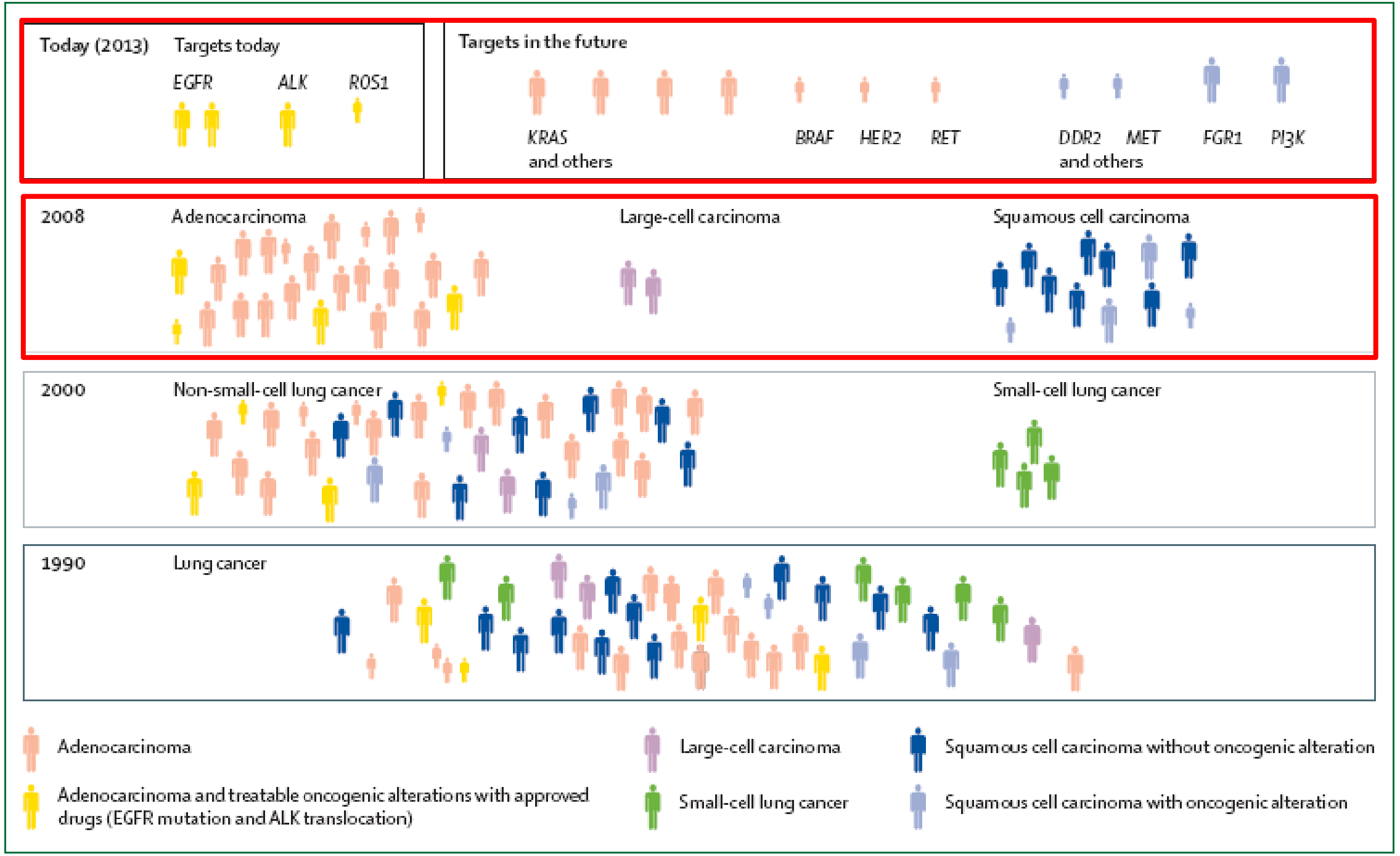
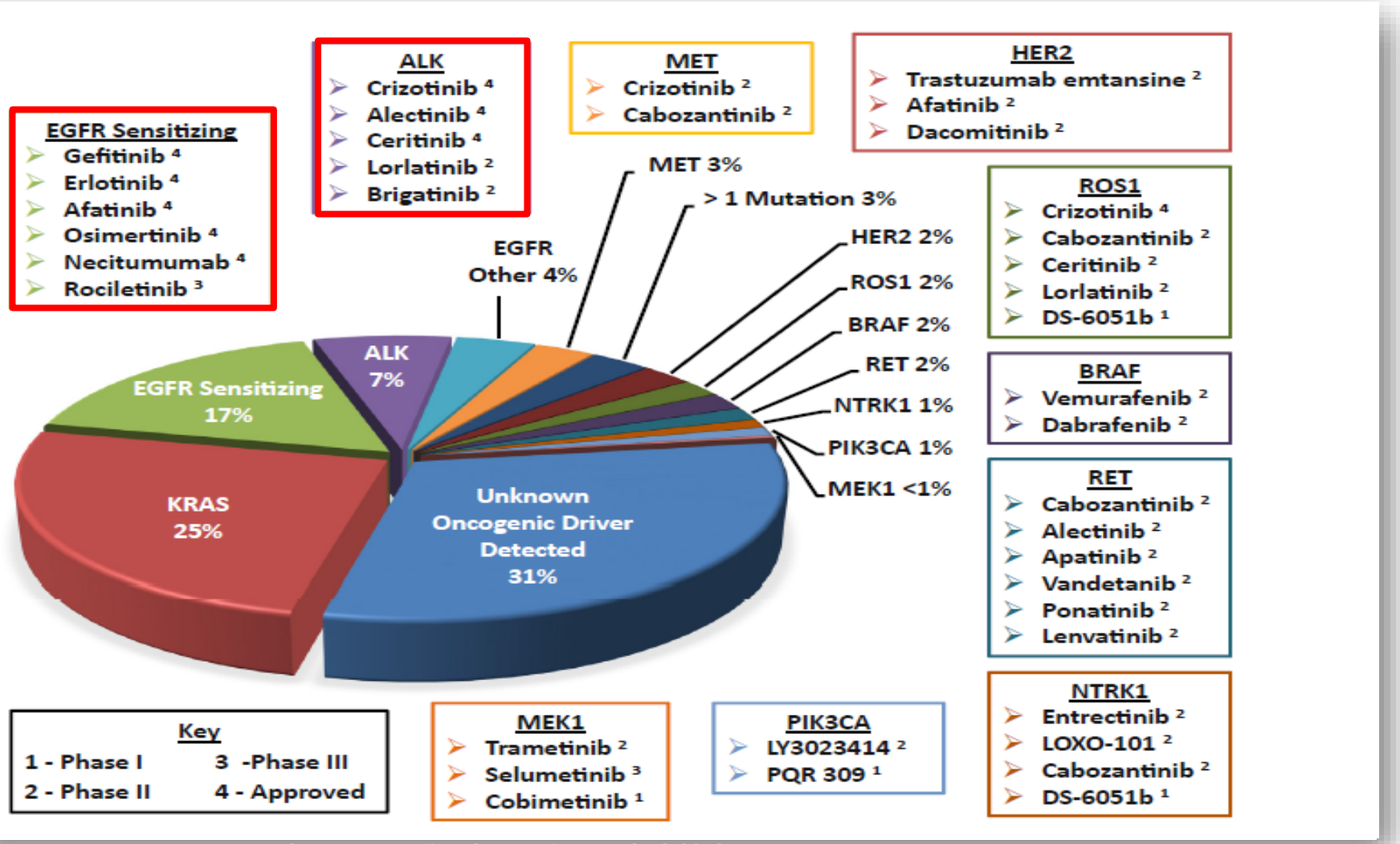
STATO DELL'ARTE IN TERAPIA ONCOLOGICA: CARCINOMA POLMONARE

