L'immunoterapia nel tumore del polmone

Francesco Cognetti

Roma, 21 Settembre 2018

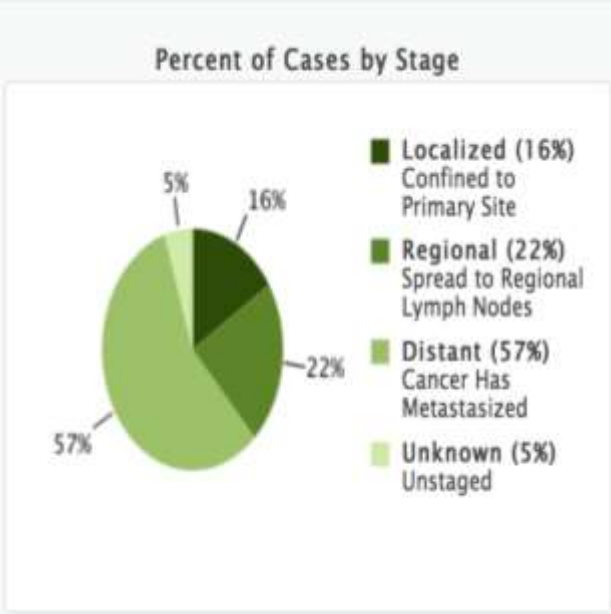
Le dimensioni del problema 2018

US Data

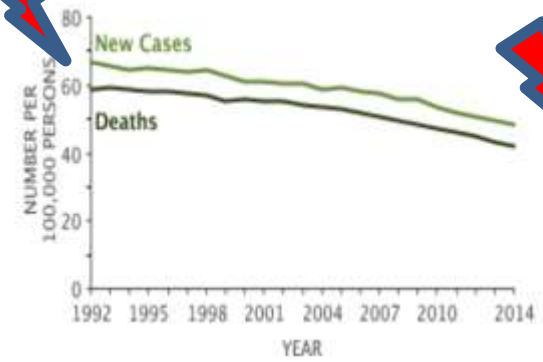
	Common Types of Cancer	Estimated New Cases 2017	Estimated Deaths 2017
1.	Breast Cancer (Female)	252,710	40,610
2.	**Lung and Bronchus Cancer**	**222,500**	**155,870**
3.	Prostate Cancer	161,360	26,730
4.	Colorectal Cancer	135,430	50,260
5.	Melanoma of the Skin	87,110	9,730
6.	Bladder Cancer	79,030	16,870
7.	Non-Hodgkin Lymphoma	72,240	20,140
8.	Kidney and Renal Pelvis Cancer	63,990	14,400
9.	Leukemia	62,130	24,500
10.	Uterine Cancer	61,380	10,920

Lung and bronchus cancer represents 13.2% of all new cancer cases in the U.S.

13.2%



Estimated New Cases in 2017	222,500
% of All New Cancer Cases	13.2%
Estimated Deaths in 2017	155,870
% of All Cancer Deaths	25.9%



Percent Surviving 5 Years
18.1%
2007-2013

https://seer.cancer.gov/statfacts/html/lungb.html

Fonte: I numeri del cancro in Italia, AIOM-AIRTUM, 2017, www.aiom

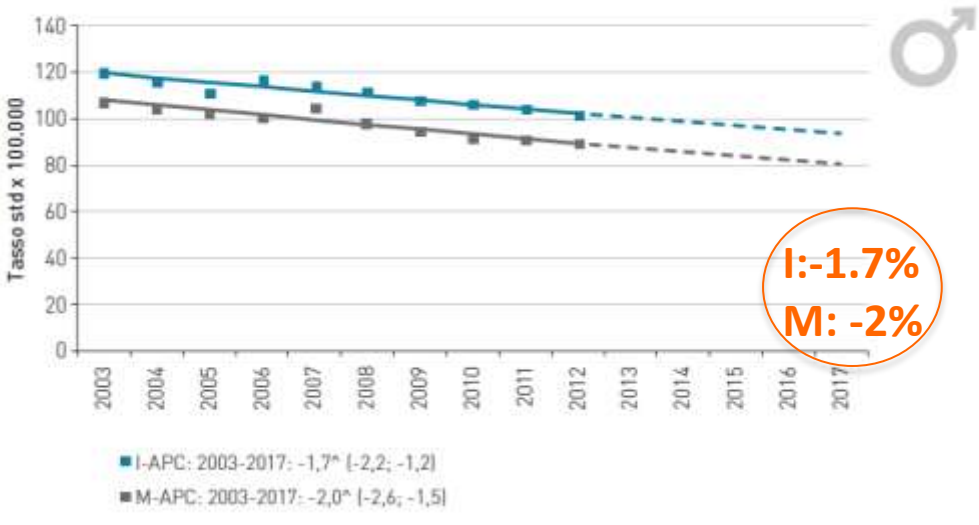
Primi cinque tumori più frequentemente diagnosticati

Rango	Maschi	Femmine	Tutta la popolazione
1°	Prostata (18%)	Mammella (28%)	Colon-retto (14%)
2°	Colon-retto (16%)	Colon-retto (13%)	Mammella (14%)
3°	Polmone (15%)	Polmone (8%)	Polmone (11%)
4°	Vescica* (11%)	Tiroide (6%)	Prostata (9%)
5°	Rene, vie urinarie** (5%)	Utero corpo (5%)	Vescica* (7%)

Prime cinque cause di morte oncologica

Rango	Maschi	Femmine	Tutta la popolazione
1°	Polmone (27%)	Mammella (17%)	Polmone (20%)
2°	Colon-retto (11%)	Colon-retto (12%)	Colon-retto (11%)
3°	Prostata (8%)	Polmone (11%)	Mammella (8%)
4°	Fegato (7%)	Pancreas (7%)	Stomaco (6%)
5°	Stomaco (6%)	Stomaco (6%)	Pancreas (6%)

Dati Italiani (incidenza e mortalità)



I:-1.7%
M: -2%

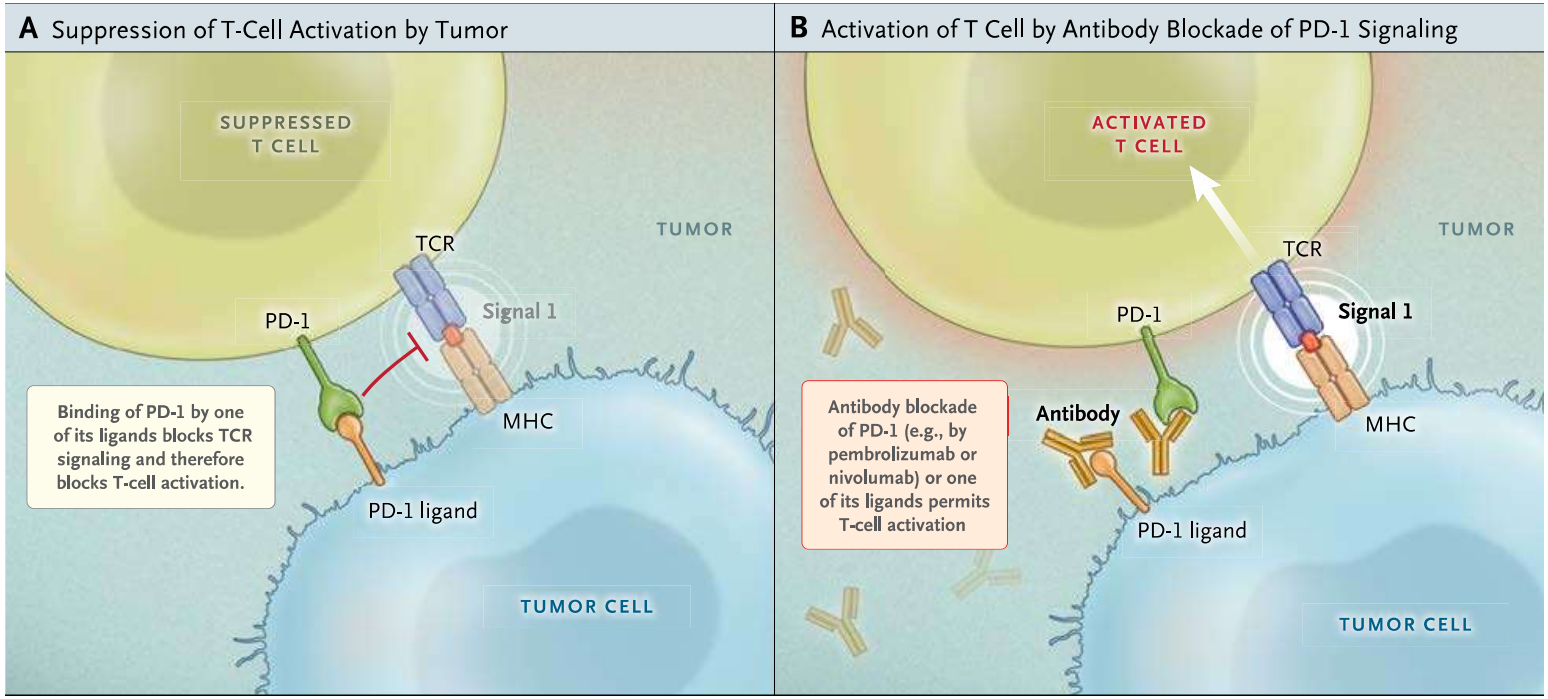
- 41.800 NUOVI casi/anno (su 369.000)
- **prima causa di morte oncologica in tutte le fasce di età negli uomini**: 14% dei decessi tra i giovani (0-49aa), 30% tra gli adulti (50-69 aa), 26% >70 aa

I: +3.1%
M:+2%

Background until 2015

- ✓ First line platinum based chemo has been standard treatment for a long decades 1990
- ✓ Maintenance chemotherapy with pemetrexed has became standard option for patient treated
- ✓ first line platinum based (either continuation or switch maintenance) JMEN e PARAMOUNT studies
- ✓ Bevacizumab is maintenance treatment after induction with carbo/paclitaxel ECOG 4599 2006
- ✓ Docetaxel has been established in the 1999 As standard second line therapy TAX 317
- ✓ Adding nintedanib tp docetaxel in second line setting prolongs PFS and OS in adenok population, especially in those progressing durind 9 months from starting first line LUME-LUNG1

2015

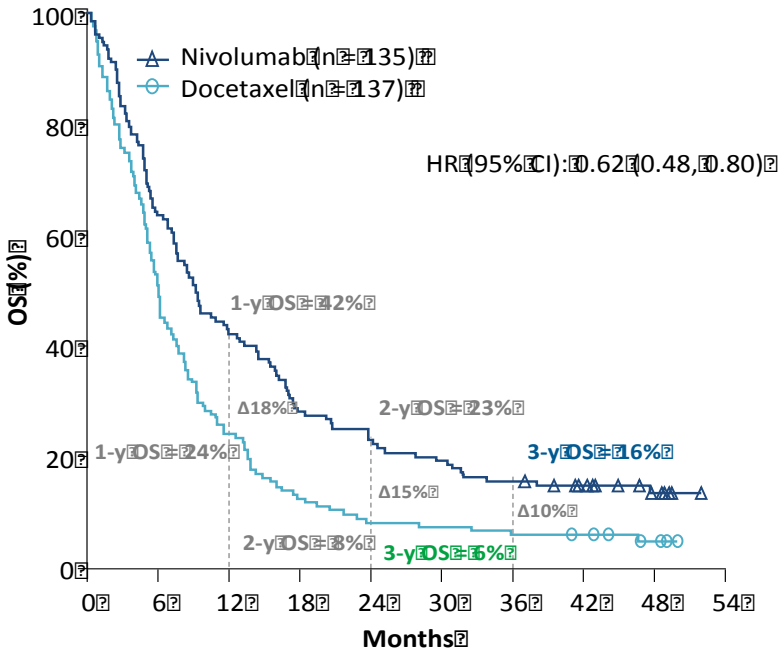

A Suppression of T-Cell Activation by Tumor
SUPPRESSED T CELL
TUMOR
TCR
PD-1
Signal 1
MHC
Binding of PD-1 by one of its ligands blocks TCR signaling and therefore blocks T-cell activation.
PD-1 ligand
TUMOR CELL
B Activation of T Cell by Antibody Blockade of PD-1 Signaling
ACTIVATED T CELL
TUMOR
TCR
PD-1
Signal 1
Antibody blockade of PD-1 (e.g., by pembrolizumab or nivolumab) or one of its ligands permits T-cell activation
Antibody
MHC
PD-1 ligand
TUMOR CELL

ORIGINAL ARTICLE

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

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

CheckMate 017 (SQ NSCLC)



