UNIVERSITÀ POLITECNICA DELLE MARCHE

Azienda Ospedaliero Universitaria OSPEDALI RIUNITI Umberto I - G.M.Lancisi - G.Salesi Ancona

Facoltà di Medicina e Chirurgia

NUOVE STRATEGIE IMMUNOTERAPICHE NEL TRATTAMENTO IN PRIMA LINEA DEL TUMORE AL POLMONE

Rossana Berardi

Clinica Oncologica

r.berardi@univpm.it

26 novembre 2019 – www.univpm.it

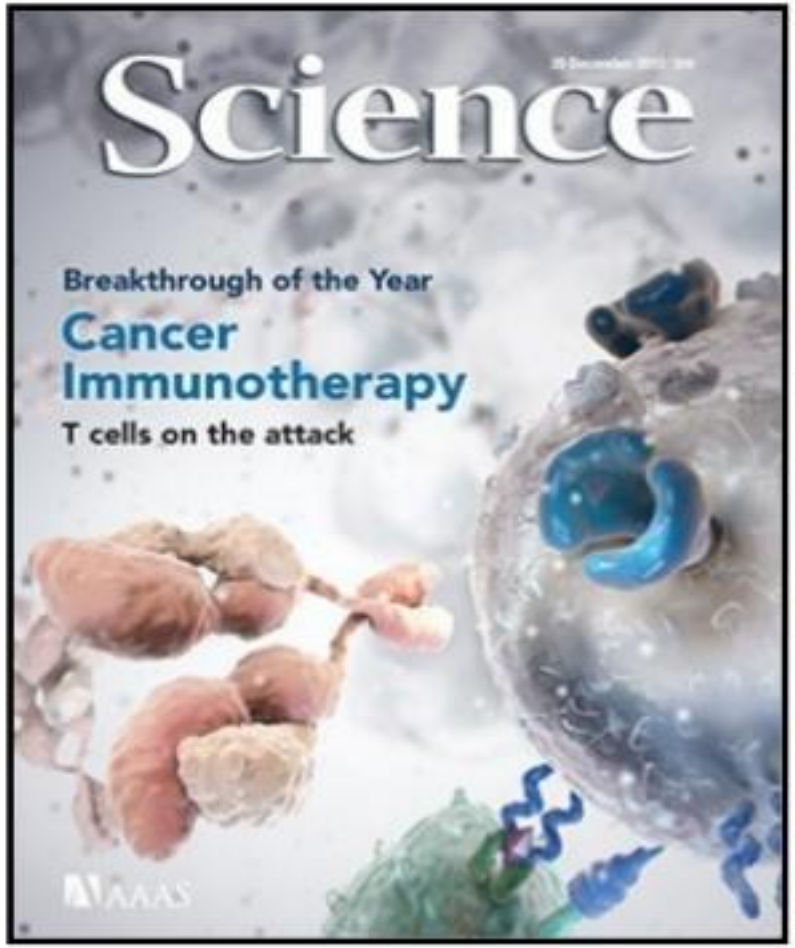
INNOVAZIONE E SOSTENIBILITÀ NEL CARCINOMA POLMONARE CONFRONTO TRA ESPERTI

2019 MOTORE SANITÀ Gestire il Cambiamento

LUNG CANCER : TIME'S UP !