Lucio Buffoni
Oncologia Polmonare
AOU San Luigi Orbassano


Today (2013)
Targets today
EGFR
ALK
ROS1
Targets in the future
KRAS
and others
BRAF
HER2
RET
DDR2
MET
and others
FGR1
PI3K
2008
Adenocarcinoma
Large-cell carcinoma
Squamous cell carcinoma
2000
Non-small-cell lung cancer
Small-cell lung cancer
1990
Lung cancer
Adenocarcinoma
Adenocarcinoma and treatable oncogenic alterations with approved drugs (EGFR mutation and ALK translocation)
Large-cell carcinoma
Small-cell lung cancer
Squamous cell carcinoma without oncogenic alteration
Squamous cell carcinoma with oncogenic alteration

Oncogene Addicted Tumor: Special Entity



Lung Cancer Mutation Consortium: WCLC 2013

ALGORITMO TERAPEUTICO NSCLC: 2017

EGFR MUT +
15%

ALK TRASLOC
4%

GEFITINIB/ERLOTINIB/AFATINIB

9-13 mesi PFS

OLIGO PD

SYSTEMIC PD

Continue TKI + LAT

OSIMERTINIB

2017

24 mesi

10-12 mesi PFS

CRIZOTINIB

11 mesi PFS

OLIGO PD

SYSTEMIC PD

Continue CRIZO+LAT

ALECTINIB
CERITINIB
…..

20 mesi

9 mesi PFS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhaufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, and J.R. Brahmer

ABSTRACT

BACKGROUND

Nivolumab, a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint–inhibitor antibody, disrupts PD-1–mediated signaling and may restore antitumor immunity.