No. of Patients at Risk

Nivolumab	135	86	57	38	31	26	21	16	8	0
Docetaxel	137	69	33	17	11	10	8	7	3	0

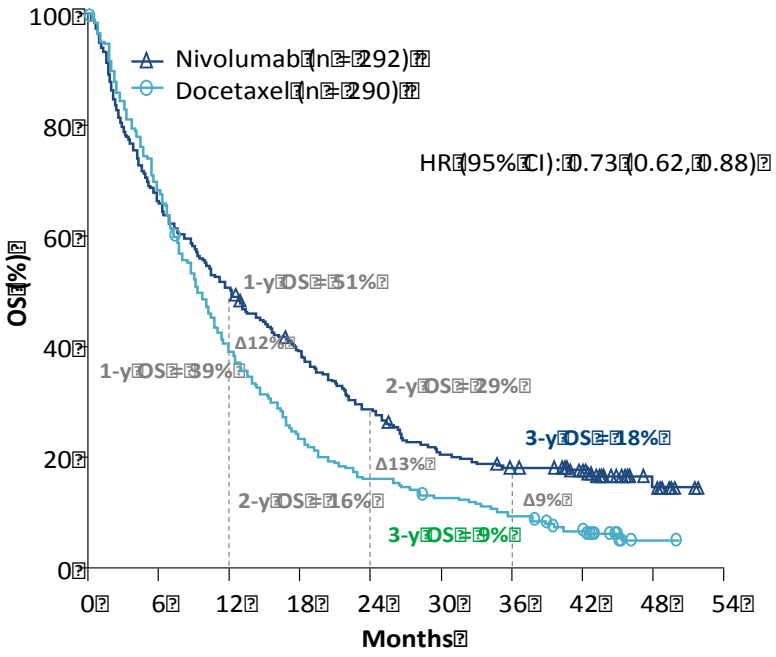
CI = confidence interval; HR = hazard ratio

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. Kohlhäufl, 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

CheckMate 057 (non-SQ NSCLC)



No. of Patients at Risk

Nivolumab	292	194	148	112	82	58	49	39	7	0
Docetaxel	290	195	112	67	46	35	26	16	1	0

3 YEARS OF FOLLOW-UP UPDATE

Courtesy of Silvia Novello

Blog

RX Factor

Cancro al polmone, la svolta: immunoterapia batte la chemio

L'**immunoterapia** con Pembrolizumab riduce il rischio di mortalità del 40% per chi è affetto da **tumore al polmone**. L'affermazione arriva dallo studio internazionale Keynote-024 presentato al Congresso della Società europea di oncologia medica. La cura è anche in grado di migliorare del 50% la sopravvivenza libera da progressione rispetto alla chemioterapia tradizionale a base di platino.

L'immunoterapia può dunque sostituire in via definitiva alla chemio per debellare il cancro al polmone? Ancora presto per dirlo con certezza ma quel che invece pare essere

OncoLine - Il canale di Oncologia

L'Europa approva l'immunoterapia per il tumore del polmone

DANIMARCA

Tumori, con nuova immunoterapia rischio di mortalità in calo del 40%

COPENAGHEN - Una stima di una riduzione del 40% del rischio di mortalità. Sono i risultati promettenti di una nuova cura di immunoterapia, che punta a stimolare il sistema immunitario contro il tumore, che utilizza la molecola pembrolizumab contro il cancro del polmone.

Lo studio, chiamato Keynote-024 e che ha coinvolto 305 pazienti, è stato presentato in sessione plenaria, data la sua rilevanza, al Congresso della Società europea di oncologia medica (Esmo) e contemporaneamente pubblicato sulla rivista The New England Journal Of Medicine.

«Uno studio importante - ha affermato Silvia Novello, professore associato di Oncologia Medica all'Università di Torino - che ha fatto registrare vantaggi enormi per i pazienti che esprimono la proteina PD-L1 sulle cellule tumorali, perché possono evitare le terapie tradizionali e la chemioterapia e accedere a farmaci innovativi con una tollerabilità migliore».

Non solo: «Sarà infatti possibile in questo modo razionalizzare le risorse, ottenendo risparmi per Servizio sanitario nazionale - conclude Novello - perché potremo trattare con il farmaco giusto i pazienti selezionati in base alla espressione di PD-L1 sulle cellule tumorali e continuare quindi il percorso nella medicina di precisione contro una neoplasia, quella del cancro al polmone, che in Italia nel 2016 registra più di 41 mila nuove diagnosi».

la Nuova Ferrara

IIS COPERNICO CARPEGGIANI - VIA PONTEGRADELLA 25

HOME › ITALIA MONDO › TUMORE AL POLMONE, NUOVA...

VAI ALLA PAGINA SU BENESSERE

BENESSERE & SALUTE

Tumore al polmone, nuova immunoterapia fa diminuire del 40% il rischio di morte

Potrà sostituire la chemioterapia. Il risultato secondo gli esperti promette di cambiare la lotta a questo tipo di neoplasia, terza per incidenza in Italia con più di 41mila nuove diagnosi stimate nel 2016

IMMUNO-ONCOLOGIA

Una nuova era nella lotta al cancro del polmone e della vescica

COPENAGHEN

Tumore polmone, con immunoterapia meno 40% rischio di morte

09/09/2016 - 19:30

Giornale di Puglia

Home » Attualità , Salute e benessere » Tumore polmone, con immunoterapia - 40% rischio di morte

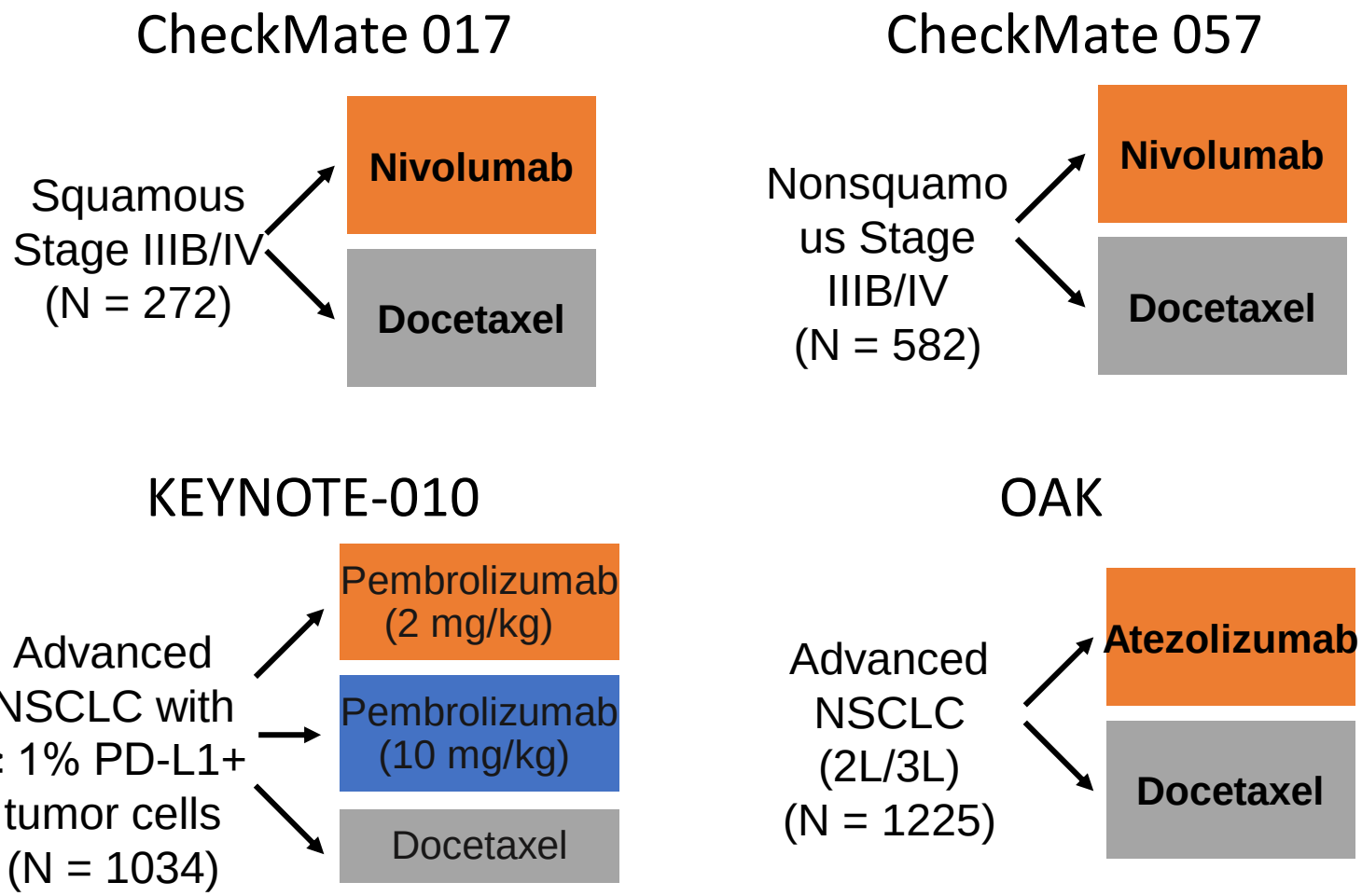
Tumore polmone, con immunoterapia - 40% rischio di morte

10/09/2016 07:12:00 PM - Nessun commento

Cancro al polmone: nuova immunoterapia riduce la mortalità del 40%

Courtesy of Silvia Novello

Immune Checkpoint Inhibitors in Pretreated Advanced NSCLC: Randomized Late-StageTrials



PDL-1

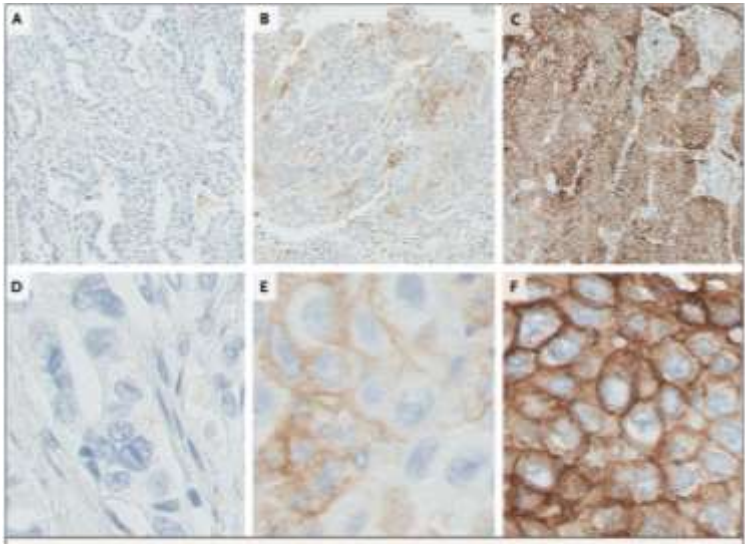
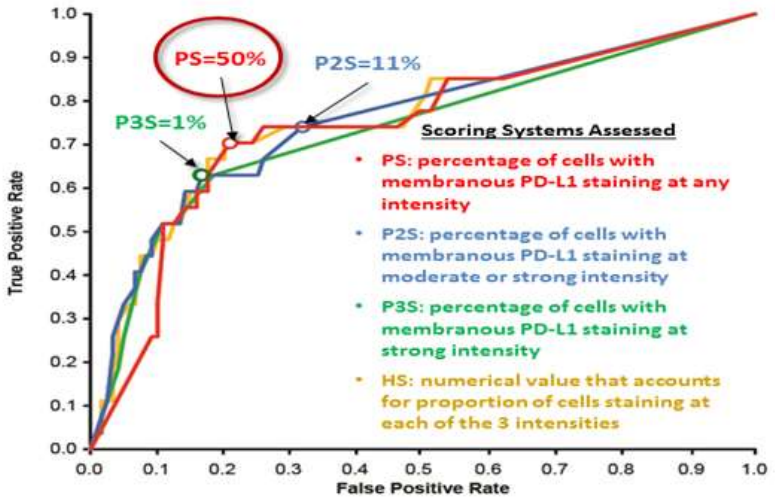


Figure 1. PD-L1 Expression in Non–Small-Cell Lung Cancers.

Results were reported as the percentage of neoplastic cells showing membranous staining of programmed cell death ligand 1 (PD-L1) (proportion score). Shown are tumor samples obtained from patients with a proportion score of 19% (Panel B), and a score of at least 50% (Panel C) (all at low magnification). g proportion scores are shown at a higher magnification in Panels D through ence of the brown chromogen. The blue color is the hematoxylin counterstain.

Training Set: Selection of PD-L1 Cutpoint and Scoring System Using a Clinical Trial IHC Assay



- Clinical trial assay (CTA) used same 22C3 antibody as prototype assay
- Cutpoint selection based on irRC by investigator review
  - Results confirmed using RECIST v1.1 by central review
- Choice of PS ≥50% based on:
  - Correlation with the Youden index
  - Ease of use
- Predictive value not improved by incorporating inflammatory T cells
- At time of cutpoint selection, 30.1% had PS ≥50%
  - 45.5% ORR per investigator irRC
  - 36.6% ORR per central RECIST v1.1

HS, H score; PS, proportion score; P2S, proportion score 2+ or 3+; P3S, proportion score 3+.

