA**
- PEMBROLIZUMAB E NIVOLUMAB SONO MEGLIO TOLLERATI DELLA CHEMIOTERAPIA**
- MAGGIO 2017: PEMBROLIZUMAB HA INDICAZIONE MA NON RIMBORSABILITA' PER NSCLC IN PRIMA LINEA**

Impact of Tumor Mutation Burden on the Efficacy of First-Line Nivolumab in Stage IV or Recurrent Non-Small Cell Lung Cancer: An Exploratory Analysis of CheckMate 026

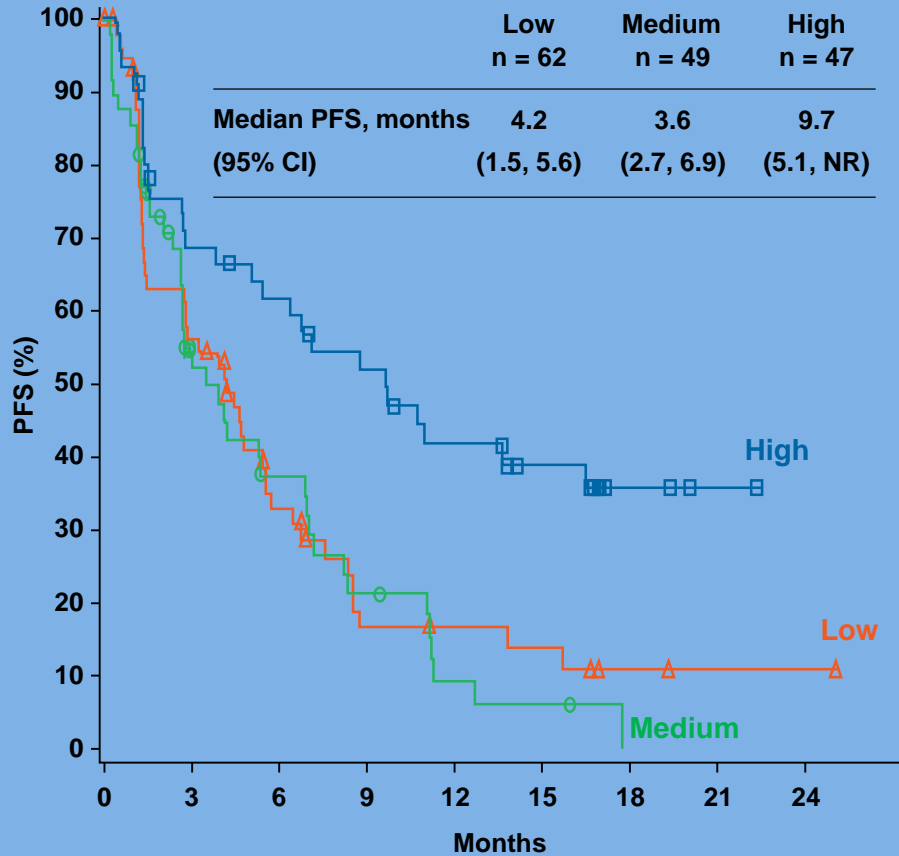
Solange Peters,¹ Benjamin Creelan,² Matthew D. Hellmann,³ Mark A. Socinski,⁴ Martin Reck,⁵ Prabhu Bhagavatheeswaran,⁶ Han Chang,⁶ William J. Geese,⁶ Luis Paz-Ares,⁷ David P. Carbone⁸

¹Oncology Department, Lausanne University Hospital, Lausanne, Switzerland; ²H. Lee Moffitt Cancer Center, Tampa, FL, USA; ³Memorial Sloan Kettering Cancer Center, New York, NY, USA; ⁴Florida Hospital Cancer Institute, Orlando, FL, USA; ⁵LungenClinic Grosshansdorf, Airway Research Center North (ARCN), German Center for Lung Research (DZL), Grosshansdorf, Germany; ⁶Bristol-Myers Squibb, Princeton, NJ, USA; ⁷Hospital Universitario Doce de Octubre, CNIO and Universidad Complutense, Madrid, Spain; ⁸Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