METHODS

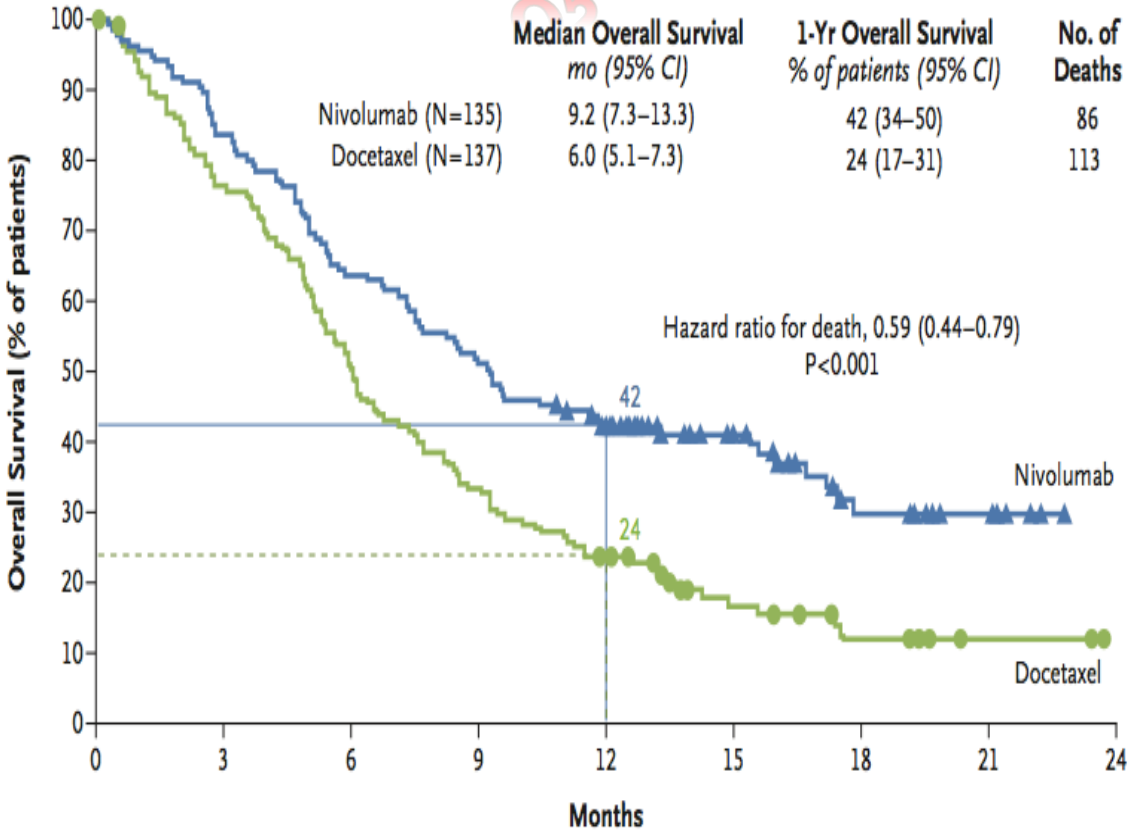
In this randomized, open-label, international phase 3 study, we assigned patients with nonsquamous non–small-cell lung cancer (NSCLC) that had progressed during or after platinum-based doublet chemotherapy to receive nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks or docetaxel at a dose of 75 mg per square meter of body-surface area every 3 weeks. The primary end point was overall survival.

Cancer is an immunological disorder

Check-Mate 17

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

OS



No. at Risk

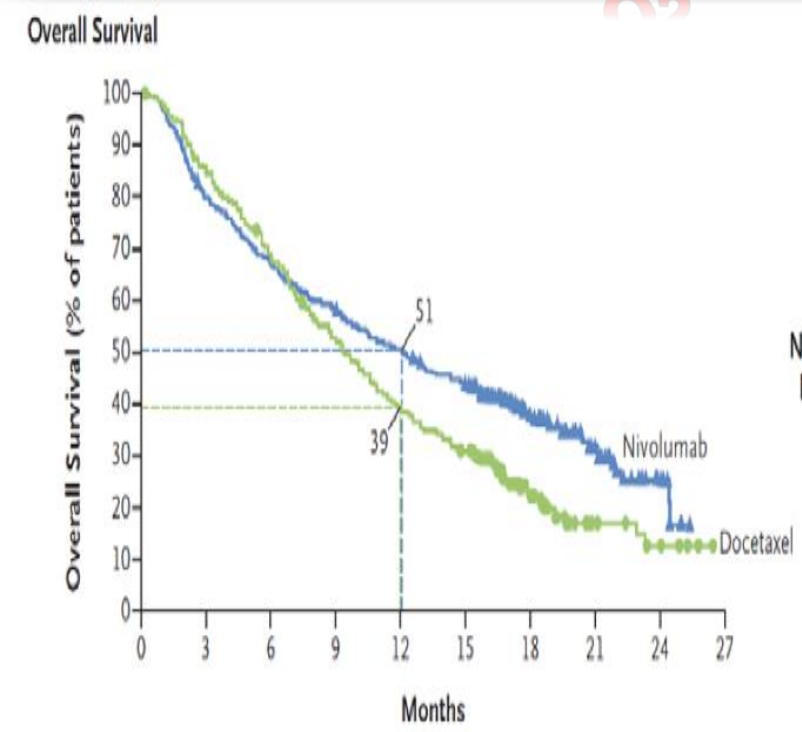
Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