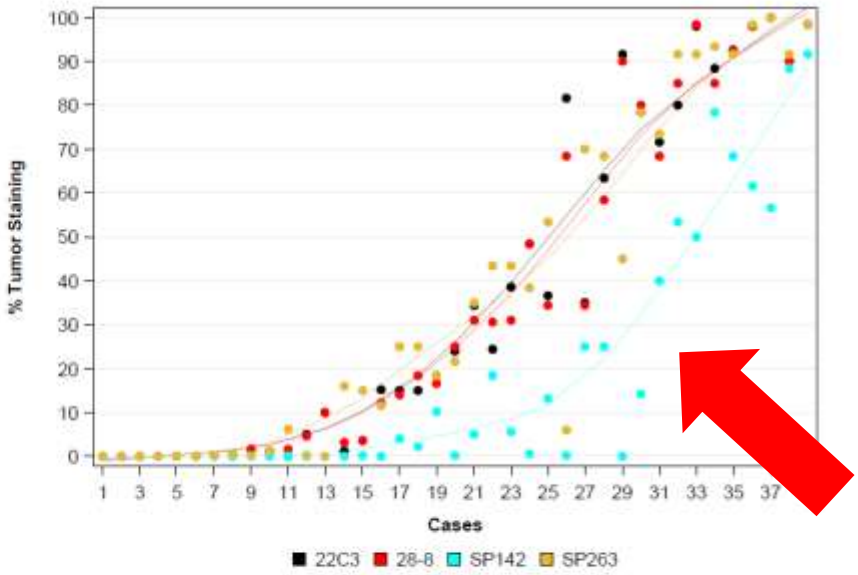
Garon_AACR 2015_18Apr15

Garon et al. N Engl J Med 2015;372:2018–2028

SOLO IL VENTANA SP142 SEMBRA DIVERSO SULLE CELLULE TUMORALI

Analytical Evaluation Results: Mean Tumor Proportion Score (TPS) per case based on three readers

- Analytical comparison of % tumor cell staining (Tumor Proportion Score), by case, for each assay
- Data points represent the mean score from three pathologists for each assay on each case
- Superimposed lines / points indicate identical TPS values
- No clinical diagnostic cut-off applied
- **Conclusion:** 3 of 4 assays are analytically similar for tumor cell staining.



Come “testare” immuno in prima linea?

SELEZIONANDO
(PDL1≥50%)

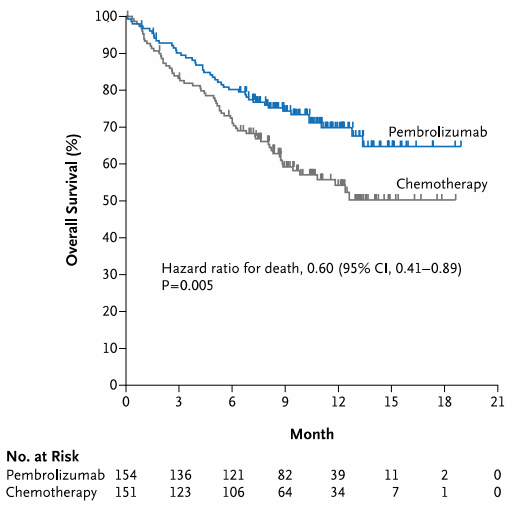
NON SELEZIONANDO
(PDL1≥1%)

KN024

The NEW ENGLAND JOURNAL of MEDICINE

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

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



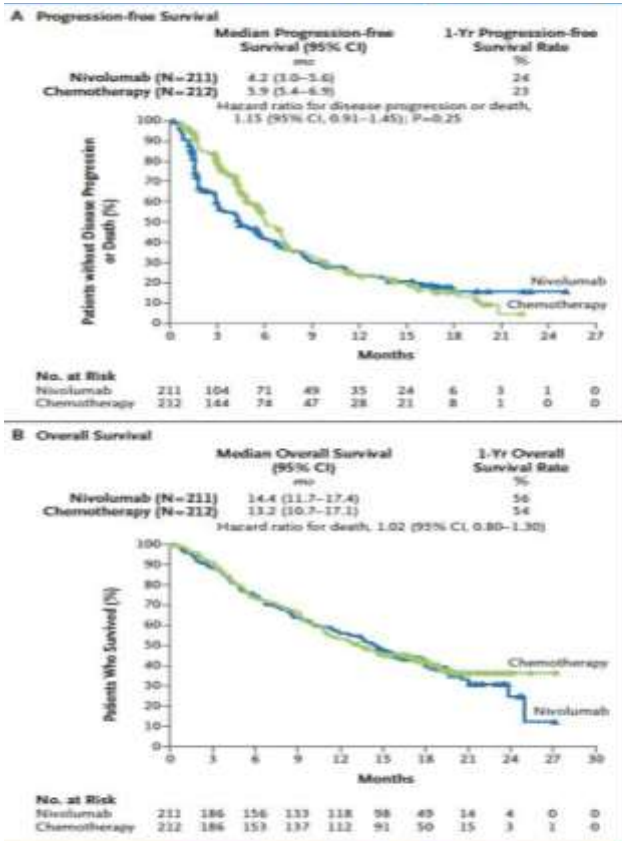
NOVEMBER 10, 2016

CM026

First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer

The NEW ENGLAND JOURNAL of MEDICINE

D.P. Carbone, M. Reck, L. Paz-Ares, B. Creelan, L. Horn, M. Steins, E. Felip, M.M. van den Heuvel, T.-E. Ciuleanu, F. Badin, N. Ready, T.J.N. Hiltermann, S. Nair, R. Juergens, S. Peters, F. Minenza, J.M. Wrangle, D. Rodriguez-Abreu, H. Borghaei, G.R. Blumenschein, Jr., L.C. Villaruz, M. Havel, J. Krejci, J. Corral Jaime, H. Chang, W.J. Geese, P. Bhagavatheeswaran, A.C. Chen, and M.A. Socinski, for the CheckMate 026 Investigators*

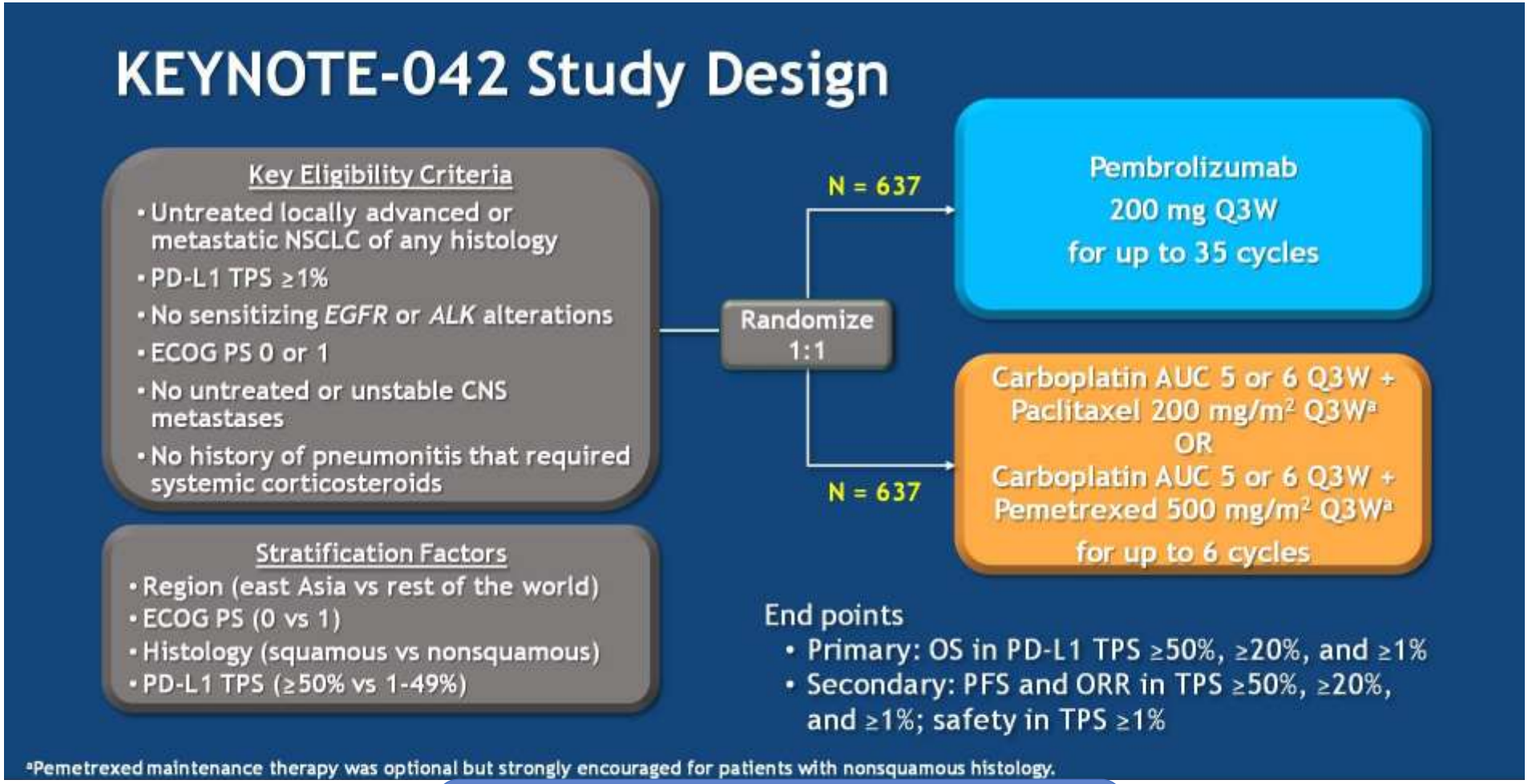


2017
KN024

NUOVO STANDARD I LINEA

(PDL-1 ≥50%)

La Plenaria all'ASCO ci ha detto che..
Se non selezioniamo per PDL-1≥50% l'immuno da sola non serve...



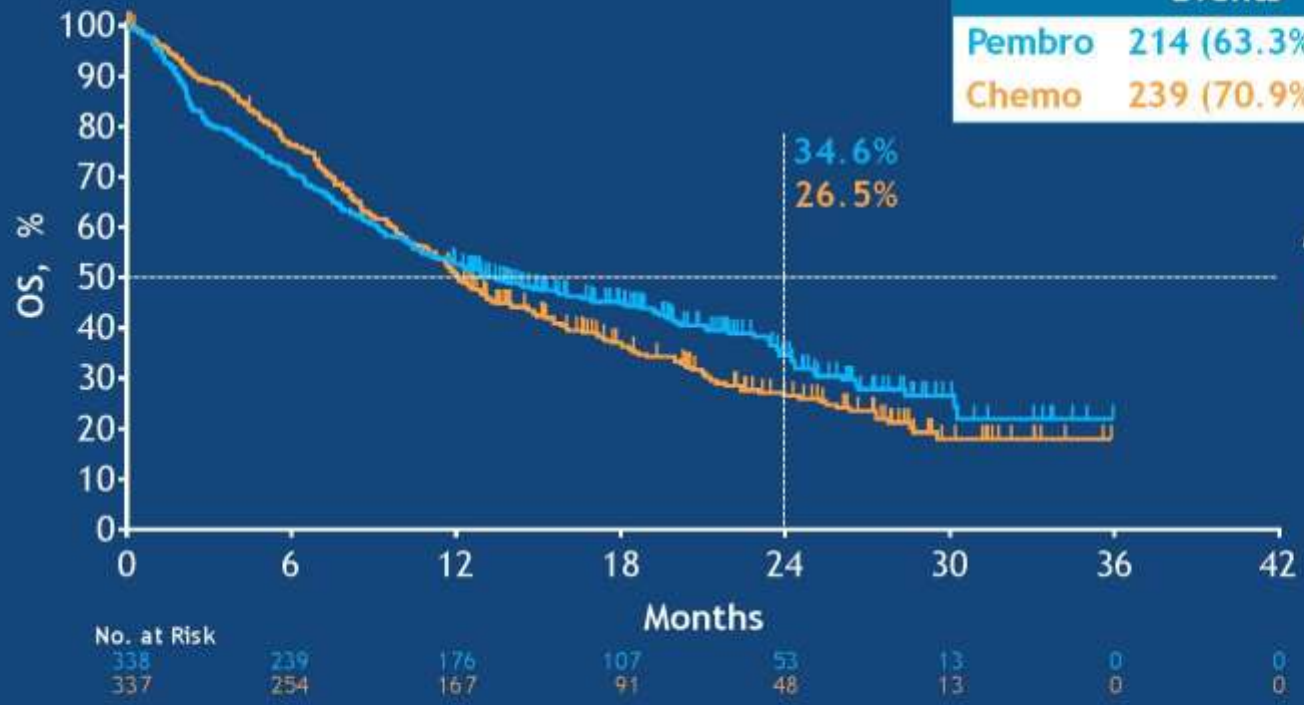
Cross over not allowed

Overall Survival: TPS ≥1%

	Events	HR (95% CI)	P
Pembro	371 (58.2%)	0.81 (0.71-0.93)	0.0018
Chemo	438 (68.8%)		

