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Note di pratica clinica ed aggiornamenti in merito ad oncogene-addiction ed immunoterapia nel NSCLC

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Aggiornamenti:

NSCLC early stage

NSCLC advanced stage

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NSCLC Early stage

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Terapia adiuvante

Invariate le indicazioni a chemio e/o radioterapia, quando indicate, negli stadi precoci

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Terapia adiuvante – aggiornamenti immuno

Tumor	Trial Name		Est. Trial readout
Lung			
1L NSCLC (non-sq)	**IMpower 150**	Tecentriq + carbo/pac +/- Avastin	2017
1L NSCLC (non-sq)	**IMpower 130**	Tecentriq + carbo + Abraxane	2017
1L NSCLC (sq)	**IMpower 131**	Tecentriq + carbo + pac/Abraxane	2017
1L NSCLC (non-sq)	**IMpower 132**	Tecentriq + cis/carbo + pem	2018
1L Dx+ NSCLC (non-sq & sq)	**IMpower 110/111**	Tecentriq monotherapy	2017
Adj NSCLC	**IMpower 010**	Tecentriq monotherapy	Post 2018
1L SCLC	**IMpower 133**	Tecentriq+ carbo + etoposide	Post 2018
2L + NSCLC	**OAK**	Tecentriq monotherapy	2016

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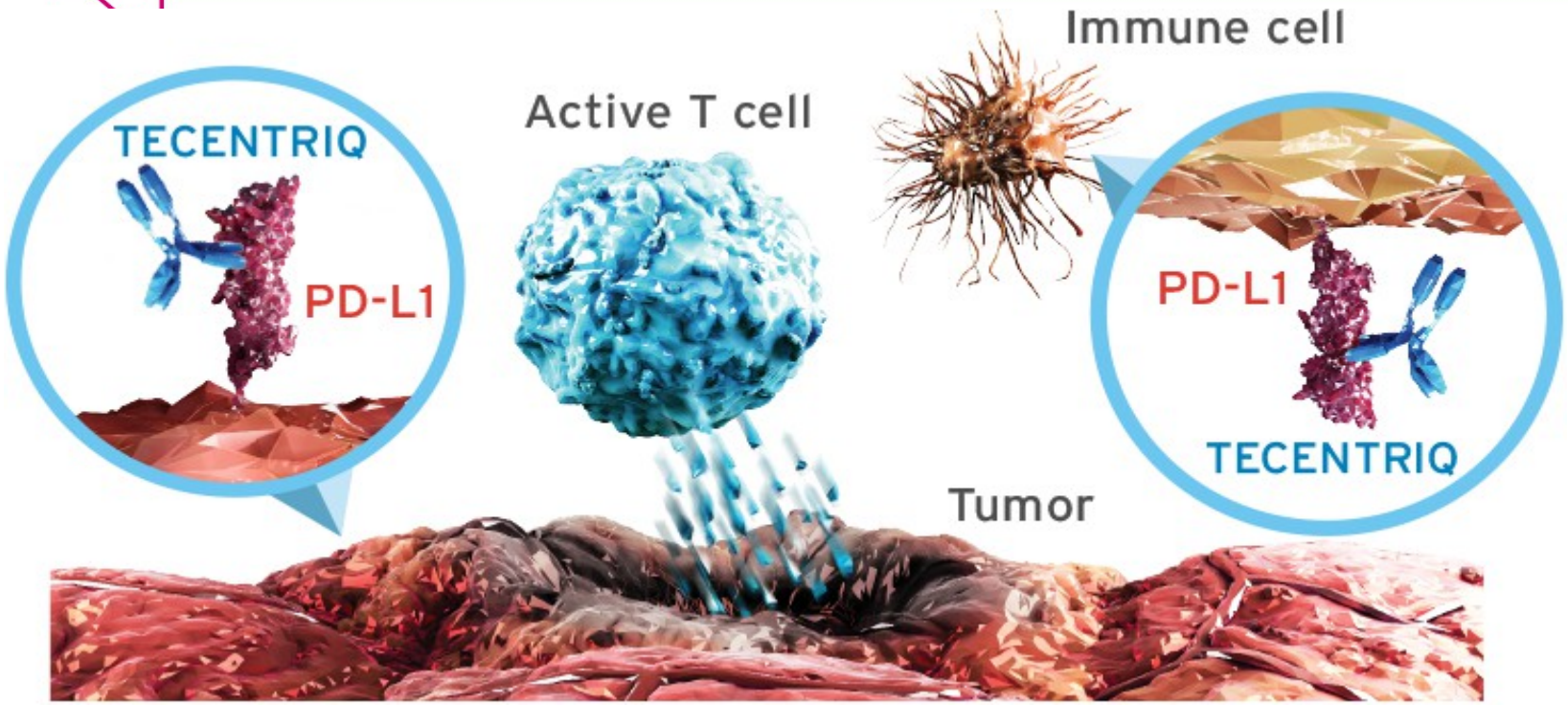
Ongoing…Impower 010



✓Pazienti ECOG PS 0-1 sottoposti ad intervento chirurgico radicale

✓Terapia adiuvante (cisplatinum-based);

✓Arruolamento consentito indipendentemente dallo stato di PD-L1;

✓Randomizzazione 1:1 → 16 cicli di atezolizumab 1200 mg q3w vs BSC dopo chemioterapia adiuvante.

✓End-point primario: DFS

✓End-point secondari: OS e safety.