ORIGINAL ARTICLE

Check-Mate 57

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

OS



	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

No. at Risk

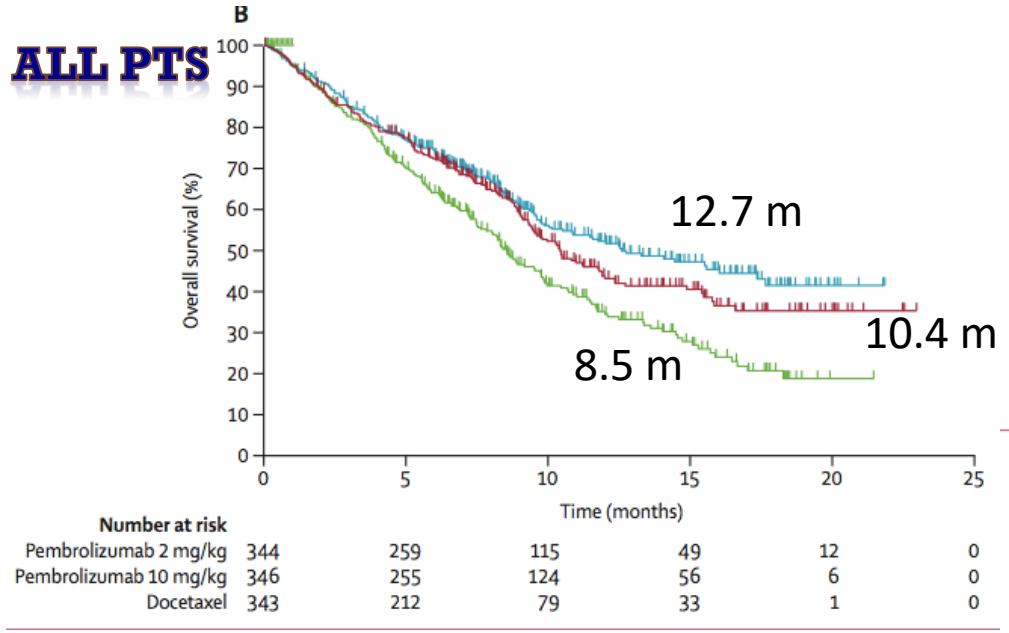
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Spigel *et al*, NEJM 2015

Key-Note 10

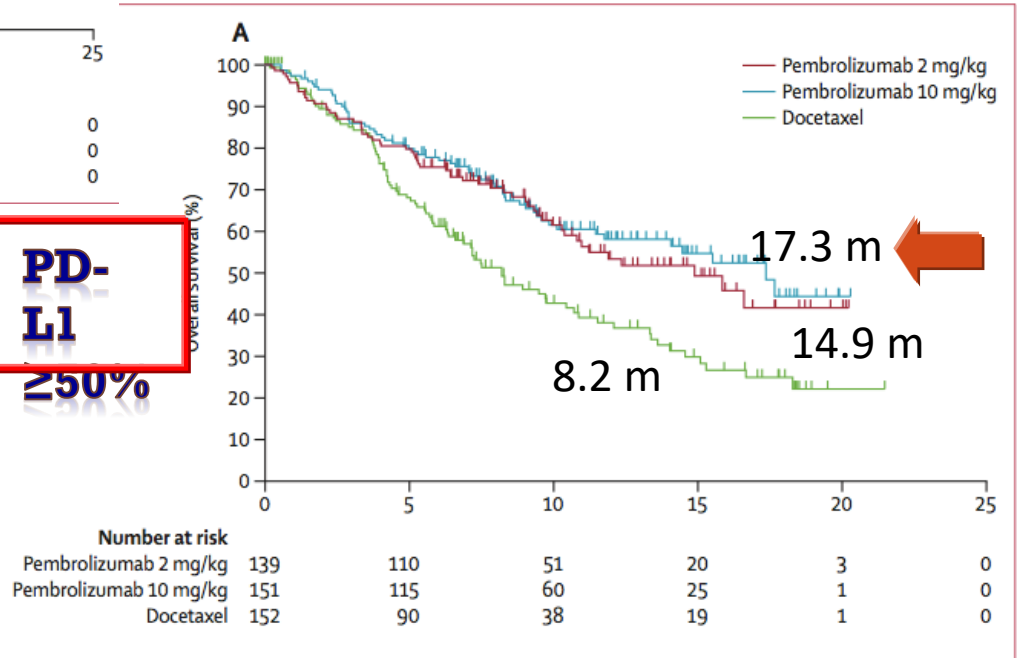
Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