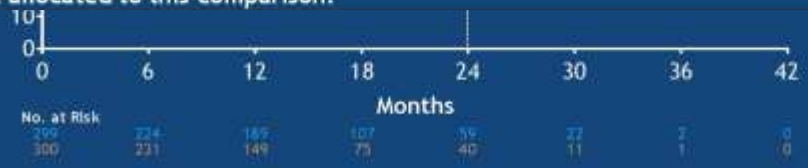
Overall Survival: TPS ≥1-49% (Exploratory Analysis[a])

	Events	HR (95% CI)
Pembro	214 (63.3%)	0.92 (0.77-1.11)
Chemo	239 (70.9%)	

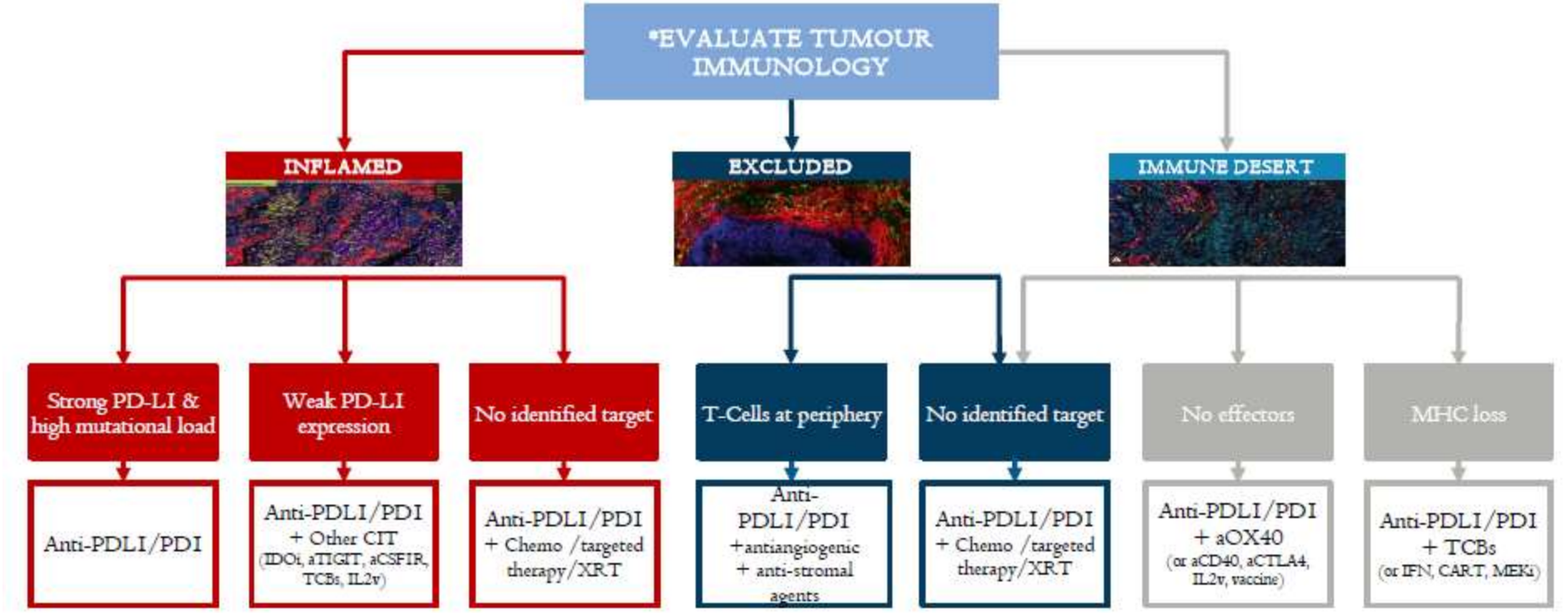


Median (95% CI)
13.4 mo (10.7-18.2)
12.1 mo (11.0-14.0)

[a]No alpha allocated to this comparison.



Precision IO? *(Modif from Kim and Chen, Ann Oncol 2016)*

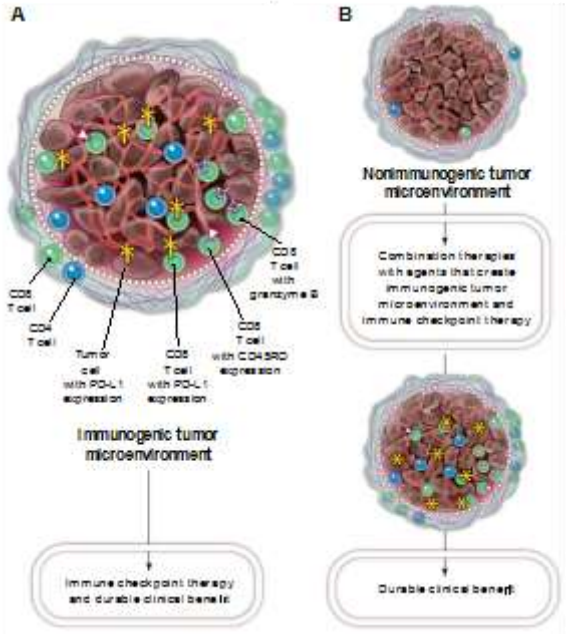


NOVITA' 2018: AACR & ASCO

PDL-1 ≥1%

Any histology

Keynote 042



PDL-1 <1%
PDL-1>1%

TMB

Any histology

Checkmate 227

ALL COMERS

Non-squamosi

Keynote 189

Impower 150

squamosi

Impower 131
Keynote 407

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

N ENGL J MED 378;22 NEJM.ORG MAY 31, 2018

Stratified by PD-L1 TPS (< 1% vs ≥ 1%), cisplatin vs carboplatin, smoking history (never vs former/current)

Patients with untreated stage IV nonsquamous NSCLC*; EGFR, ALK* neg; ECOG PS 0 or 1; any PD-L1 expression; no prior systemic treatment; no symptomatic brain metastases (N = 616)

Cisplatin 75 mg/m^2 or **Carboplatin AUC 5** + **Pemetrexed** 500 mg/m^2 + **Pembrolizumab** 200 mg Q3W for 4 cycles (n = 410)

Cisplatin 75 mg/m^2 or **Carboplatin AUC 5** + **Pemetrexed** 500 mg/m^2 + **Placebo** (normal saline) Q3W for 4 cycles (n = 206)

Maintenance

Pemetrexed 500 mg/m^2 Q3W + **Pembrolizumab** 200 mg Q3W for up to a total of 35 cycles

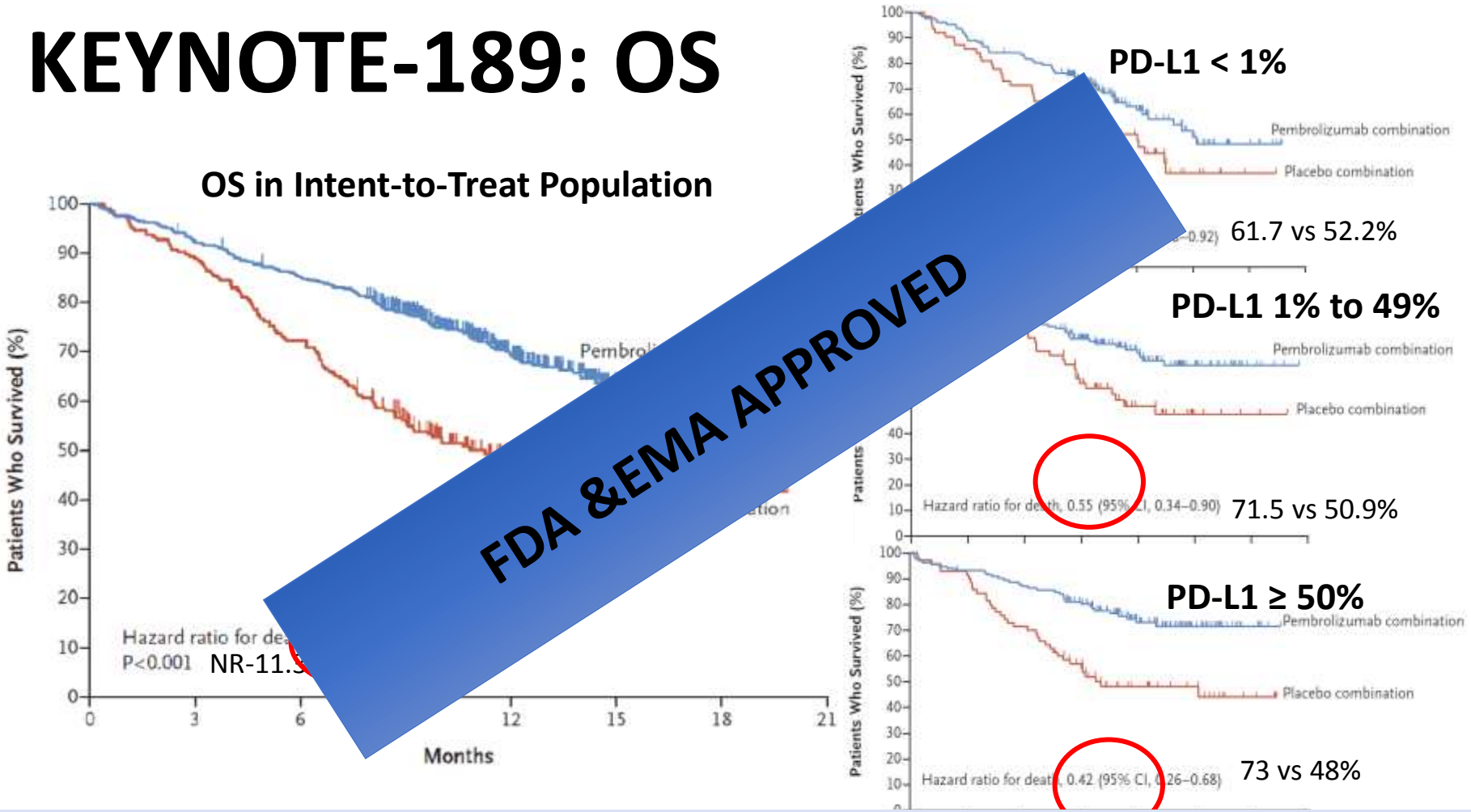
Pemetrexed 500 mg/m^2 + **Placebo** (normal saline) Q3W for up to a total of 35 cycles

PD

Pembrolizumab 200 mg Q3W for up to a total of 35 cycles

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

KEYNOTE-189: OS



Follow-up immaturo (mFU 10.5 mesi), OS ancora non raggiunta nel braccio sperimentale

Rimane un quesito importante: nei PDL-1≥50% è meglio chemio-immuno o immuno da sola?

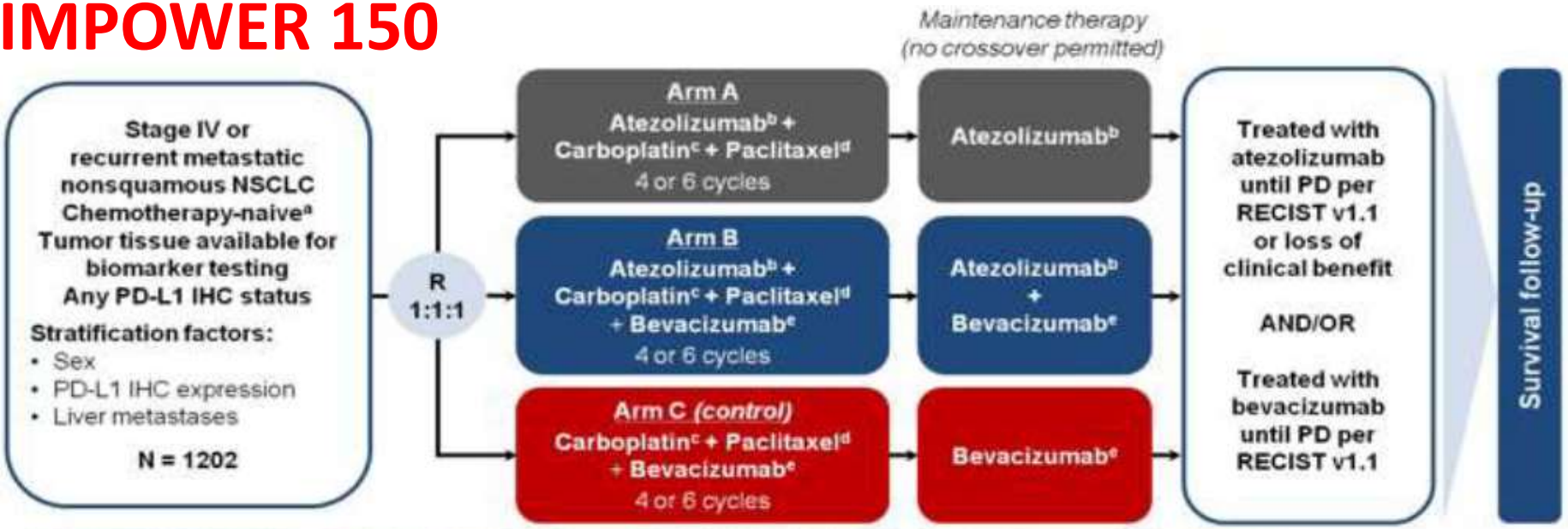
KN 189 SAFETY

- DISCONTINUATION because of sAEs was almost doubled in exp arm vs standard arm (13.8 vs 7.9 exp. Arm in induction part and 20.2 vs 10.4 in maintenance arm)
- HIGH number of deaths for Aes (27/405: 6.7% exp arm and 12/202: 5.9% standard arm)
- More frequent febrile neutropenia in pembrolizumab-arm
- Rash and diarrhoea >10% in pembro arm
- Acute kidney failure in 5.2 vs 0.5 arm (**additive** effect of platinum/pemetrexed/pembro?)
- 3 FATAL PNEUMONITIS in pembro arm