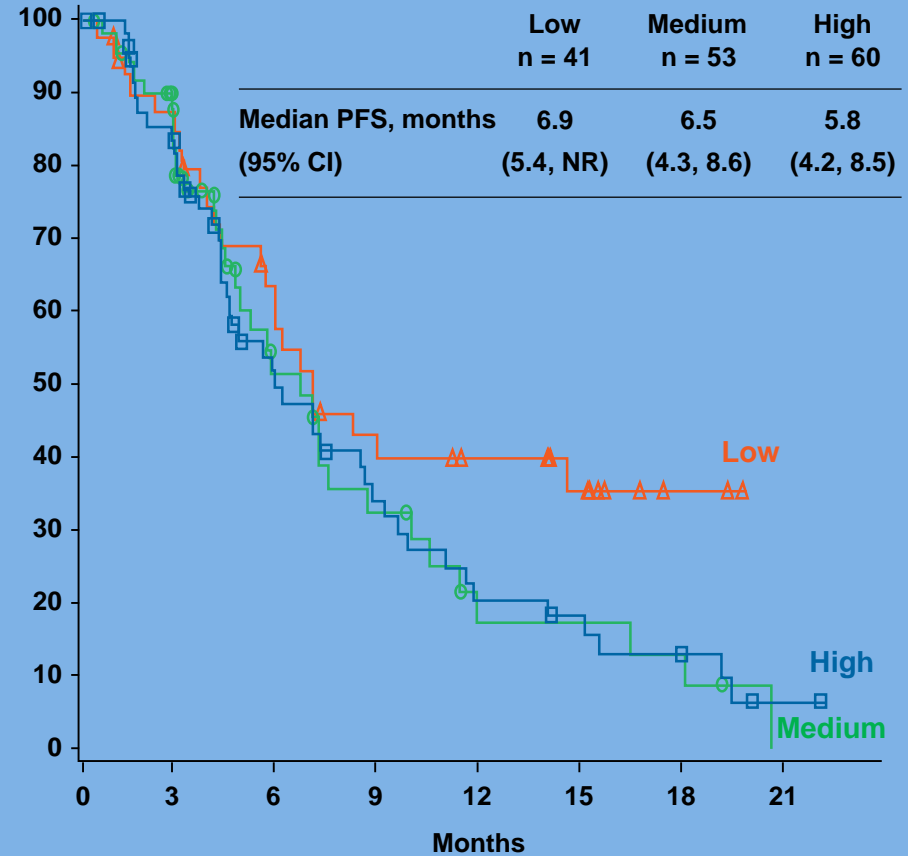
PFS by Tumor Mutation Burden Tertile

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

Nivolumab Arm



Chemotherapy Arm



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

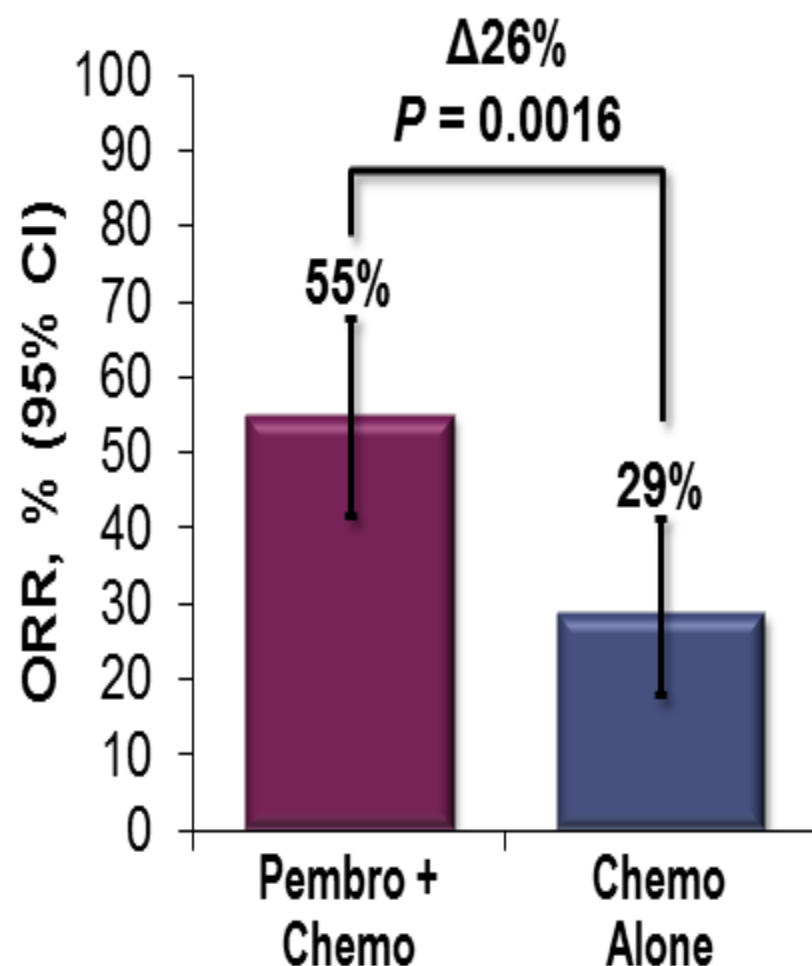
Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study



*Corey J Langer, Shirish M Gadgeel, Hossein Borghaei, Vassiliki A Papadimitrakopoulou, Amita Patnaik, Steven F Powell, Ryan D Gentzler, Renato G Martins, James P Stevenson, Shadia I Jalal, Amit Panwalkar, James Chih-Hsin Yang, Matthew Gubens, Lecia V Sequist, Mark M Awad, Joseph Fiore, Yang Ge, Harry Raftopoulos, Leena Gandhi, for the KEYNOTE-021 investigators**

Confirmed Objective Response Rate

(RECIST v1.1 by Blinded, Independent Central Review)



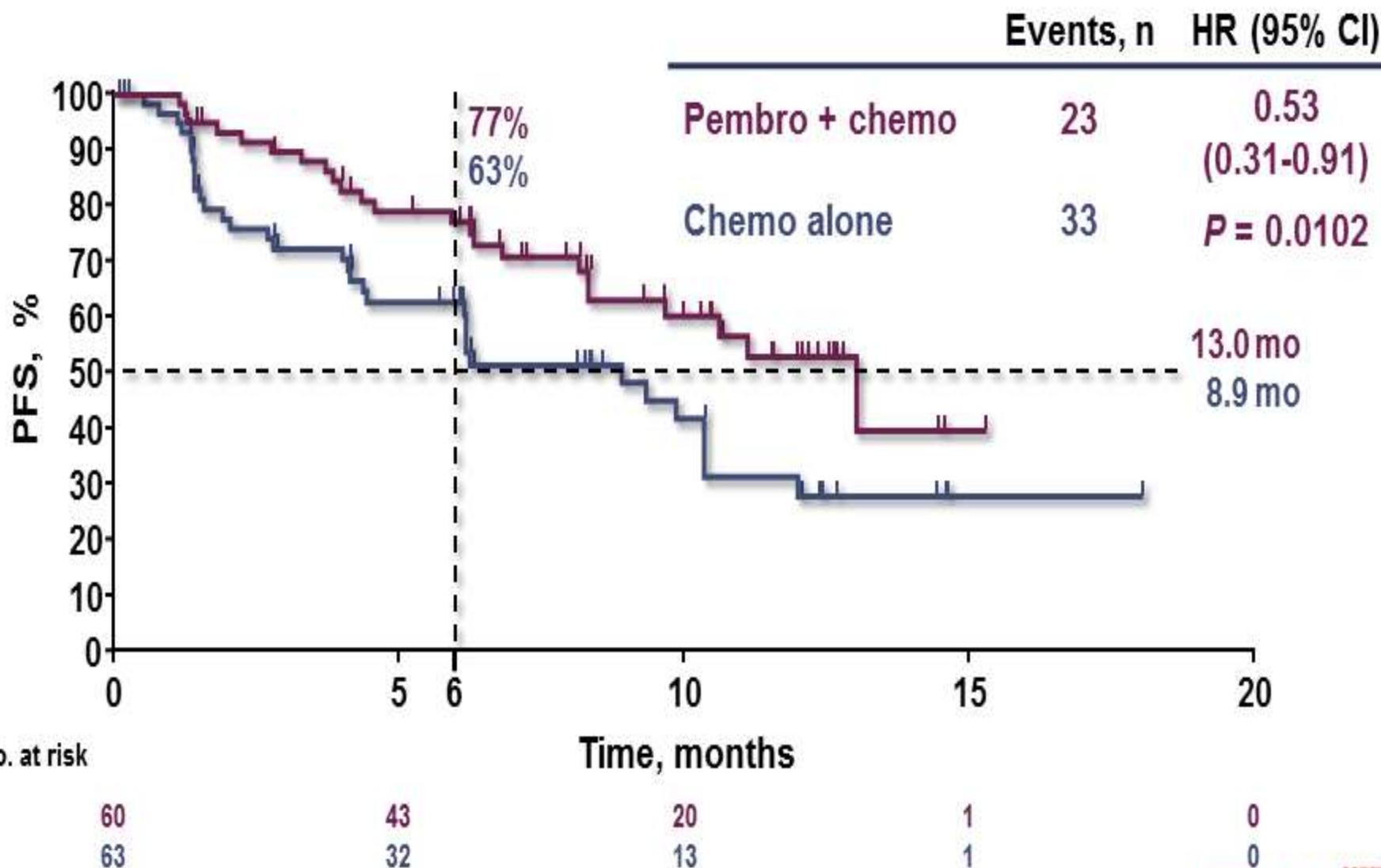
	Pembro + Chemo Responders n = 33	Chemo Alone Responders n = 18
TTR, mo median (range)	1.5 (1.2-12.3)	2.7 (1.1-4.7)
DOR, mo median (range)	NR (1.4+-13.0+)	NR (1.4+-15.2+)
Ongoing response, ^a n (%)	29 (88)	14 (78)

DOR = duration of response; TTR = time to response.