IMMUNOTHERAPY

IMMUNOTERAPIA: RIVOLUZIONE DEL PARADIGMA TERAPEUTICO

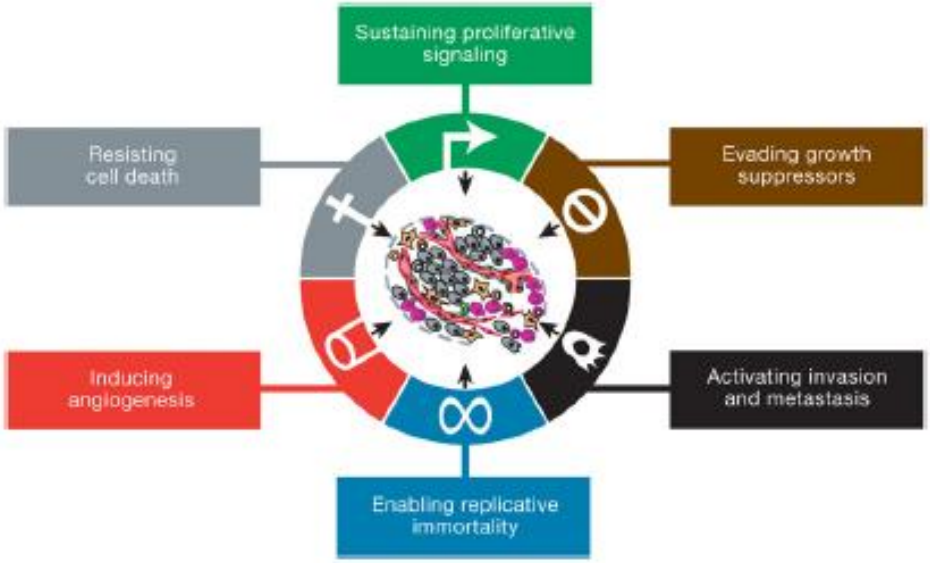


2013

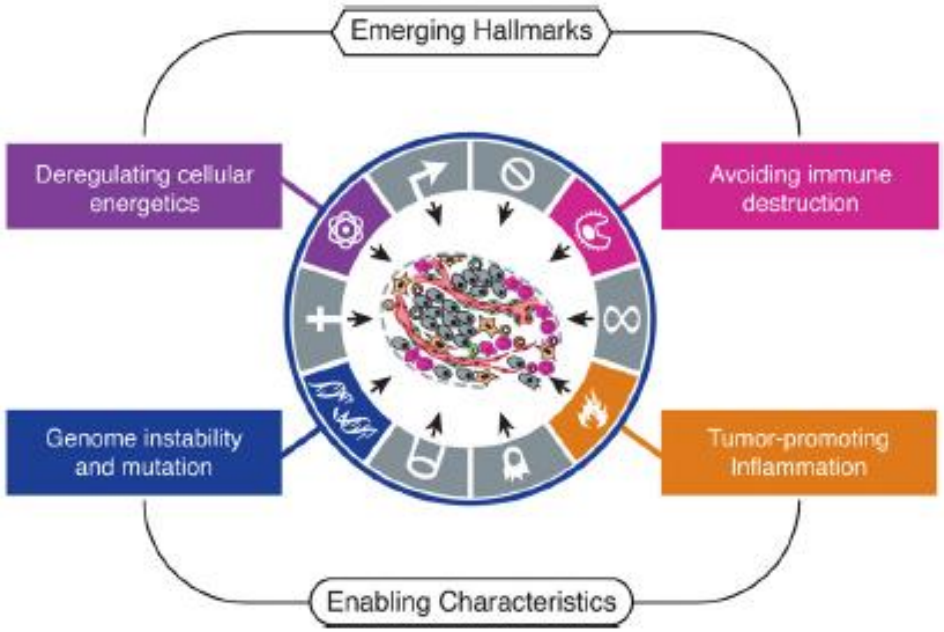
2014

THE HALLMARKS OF CANCER

2001



2011



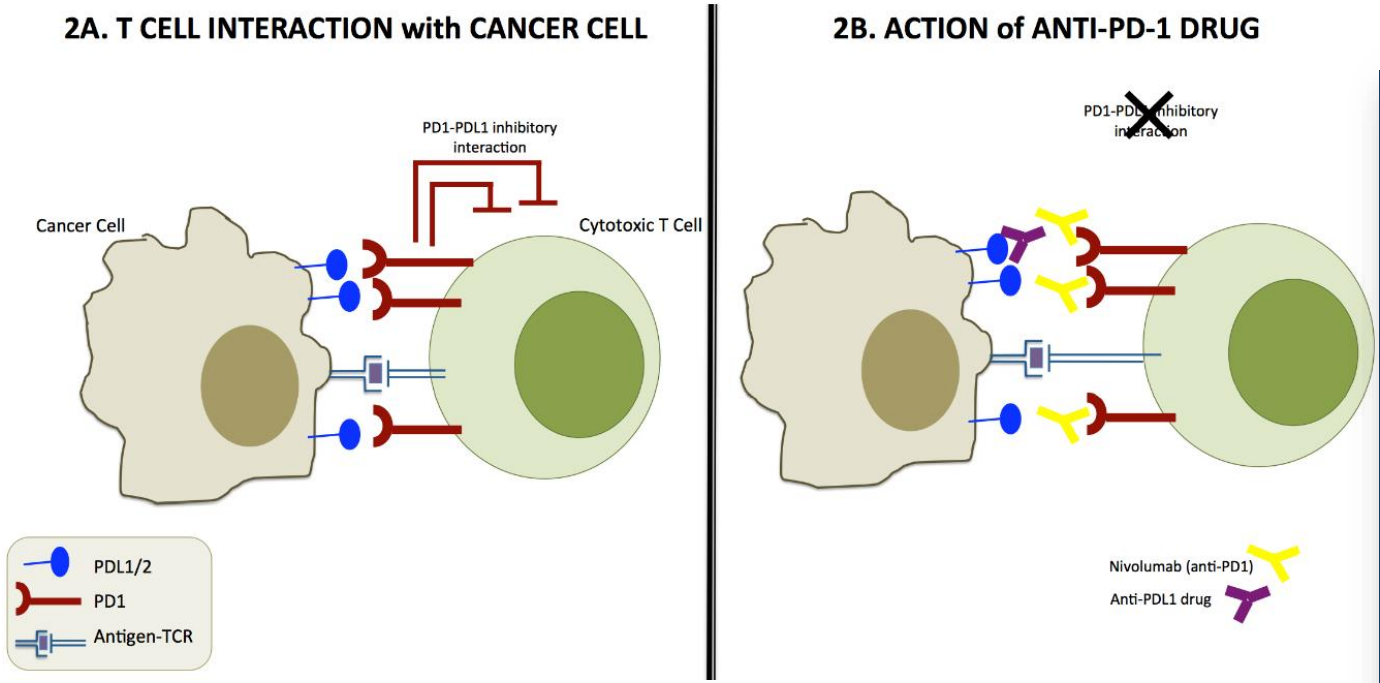
10 years later…

Hanahan D, Weinberg RA, Cell - 2011

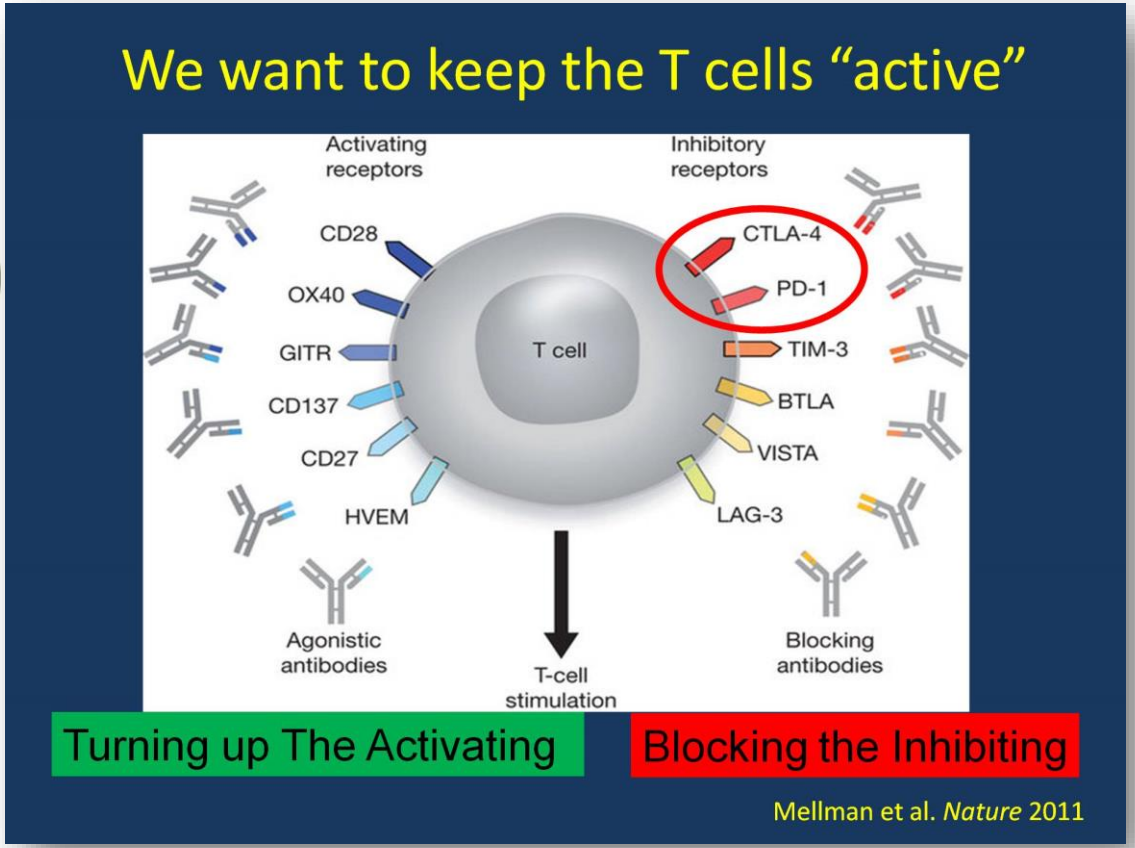
CHECKPOINT INHIBITORS: THE NEW PLAYERS IN THE NSCLC FIELD

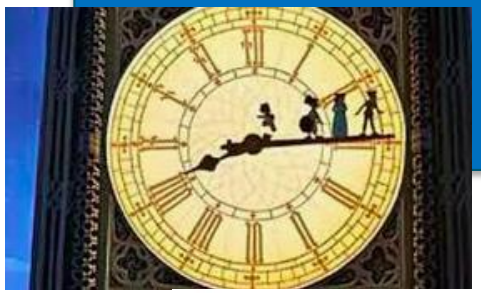
CHECKPOINT INHIBITORS: TUMORS EXPRESS "CHECKPOINT" PROTEINS ON THEIR CELL SURFACE TO ESCAPE DETECTION FROM THE IMMUNE SYSTEM

→ TARGETED INHIBITION TOWARDS THESE RECEPTORS ENHANCES T CELL RESPONSE TOWARDS THE TUMOR

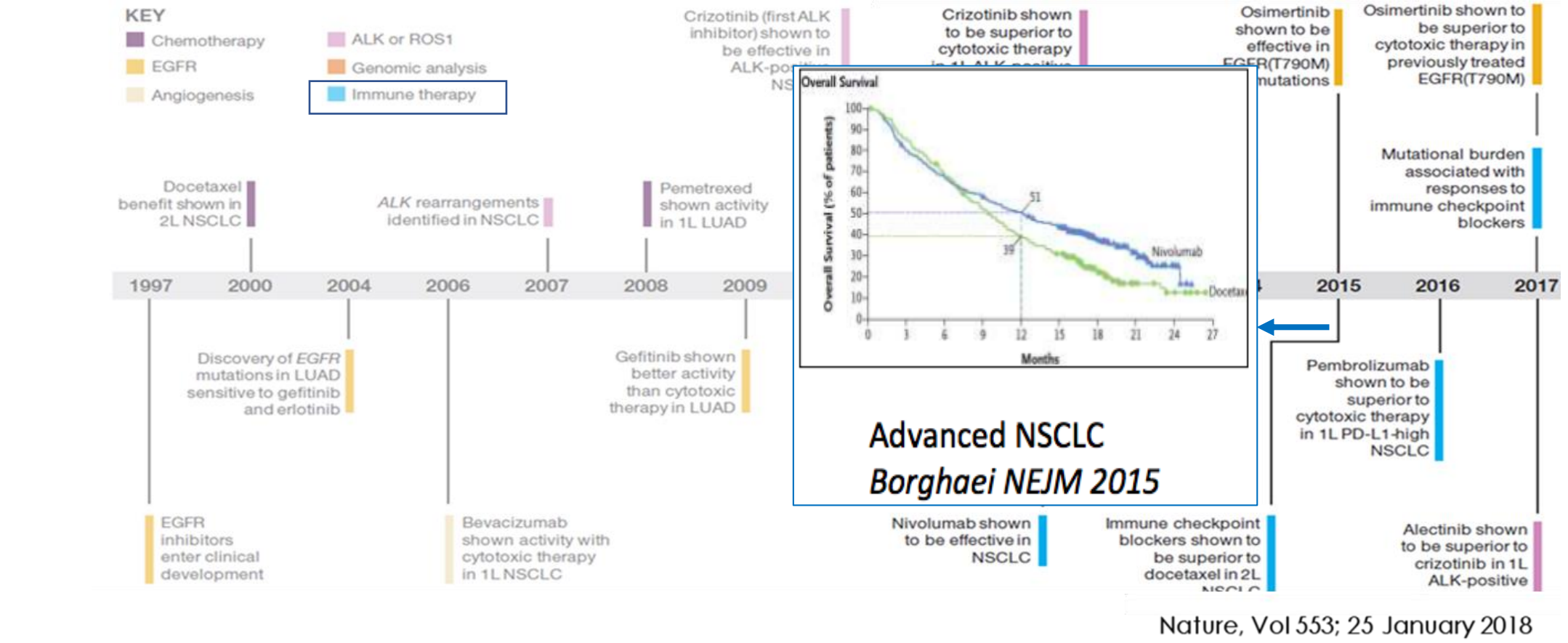


http://sitn.hms.harvard.edu/flash/2014/blocking-the-brakes-helping-your-immune-system-battle-cancer/





IMMUNOTHERAPY IN LUNG CANCER: CRONOSTORIA

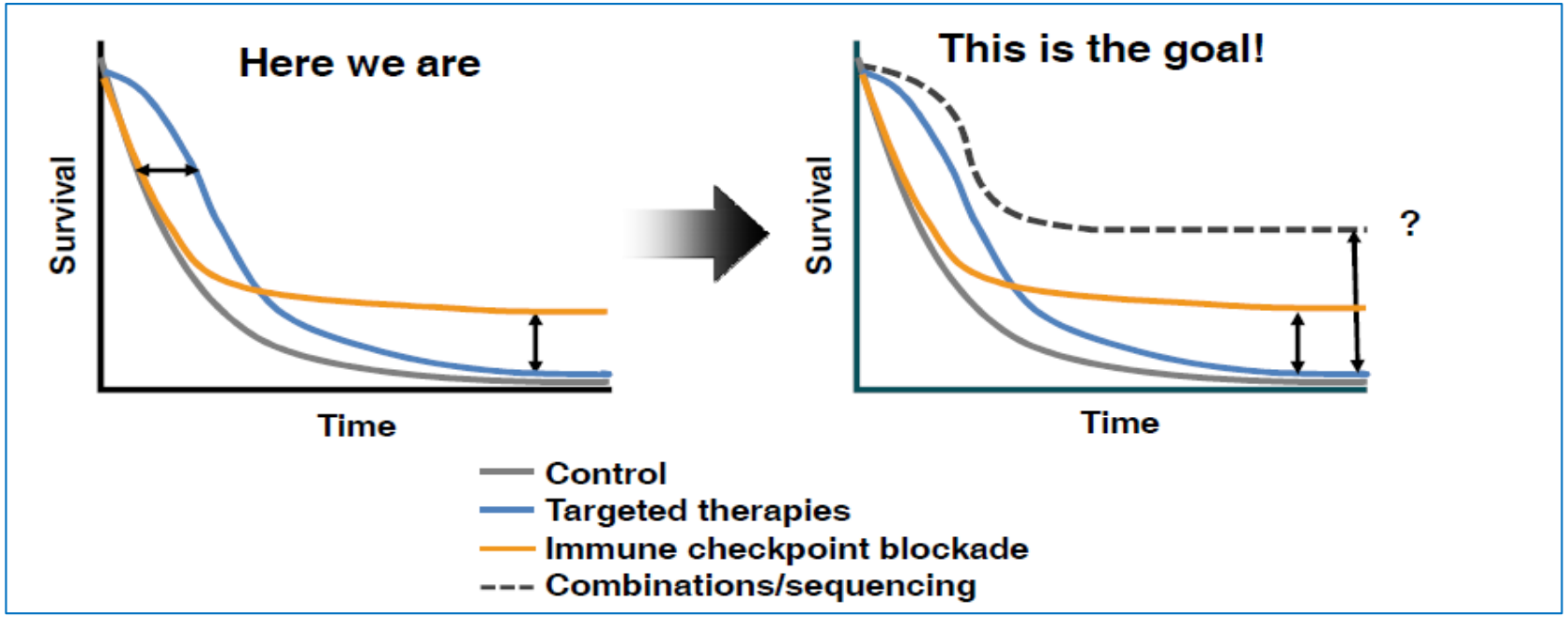


Nature, Vol 553; 25 January 2018

Immunocheck-point inhibitors: netto miglioramento in termini di sopravvivenza, circa 20% di lungo sopravviventi

ADVANCED NSCLC: CURRENT THERAPEUTIC SCENARIO

Chemotherapy*†	Targeted TKI Therapy	Checkpoint Inhibitors
Histologic subtype	EGFR ALK ROS1 BRAF V600E	Anti–PD-1 Anti–PD-L1
1970s - today	2000s - today	2015 - today

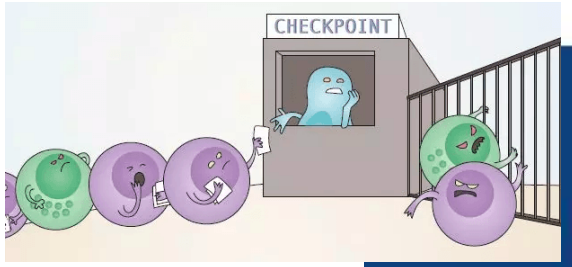


Immunoterapia e tumore del polmone
Linee guida AIOM 2019

Globalmente considerati, i risultati di questi studi suggeriscono come l'immunoterapia (da sola o in associazione) possa diventare uno standard nel trattamento di prima linea di una parte significativa di pazienti con nuova diagnosi di NSCLC avanzato. Tuttavia, al momento della stesura di queste linee guida (ottobre 2019), l'unico agente immunoterapico approvato e rimborsato in Italia in prima linea per il trattamento del NSCLC avanzato è il pembrolizumab in monoterapia, limitatamente ai pazienti senza alterazioni di *EGFR* e *ALK* e con espressione di PD-L1 $\geq$ 50%.
Pertanto, nei pazienti con buon performance status (0-1), senza alterazioni molecolari drivers, e con livello di espressione di PD-L1 < 50%, l'unico trattamento possibile ad oggi in Italia resta la chemioterapia.