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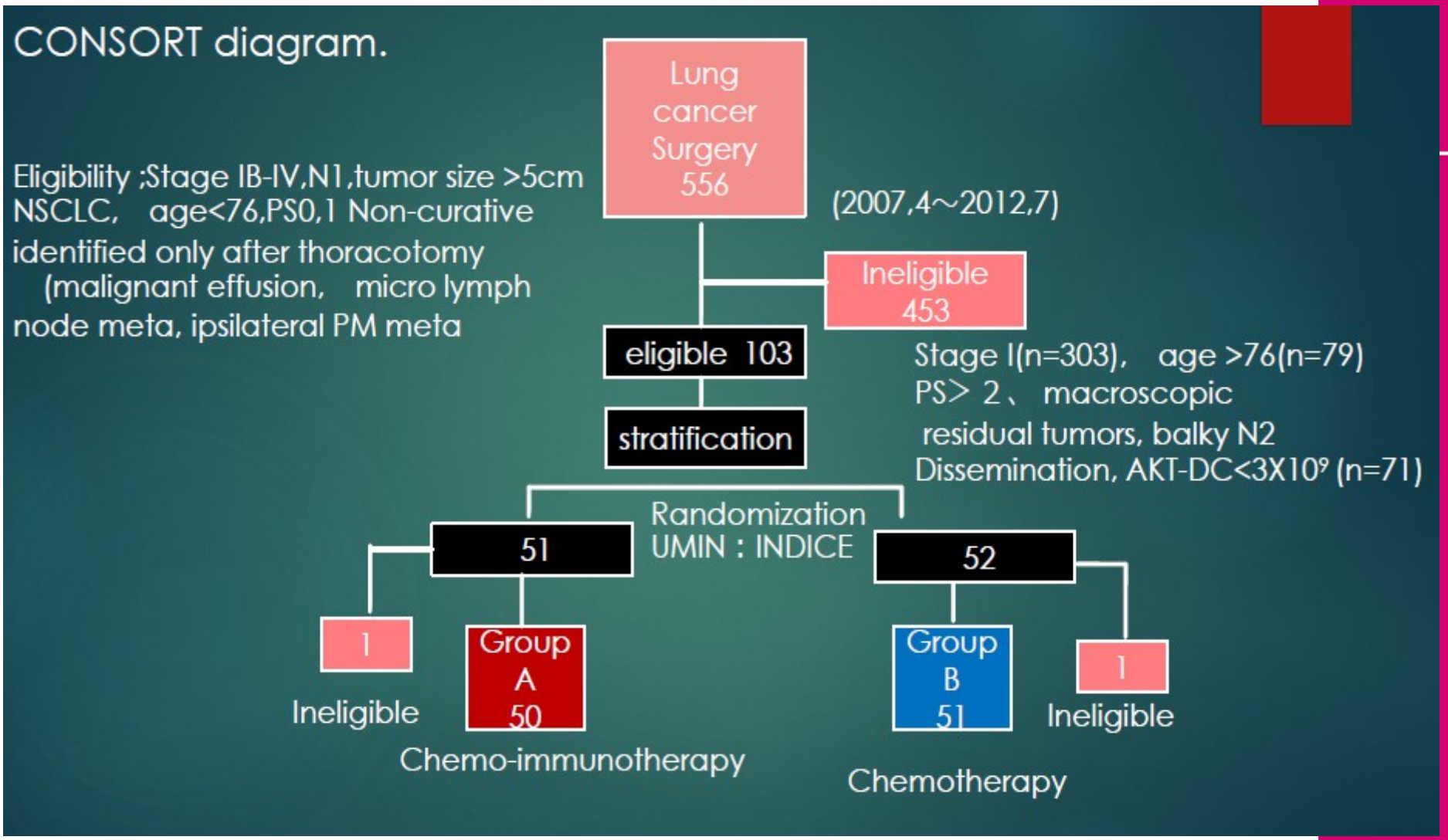
Terapia adiuvante.. in evoluzione

1144-O Phase III randomized controlled trial of adjuvant chemoimmunotherapy in patients with resected primary lung cancer

Hideki Kimura[a],Yukiko Matsui[b], Aki Ishikawa [c] Masato Shingyouji [b]; Takahiro Nakajima [c]; Toshihiko Iizasa, [b]
A: Saiseikai-Narashino Hospital, B: Chiba Cancer Center,
C:Graduate School of Medicine, Chiba University



L'immunoterapia in questo studio:
cellule T killer autologhe attivate e cellule dendridiche ottenute dai linfonodi regionali dei pazienti.

Terapia adiuvante – aggiornamenti in merito a TKI

Studi di fase III

- ADJUVANT (CTONG1104; NCT01405079)
  - Gefitinib versus vinorelbine/platin in NSCLC II-IIIA (N1-N2)
  - Yi-Long Wu
  - 220 patients; exon 19 deletions, L858R
  - Disease-free survival **Significativamente prolungato!**
- WJOG6410L
  - Gefitinib versus vinorelbine/cisplatin in NSCLC II-III
  - 230 patients; exon 19 deletions or L858R without T790 mutation
  - Disease-free survival (HR=0.65)

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Early stage - conclusioni

Invariate le indicazioni a chemio e/o radioterapia, quando indicate, negli stadi precoci

Non indicazioni per TKIs ed immunoterapia, al momento, al di fuori di studi clinici

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Stadio III

Discussione di tutti gli stadi III

al GIC polmone

Cosa cambierà…

PACIFIC: A DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III STUDY OF DURVALUMAB AFTER CHEMORADIATION THERAPY IN PATIENTS WITH STAGE III, LOCALLY ADVANCED, UNRESECTABLE NSCLC

Luis Paz-Ares[1], Augusto Villegas[2], Davey Daniel[3], David Vicente[4], Shuji Murakami[5], Rina Hui[6], Takashi Yokoi[7], Alberto Chiappori[8], Ki Hyeong Lee[9], Maike de Wit[10], Byoung Chul Cho[11], Maryam Bourhaba[12], Xavier Quantin[13], Takaaki Tokito[14], Tarek Mekhail[15], David Planchard[16], Haiyi Jiang[17], Yifan Huang[17], Phillip A. Dennis[17], Mustafa Özgüroğlu[18]