ALL PTS



OS

PD-L1 ≥50%



Herbst *al*, Lancet 2015

ALGORITMO TERAPEUTICO NSCLC: 2017

NSCLC IIIB-IV

EGFR e ALK WT

PS 0-1/Età < 70

Non-SCC

SCC

CT + Beva
P – Pem

P - Gem
P - Doc

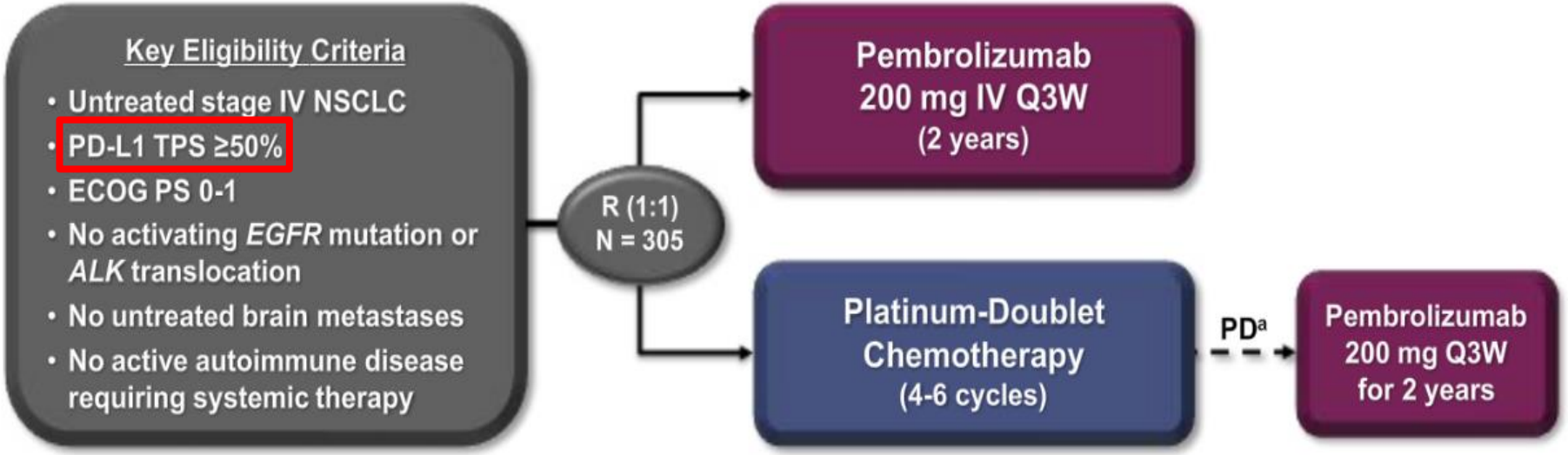
Docetaxel +/-
Nintedanib

Docetaxel

Nivolumab
Pembrolizumab PDL1>1%

2016-17

KEYNOTE 024: STUDY DESIGN



Key End Points

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

Secondary: OS, ORR, safety

Exploratory: DOR

Platinum-Doublet Chemotherapy Options

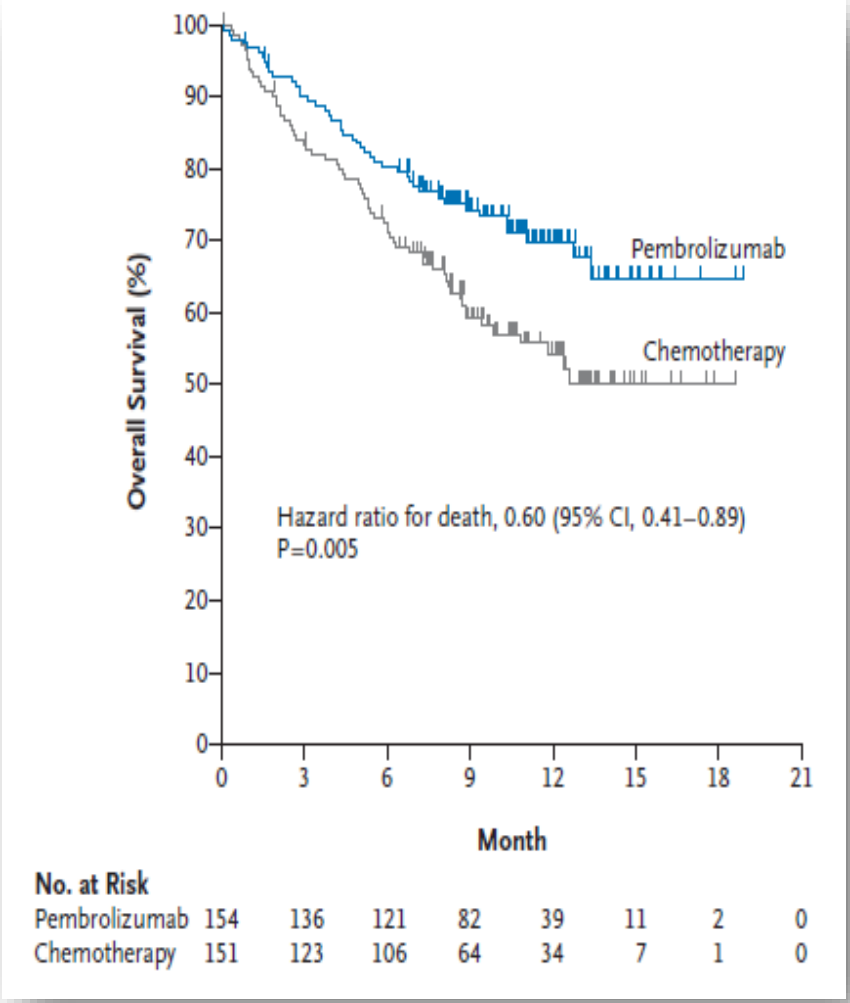
- Pemetrexed 500 mg/m² on day 1 of 21-day cycles + Carboplatin AUC 5 or 6 on day 1 of 21-day cycles
- Pemetrexed 500 mg/m² on day 1 of 21-day cycles + Cisplatin 75 mg/m² on day 1 of 21-day cycles

  (Nonsquamous NSCLC only)
- Paclitaxel 200 mg/m² on day 1 of 21-day cycles + Carboplatin AUC 5 or 6 on day 1 of 21-day cycles
- Gemcitabine 1250 mg/m² on days 1 and 8 of 21-day cycles + Carboplatin AUC 5 or 6 on day 1 of 21-day cycles
- Gemcitabine 1250 mg/m² on days 1 and 8 of 21-day cycles + Cisplatin 75 mg/m² on day 1 of 21-day cycles