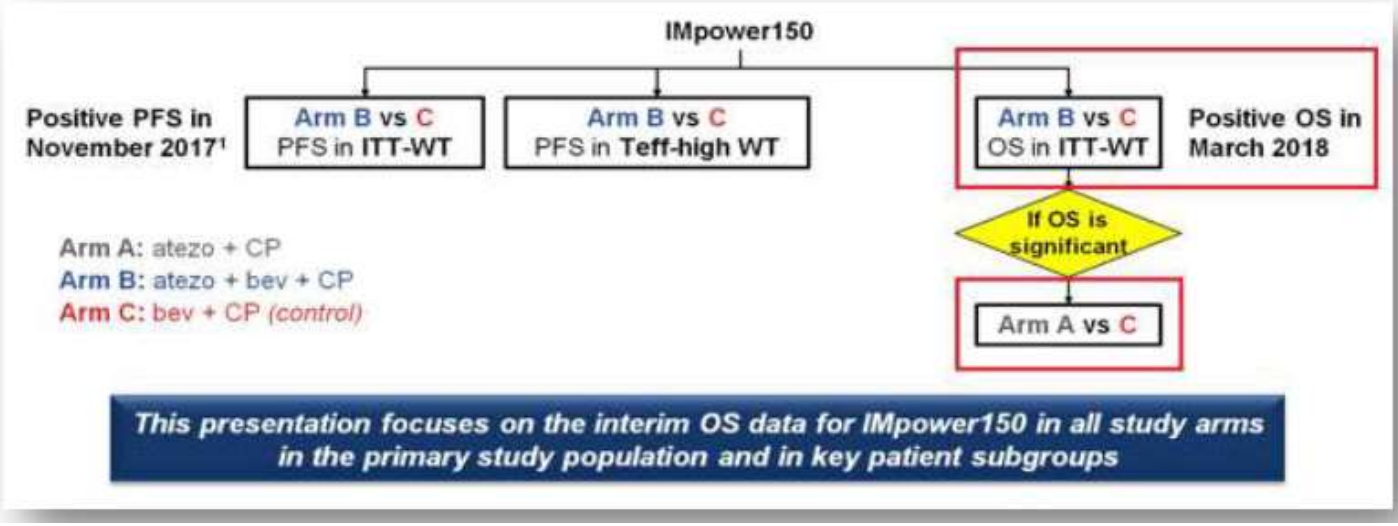
Follow-up immaturo (mFU 10.5 mesi), OS ancora non raggiunta nel braccio sperimentale

Rimane un quesito importante: nei PDL-1≥50% è meglio chemio-immuno o immuno da sola?

IMPOWER 150



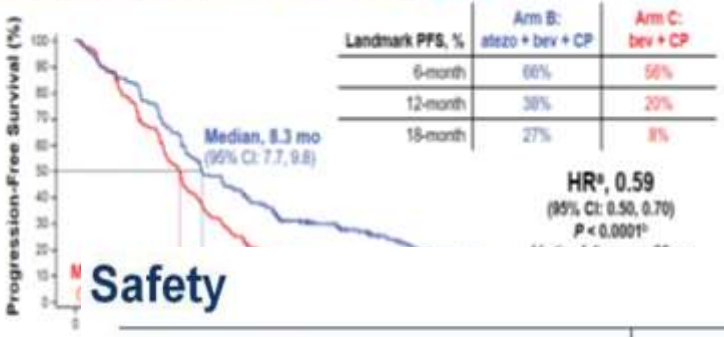
[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. [b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w. [d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.



Co-Primary Endpoint Analysis

Presented By Mark Socinski at 2018 ASCO Annual Meeting

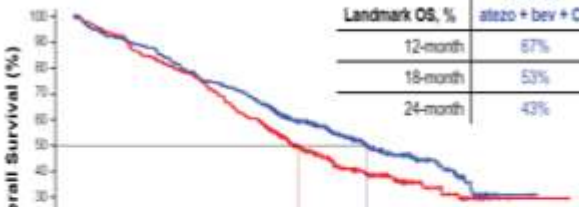
Updated PFS Analysis in the ITT-WT (Arm B vs Arm C)



Landmark PFS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
6-month	66%	56%
12-month	38%	20%
18-month	27%	8%

HR[a], 0.59
(95% CI: 0.50, 0.70)
P < 0.0001[b]

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



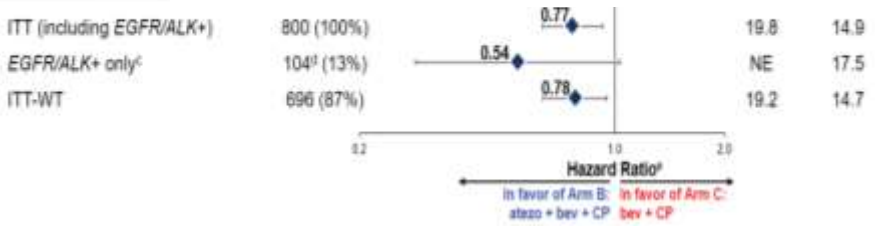
Landmark OS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
12-month	67%	61%
18-month	53%	41%
24-month	43%	34%

HR[a], 0.78
(95% CI: 0.64, 0.96)
P = 0.0164
n follow-up: ~20 mo

Safety

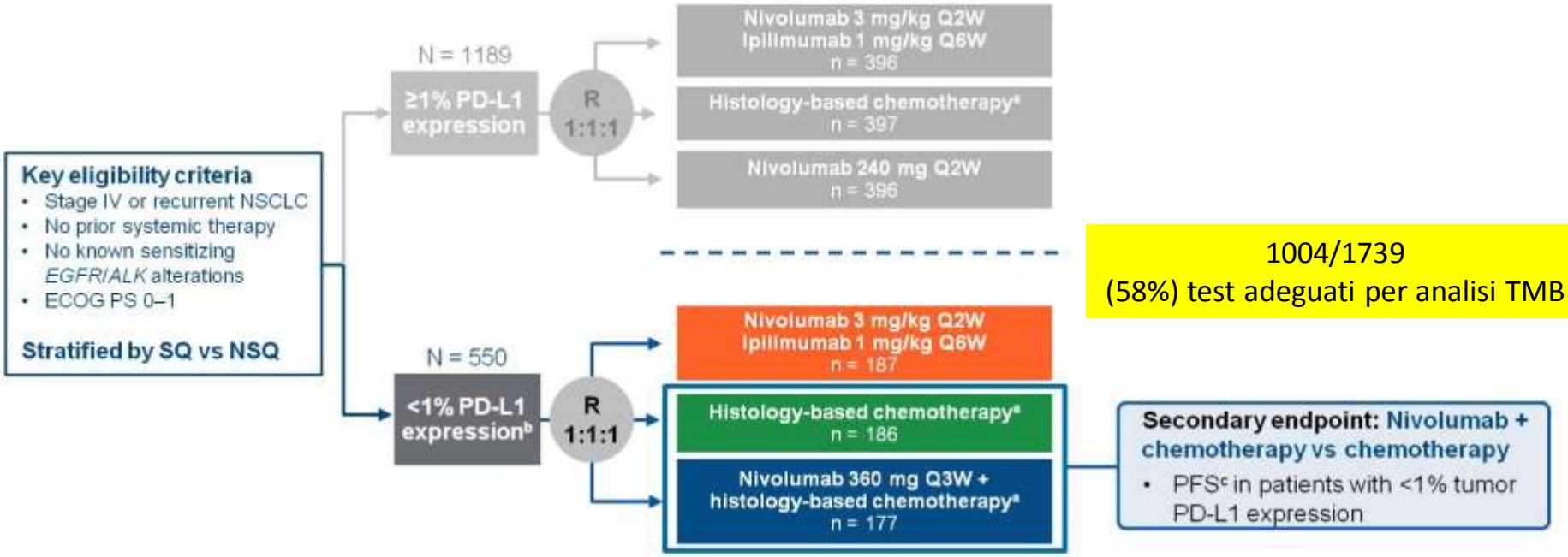
Incidence, n (%)	Arm A: atezo + CP (n = 400)		Arm B: atezo + bev + CP (n = 393)		Arm C (*control*): bev + CP (n = 394)	
Median doses received (range), n						
Atezolizumab	10 (1-43)		12 (1-44)		NA	
Bevacizumab	NA		10 (1-44)		8 (1-38)	
Treatment-related AE[a]	377 (94%)		370 (94%)		377 (96%)	
Grade 3-4	172 (43%)		223 (57%)		191 (49%)	
Grade 5[b]	4 (1%)		11 (3%)		9 (2%)	
Serious AE	157 (39%)		174 (44%)		135 (34%)	
AE leading to withdrawal from any treatment	53 (13%)		133 (34%)		98 (25%)	
Immune-related AEs[c] in > 5 patients in any arm	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**
Rash	119 (30%)	14 (4%)	117 (30%)	9 (2%)	53 (14%)	2 (1%)
Hepatitis[d]	42 (11%)	12 (3%)	54 (14%)	20 (5%)	29 (7%)	3 (1%)
Laboratory abnormalities	36 (9%)	10 (3%)	48 (12%)	18 (5%)	29 (7%)	3 (1%)
Hypothyroidism	34 (9%)	1 (<1%)	56 (14%)	1 (<1%)	18 (5%)	0
Pneumonitis[d]	23 (6%)	8 (2%)	13 (3%)	6 (2%)	5 (1%)	2 (1%)
Hyperthyroidism	11 (3%)	0	16 (4%)	1 (<1%)	5 (1%)	0
Colitis	3 (1%)	2 (1%)	11 (3%)	7 (2%)	2 (1%)	2 (1%)

- The safety profiles of ABCP and ACP were similar to A, B and C+P individually; no new safety signals were identified with the combinations



- 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

CheckMate 227 Part 1 Study Design



1004/1739
(58%) test adeguati per analisi TMB

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

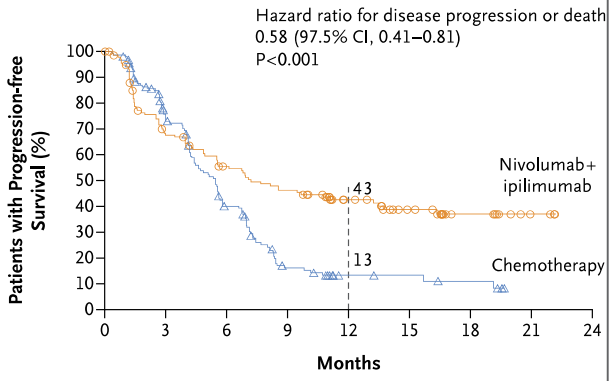
Database lock: January 24, 2018; minimum follow-up: 11.2 months

[a]**NSQ:** 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; [b]One patient was randomized with <1% tumor PD-L1 expression in IVRS, but was subsequently found to have ≥1% tumor PD-L1 expression; [c]Per BICR

TMB≥10

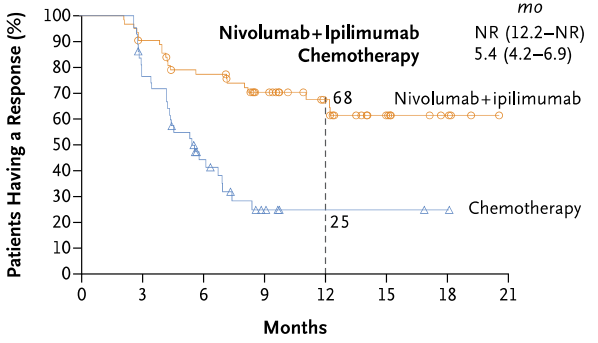
N: 444 (44.2%)