^aAlive without subsequent disease progression.

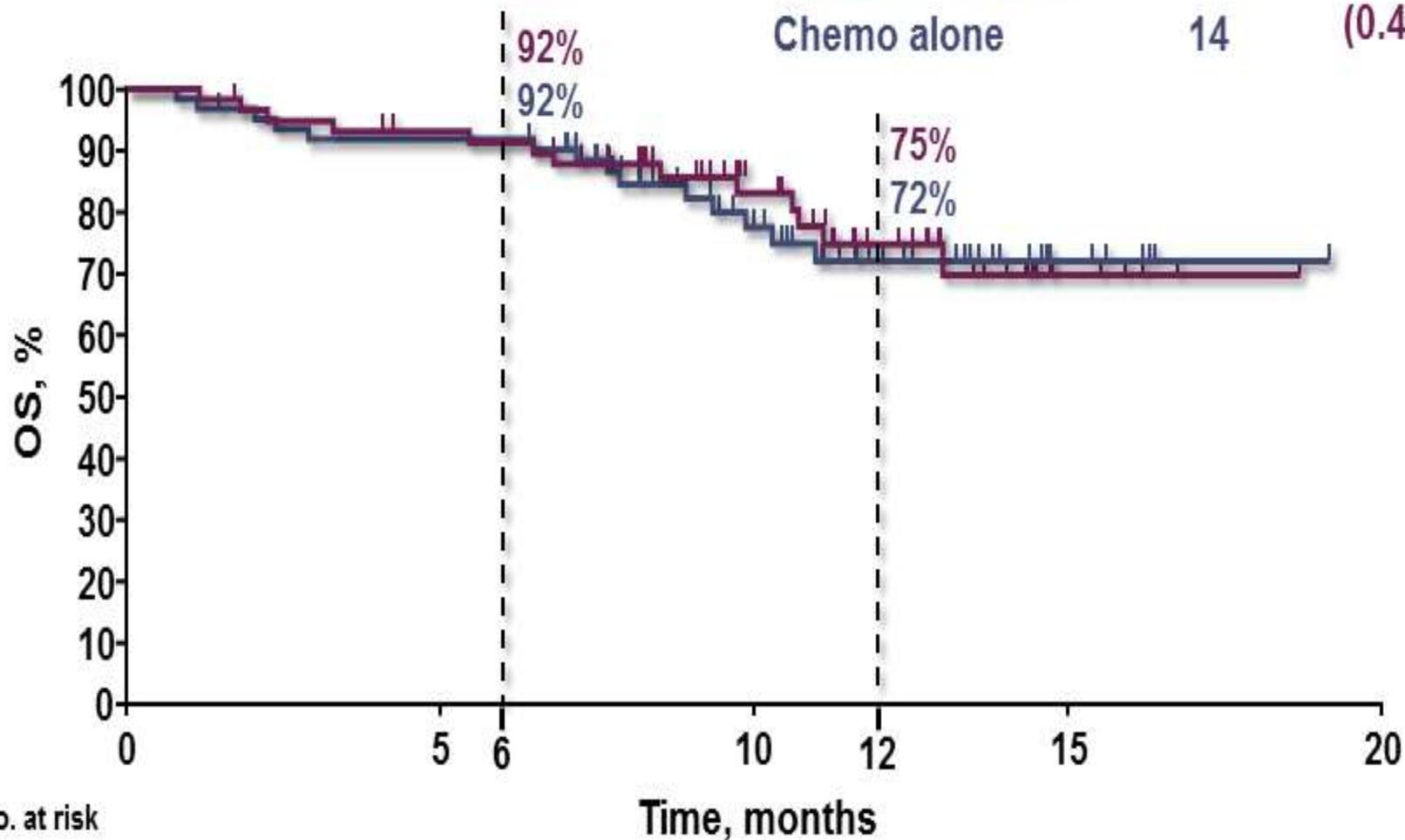
Progression-Free Survival

(RECIST v1.1 by Blinded, Independent Central Review)



Overall Survival

	Events, n	HR (95% CI)
Pembro + chemo	13	0.90
Chemo alone	14	(0.42-1.91)