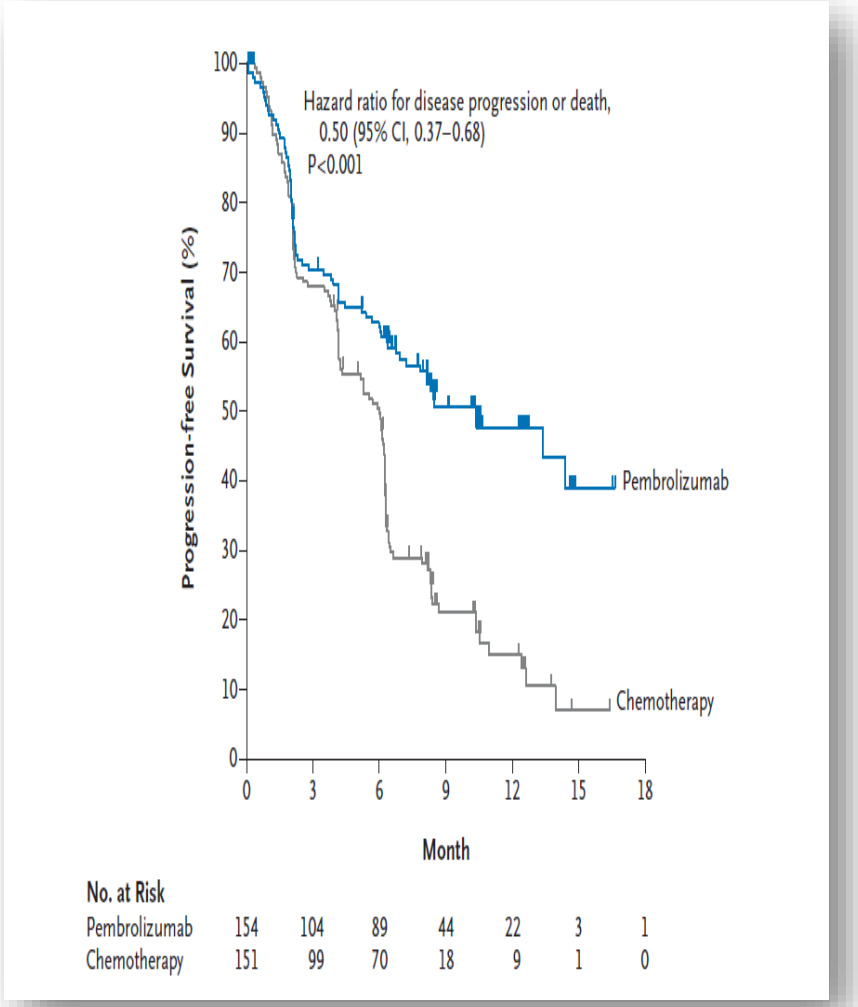
Reck M, ESMO 2016

I LINE: SINGLE IMMUNO AGENT VS STANDARD CT

Overall Survival



Progression Free Survival



Reck M, NEJM 2016; Reck M, ESMO 2016

ALGORITMO TERAPEUTICO NSCLC: 2017

NSCLC IIIB-IV

EGFR e ALK WT

PS 0-1/Età < 70

Non-SCC

CT + Beva
P – Pem