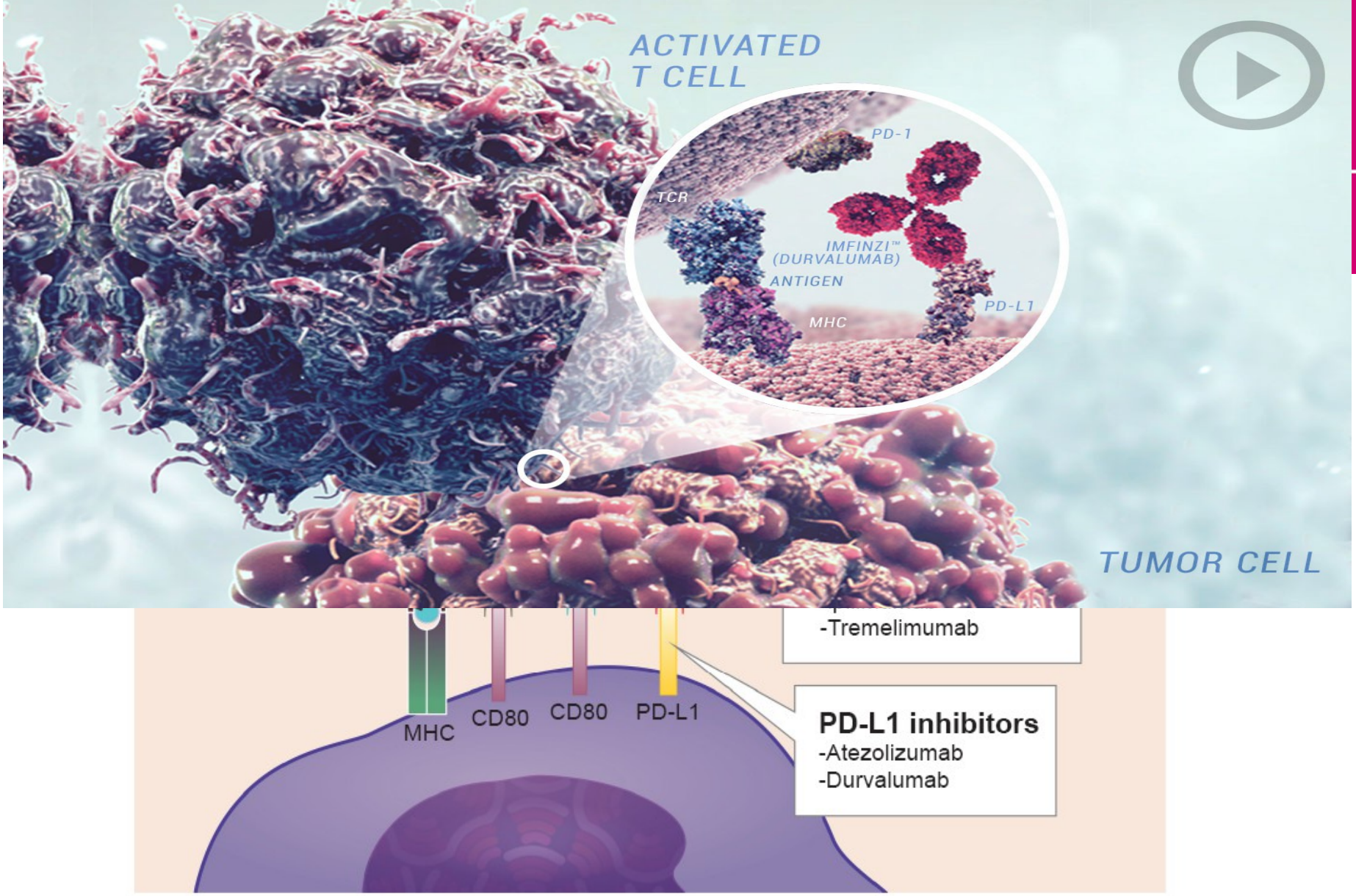

Figure 2 Mechanism of action of immune checkpoint inhibitors.

Notes: T_{regs} depend on the activity of CTLA-4, PD-1, and PD-L1 to induce immunosuppression. Ipilimumab and tremelimumab are monoclonal antibodies that inhibit CTLA-4, while nivolumab, pembrolizumab, atezolizumab, and durvalumab inhibit PD-1 and PD-L1. These drugs act by reducing immuno checkpoint activity on a T_{reg}-rich microenvironment, thus diminishing tumor evasion.

Abbreviations: T_{regs}, regulatory T-cells; TCR, T-cell receptor; MHC, major histocompatibility complex.

MADRID 2017 ESMO congress

PACIFIC: Study Design

Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- Patients with stage III, locally advanced, unresectable NSCLC

Durvalumab 10 mg/kg q2w for

Co-primary endpoints

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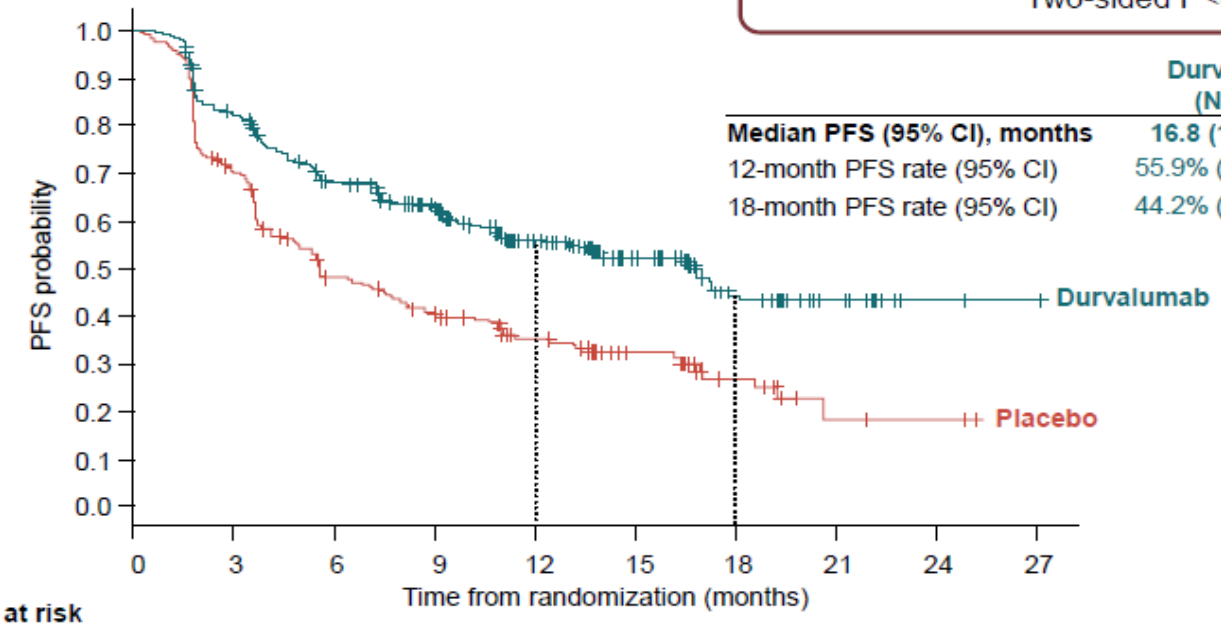
PFS by BICR (Primary Endpoint; ITT)

Stratified hazard ratio, 0.52 (95% CI, 0.42–0.65)
Two-sided P<0.0001

	Durvalumab (N=476)	Placebo (N=237)
Median PFS (95% CI), months	**16.8 (13.0–18.1)**	**5.6 (4.6–7.8)**
12-month PFS rate (95% CI)	55.9% (51.0–60.4)	35.3% (29.0–41.7)
18-month PFS rate (95% CI)	44.2% (37.7–50.5)	27.0% (19.9–34.5)



No. at risk										
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

Interim Analysis

Median follow-up:

14.5 months

(range 0.2–29.9)

BICR, blinded independent central review; CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival

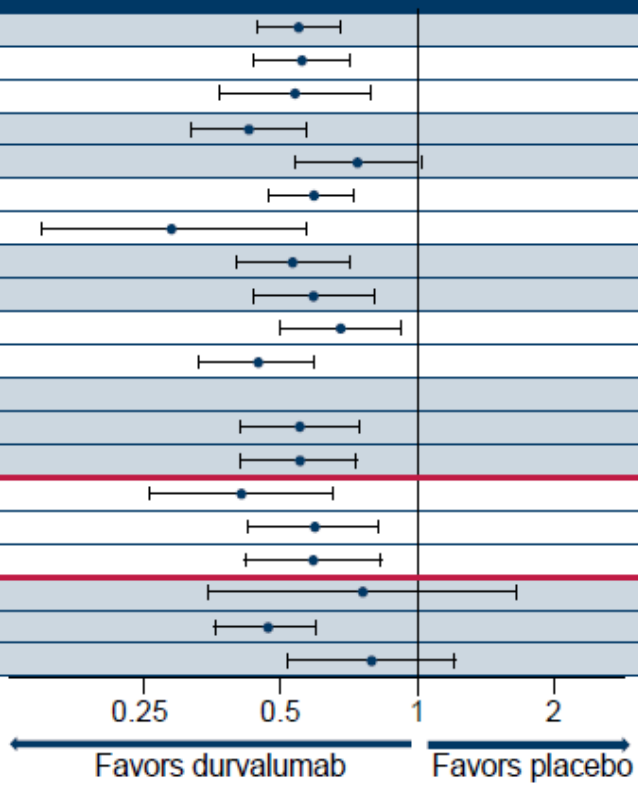
Other Outcomes

Objective Response

Time to Distant Metastasis or Death by BICR (ITT)

PFS Subgroup Analysis by BICR (ITT)