No. at risk

60

63

53

57

33

31

5

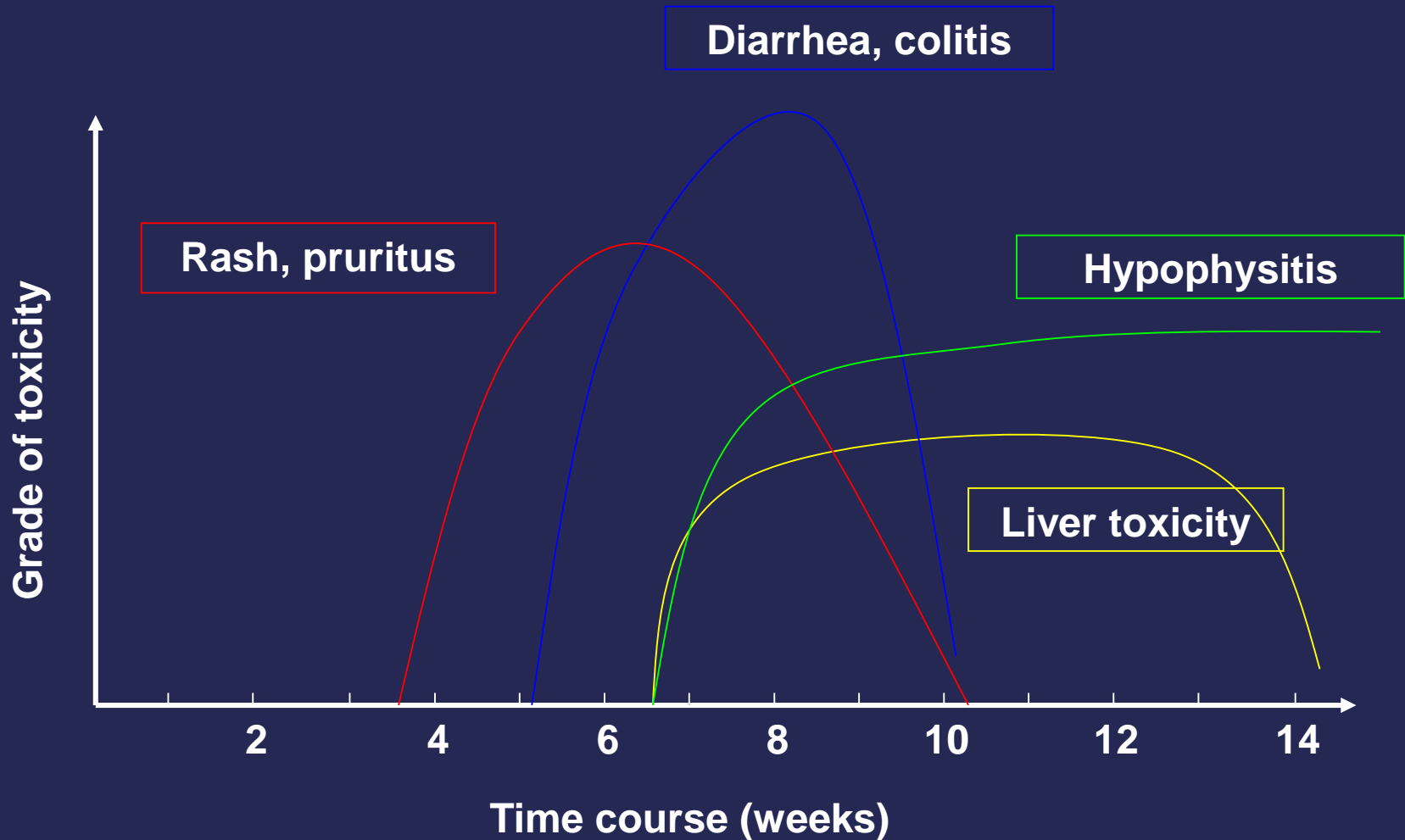
6

0

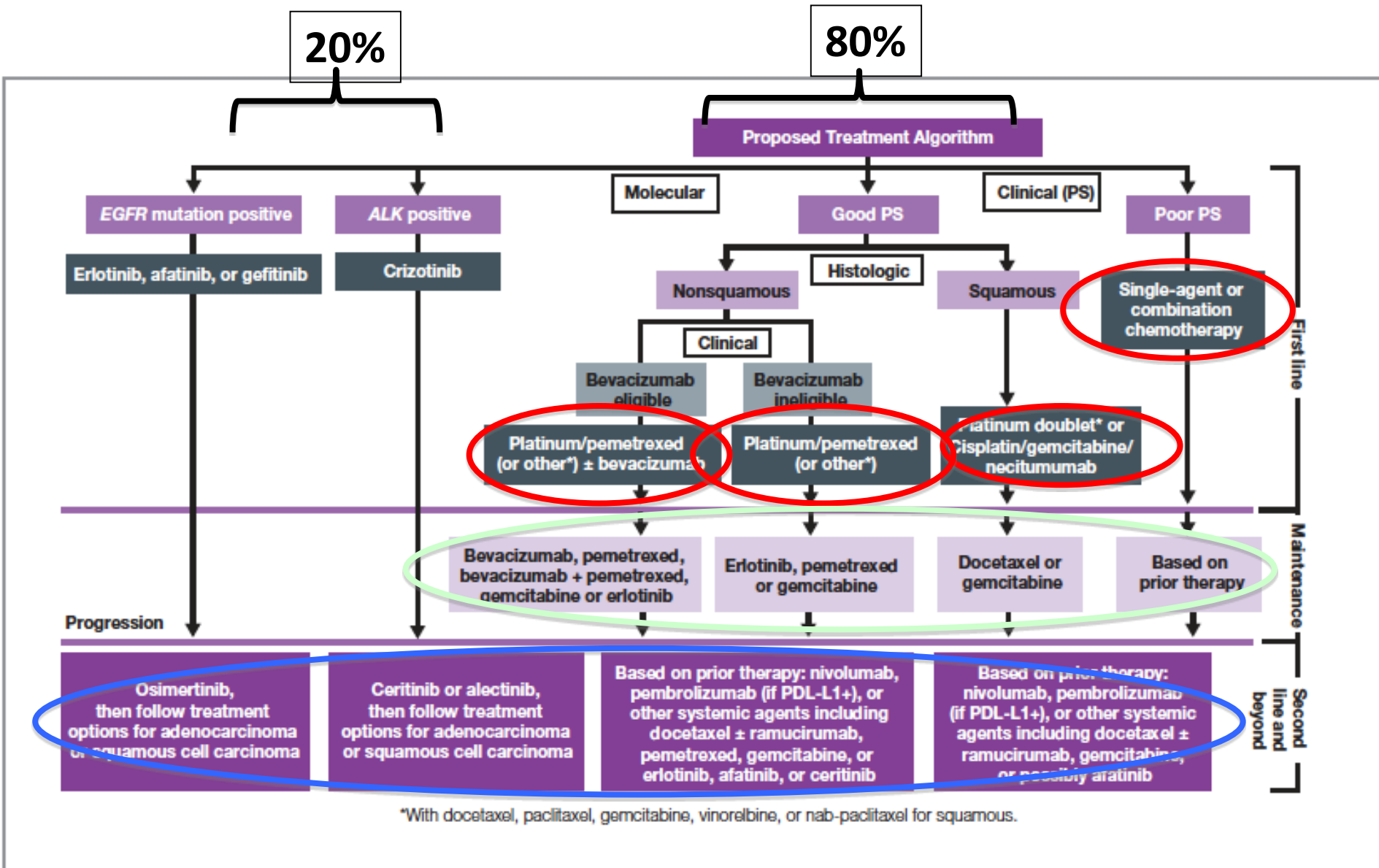
0

Time, months

Kinetics of Appearance of irAEs



LA CHEMIOTERAPIA NELLO SCENARIO TERAPEUTICO ATTUALE DEL NSCLC



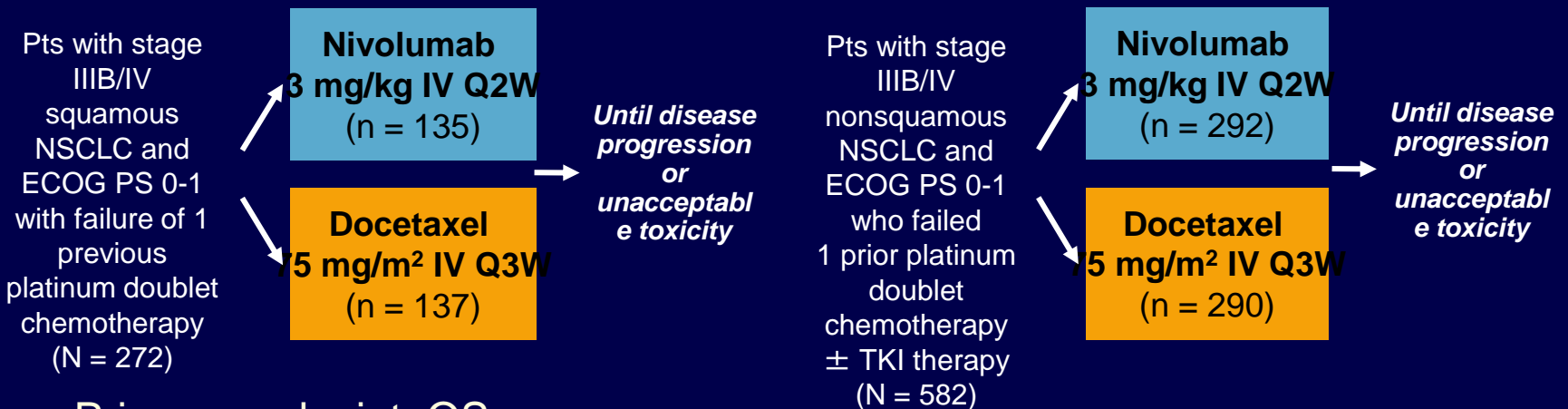
LA CHEMIOTERAPIA NEL NSCLC : "ALIVE AND WELL"