Docetaxel +/-
Nintedanib

SCC

P - Gem
P - Doc

Docetaxel

Nivolumab
Pembrolizumab PDL1>1%

EGFR e ALK WT

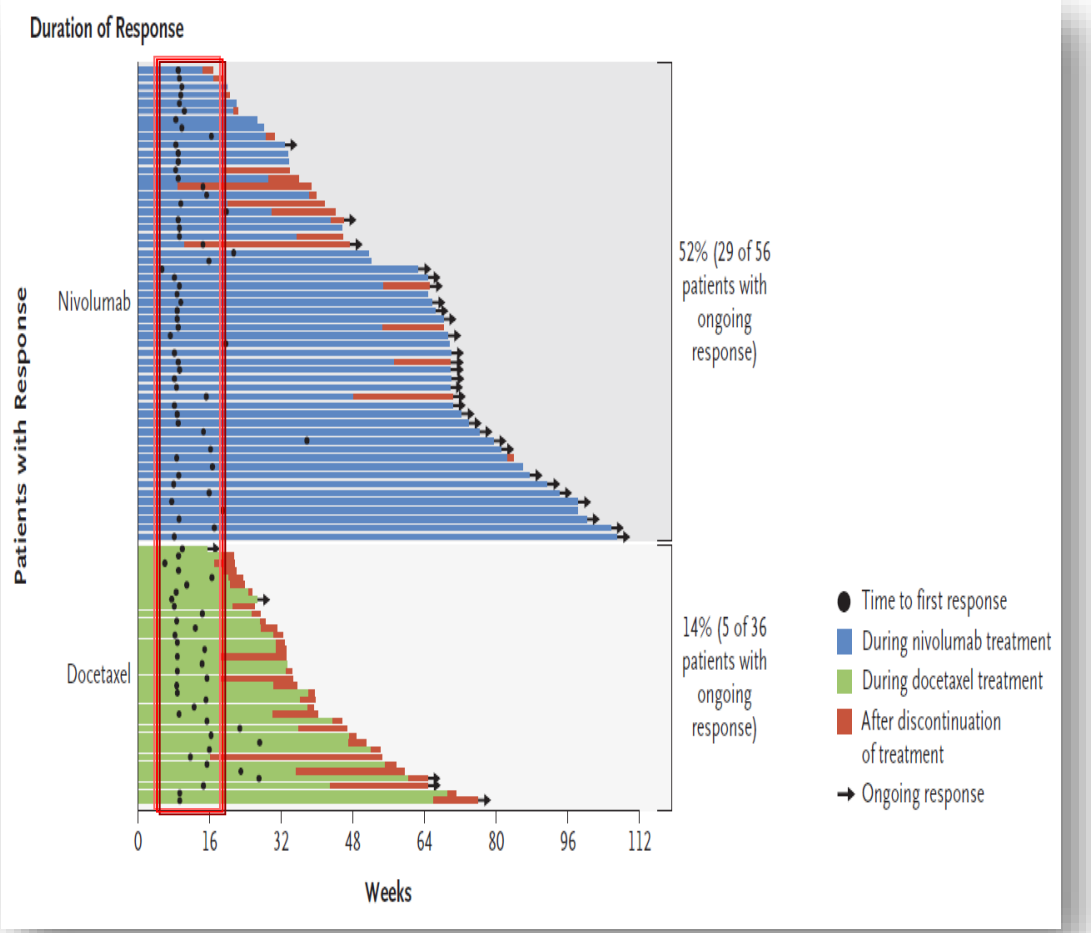
PDL1 > 50%

CHEMIOTERAPIA

PEMBROLIZUMAB

CHEMIOTERAPIA

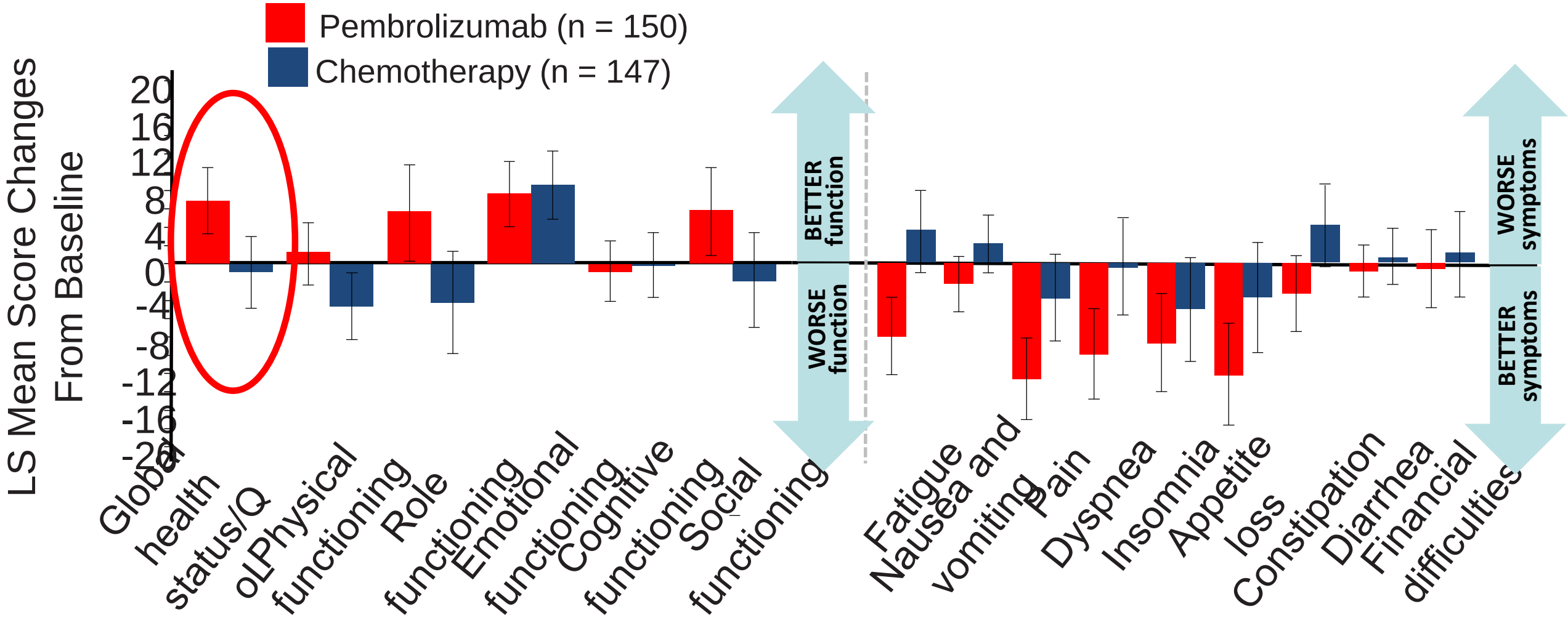
CHECKMATE 057: RESPONSE AND DURATION OF RESPONSE