		Durvalumab No. of patients	Placebo No. of patients	Unstratified HR* (95% CI)
	All patients	476	237	0.55 (0.45–0.68)
Sex	Male	334	166	0.56 (0.44–0.71)
	Female	142	71	0.54 (0.37–0.79)
Age at randomization	<65 years	261	130	0.43 (0.32–0.57)
	≥65 years	215	107	0.74 (0.54–1.01)
Smoking status	Smoker	433	216	0.59 (0.47–0.73)
	Non-smoker	43	21	0.29 (0.15–0.57)
Disease stage	Stage IIIA	252	125	0.53 (0.40–0.71)
	Stage IIIB	212	107	0.59 (0.44–0.80)
Histology	Squamous	224	102	0.68 (0.50–0.92)
	Non-squamous	252	135	0.45 (0.33–0.59)
Best response to cCRT	CR	9	7	–
	PR	232	111	0.55 (0.41–0.75)
	SD	222	114	0.55 (0.41–0.74)
PD-L1 status	≥25%	115	44	0.41 (0.26–0.65)
	<25%	187	105	0.59 (0.43–0.82)
	Unknown	174	88	0.59 (0.42–0.83)
EGFR status	Mutant	29	14	0.76 (0.35–1.64)
	Wild-type	315	165	0.47 (0.36–0.60)
	Unknown	132	58	0.79 (0.52–1.20)



*Hazard ratio and 95% CI not calculated if the subgroup has less than 20 events.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; HR, hazard ratio; ITT, intention-to-treat; EGFR, epidermal growth factor receptor

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NSCLC
Advanced stage

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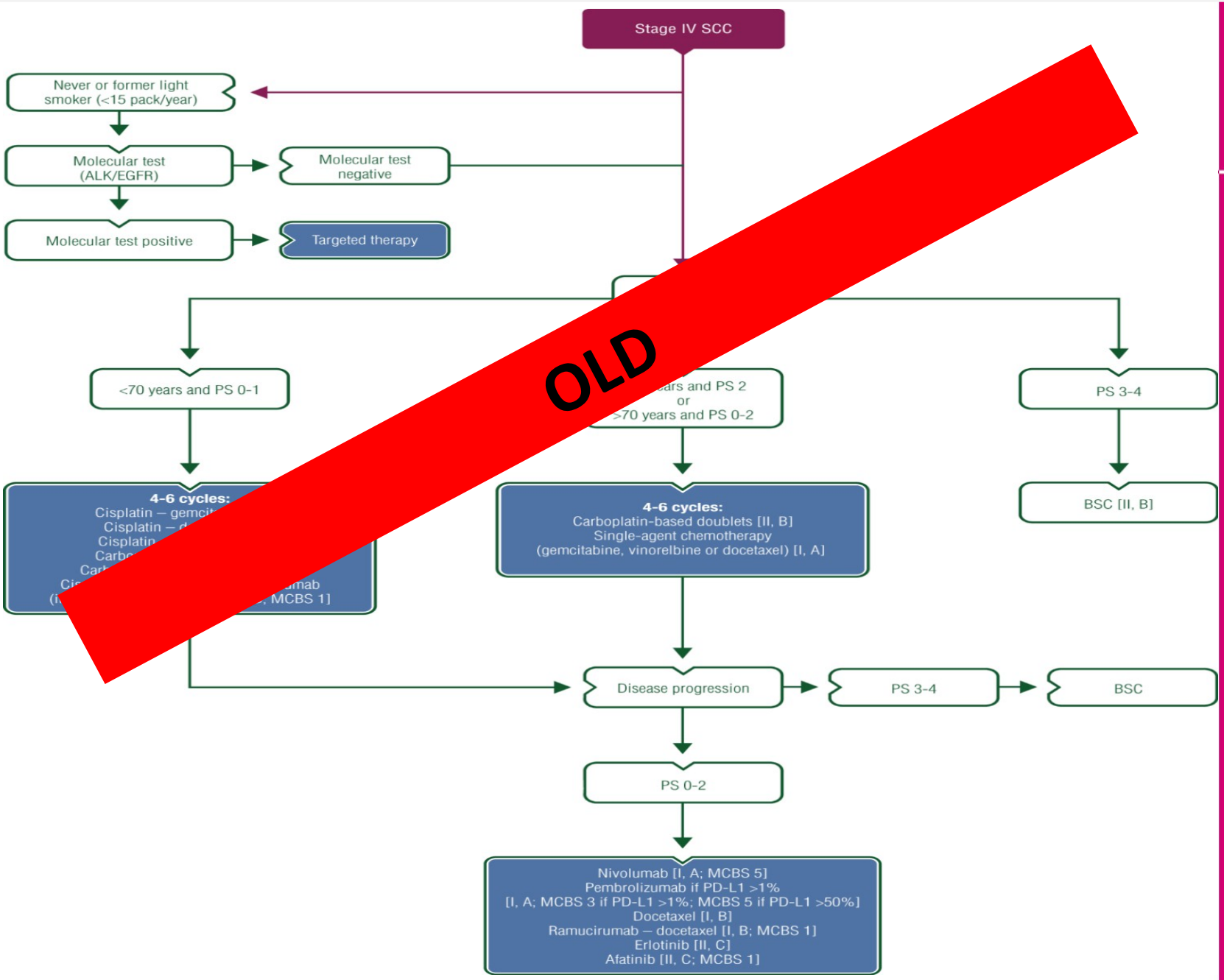
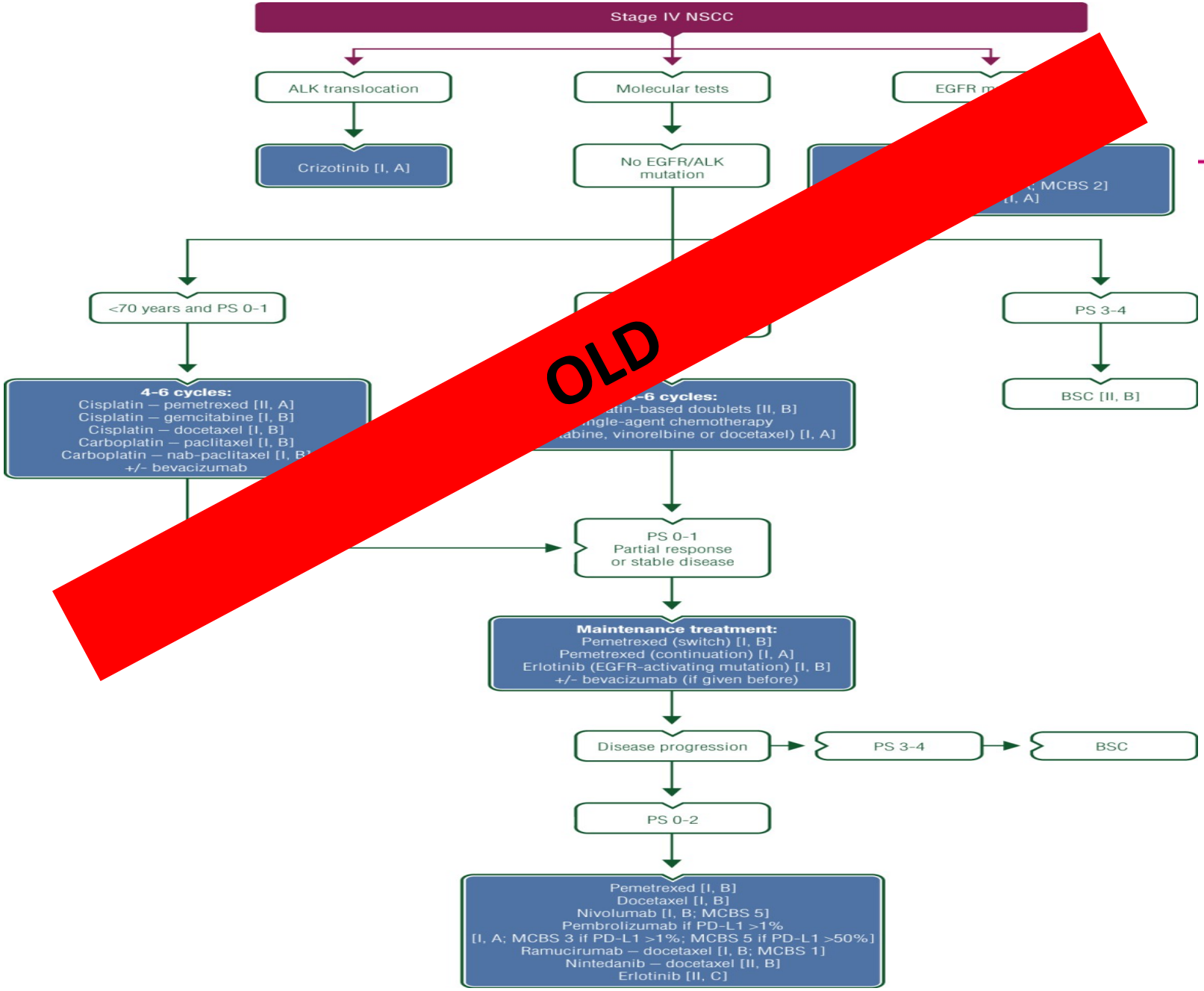


Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†Ann Oncol. 2016;27(suppl_5):v1-v27. doi:10.1093/annonc/mdw326



Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†Ann Oncol. 2016;27(suppl_5):v1-v27. doi:10.1093/annonc/mdw326

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Terapia della malattia metastatica.. in evoluzione

<u>Indicazione a richiedere mutazioni EGFR:</u>

Adenocarcinoma
Carcinoma a grandi cellule
Carcinoma misto con cellule di adenocarcinoma
Carcinoma NAS

<u>Indicazione a richiedere riarrangiamento di ALK:</u>

Adenocarcinoma
Carcinoma a grandi cellule
Carcinoma misto con cellule di adenocarcinoma
Carcinoma NAS

<u>Indicazione a richiedere determinazione PD-L1:</u>

Tutte le istologie

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ORIGINAL ARTICLE

First-Line Nivolum
Cell Lung Ca

Studio ne

David P. Carb M.D., Ph.D., Luis
M.D., Ma queta Felip, M.D., Michel
M.D., Firas Ready, M.D., T. Jeroen N. Hilter
M.D., Ph.D., eters, M.D., Ph.D., Elisa Minenza, M.D.
M.D., Hossein Borghaei, D.O., George R. Blumenschein, Jr., M
Krejci, M.D., Jesus Corral Jaime, M.D., Han Chang, Ph.D., Wil
Ph.D., Allen C. Chen, M.D., and Mark A. Socinski, M.D., for the
N Engl J Med 2017; 376:2415-2426 | June 22, 2017 | DOI: 10.1

BACKGROUND

Nivolumab has been associated with longer overall su
docetaxel among patients with previously treated non-
cancer (NSCLC). In an open-label phase 3 trial, we co

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ORIGINAL ARTICLE

Pembrolizumab versus Chemotherapy f itive Non–Small-Cell Lung Cancer

Studio positivo

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abre M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya G Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., R and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*

N Engl J Med ember 10, 2016 | DOI: 10.1056/NEJMoa1606774

Comments (gn November 16, 2016

Share:

Abstract | Article | References | Citing Articles (386) | Comments (1) | Letters | Metrics

Approximately 23 to 28% of patients with advanced non–small-cell lung cancer (NSCLC) have a high level of programmed death ligand 1 (PD-L1) expression, which is defined as membranous PD-L1 expression on at least 50% of tumor cells, regardless of the staining intensity (i.e., a PD-L1 tumor proportion score of 50% or greater).[1,2] Data from the phase 1 KEYNOTE-001 and phase 3 KEYNOTE-010 studies indicated that patients with advanced NSCLC and a PD-L1 tumor proportion score of 50% or greater were more likely than those with lower tumor proportion scores to have a response to pembrolizumab, a highly selective, humanized monoclonal antibody against programmed death 1 (PD-1) that prevents PD-1 from engaging PD-L1 and PD-L2.[1-3]