Aiom
Associazione Italiana di Oncologia Medica

1st line Checkpoint inhibitors for NSCLC: summary of evidence



Phase 3 trials of first-line immunotherapy

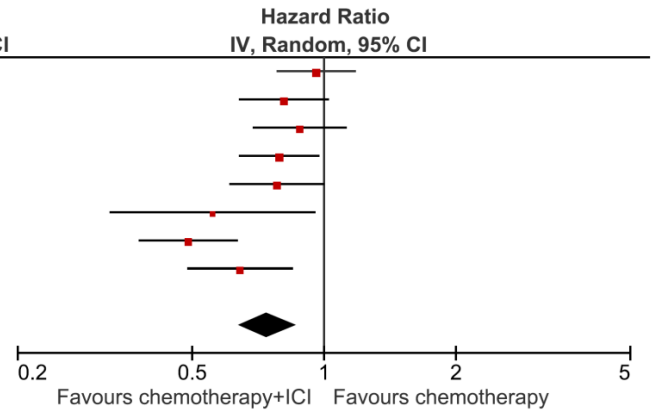
Comparison	Selection	ORR	PFS	OS
Pembrolizumab vs. platinum doublet	PD-L1 ≥ 50%	44.8% vs 27.8%	HR=0.50 p<0.01	HR=0.60 p<0.01
Carboplatin/pemetrexed +/- pembrolizumab or placebo	PD-L1:unselected Nonsquamous	47.6% vs.18.9% p<0.01	HR=0.52 p<0.01	HR=0.49 p<0.01
Pembrolizumab vs platinum doublet	PD-L1≥ 1%	27.3% vs. 26.5%	HR=1.07 NS	0.81 p<0.01
Carboplatin, paclitaxel, bevacizumab +/- atezolizumab	PD-L1:unselected Nonsquamous	64% vs 48%	HR=0.62 p<0.01	Positive
Carboplatin (nab-paclitaxel or paclitaxel) +/- pembrolizumab	PD-L1: unselected Squamous	58.4% vs 35.0% p<0.01	HR=0.56 p<0.01	HR=0.64 p<0.01
Nivolumab/ipilimumab vs. platinum doublet	TMB high ≥ 10 mutations/Mb	45.3% vs 26.9%	HR=0.58 p<0.01	Immature

Reck et al NEJM 2016, Gandhi et al NEJM 2018, Lopes et al ASCO 2018, Reck et al ESMO-Immuno-oncology 2017, Kowanetz et al AACR 2018 Paz-Ares et al ASCO 2018, Socinski et al ASCO 2018, Hellman et al NEJM 2018

NSCLC: First-line chemo + immuno vs Chemo
Overall survival
Any PD-L1 expression

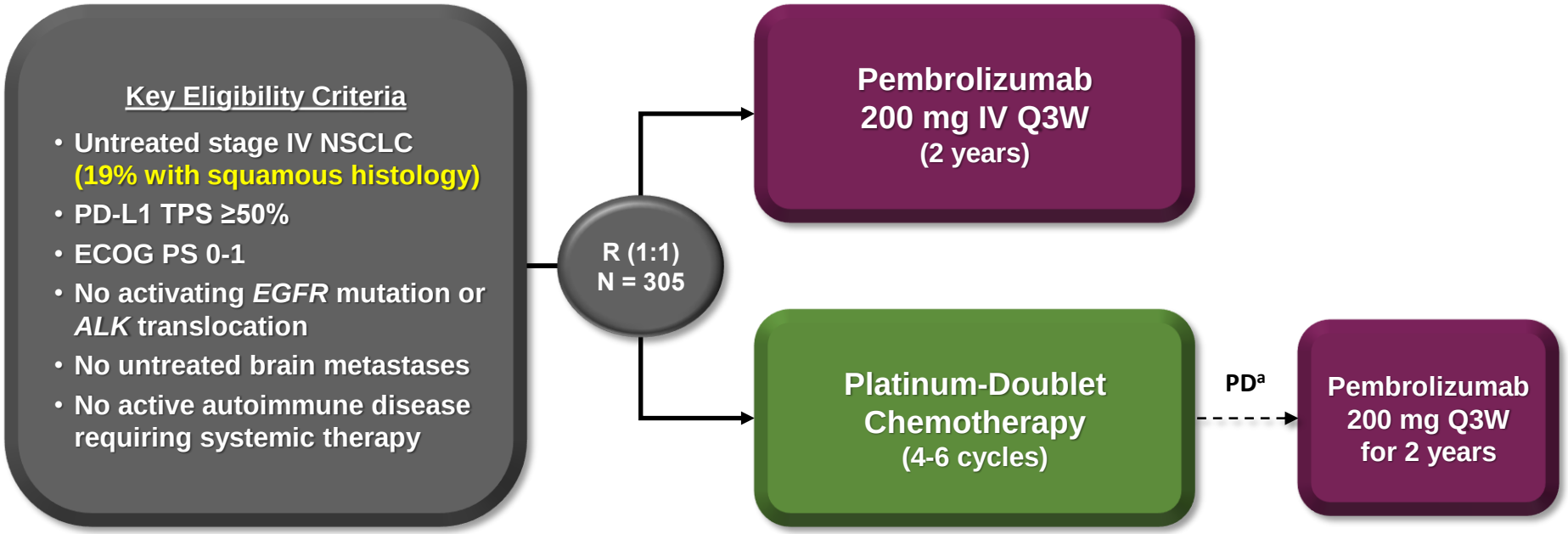
Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy + ICI Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
IMpower 131	-0.0408	0.1059	343	340	14.7%	0.96 [0.78, 1.18]
IMpower 132	-0.2107	0.1202	292	286	13.6%	0.81 [0.64, 1.03]
IMpower 150 A vs C	-0.1278	0.1254	349	337	13.3%	0.88 [0.69, 1.13]
IMpower130	-0.2357	0.1074	451	228	14.5%	0.79 [0.64, 0.98]
IMpower150 B vs C	-0.2485	0.1265	359	337	13.2%	0.78 [0.61, 1.00]
KEYNOTE-021	-0.587	0.2755	60	63	5.8%	0.56 [0.32, 0.95]
KEYNOTE-189	-0.7133	0.1324	410	206	12.8%	0.49 [0.38, 0.64]
KEYNOTE-407	-0.4416	0.1418	278	281	12.1%	0.64 [0.49, 0.85]
Total (95% CI)			**2542**	**2078**	**100.0%**	**0.74 [0.64, 0.87]**

Heterogeneity: Tau² = 0.03; Chi² = 20.34, df = 7 (P = 0.005); I² = 66%
Test for overall effect: Z = 3.76 (P = 0.0002)



Addeo A, Banna GL, Metro G, Di Maio M.
Chemotherapy in Combination With Immune Checkpoint Inhibitors for the First-Line Treatment of Patients With Advanced Non-small Cell Lung Cancer: A Systematic Review and Literature-Based Meta-Analysis.
Front Oncol. 2019 Apr 16;9:264. doi: 10.3389/fonc.2019.00264.

ADVANCED NSCLC
KEYNOTE-024: Pembrolizumab as First-line Treatment



Key End Points

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

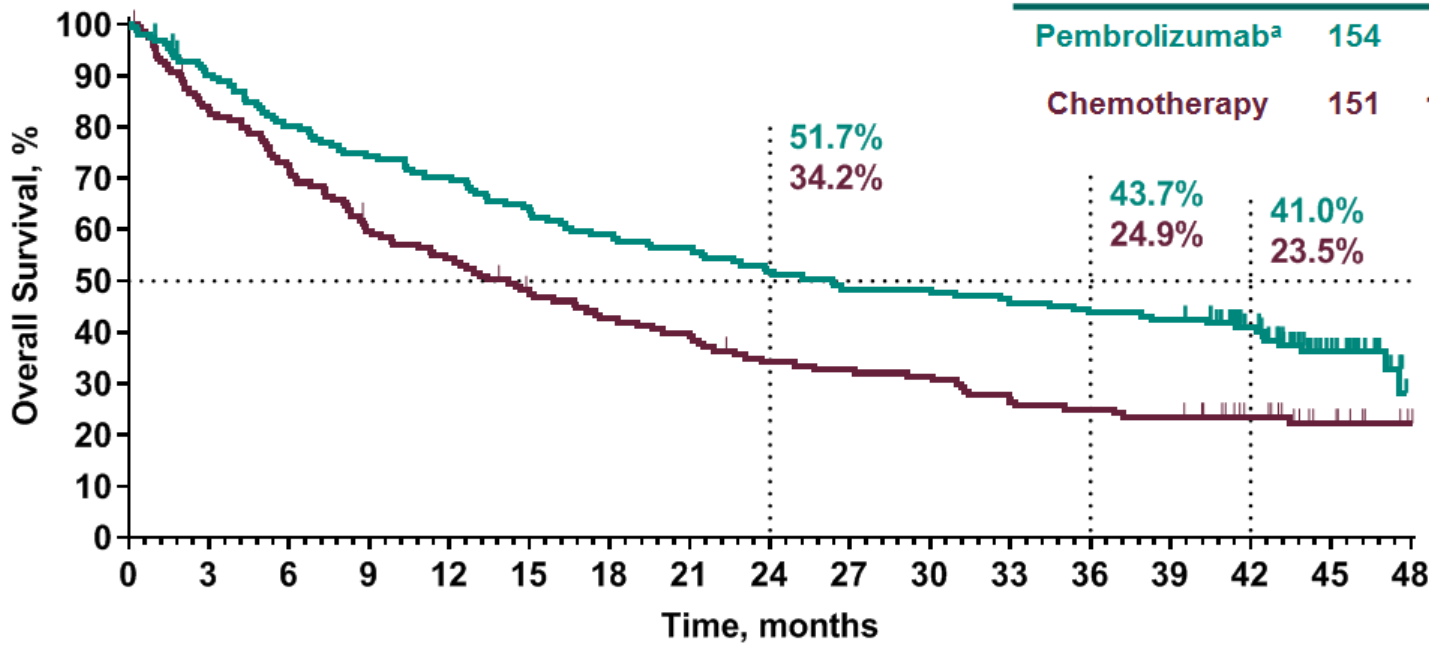
Secondary: OS, ORR, safety

Exploratory: DOR

Reck M et al, N Engl J Med 2016;375(19):1823-1833.

Reck KN024 WCLC 2019

Overall Survival: Updated Analysis



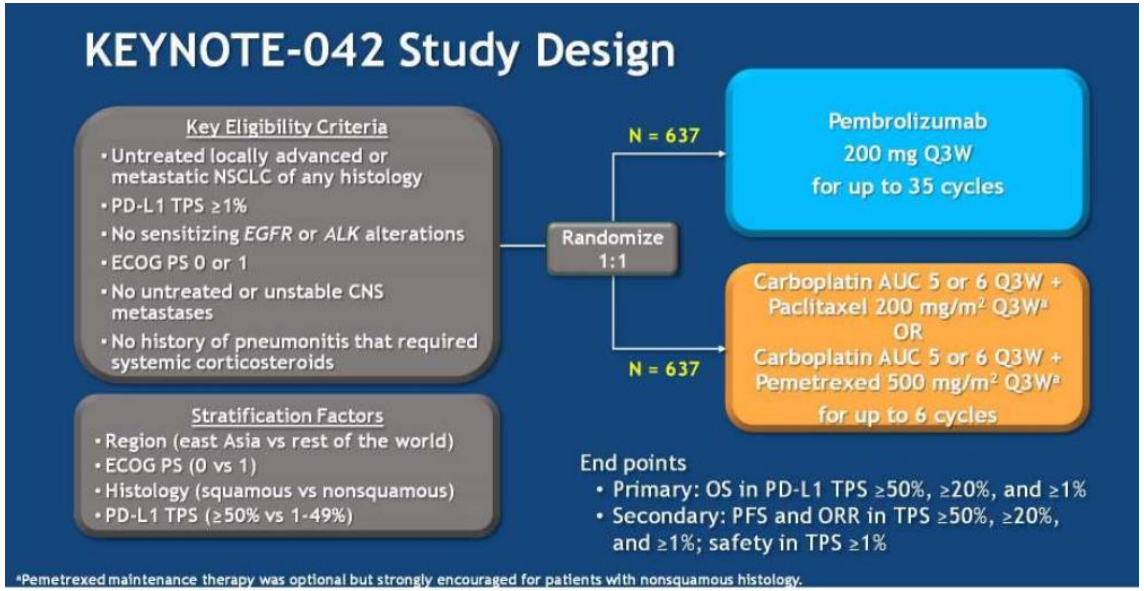
	N	Events, n (%)	HR (95% CI)
Pembrolizumab[a]	154	97 (63)	0.65 (0.50–0.86) *P* = 0.001[b]
Chemotherapy	151	113 (75)	

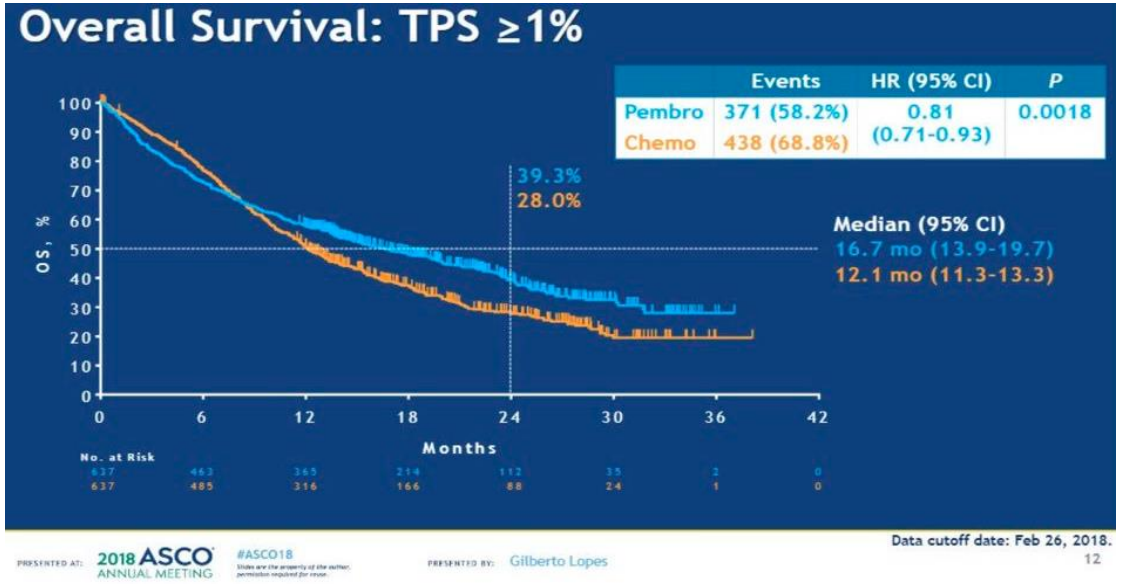
Median (95% CI)
26.3 mo (18.3–40.4 mo)
14.2 mo (9.8–18.3 mo)