CheckMate 017 and 057: Nivolumab vs Docetaxel in Previously Treated Advanced NSCLC

- Open-label, randomized phase III trials

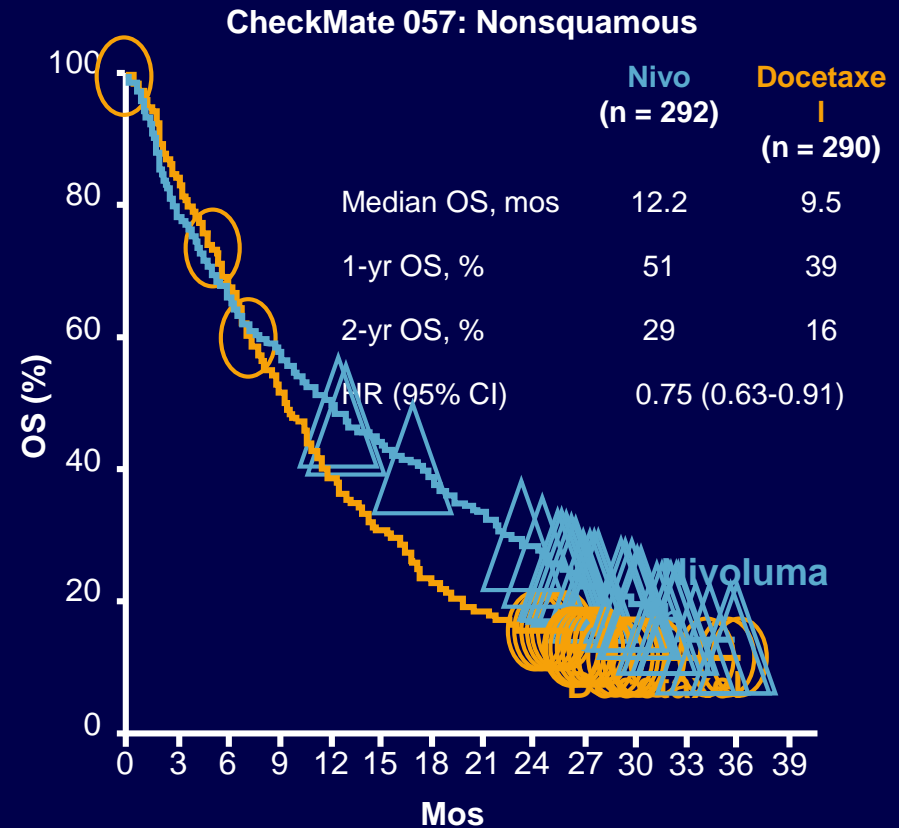
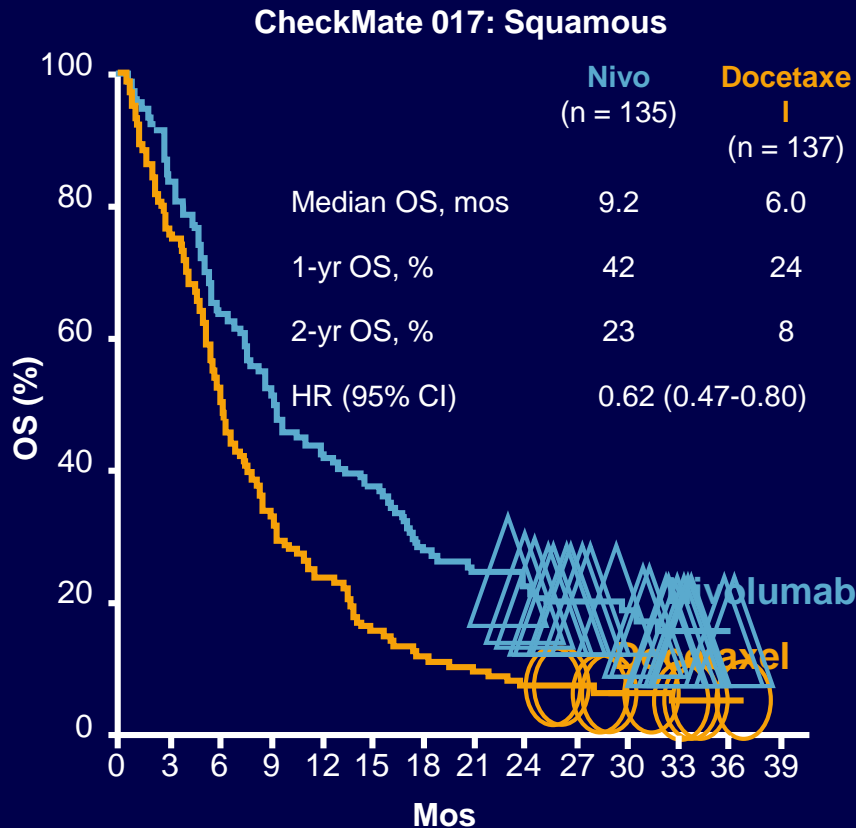
CheckMate 017: Squamous NSCLC