A Progression-free Survival



No. at Risk									
Nivolumab + ipilimumab	139	85	66	55	36	24	11	3	0
Chemotherapy	160	103	51	17	7	6	4	0	0

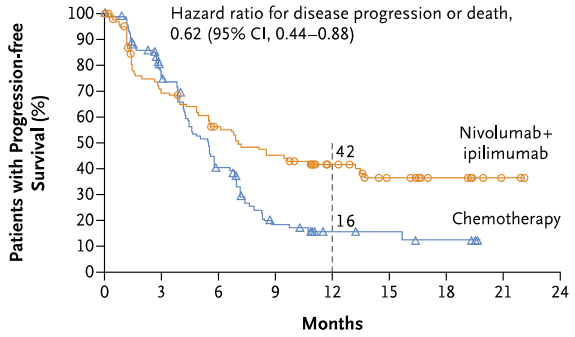
B Duration of Response



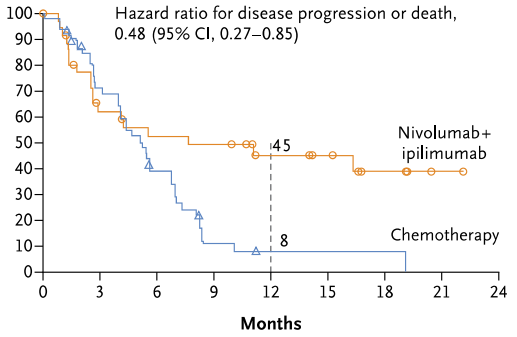
No. at Risk								
Nivolumab + ipilimumab	63	56	46	32	22	10	5	0
Chemotherapy	43	32	15	5	2	2	1	0

A Tumor PD-L1 Expression

PD-L1 Expression of ≥1%



PD-L1 Expression of <1%

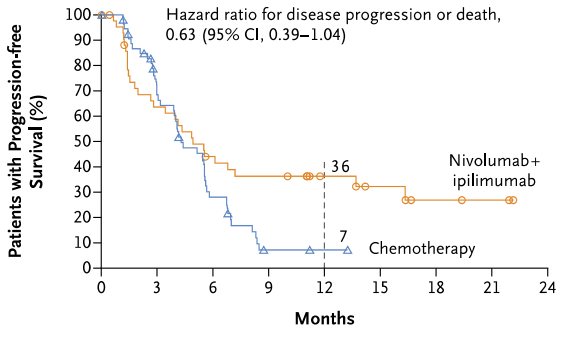


No. at Risk									
Nivolumab + ipilimumab	101	65	50	40	26	16	7	2	0
Chemotherapy	112	73	35	13	6	5	3	0	0

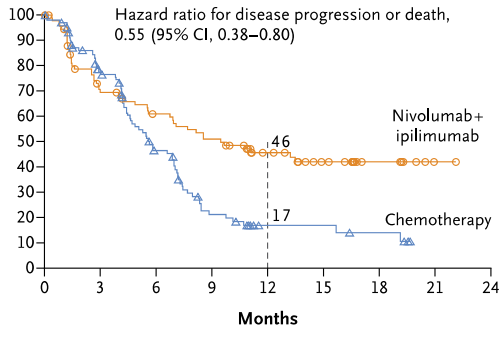
No. at Risk									
Nivolumab + ipilimumab	38	20	16	15	10	8	4	1	0
Chemotherapy	48	30	16	4	1	1	1	0	0

B Tumor Histologic Type

Squamous



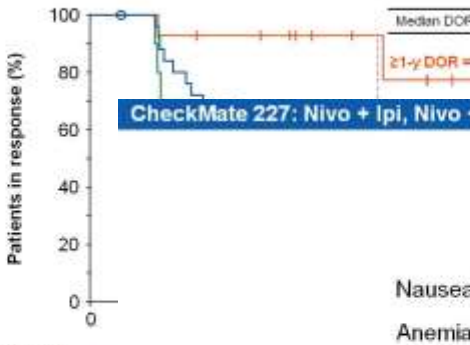
Nonsquamous



No. at Risk									
Nivolumab + ipilimumab	44	26	17	14	9	6	3	2	0
Chemotherapy	56	33	13	2	1	0	0	0	0

No. at Risk									
Nivolumab + ipilimumab	95	59	49	41	27	18	8	1	0
Chemotherapy	104	70	38	15	6	6	4	0	0

DOR: Nivolumab + Chemotherapy and Nivolumab + Ipilimumab in Patients With TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression



	Nivo + chemo (n = 26)	Nivo + ipi (n = 14)	Chemo (n = 10)
Median DOR,[a] mo	7.4	NR	4.4

≥1-y DOR = 93%

Nivolumab + Ipilimumab

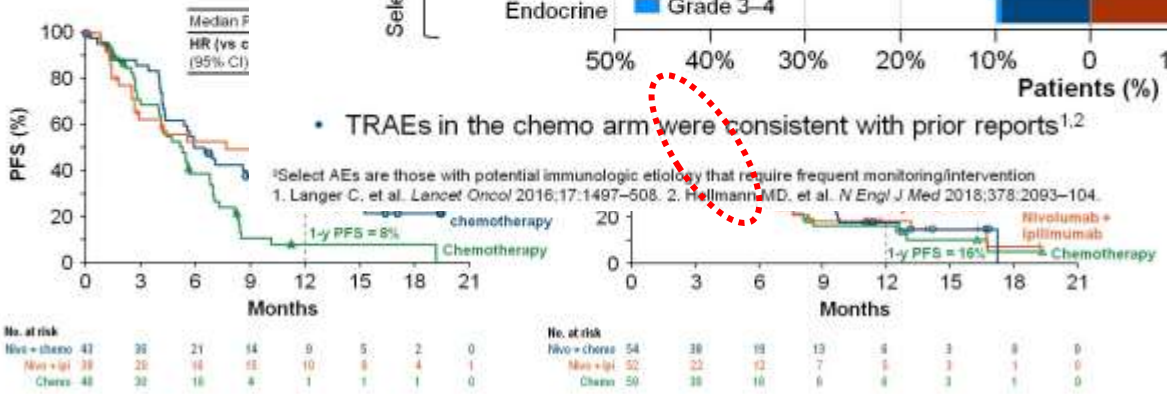
- ORR was 60.5%

Exploratory analysis
[a]95% CI: nivo + chemo (4.0, NR mo), nivo + ipi (12.2, NR

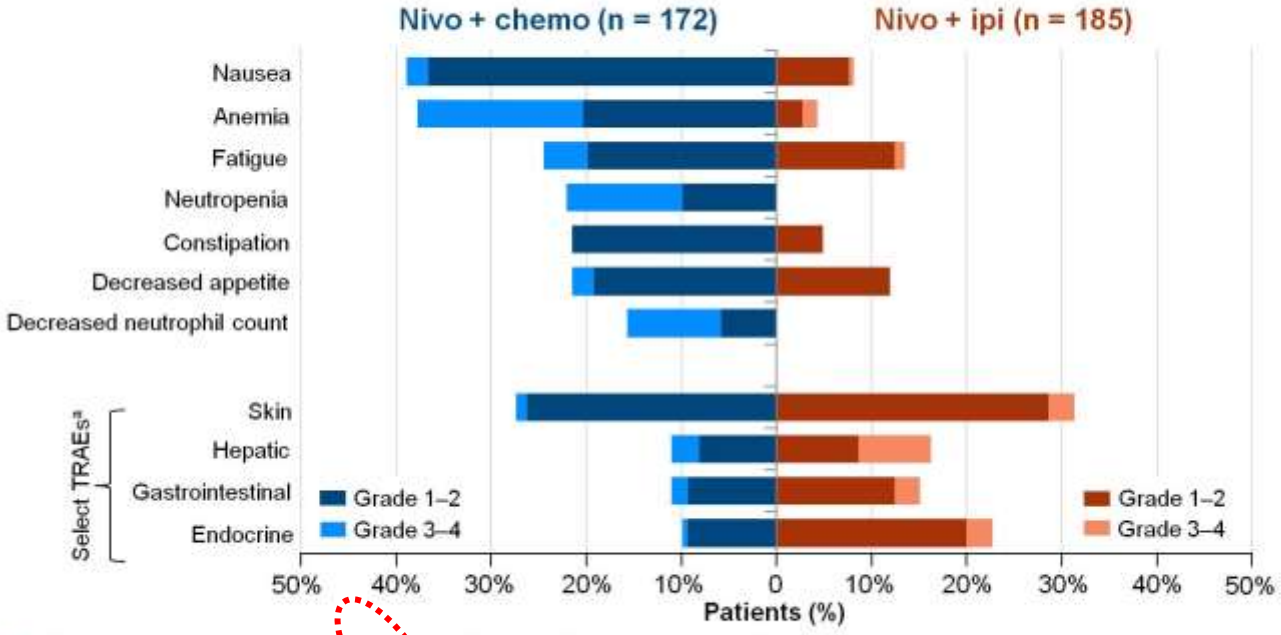
CheckMate 227: Nivo + Ipi, Nivo

PFS: Nivolur

TMB ≥10 mut/Mb and



Most Frequent TRAEs (≥15%)



- TRAEs in the chemo arm were consistent with prior reports[1,2]

[a]Select AEs are those with potential immunologic etiology that require frequent monitoring/intervention

1. Langer C. et al. *Lancet Oncol* 2016;17:1497–508. 2. Hellmann MD. et al. *N Engl J Med* 2018;378:2093–104.

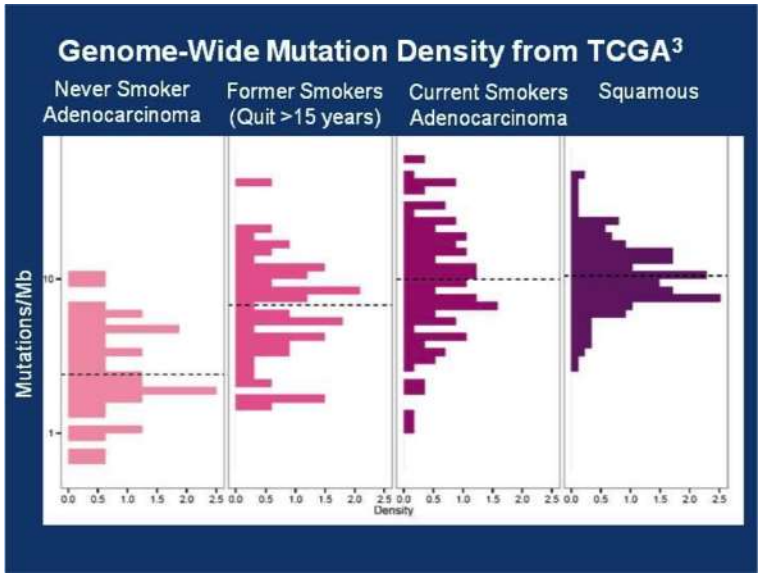
Exploratory analysis
[a]95% CI: nivo + chemo (4.3, 9.1 mo), nivo + ipi (2.7, NR mo); chemo (4.0, 6.8 mo); [b]95% CI: nivo + chemo (4.2, 6.9 mo), nivo + ipi (1.8, 5.4 mo); chemo (3.9, 6.2 mo)

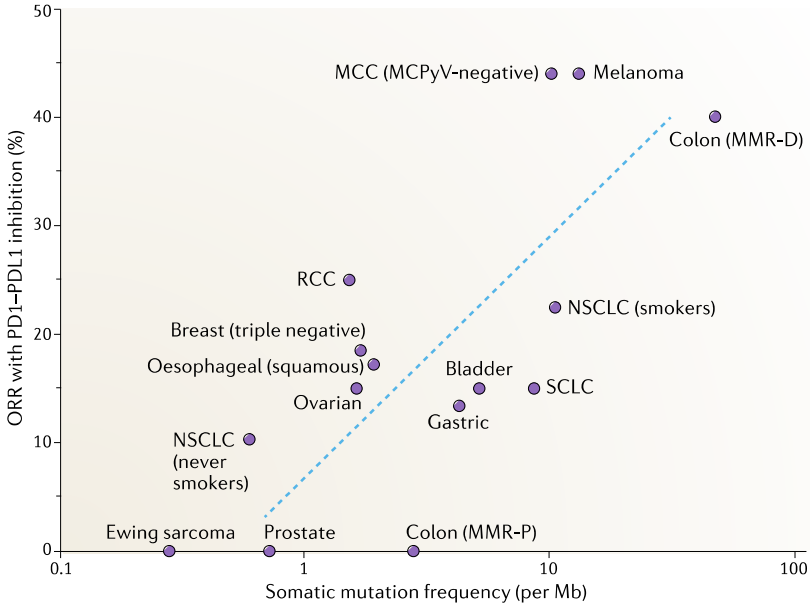
Per orientarsi nella valanga di novità rimangono sempre validi i fattori clinici..