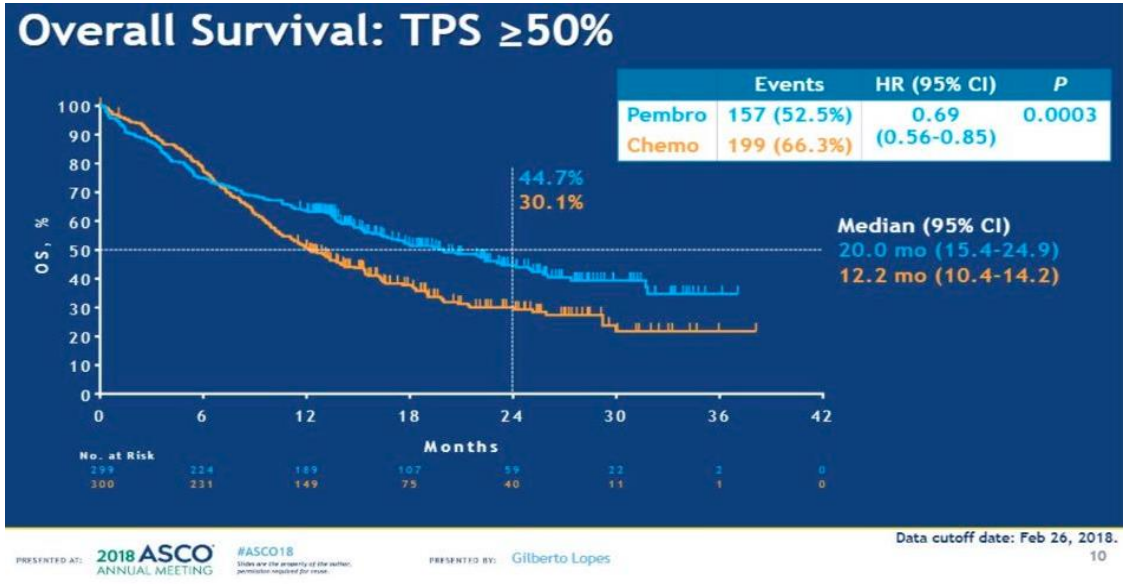
No. at risk																	
Pembrolizumab	154	136	121	112	106	96	89	85	78	73	73	69	66	64	50	24	5
Chemotherapy	151	124	108	88	80	69	61	56	48	46	44	37	35	33	24	14	6

[a]Effective crossover rate from chemotherapy to anti–PD-L1 therapy, 64.9% (98 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 21 patients received subsequent anti–PD-L1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-L1 therapy). [b]Nominal *P* value.
Data cutoff: February 15, 2019.

ADVANCED NSCLC
KEYNOTE-042: Pembrolizumab as First-line Treatment with PD-L1 TPS ≥ 1%







TWO IS MEGL CHE ONE

IMMUNOTHERAPY + CHEMOTHERAPY : WHY NOT?

KEYNOTE 189: 1° line stage IV NSCLC regardless PD-L1

The NEW ENGLAND JOURNAL of MEDICINE

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*

TWO IS MEGL CHE ONE

IMMUNOTHERAPY + CHEMOTHERAPY : WHY NOT?

KEYNOTE 189: 1° line stage IV NSCLC regardless PD-L1

Key Eligibility Criteria
- Untreated stage IV nonsquamous NSCLC
- No sensitizing *EGFR* or *ALK* alteration
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

Stratification Factors
- PD-L1 expression (TPS[a] <1% vs ≥1%)
- Platinum (cisplatin vs carboplatin)
- Smoking history (never vs former/current)

R (2:1)

N = 410

Pembrolizumab 200 mg + Pemetrexed 500 mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m² Q3W for 4 cycles

Pembrolizumab 200 mg Q3W for up to 31 cycles + Pemetrexed 500 mg/m² Q3W

N = 206

Placebo (normal saline) + Pemetrexed 500 mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m² Q3W for 4 cycles

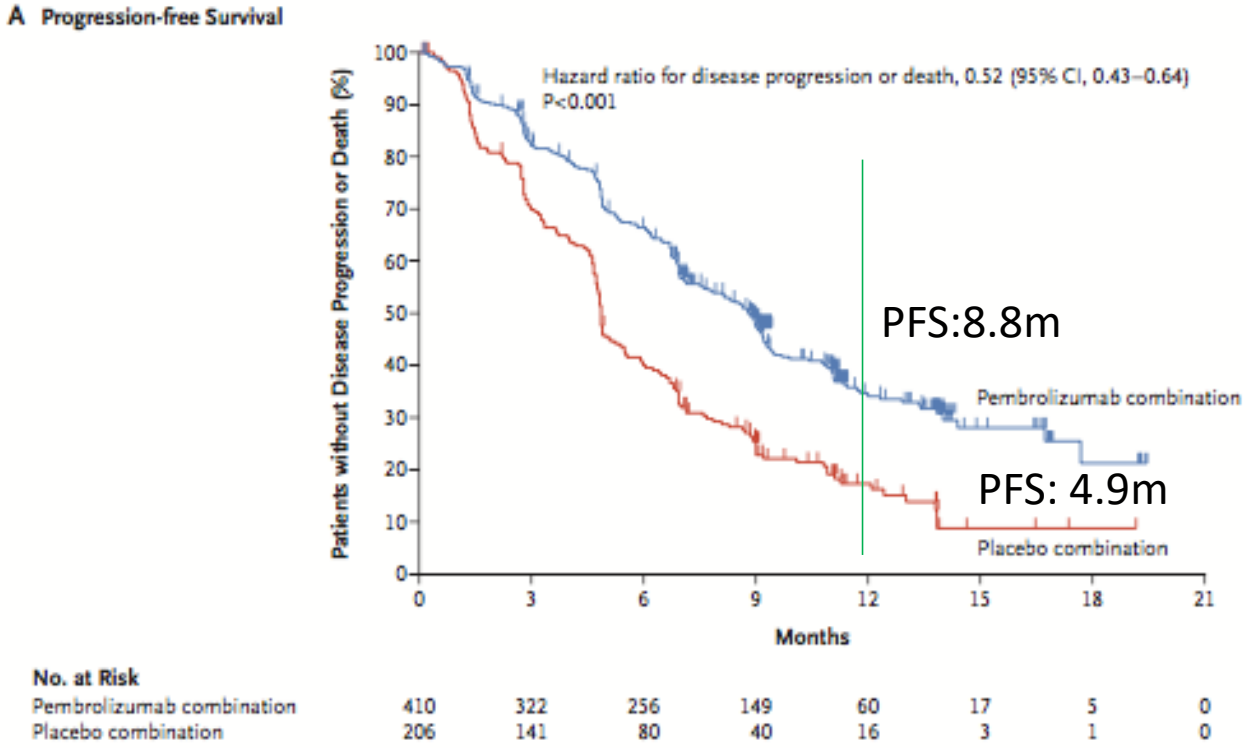
Placebo (normal saline) for up to 31 cycles + Pemetrexed 500 mg/m² Q3W

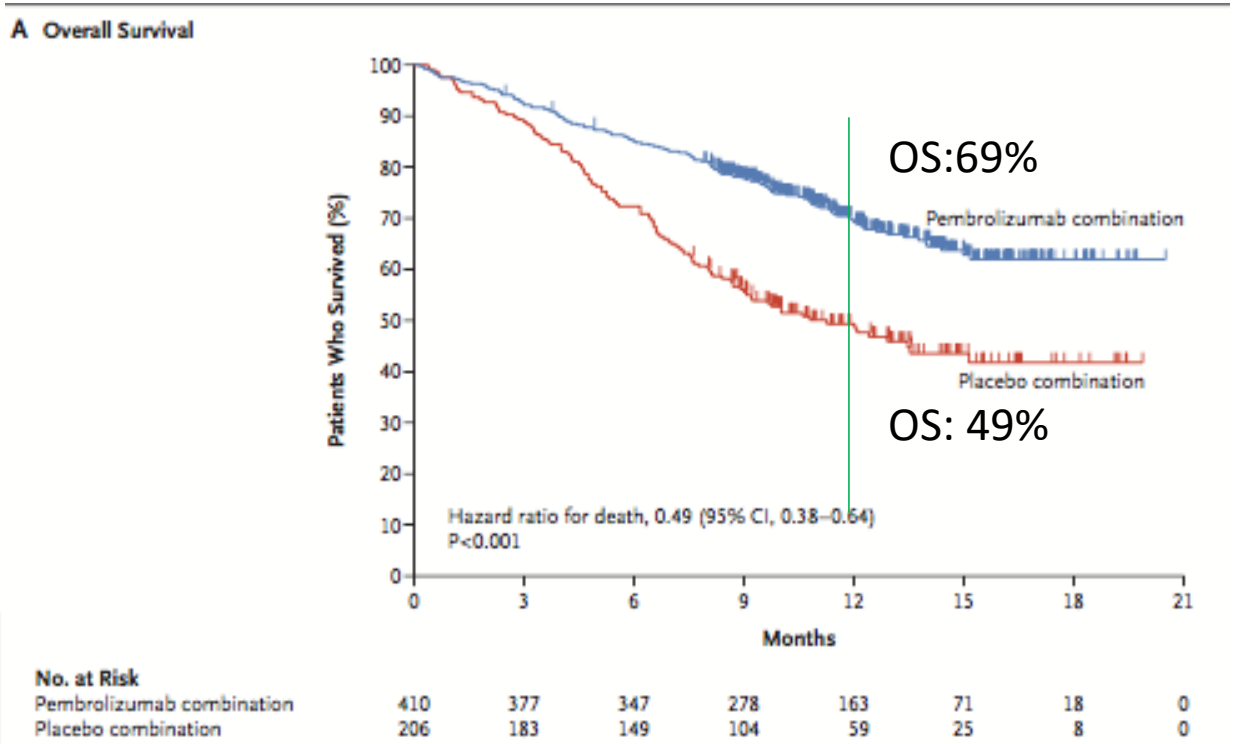
PD[b]

Pembrolizumab 200 mg Q3W for up to 35 cycles

Gandhi NEJM 2019

KEYNOTE 189: SURVIVAL OUTCOMES

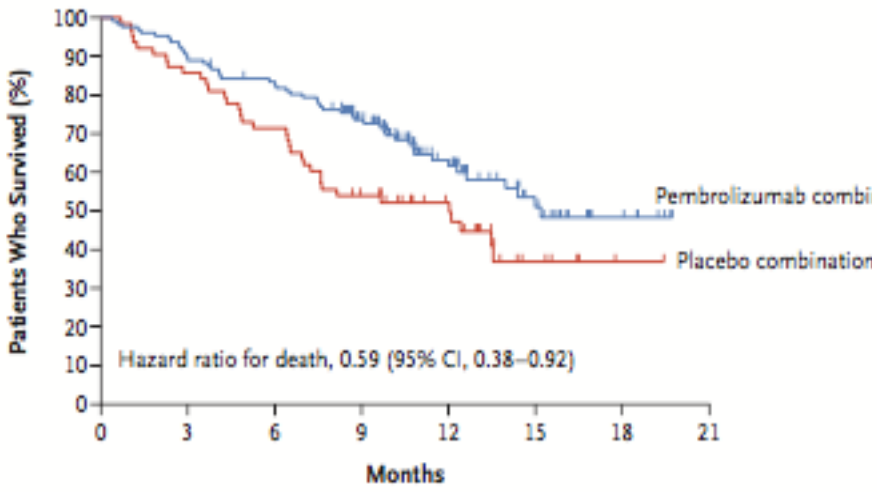




NB 47.6% **Response rate** in the pembrolizumab-combination group **vs** 18.9% in the placebo-combination group (P<0.001).