CheckMate 057: Nonsquamous NSCLC



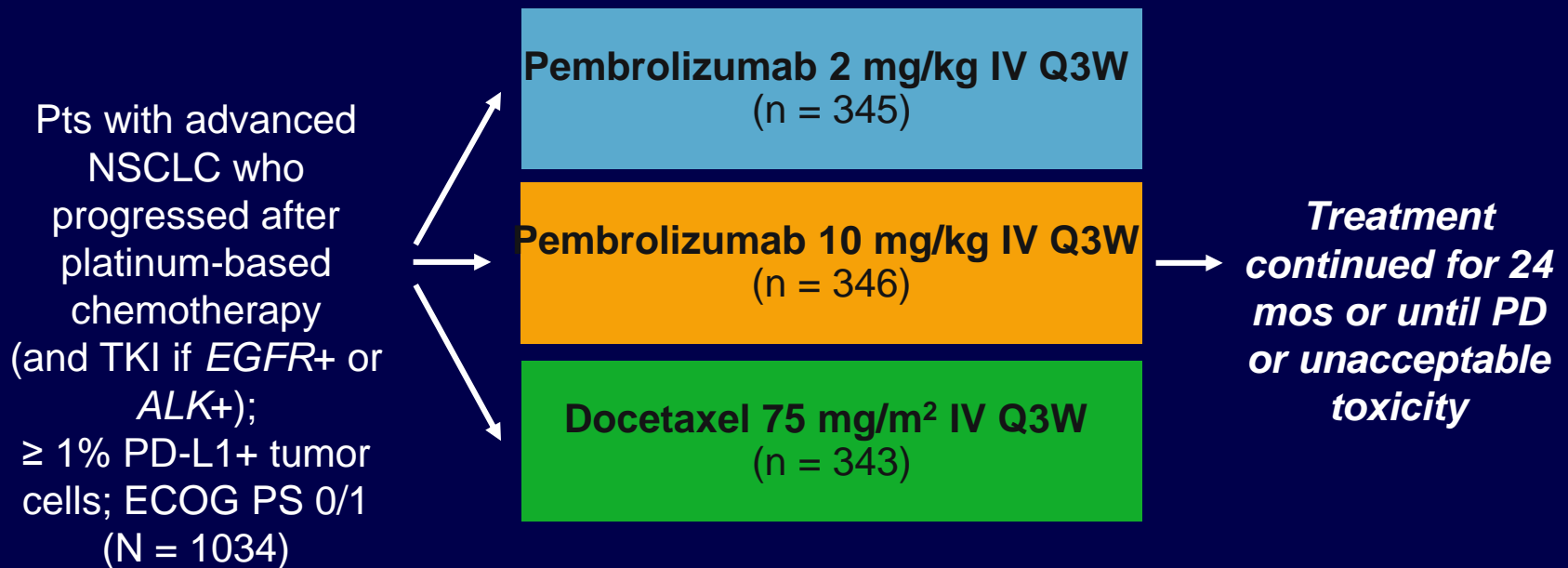
- Primary endpoint: OS
- Secondary endpoints: ORR, PFS, efficacy by PD-L1 expression, safety, QoL

CheckMate 017 and 057: OS With a Minimum 2-Yr Follow-up



KEYNOTE-010: Pembrolizumab vs Docetaxel in Advanced PD-L1–Positive NSCLC

- Multicenter, randomized, open-label phase II/III trial

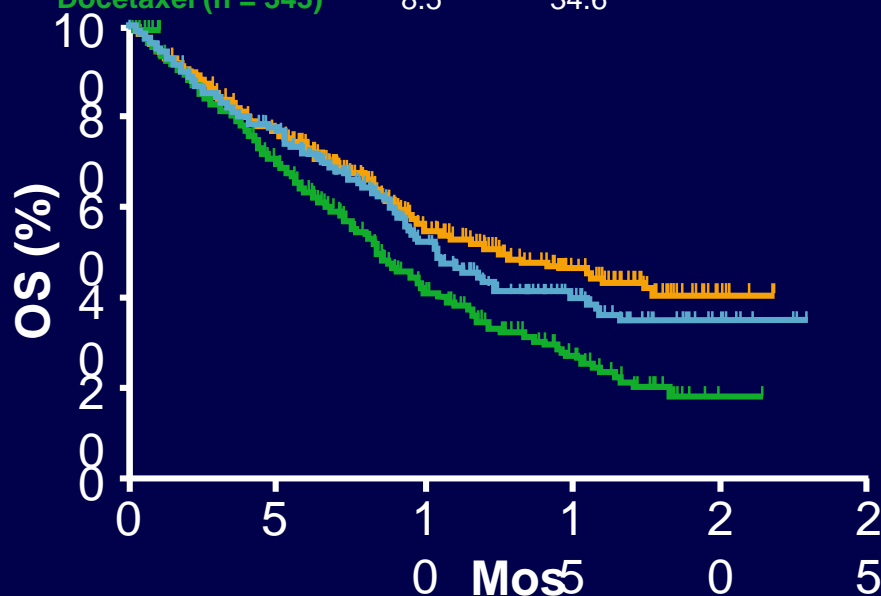


- Primary endpoints: OS, PFS
- Secondary endpoints: DoR, ORR, safety

KEYNOTE-010: OS in Pts With PD-L1 TPS $\geq 1\%$ and TPS $\geq 50\%$

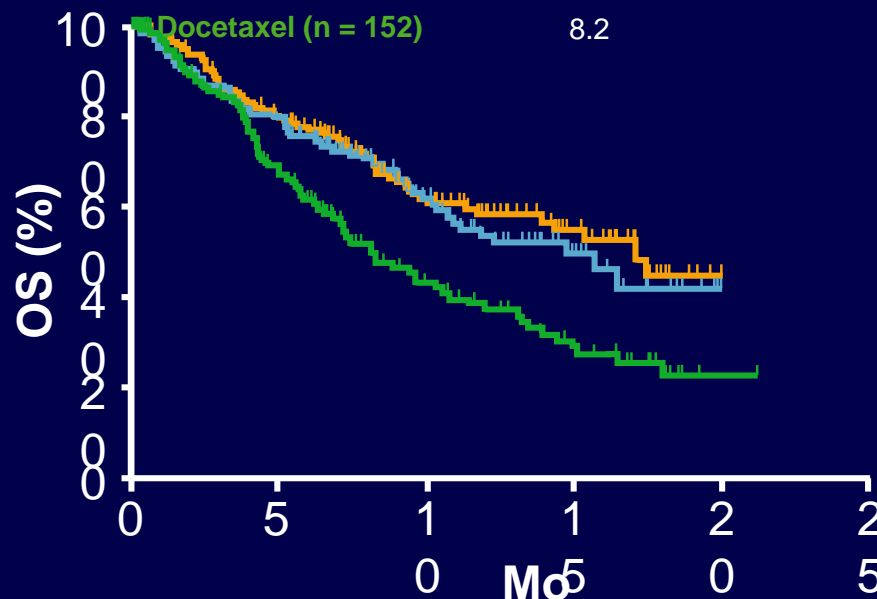
Pts With PD-L1 TPS $\geq 1\%$

	mOS, Mos	1-Yr OS, %	HR (95% CI)
Pembrolizumab 2 mg/kg (n = 344)	10.4	43.2	0.71 (0.58-0.88)
Pembrolizumab 10 mg/kg (n = 346)	12.7	52.3	0.50 (0.49-0.75)
Docetaxel (n = 343)	8.5	34.6	