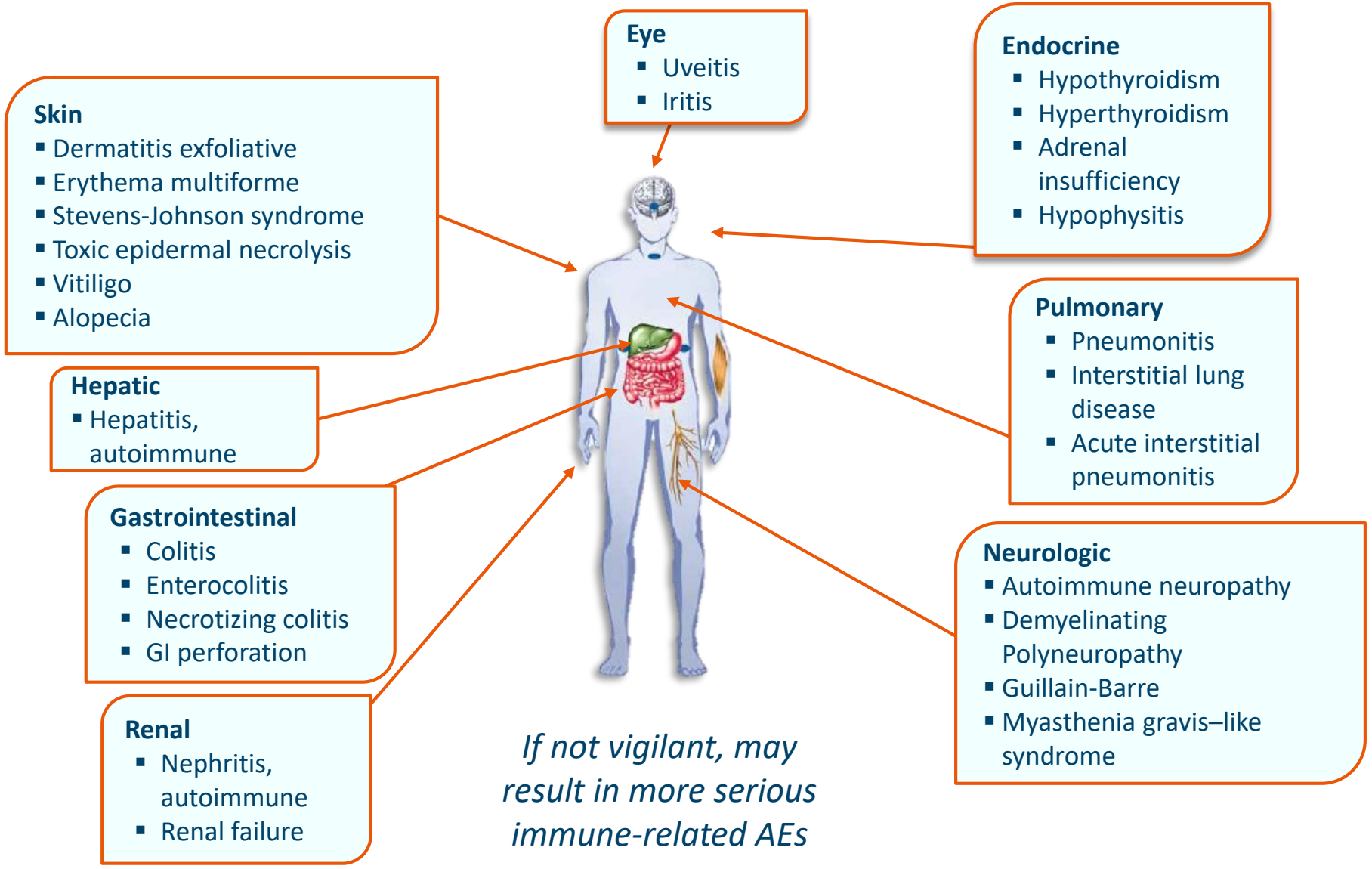
Variable	Nivolumab (N = 292)	Docetaxel (N = 290)
Objective response†		
No. of patients	56	36
% of patients (95% CI)	19 (15–24)	12 (9–17)
Estimated odds ratio (95% CI)	1.7 (1.1–2.6)	
P value	0.02	
Best overall response — no. (%)		
Complete response	4 (1)	1 (<1)
Partial response	52 (18)	35 (12)
Stable disease	74 (25)	122 (42)
Progressive disease	129 (44)	85 (29)
Could not be determined	33 (11)	47 (16)
Time to response — mo‡§		
Median	2.1	2.6
Range	1.2–8.6	1.4–6.3
Duration of response — mo‡¶		
Median	17.2	5.6
Range	1.8 to 22.6+	1.2+ to 15.2+

Borghaei H , NEJM 2015

Supportive PRO Analysis: Change From Baseline to Week 15 EORTC QLQ-C30 Functioning and Symptom Scales



IMMUNE-RELATED AES WITH IMMUNOTHERAPY



ALGORITMO TERAPEUTICO NSCLC: I LINEA 2017

NSCLC IIIB-IV

CHEMIOTERAPIA 2008	IMMUNOTERAPIA 2017	TARGETTERAPIES 2009
55%	**25%**	**20%**
EGFR WT ALK NT ROS1 NT Età media più alta All histologies Fumatori/Ex fumatori	EGFR WT ALK/ROS1 NT **PDL1 > 50%** Età media più alta All histologies Fumatori	EGFR mut+ ALK traslocato ROS1+ Età media più bassa Adenocarcinoma Non fumatori

CONCLUSIONI NSCLC 2017…

- **Non Oncogene Addicted:**
  Immunotherapy is a standard of care with IMPRESSIVE efficacy, rapid ONSET, LONG effect, MILD and PECULIAR toxicities
- FUTURE:
  - PREDICTIVE BIOMARKERS (PDL1 + TMB)
  - COMBINATIONS with CHEMOTHERAPY or IMMUNOTHERAPY (**Anti PDL1/Anti CTLA4**)
- **Oncogene Addicted:**
  EGFR +:
  - TKIs I gen -> TKIs 3 gen PFS 24 mesi e OS 3-4 anni
  - TKIs 3 gen in I line to prevent PD and Brain Mets?
- ALK +:
  - Crizo I line ->Alectinib/Ceritinib ->Lorlatinib/Brigatinib PFS 20 mesi OS 4 anni
  - Alectinib I line to prevent PD and Brain Mets?