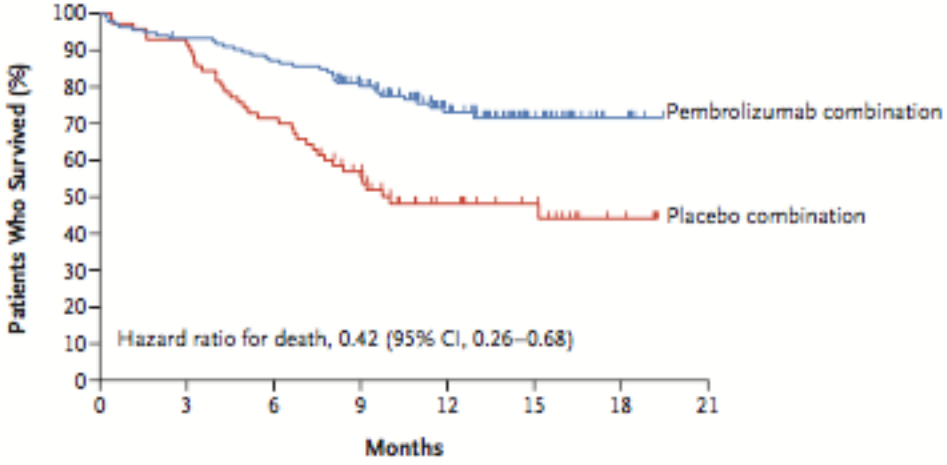
KEYNOTE 189 : PD-L1 YES or NO ?

A Tumor Proportion Score of <1%



No. at Risk								
Pembrolizumab combination	127	113	104	79	42	20	6	0
Placebo combination	63	54	45	32	21	6	1	0

C Tumor Proportion Score of ≥50%



No. at Risk								
Pembrolizumab combination	132	122	114	96	56	25	6	0
Placebo combination	70	64	50	35	19	13	4	0

THE BENEFIT OF THE PEMBROLIZUMAB COMBINATION WAS OBSERVED IN ALL SUBGROUPS: **INCLUDING THOSE WITH A PD-L1 TUMOR PROPORTION SCORE < 1%**

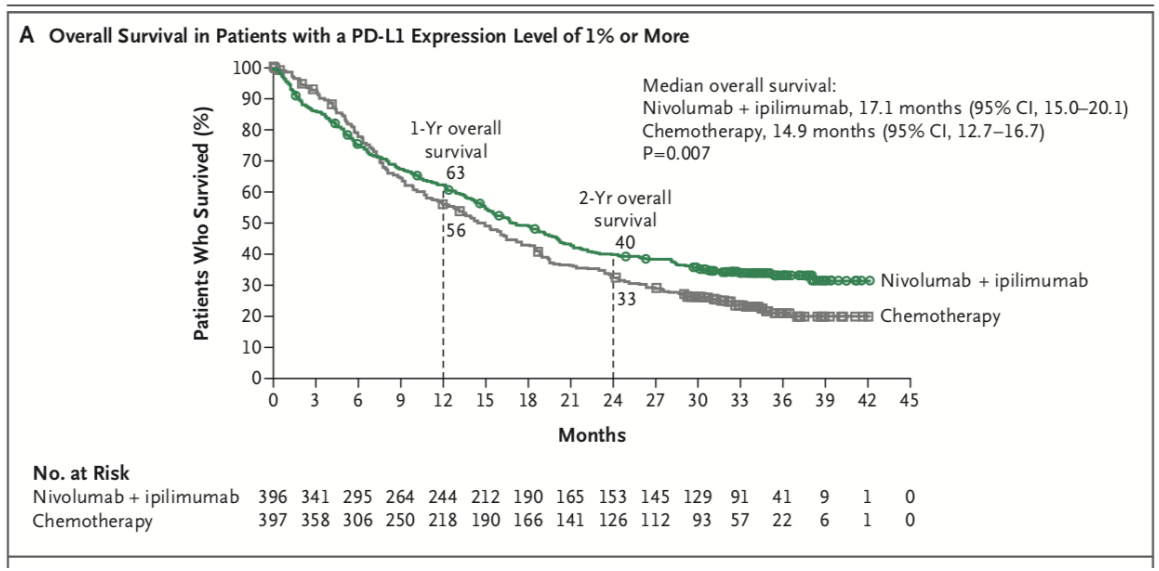
TWO IS MEGL CHE ONE

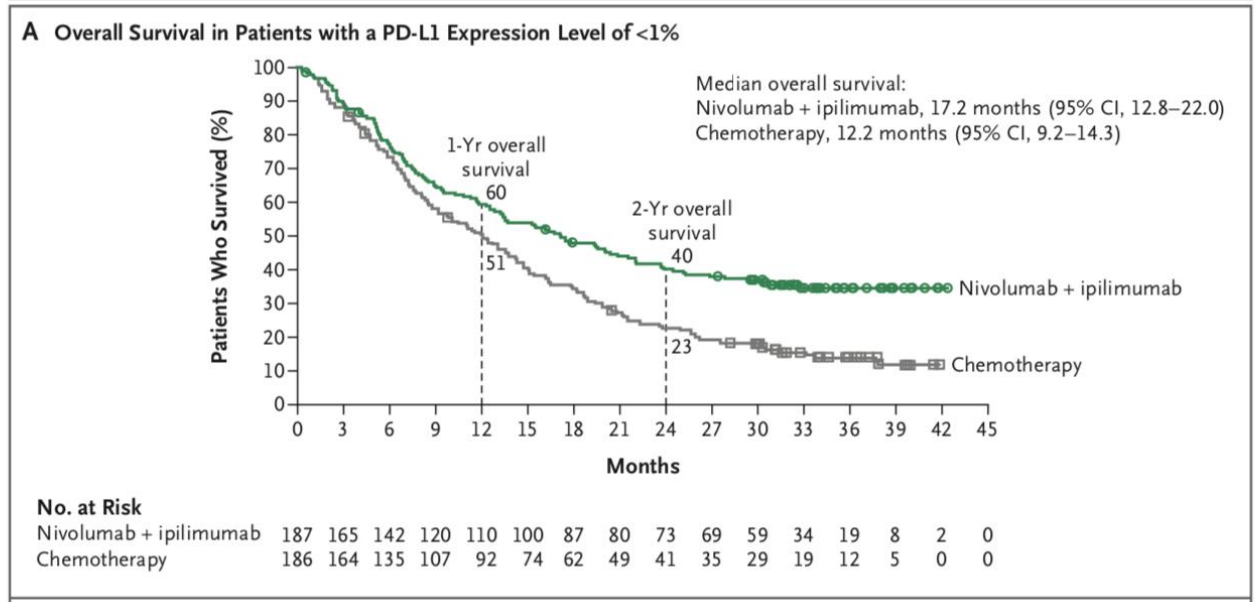
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer

M.D. Hellmann, L. Paz-Ares, R. Bernabe Caro, B. Zurawski, S.-W. Kim, E. Carcereny Costa, K. Park, A. Alexandru, L. Lupinacci, E. de la Mora Jimenez, H. Sakai, I. Albert, A. Vergnenegre, S. Peters, K. Syrigos, F. Barlesi, M. Reck, H. Borghaei, J.R. Brahmer, K.J. O'Byrne, W.J. Geese, P. Bhagavatheeswaran, S.K. Rabindran, R.S. Kasinathan, F.E. Nathan, and S.S. Ramalingam





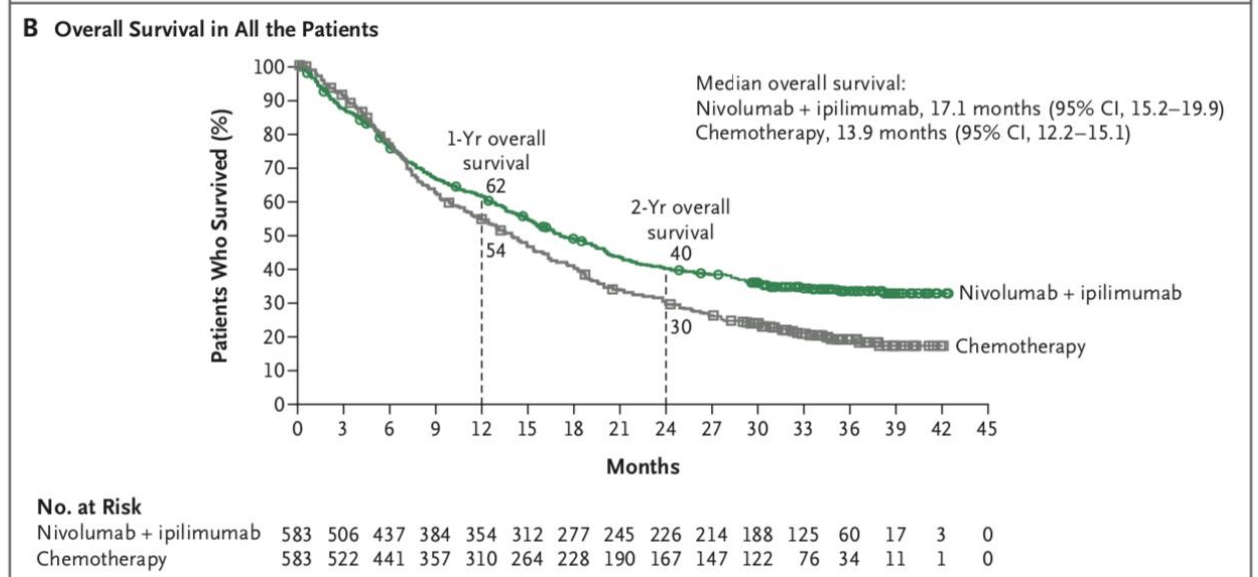
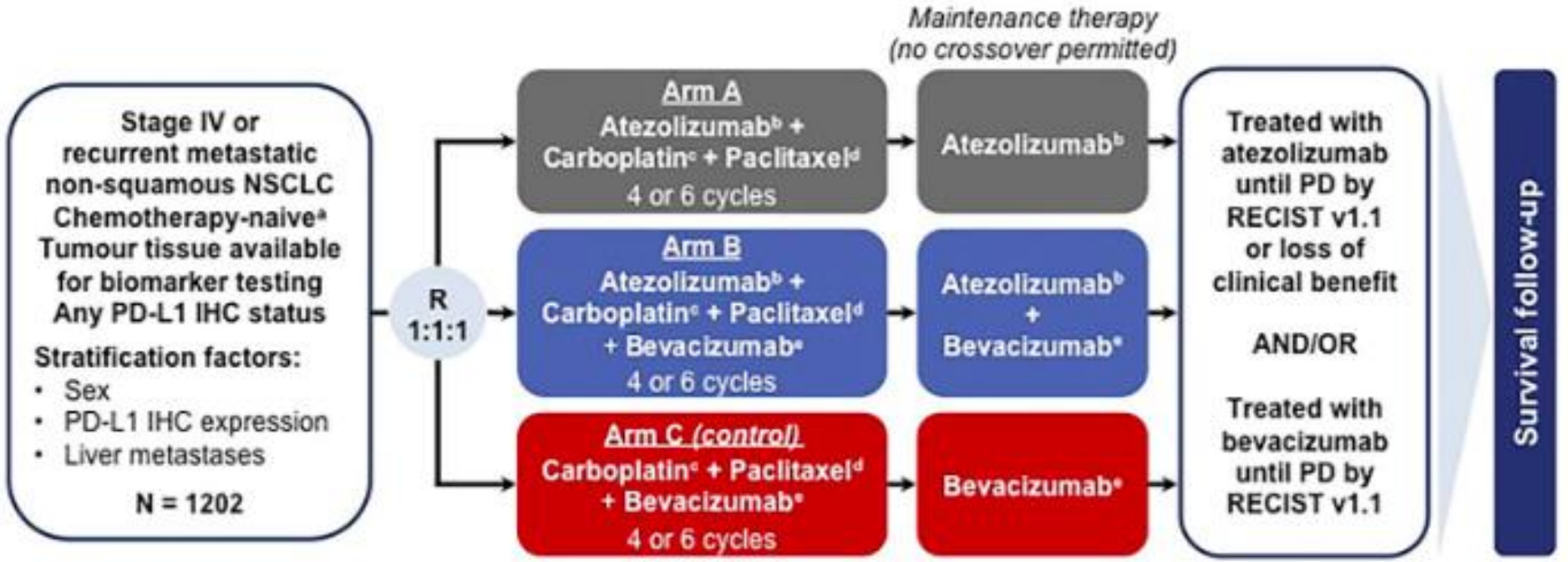


Figure 2. Overall Survival in Patients with a Tumor PD-L1 Expression Level of Less Than 1% and in All the Patients.
Shown is the median duration of overall survival in patients in the group that received nivolumab plus ipilimumab and in the group that received chemotherapy among those who had a tumor PD-L1 expression level of less than 1% (Panel A) and among those in the overall population (Panel B). Also shown are the 1-year and 2-year rates of survival in the two groups.