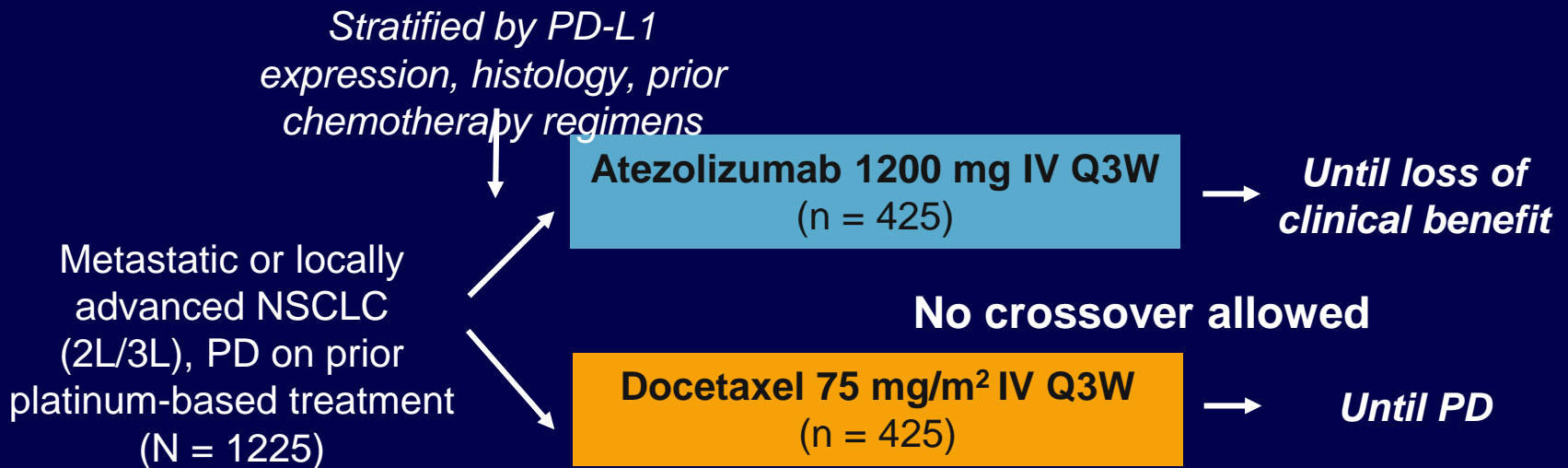
Pts With PD-L1 TPS $\geq 50\%$

	mOS, Mos	HR (95% CI)
Pembrolizumab 2 mg/kg (n = 139)	14.9	0.54 (0.38-0.77)
Pembrolizumab 10 mg/kg (n = 151)	17.3	0.50 (0.36-0.70)
Docetaxel (n = 152)	8.2	



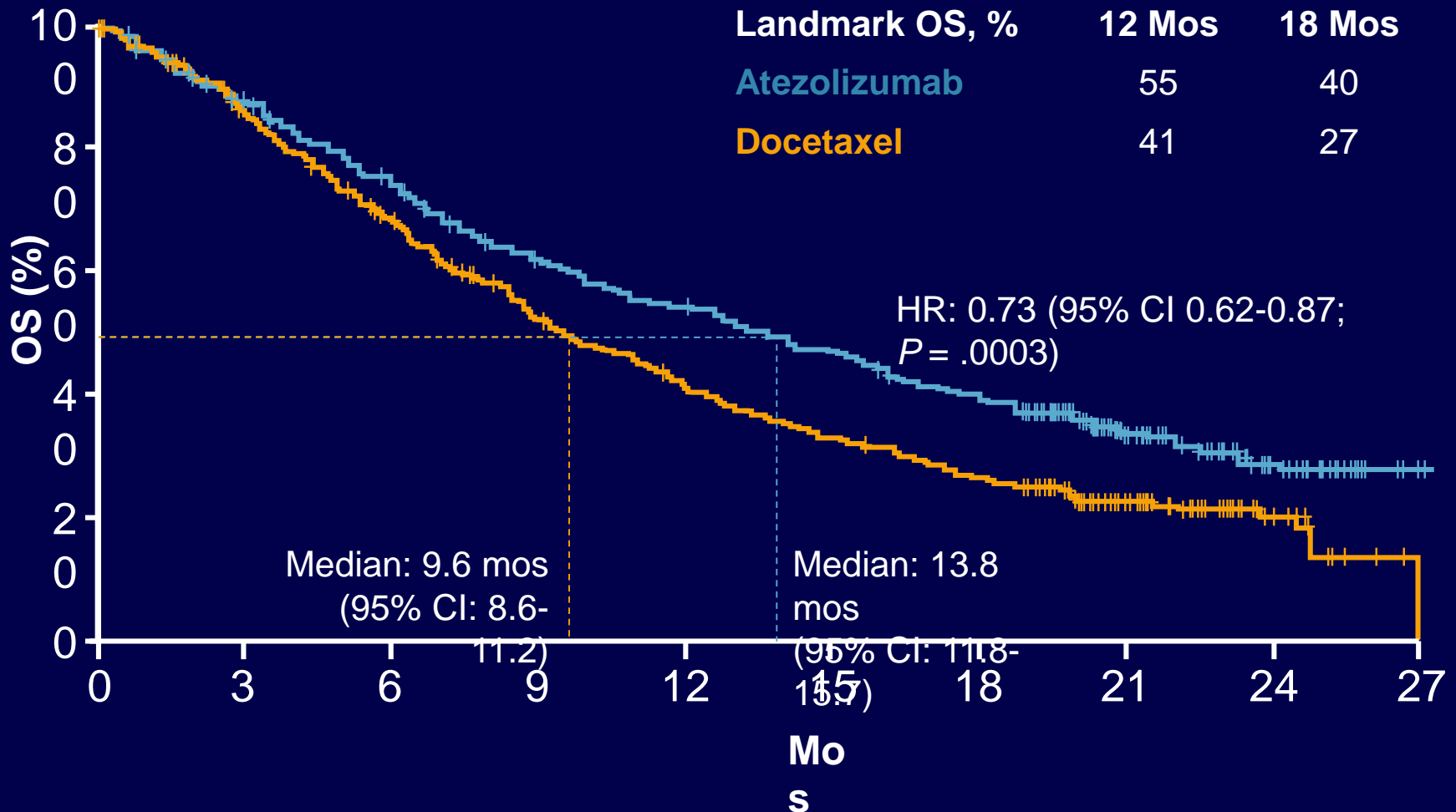
OAK: Atezolizumab vs Docetaxel in Progressive Advanced NSCLC

- Multicenter, randomized, open-label phase III trial



- Primary endpoints (first 850 pts enrolled): OS in ITT population; OS in pts with $\geq 1\%$ PD-L1 expression
- Secondary endpoints: ORR, PFS, DoR, safety

OAK: OS in ITT Population



IMMUNOTERAPIA DI LINEE SUCCESSIVE ALLA PRIMA NEL NSCLC

**NEL TUMORE POLMONARE NON MICROCITOMA
LE EVIDENZE DI LETTERATURA INDICANO CHE**

- NIVOLUMAB E' SUPERIORE ALLA CHEMIOTERAPIA**
- PEMBROLIZUMAB E' SUPERIORE ALLA CHEMIOTERAPIA**
- ATEZOLIZUMAB E' SUPERIORE ALLA CHEMIOTERAPIA**
- TUTTI GLI ANTICORPI SONO MEGLIO TOLLERATI DELLA CHEMIOTERAPIA**
- MAGGIO 2017: NIVOLUMAB HA INDICAZIONE E RIMBORSABILITA' PER NSCLC PRETRATTATO (qualunque istologia)**