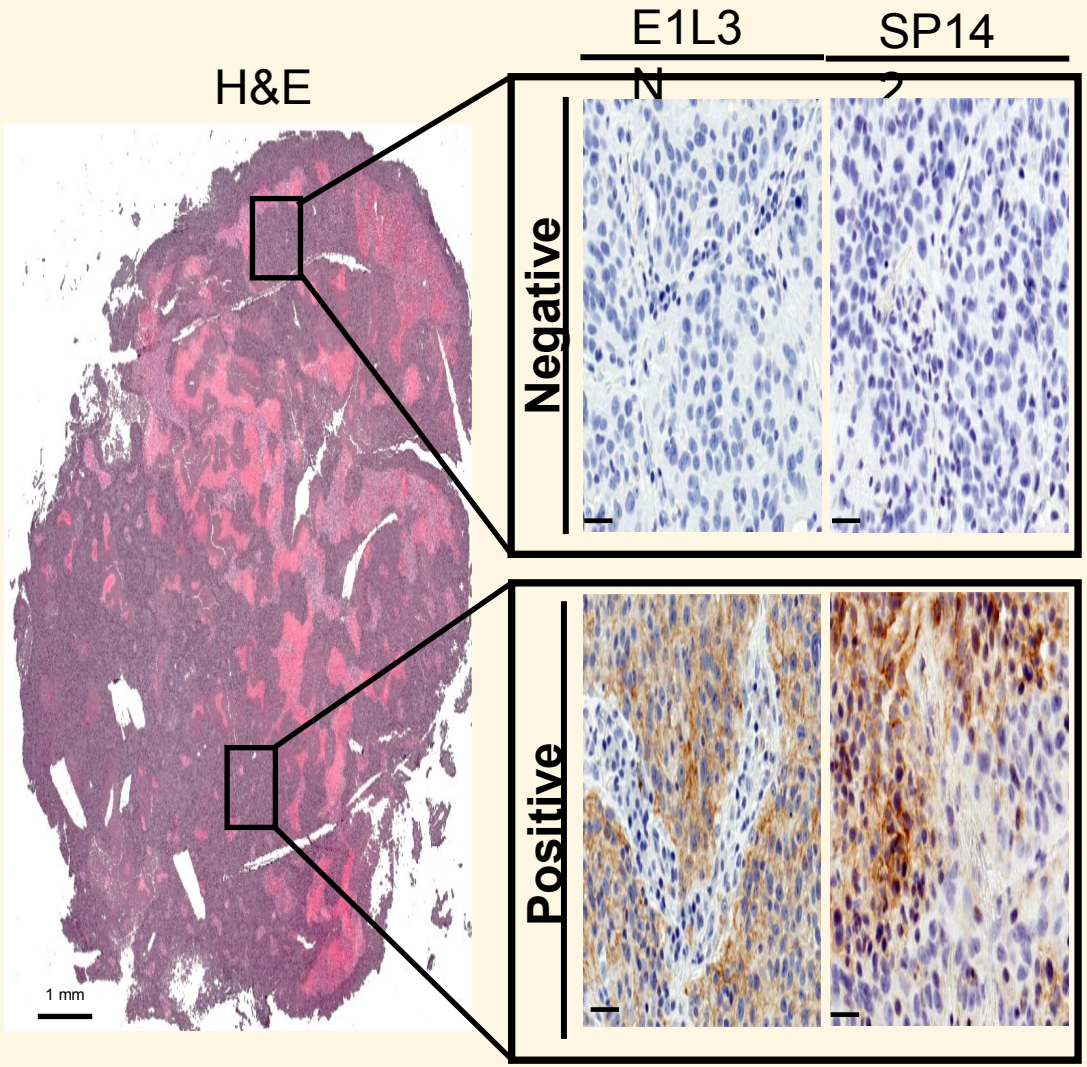
CheckMate 026 vs. Keynote 024

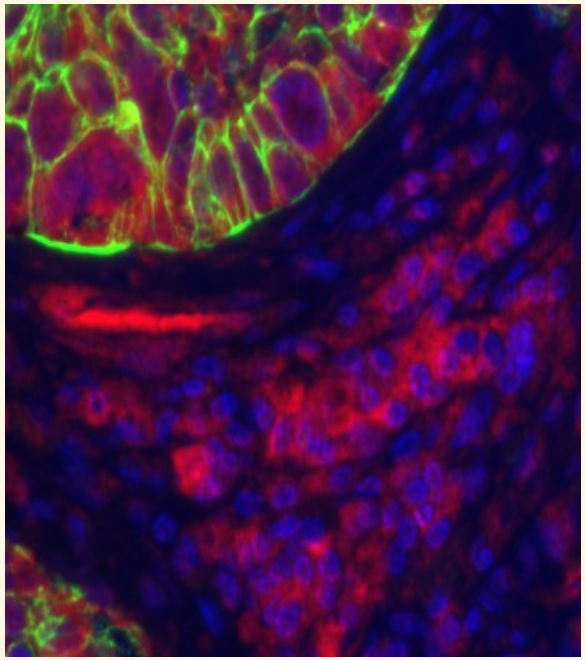
	Keynote 024	CheckMate 026
Tumor biopsy	After metastatic diagnosis	Within 6 months
PD-L1 cut off	50% (22C3 clone)	5% (28-8 clone)
Prevalence	30%	50%
Imaging interval	Q 9 weeks	Q 6 weeks for first 48 weeks
Primary endpoint	PFS (RECIST)	PFS (IRRC)
Never smokers (PD-1)	3%	11%
Squamous histology	19%	24%
Time from diagnosis to treatment	?	2 months
Prior radiation	? [1]	37.6 %

[1] Prior radiation therapy of > 30 Gy disallowed within 6 months of first dose of trial treatment

Socinski et al, ESMO 2016
Reck et al, ESMO 2016, NEJM 2016

PD-L1 presenta espressione eterogenea e varia sulla base dell'anticorpo utiilizzato





Immunofluorescence shows stroma and epithelial staining are often concordant and adjacent

Green = Cytokeratin

Blue = Nuclei

Red = PD-L1 (SP142)

McLaughlin, K Schalper, R. Herbst and D Rimm (Yale Pathology)

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Predittori di beneficio – work in progress

- **Score di PD-L1**

- **Mutational burden:**
  - minore in pazienti con mutazioni attivanti di EGFR e/o riarrangiamento di ALK

- **Fumo di sigaretta (al momento indicatore surrogato del mutational burden):**
  - forti fumatori
  - lungo periodo di esposizione al fumo di sigaretta

Mark G. Kris mmunotherapy as First-Line Lung Cancer Treatment? Weighing Benefit Is Key in Deciding. Medscape Dec 2016

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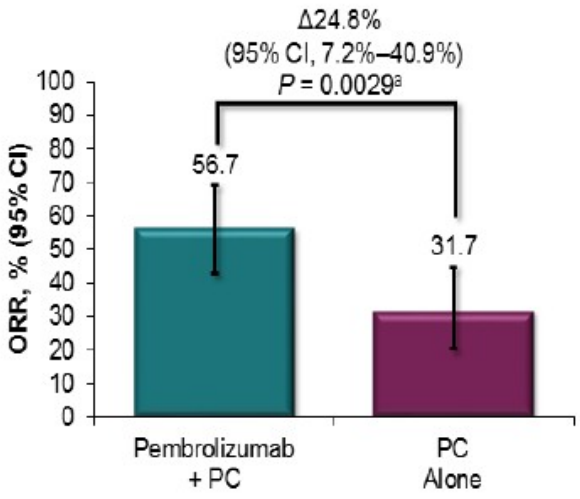
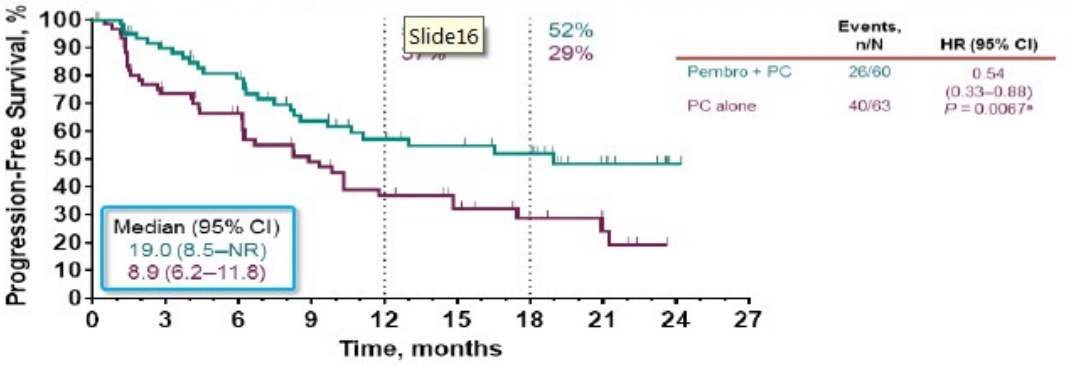
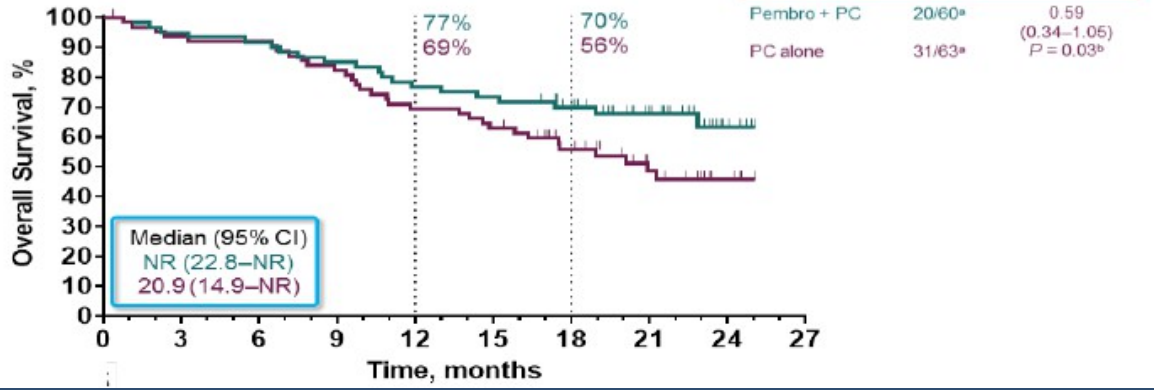
Updated Results From KEYNOTE-021 Cohort G: A Randomized, Phase 2 Study of Pemetrexed and Carboplatin With or Without Pembrolizumab As First-Line Therapy for Advanced Nonsquamous Non–Small-Cell Lung Cancer