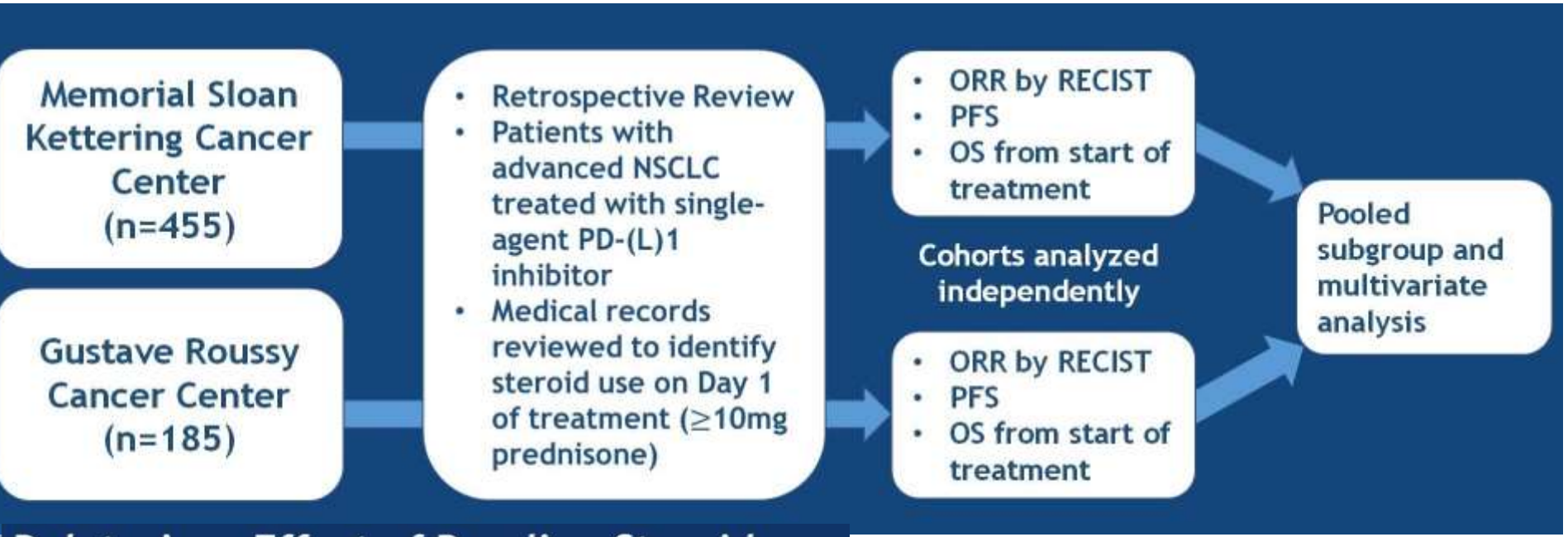
- Età (comorbidità)
- PS
- Esposizione al fumo
- Steroidi
- Sesso?
- Carico di malattia?
- Pazienti “oncogene addicted”

IL FUMO


Smoking Status, TMB & PD-L1
TMB and PD-L1 based on smoking status
P = 0.002
Mutations/Mb
Never/Light Smokers
Heavy Smokers
P = 0.734
PD-L1 Expression (%)
Never/ Light Smokers
Heavy Smokers

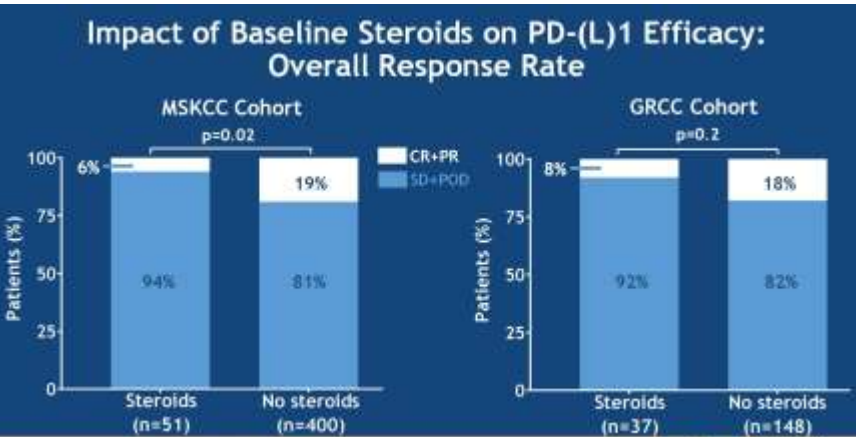

Genome-Wide Mutation Density from TCGA[3]
Never Smoker Adenocarcinoma
Former Smokers (Quit >15 years)
Current Smokers Adenocarcinoma
Squamous
Mutations/Mb
Density

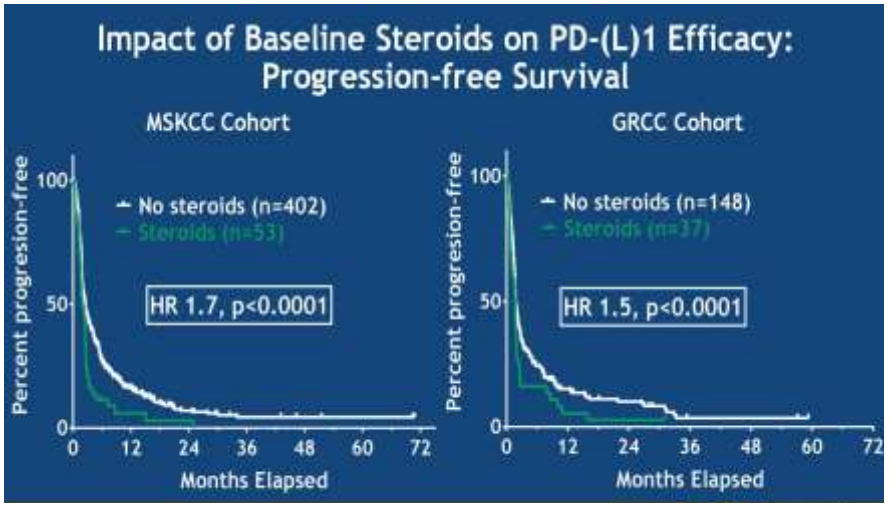

MCC (MCPyV-negative)
Melanoma
Colon (MMR-D)
RCC
NSCLC (smokers)
Breast (triple negative)
Oesophageal (squamous)
Bladder
SCLC
Ovarian
Gastric
NSCLC (never smokers)
Ewing sarcoma
Prostate
Colon (MMR-P)
ORR with PD1–PDL1 inhibition (%)
Somatic mutation frequency (per Mb)



Deleterious Effect of Baseline Steroids on Efficacy of PD-(L)1 Blockade in Patients with Non-Small Cell Lung Cancer

Patient Characteristics	MSKCC % (n=455)	GRCC % (n=185)
Median age (range)	66 (31-93)	61 (29-84)
Men	48 (220)	66 (122)
Performance status		
ECOG 0	19 (86)	12 (22)
ECOG 1	70 (320)	66 (122)
ECOG ≥ 2	11 (49)	22 (41)
Smoking status		
Former/current	83 (376)	87 (161)
Never	17 (79)	10 (19)
Histology		
Adenocarcinoma	76 (347)	73 (116)
Squamous	18 (80)	26 (49)
NSCLC-Other	6 (28)	11 (20)
Indication for steroid use ≥ 10mg	12% (n = 53)	20% (n = 37)
Dyspnea	30 (15)	41 (15)
Fatigue	33 (18)	3 (1)
Brain metastases	13 (7)	27 (10)
Pain	9 (5)	11 (6)
Other	15 (8)	14 (5)





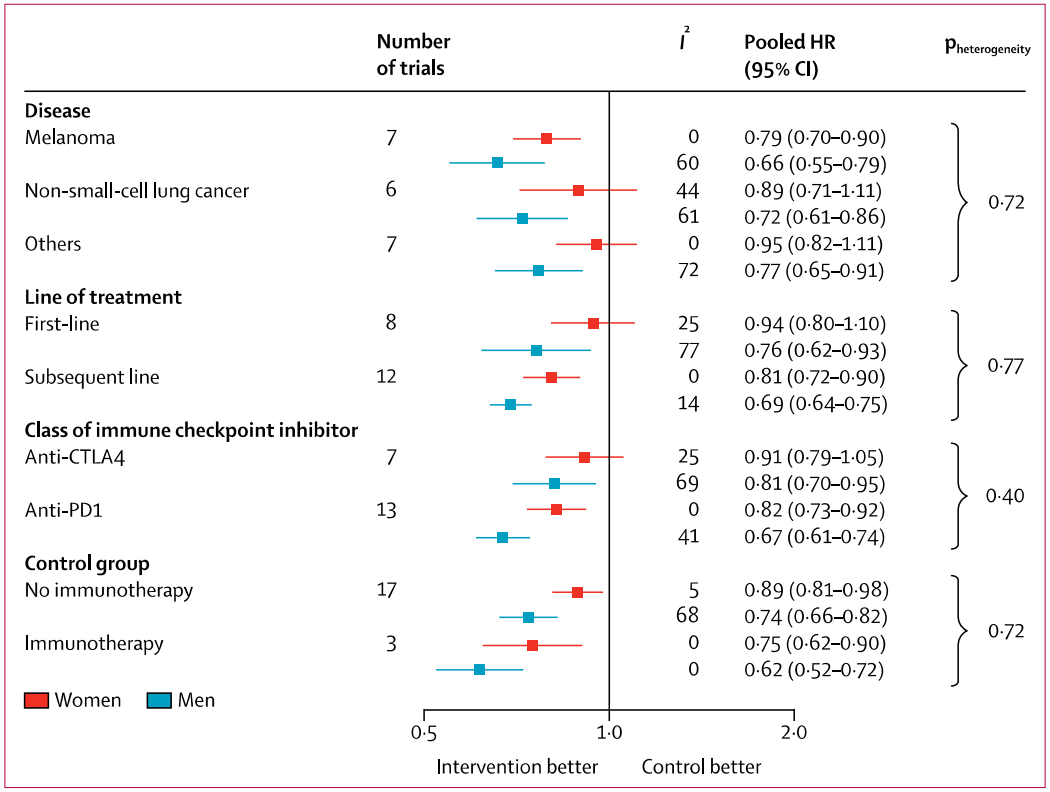
Patient characteristics	ORR Odds Ratio (95% CI)	p-value	PFS Hazard Ratio (95% CI)	p-value	OS Hazard Ratio (95% CI)	p-value
Smoking status (never vs ever)	0.33 (0.15-0.74)	0.007	1.64 (1.30-2.04)	<0.001	1.03 (0.81-1.33)	0.78
Performance status (ECOG ≥2 vs 0/1)	0.29 (0.11-0.75)	0.11	1.97 (1.55-2.50)	<0.001	2.29 (1.75-2.98)	<0.001
History of brain metastases (yes vs no)	0.88 (0.52-1.49)	0.6	1.16 (0.96-1.41)	0.1	1.37 (1.11-1.7)	0.003
Steroid use (yes vs no)	0.42 (0.17-1.01)	0.053	1.31 (1.03-1.67)	0.03	1.66 (1.28-2.16)	<0.001

L'USO DEGLI STEROIDI AT BASELINE è PROGNOSTICO O PREDITTIVO?
MOLTA CAUTELA NELL'UTILIZZO
CONSIDERARE ANCHE LE ALTE DOSI FATTE IN PREMEDICAZIONE NEGLI SCHEMI CON CHEMIOTERAPIA

Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis

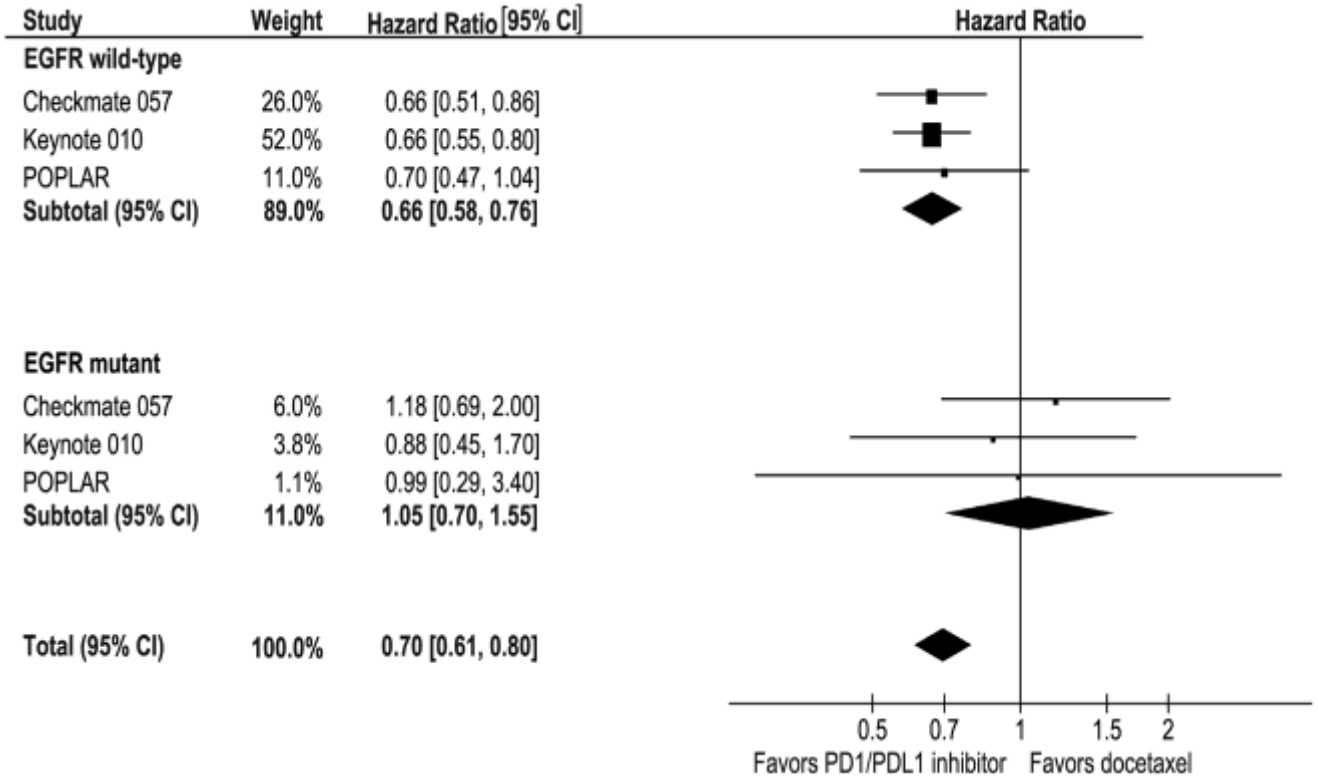
Fabio Conforti, Laura Pala, Vincenzo Bagnardi, Tommaso De Pas, Marco Martinetti, Giuseppe Viale, Richard D Gelber, Aron Goldhirsch

Non-small-cell lung cancer				
Borghaei et al (2015)[49]	>1	Nivolumab (n=292)	Docetaxel (n=290)	0·78 (0·58–1·04)
Brahmer et al (2015)[47]	>1	Nivolumab (n=135)	Docetaxel (n=137)	0·73 (0·56–0·96)
Herbst et al (2016)[45]	>1	Pembrolizumab (n=690)	Docetaxel (n=343)	0·67 (0·36–1·25) 0·57 (0·41–0·78) 0·69 (0·51–0·94) 0·65 (0·52–0·81)
Reck et al (2016)[44]	1	Pembrolizumab (n=154)	ICC (n=151)	0·96 (0·56–1·64) 0·54 (0·36–0·80)
Carbone et al (2017)[43]	1	Nivolumab (n=271)	ICC (n=270)	1·15 (0·79–1·66) 0·97 (0·74–1·26)
Govindan et al (2017)[48]	1	Ipilimumab plus paclitaxel plus carboplatin (n=388)	Paclitaxel plus carboplatin plus placebo (n=361)	1·33 (0·84–2·11) 0·85 (0·71–1·02)



Checkpoint Inhibitors in Metastatic *EGFR*-Mutated Non-Small Cell Lung Cancer—A Meta-Analysis

Chee Khoon Lee, PhD,[a,b,*] Johnathan Man, M.B.B.S.,[b] Sally Lord, MSc,[a,c]
Matthew Links, PhD,[b] Val Gebski, MStat,[a] Tony Mok, MD,[d]
James Chih-Hsin Yang, PhD[e]



Tumor mutation burden (TMB) in lung cancer (LC) and relationship with response to PD-1/ PD-L1 targeted therapies

Abs #9017

FOUNDATION MEDICINE®

Methods: Comprehensive genomic profiling (CGP) was performed on FFPE specimens during the course of clinical care. TMB (mutations/Mb) was assessed as the number of somatic, coding, base substitution and indel alterations per Mb of genome. The top quartile of LC was classified as TMB high. Microsatellite instable (MSI-H) or stable (MSS) status was determined using a proprietary computational algorithm.

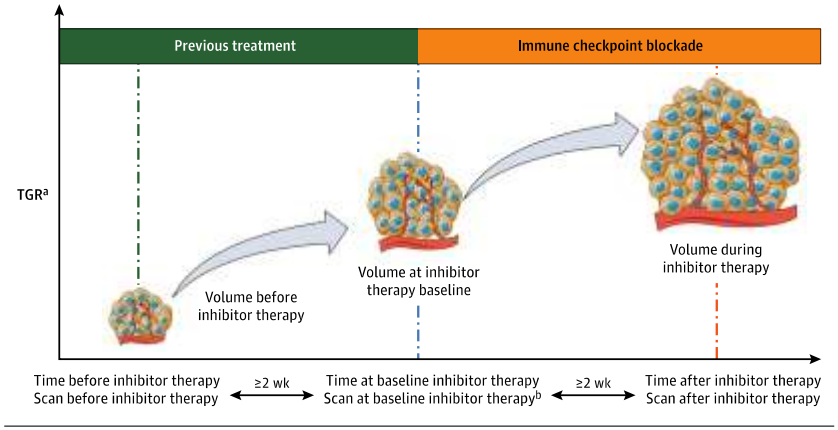
11662 Lung cancer specimens were sequenced using hybrid capture NGS test. MSI and TMB were calculated

Frequency of LC Patients with selected variants between TMB-high vs. TMB-low cohorts

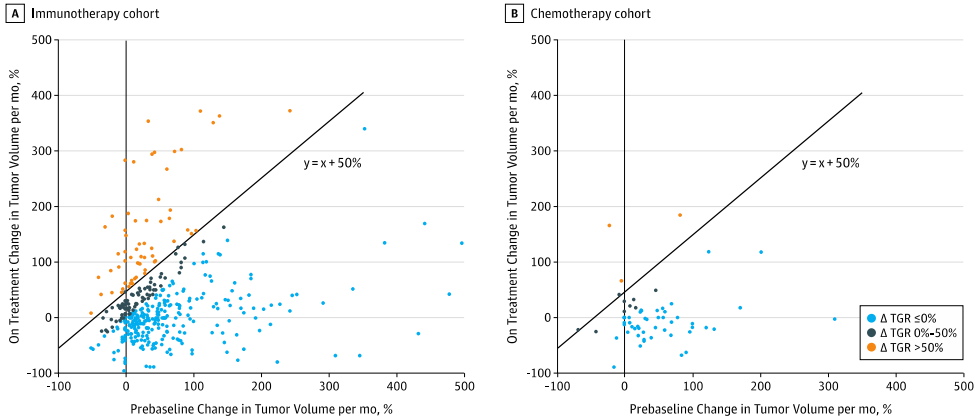
Variant	Mean TMB	TMB-high		TMB-low		P-value
		No. of cases	%	No. of cases	%	
EGFR ex19del	4.5	36	5	354	46	<0.0001
EGFR L858R	4.6	22	4	242	49	<0.0001
EGFR T790M	4.4	8	3	132	44	<0.0001
EGFR mutation (other)	4.5	24	5	267	52	<0.0001
EML4-ALK	2.8	3	1	216	69	<0.0001
non-EML4-ALK	2.8	2	4	46	84	<0.0001
ROS1 rearrangement	3.9	5	4	71	59	<0.0001
MET ex14	6.2	22	8	118	41	<0.0001
BRAF V600E	6.8	20	10	99	48	<0.0001
BRAF non-V600E	9.7	104	36	49	17	<0.0001
KRAS mutation	10.3	934	30	622	20	<0.0001
BRCA1 alteration	19.2	62	42	29	20	0.0005
BRCA2 alteration	13.8	77	32	49	20	0.0126
POLE mutation	25.1	8	62	2	15	0.0578
PD-L1 amplification	15.6	44	52	3	4	<0.0001

Hyperprogressive disease

Figure 1. Hypothetical Tumor Volume Variation and Definition of Hyperprogressive Disease (HPD) in the Immunotherapy Cohort



Recist 1.1. defined as progressive disease during treatment and ΔTGR exceeding 50%, corresponding to an absolute increase in TGR exceeding 50% per month



A, Light blue spots show 266 patients with regressing or stable tumors, dark blue spots show 78 patients with progressing tumors, and orange spots show 62 patients with accelerated tumor growth during programmed cell death (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitor therapy. B, Light blue spots show 47 patients with regressing or stable tumors, dark blue spots show 9 patients with progressing tumors, and orange spots show 3 patients with accelerated tumor growth during chemotherapy. Diagonal lines separate patients with delta TGR exceeding 50% from patients with delta TGR of 50% or less.

JAMA Oncology Published online September 6, 2018

Research Article

Antibody-Fc/FcR Interaction on Macrophages as a Mechanism for Hyperprogressive Disease in Non-Small Cell Lung Cancer Subsequent to PD-1/PD-L1 Blockade

Giuseppe Lo Russo, Massimo Moro, Michele Sommariva, Valeria Cancila, Mattia Boeri, Giovanni Centonze, Simona Ferro, Monica Ganzinelli, Patrizia Gasparini, Veronica Huber, Massimo Milione, Luca Porcu, Claudia Proto, Giancarlo Pruneri, Diego Signorelli, Sabina Sangaletti, Lucia Sfondrini, Chiara Storti, Elena Tassi, Alberto Bardelli, Silvia Marsoni, Valter Torri, Claudio Tripodo, Mario P Colombo, Andrea Anichini, Licia Rivoltini, Andrea Balsari, Gabriella Sozzi, and Marina Garassino

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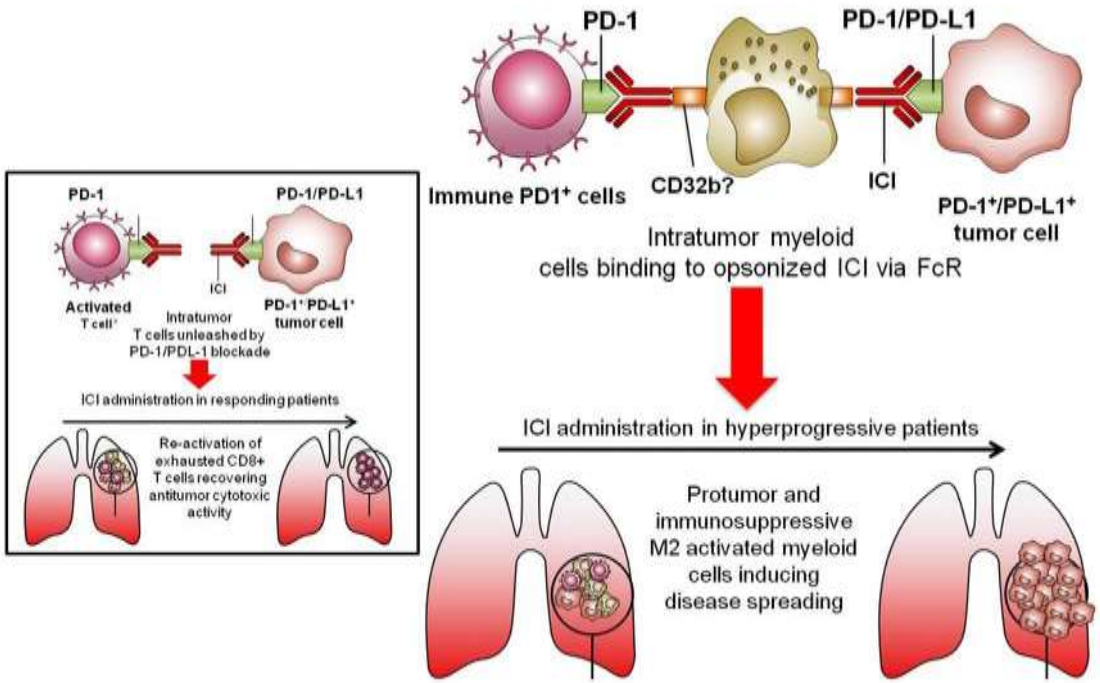

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Conclusioni

- L'immunoterapia ha sicuramente cambiato il nostro modo di trattare i pazienti affetti da NSCLC, modificandone la storia naturale

- Nonostante l'innovazione prodotta dall'immunoterapia, non possiamo ancora parlare di «guarigione», ma di effetti anche a lungo termine

- Le combinazioni (chemio-immuno, anti-PD-1/anti-CTLA4, chemio/biologico/immuno) potranno ulteriormente migliorare i risultati ottenuti, soprattutto nei pazienti scarsamente responsivi

- Per quel che riguarda i tumori localmente avanzati, lo studio PACIFIC ha dimostrato L'efficacia della immunoterapia come strategia di mantenimento dopo chemio-radioterapia definitiva

- Sono ongoing studi nelle fasi più precoci di malattia

- **IL MODO MIGLIORE DI ABBATTERE LA MORTALITA' PER TUMORE POLMONARE E' NON FUMARE**