THREE IS A MAGIC NUMBER

ESMO 2018: NON-SQUAMOUS NSCLC 1°LINE
ATEZOLIZUMAB + CHEMO + BEV vs CHEMO + BEV



The principal question is to assess whether the addition of atezolizumab to Arm C provides clinical benefit

[a] Patients with a sensitising *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/m² IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

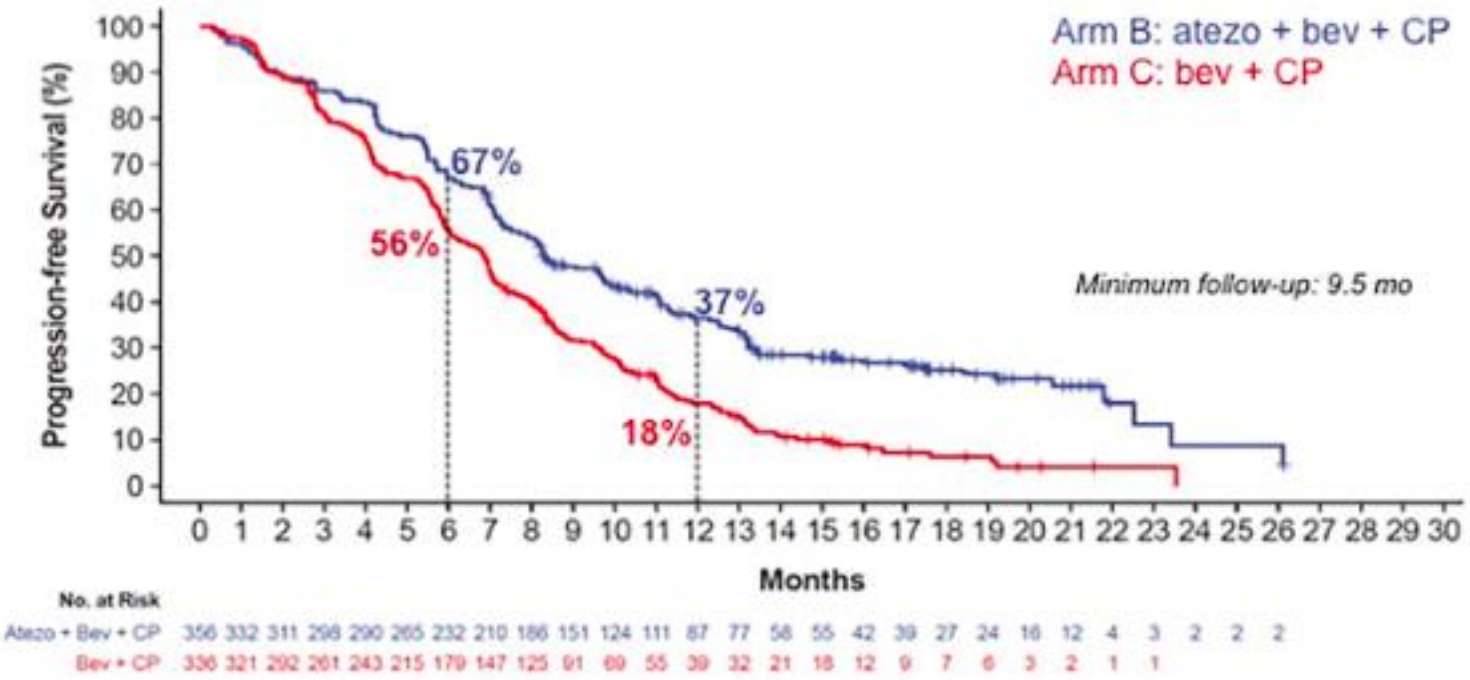
Reck M, et al. IMpower150 PFS analysis.

THREE IS A MAGIC NUMBER

the future you want

ESMO 2018: NON-SQUAMOUS NSCLC 1°LINE
ATEZOLIZUMAB + CHEMO + BEV vs CHEMO + BEV

PFS OUTCOMES



INV, investigator.
Data cutoff: September 15, 2017

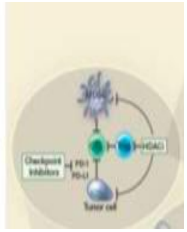
Reck M, et al. IMpower150 PFS analysis.

TOMORROWLAND : IMMUNOTHERAPY [2]

New emerging pathways for future combination with anti-PD-1/PD-L1 compounds

- Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor
- ENT leads to downregulation of immunosuppressive cell types in the tumor microenvironment
- Synergy with anti-PD-1 inhibition in preclinical models

HDAC inhibitor
(eg., entinostat [Ph 2])



Entinostat in combination with anti-PD-(L)1 therapy

ENCORE-601: Open-label study evaluating ENT + PEMBRO in patients with recurrent or metastatic NSCLC and prior progression on anti-PD-1/PD-L1 therapy

Phase 1b:
Dose & safety confirmation

Phase 2:
ENT 5 mg PO QW +
PEMBRO 200 mg IV Q3W

- NSCLC Progressing on Anti-PD-1/PD-L1
- NSCLC Anti-PD-1/PD-L1–naive
- Melanoma Progressing on Anti-PD-1/PD-L1
- Mismatch Repair-Proficient CRC Anti-PD-1/PD-L1-naive

Inclusion Criteria:

- Recurrent or metastatic NSCLC, measurable by RECIST 1.1
- Prior progression on anti-PD(L1) treatment
- Prior chemotherapy in the advanced/metastatic setting
- Prior ALK or EGFR treatment if indicated
- ECOG Performance Status < 2
- Willingness to baseline and on-Tx biopsy and blood samples

Phase 2 Primary Endpoint

- ORR (irRECIST)

Phase 2 Secondary Endpoints

- PFS, OS, safety & tolerability

76 patients enrolled (72 efficacy evaluable*), last patient enrolled December 2017

- Sample size was based on single proportion binomial test, assuming a true ORR of 15% & lower threshold of 5%, with 90% power and a 1-sided significance level of 5%.

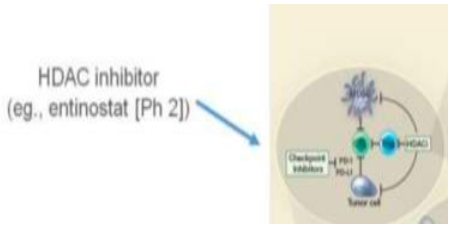
*4 patients were non-evaluable due to withdrawal of consent or discontinuations for administrative reasons prior to the first tumor assessment.

ALK, anaplastic lymphoma kinase; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ENT, entinostat; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression-free survival; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumors; QW, once a week; Q3W, every 3 weeks.

TOMORROWLAND : IMMUNOTHERAPY [2]

New emerging pathways for future combination with anti-PD-1/PD-L1 compounds

- Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor
- ENT leads to downregulation of immunosuppressive cell types in the tumor microenvironment
- Synergy with anti-PD-1 inhibition in preclinical models



Entinostat in combination with anti-PD-(L)1 therapy

Conclusions: ENT + PEMBRO in PD-(L)1 Pre-treated NSCLC

- ENT + PEMBRO demonstrated anti-tumor activity (ORR 10%) in patients with NSCLC who have progressed on prior PD-(L)1 blockade
  - Prespecified ORR target not reached; may represent clinically meaningful activity
  - An additional 50% of patients achieved disease stabilization
- Responses to ENT+ PEMBRO were independent of baseline PD-L1 expression

- Peripheral monocyte frequency as a predictor of anti-tumor immune response has been shown[1]

AACR 2019

SELEZIONE DEL PAZIENTE : ESISTONO FATTORI PREDITTIVI DI RISPOSTA

Precision Medicine ?

MAGGIORE È L'ESPRESSIONE DEL PD-L1 PIÙ È ALTA LA PROBABILITÀ DI RISPONDERE ALL'IMMUNOTERAPIA !

Ma… ANCHE PAZIENTI PD-L1 NEGATIVI POSSONO BENEFICIARE DELL' IMMUNOTERAPIA

E poi... Ruolo del Tumor Mutational Burden, del microambiente tumorale e…

SELEZIONE DEL PAZIENTE : ESISTONO FATTORI PREDITTIVI DI RISPOSTA

Mancano studi di confronto:
QUALE STRATEGIA MIGLIORE PER CIASCUN PAZIENTE?

(IM)Precision Medicine ?

MAGGIORE È L'ESPRESSIONE DEL PD-L1 PIÙ È ALTA LA PROBABILITÀ DI RISPONDERE ALL'IMMUNOTERAPIA !

Ma…

ANCHE PAZIENTI PD-L1 NEGATIVI POSSONO BENEFICIARE DELL' IMMUNOTERAPIA

E poi...

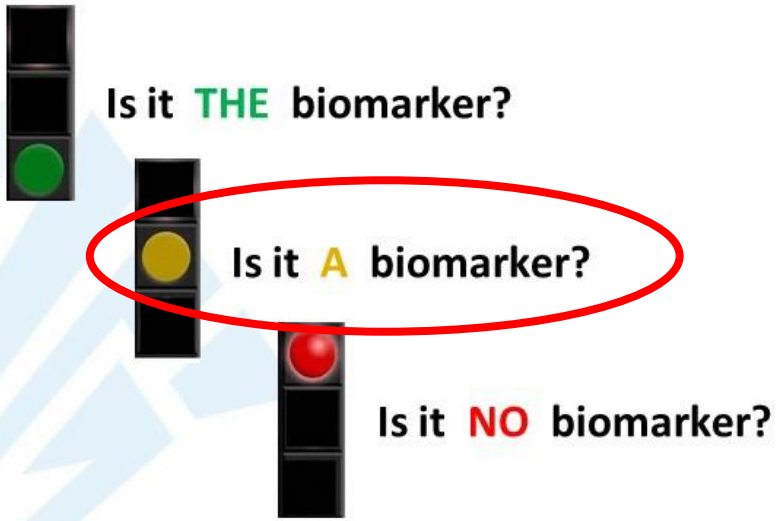
Ruolo del Tumor Mutational Burden, del microambiente tumorale e…

PD-L1: THE ONE and ONLY ?