Progression-Free Survival (RECIST v1.1 by Blinded, Independent Central Review)



Overall Survival



Borghaei ESMO 2017

Segnalazioni per neurochirurghi e radioterapisti

✓I trials clinici di immunoterapia hanno escluso generalmente pazienti con metastasi sintomatiche o per i quali risultava necessaria una terapia con corticosteroidi.

✓Non siano ancora del tutto allenati al management delle complicazioni da immunoterapia quali edema, necrosi tumorale, in sede encefalica.

✓Non conosciamo il ruolo effettivo dell'immunoterapia nelle metastasi encefaliche.

Ulahannan et al. Ann Oncol 2017

Phase II Trial of Pembrolizumab for Untreated Brain Metastases

Key Eligibility:
- Advanced NSCLC or melanoma
- At least 1 untreated or progressive brain metastasis 5-20mm
- No neurologic symptoms or steroid requirement
- PS 0-1
- PD-L1 expression after the most recent systemic therapy

Pembrolizumab 10mg/kg q2 weeks

Brain metastasis PD → **Consider radiation or surgery to progressing lesions**

Brain metastasis CR, PR, or SD → **Continue pembrolizumab if systemic control achieved**

Safety evaluation at 4 weeks:
- Brain MRI

Response evaluation every 8 weeks:
- Brain MRI
- CT chest/abdomen/pelvis

Primary Endpoint:
Brain Metastasis Response Rate

Secondary Endpoints:
Overall response rate, safety, PFS, OS

- Brain metastasis response by modified RECIST allows up to 5 target lesions with diameter ≥5mm
- Data presented from an interim analysis with cut-off date June 30, 2015

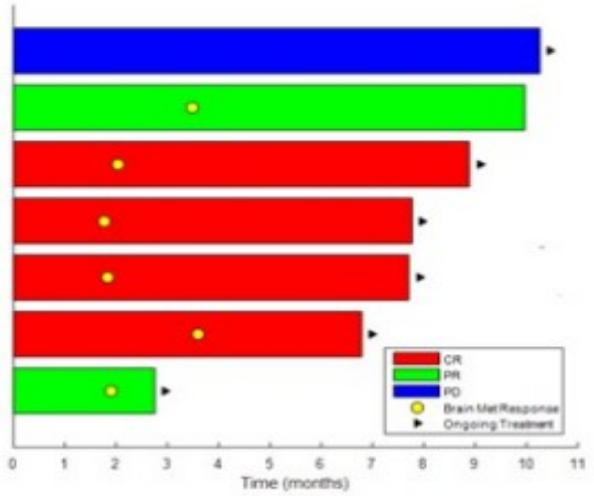
Sarah B. Goldberg, et al; WCLC 2015, ORAL 31

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

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

Phase II Trial of Pembrolizumab for Untreated Brain Metastases

Total evaluable patients	Brain Metastasis Responses (CR + PR)			Duration of BrM Response	Systemic Responses (CR + PR)		
N	No. of patients	%	95% CI	Individual duration (months)	No. of patients	%	95% CI
18	6*	33	0.14-0.59	3.2+, 6.0+, 6.1+, 6.6, 7.0+	6	33	0.14-0.59



Sarah B. Goldberg , et al; WCLC 2015, ORAL 31

- ✓Elevatissima selezione della popolazione,
- ✓Tempo tra somministrazione di pembro ed RT non specificato,
- ✓Dati positivi ma necessari ulteriori approfondimenti.

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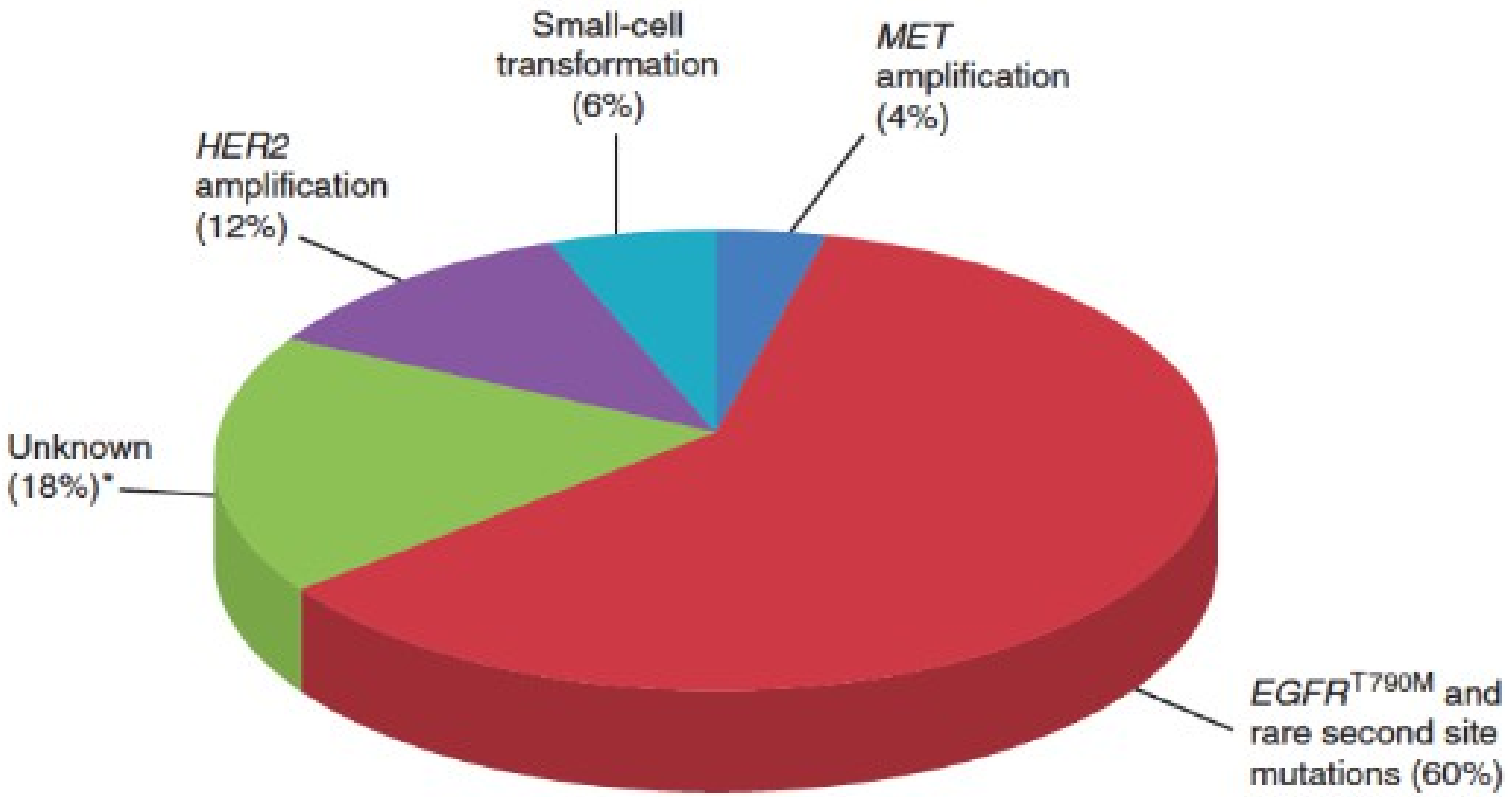
Algoritmo in pazienti oncogene-addicted