Select Ongoing Randomized Phase III Trials of PD-1/PD-L1 Therapy in Advanced NSCLC

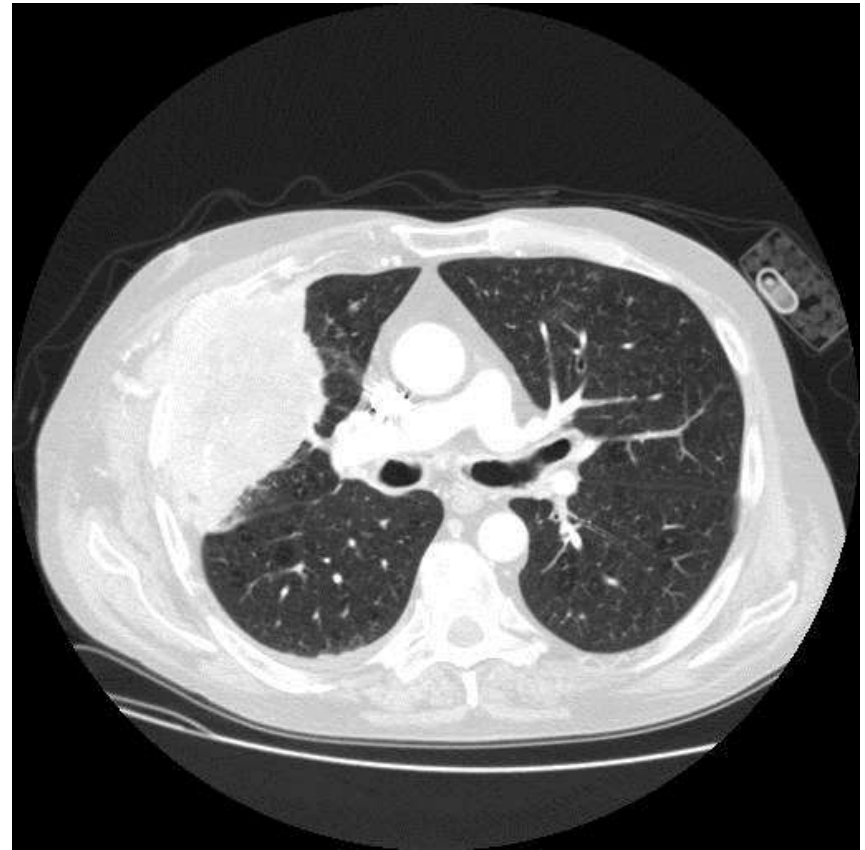
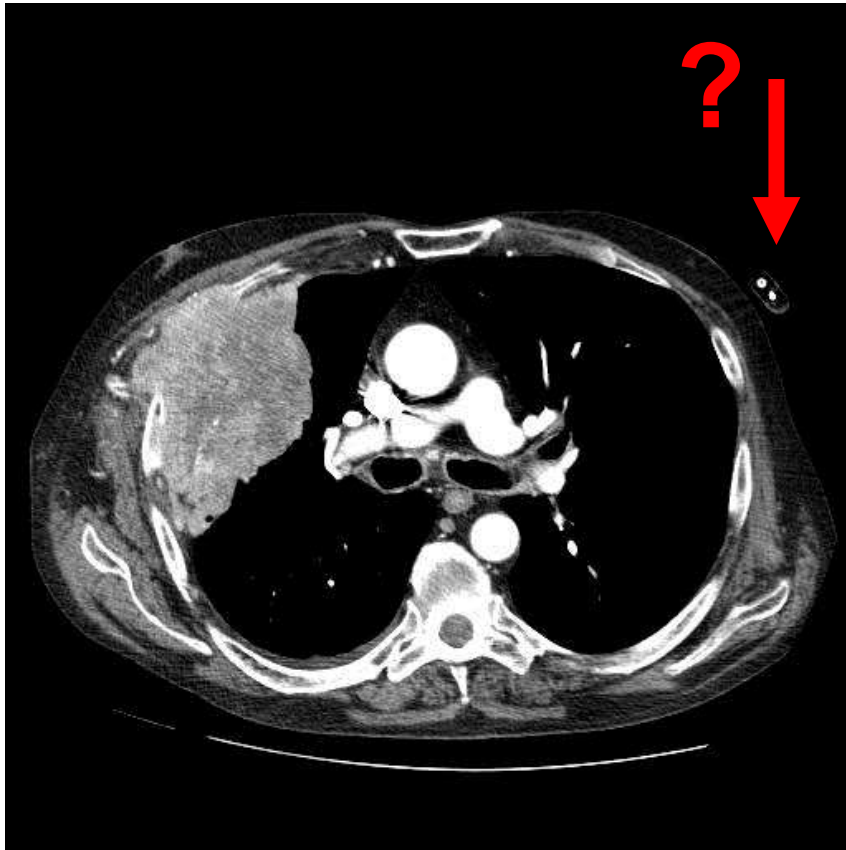
Trial*	Disease Setting	Treatment
CheckMate 227 (NCT02477826)	First line	Nivolumab or nivolumab + ipilimumab or nivolumab + Plt doublet CT vs Plt doublet CT
KEYNOTE-042 (NCT02220894)	First line/PD-L1+	Pembrolizumab vs Plt doublet CT
KEYNOTE-189 (NCT02578680)	First line (nonsq)	Plt/pemetrexed ± pembrolizumab
KEYNOTE-407 (NCT02775435)	First line (sq)	Cb/pac or nab-pac ± pembrolizumab
IMpower 110 (NCT02409342)	First line/PD-L1+	Atezolizumab vs Plt doublet CT
IMpower 130 (NCT02367781)	First line (nonsq)	Cb/nab-pac vs Cb/nab-pac ± atezolizumab
IMpower 131 (NCT02367794)	First line (sq)	Cb/pac or nab-pac + atezolizumab vs Cb/nab-pac
IMpower 132 (NCT02657434)	First line (nonsq)	Plt/pemetrexed ± atezolizumab
IMpower 150 (NCT02366143)	First line (nonsq)	Atezolizumab + Cb/pac ± bev vs Cb/pac/bev
JAVELIN Lung 100 (NCT02576574)	First line/PD-L1+	Avelumab vs Plt doublet CT
JAVELIN Lung 200 (NCT02395172)	Post-CT/PD-L1+	Avelumab vs docetaxel
NEPTUNE (NCT02542293)	First line	Durvalumab + tremelimumab vs Plt doublet CT

*All trials enrolling pts as of February 2017.

Slide credit: clinicaloptions.com



Prevenzione primaria?



Grazie per l'attenzione