Takezawa et al. Cancer Discovery 2012

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Algoritmo in pazienti oncogene-addicted

NSCLC oncogene-addicted trattati con TKI

Oligo-Progressione

Progressione sistemica

Eventuale Terapia locale e prosecuzione di trattamento sistemico

PD Sistemica

Re-biopsia solida o liquida

Trattamento conseguente

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Biopsia liquida

✓La percentuale di concordanza dipende dal metodo utilizzato ,

✓La modalità di acquisizione del campione può influenzare i risultati dell'analisi,

✓Sono stati riportati esiti differenti tra l'analisi delle cellule tumorali circolanti e l'analisi su tessuto,

✓Secondo alcuni studi la sensibilità del test si attesta al 67.4% e la specificità al 93.5%.

Segnalazioni per i radiologi

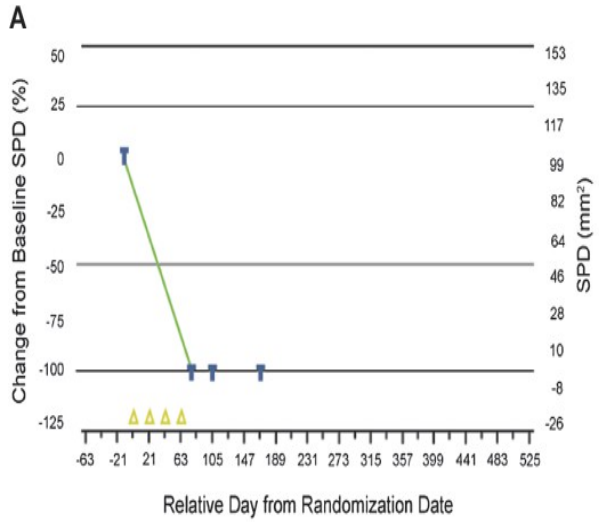
Comparison: RECIST-irRC criteria

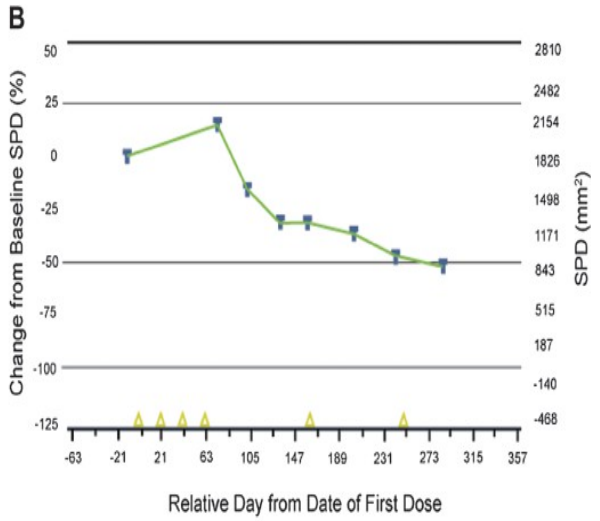
	RECIST	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
Complete Response (CR)	Disappearance of all extranodal target lesions. All pathological lymph nodes must have decreased to <10 mm in short axis.	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
Partial Response (PR)	At least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
Progressive Disease (PD)	SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) The SLD must also demonstrate an absolute increase of at least 5 mm. (Two lesions increasing from 2 mm to 3 mm, for example, does not qualify)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

Valutazione della risposta

A –B pattern di risposta convenzionali
C-E- pattern di risposta con immunoterapia

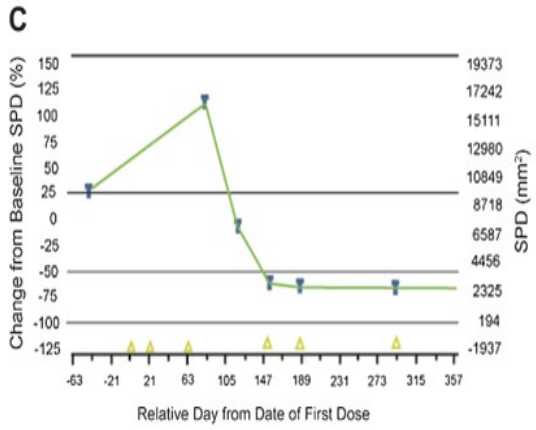
Risposta rapida

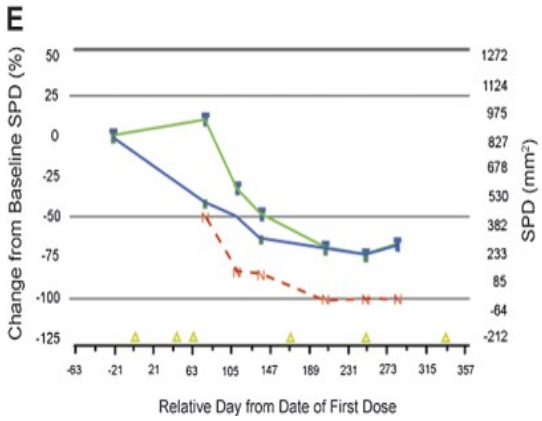




Risposta durevole con progressiva riduzione della massa tumorale

Incremento della quota tumorale seguita da risposta





Lesione esistente al baseline (blu) e nuove lesioni (rosse). Quota tumorale definitiva (verdi). Nonostante le nuove lesioni, la quota tumorale definitiva è in progressiva riduzione

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Grazie

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