Lung cancer immunotherapy

> defining expectations with anti PD-1/PD-L1 therapy

PD-L1 immunohistochemistry

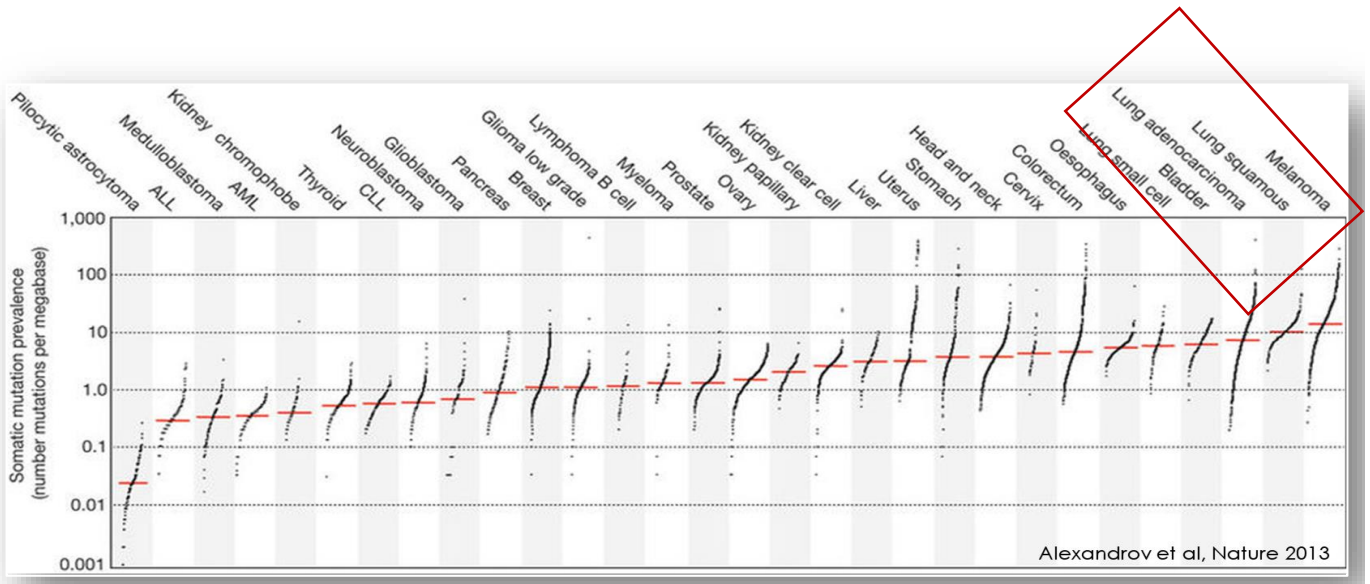


PD-L1 IHC is an "enrichment" biomarker !!

Respiratory Oncology Unit
Univ. Hospital Leuven
Leuven Lung Cancer Group
http://www.LLCG.be

Modified from Johan Vansteenkiste (Belgio) WCLC 6-12-16 SC22

TMB: TUMOR MUTATIONAL BURDEN



Genome Medicine

RESEARCH Open Access

Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden

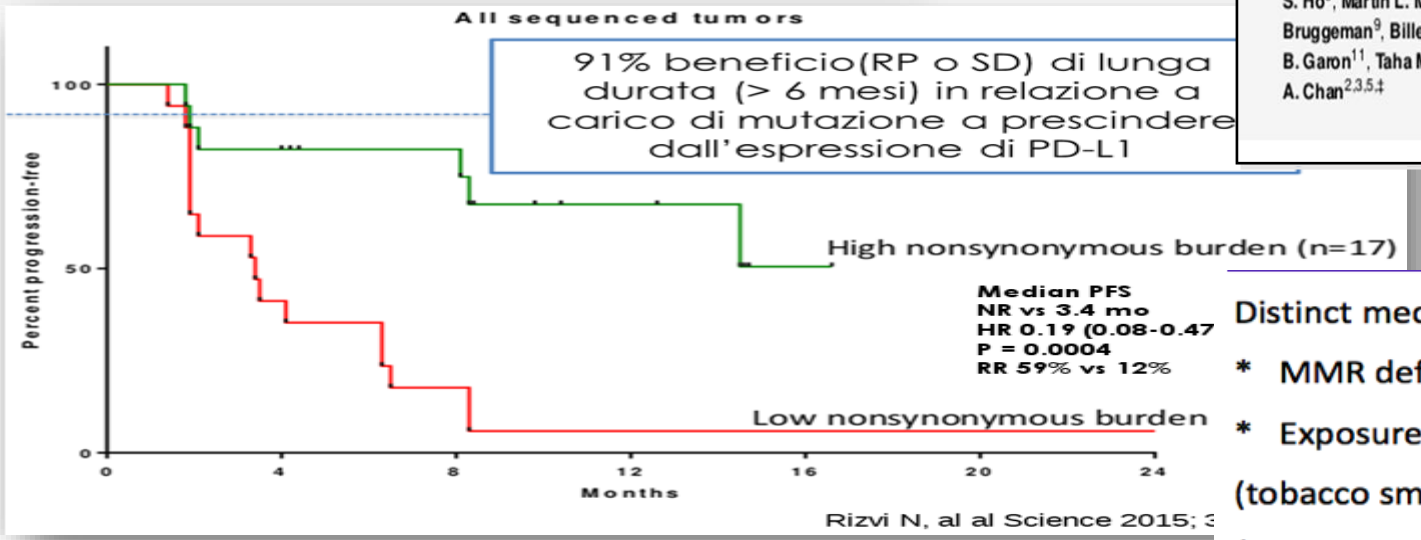
Zachary R. Chalmers[11], Caitlin
Brittany Campbell[4], Adam Sh
Mark Kennedy[1], Daniel S. Lieb
Vincent A. Miller[3], Phillip J. St

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], and Timothy A. Chan[2,3,5,‡]

Science. 2015 April 3; 348(6230): 124–128.

TUMORI CHE RISPONDONO MEGLIO HANNO UN ALTO CARICO MUTAZIONALE



Distinct mechanisms of DNA mutation:

* MMR deficiency
* Exposure to environmental mutagens (tobacco smoke and UV light)
* Virus – associated tumors

BARCELONA 2019 ESMO congress

Association Between Tissue TMB and Clinical Outcomes with Pembrolizumab Monotherapy in PD-L1-Positive Advanced NSCLC in the KEYNOTE-010 and 042 Trials

Roy S. Herbst[1], Gilberto Lopes[2], Dariusz M. Kowalski[3], Makoto Nishio[4]; Yi-long Wu[5], Gilberto de Castro Jr[6], Paul Baas[7], Dong-Wan Kim[8], Matthew A. Gubens[9], Razvan Cristescu[10], Deepti Aurora-Garg[10], Andrew Albright[10], Mark Ayers[10], Andrey Loboda[10], Jared Lunceford[10], Julie Kobie[10], Gregory Lubiniecki[10], M. Catherine Pietanza[10], Bilal Pip

[1]Yale University School of Medicine, Yale Cancer Center, New Haven, CT, USA; [2]Sylvester University of Miami, Miami, FL, USA; [3]The Maria Sklodowska Curie Memorial Cancer Centr Poland; [4]Department of Thoracic Medical Oncology, The Cancer Institute Hospital of Japan Tokyo, Japan; [5]Guandong Lung Cancer Institute, Guangdong General Hospital, and Guang Guangdong, China; [6]Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil; [7]Neth Netherlands; [8]Seoul National, University Hospital, Seoul, Republic of Korea; [9]University of [10]Merck &Co., Inc, Kenilworth, NJ, USA; [11]State Key Laboratory of Translational Oncology, Hong Kong, China

IASLC 2019 World Conference on Lung Cancer
September 7–10, 2019 | Barcelona, Spain
wclc2019.iaslc.com | #WCLC19
Conquering Thoracic Cancers Worldwide

Evaluation of TMB in KEYNOTE-189: Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy for Nonsquamous NSCLC

Marina C. Garassino,[1] Delvys Rodriguez-Abreu,[2] Shirish M. Gadgeel,[3] Emilio Esteban,[4] Enriqueta Felip,[5] Giovanna Speranza,[6] Martin Reck,[7] Rina Hui,[8] Michael Boyer,[9] Razvan Cristescu,[10] Deepti Aurora-Garg,[10] Andrew Albright,[10] Andrey Loboda,[10] Julie Kobie,[10] Jared Lunceford,[10] Mark Ayers,[10] Gregory M. Lubiniecki,[10] Bilal Piperdi,[10] M. Catherine Pietanza,[10] Edward B. Garon[11]

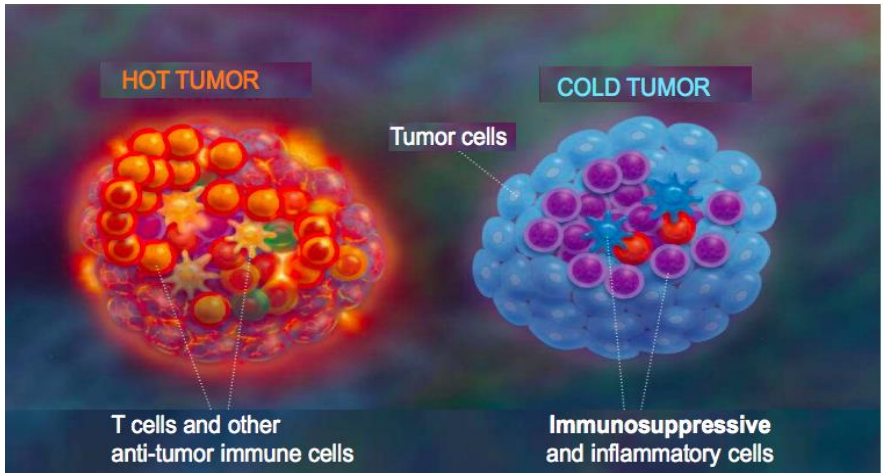
[1]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [2]Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain; [3]Karmanos Cancer Institute, Detroit, MI, USA (currently at University of Michigan, Ann Arbor, MI, USA); [4]Hospital Universitario Central de Asturias, Oviedo, Spain; [5]Vall d'Hebron University, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [6]Centre integré de cancérologie de la Montérégie, Université de Sherbrooke, Greenfield Park, QC, Canada; [7]LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [8]Westmead Hospital and University of Sydney, Sydney, NSW, Australia; [9]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [10]Merck & Co., Inc., Kenilworth, NJ, USA; [11]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

TIME : TUMOR IMMUNE MICRO-ENVIRONMENT

Tumori caratterizzati da:

ELEVATO INFILTRATO LINFOCITARIO PERITUMORALE ricco di EXHAUSTED LYMPHOCYTES.

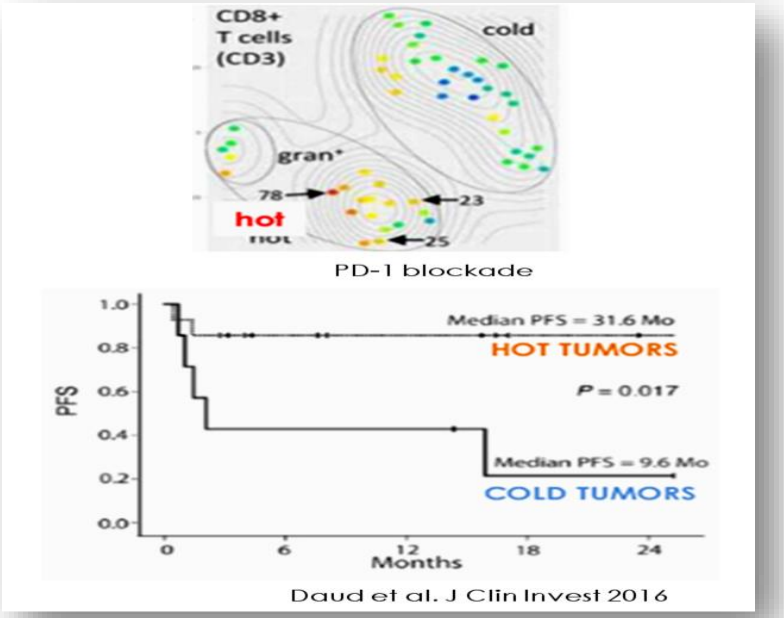
MAGGIORE PROBABILITÀ DI RISPOSTA AL TRATTAMENTO IMMUNOTERAPICO

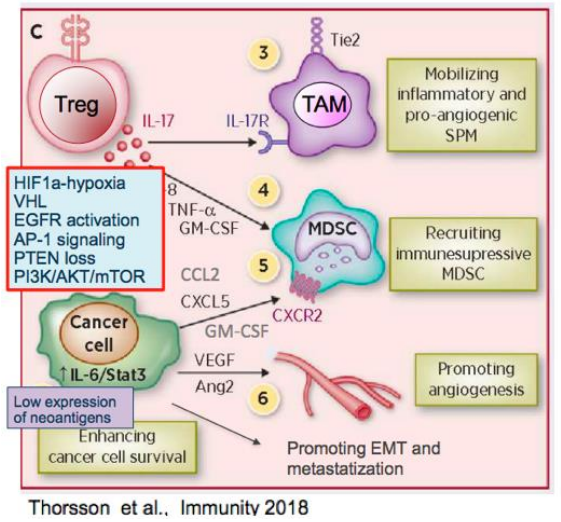


Tumori che stimolano l'arruolamento di cellule immunosoppressive nel microambiente tumorale favorendo:

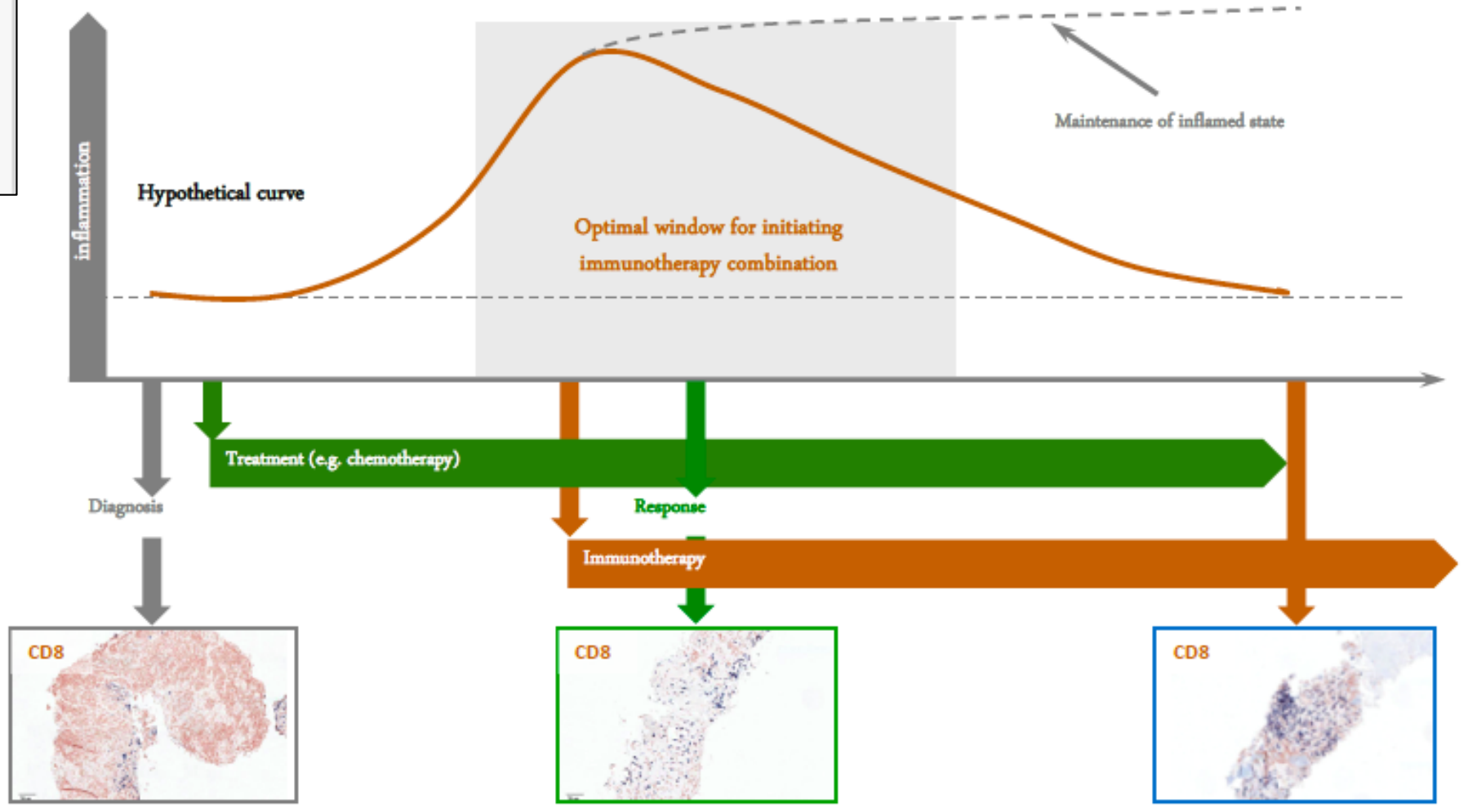
- **Angiogenesi**
- **Epitelial - Mesenchymal Transition**
- **Immunosoppressione**

POSSIAMO CONVERTIRE UN COLD TUMOR IN HOT TUMOR?





Terapie di combinazione e/o sequenziale mantengono il tumore “infiammato”

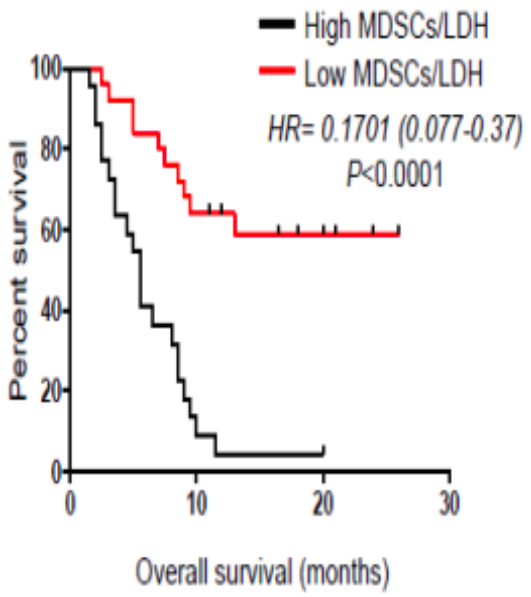


CD8 staining images are illustrative

Limiti dell'immunoterapia nel paziente oncologico: esistono fattori predittivi di risposta su sangue?

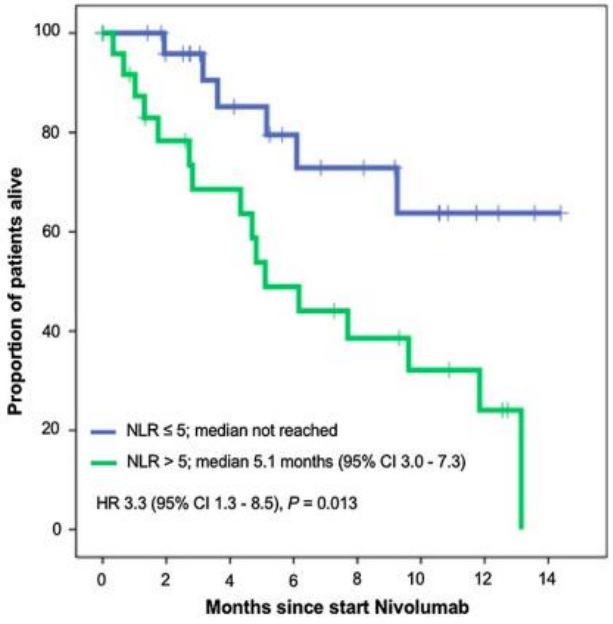
Cellule mieloidi circolanti

Monociti MDCS/LDH



Sade-Feldman et al., Clin Cancer Res 2016

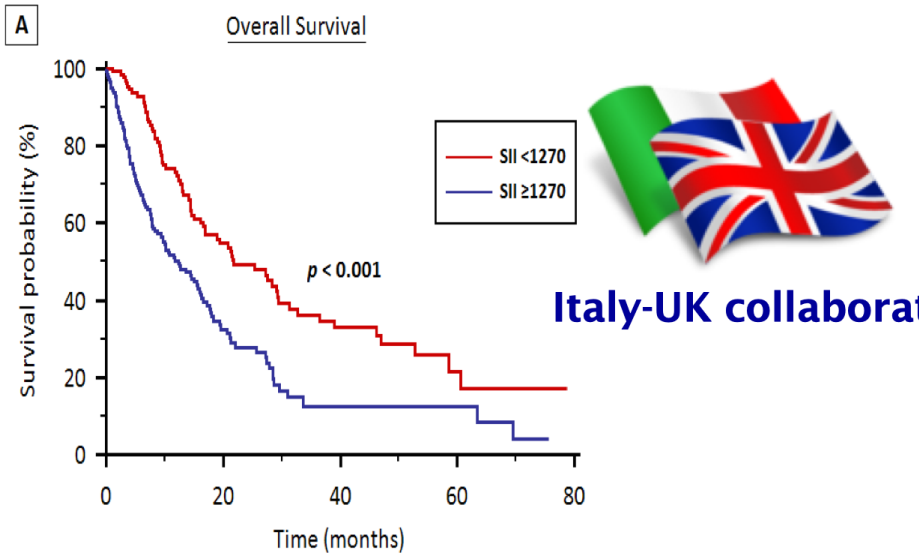
Neutrophil/lymphocytes ratio



Diem et al. Lung cancer 2011

Neutrofili **Linfociti**

Piastrine



Italy-UK collaboration

Berardi et al. Annals of Translational Medicine, 2019

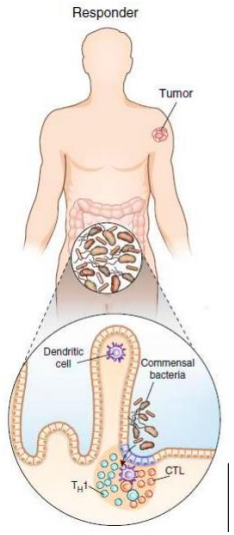
Attivazione del sistema immunosoppressivo rappresenta un fattore prognostico e predittivo negativo di risposta al trattamento immunoterapico.

PROSPETTIVE: COSA PUÒ INFLUENZARE IL SISTEMA IMMUNITARIO?

The intestinal microbiome influences checkpoint blockade

Cynthia L Sears & Drew M Pardoll

Studies in metastatic melanoma, non-small-cell lung carcinoma and renal cell carcinoma indicat
within the gut microbiota enhance clinical responses to checkpoint blockade.



Anti-PD1 in the wonder-gut-land

Cell Research advance online publication 16 January 2018; doi:10.1038/cr.2018.12

Genetics
Lifestyle
Immune status
Antibiotics
Previous treatments

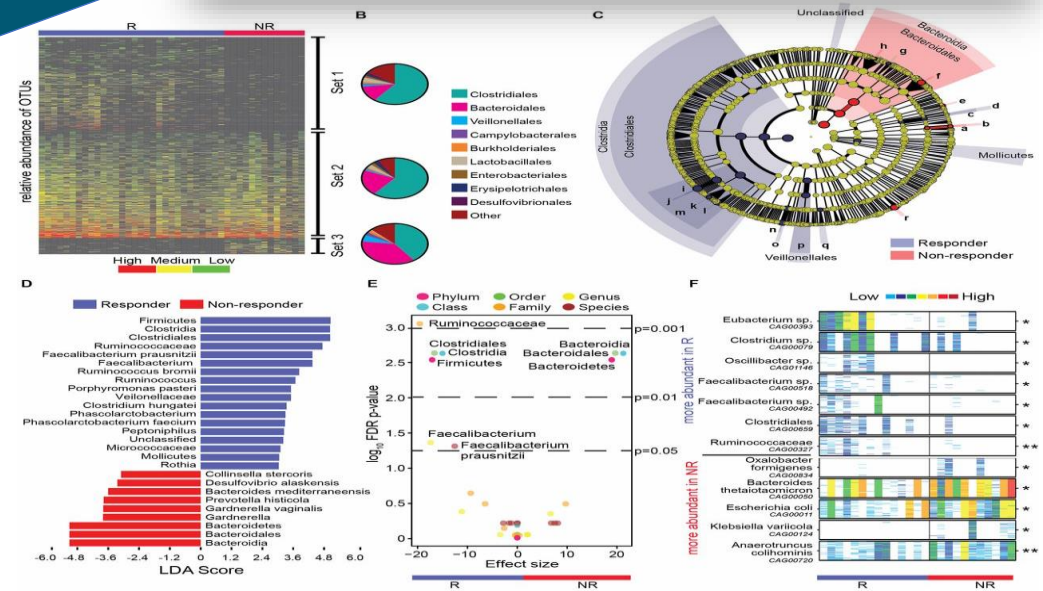
Gut microbiome composition

Bacteroidales
Antibiotics
Low alpha-diversity

Response to anti-PD1 cancer immunotherapy

Cell Research (2018):1-2.

PHASE I FMT (FECAL MICROBIOTA TRANSPLANTATION) TRIAL NCT 03353402 - DESIGN



PROSPETTIVE: IMMUNOTOXICITY BOARD

Study ID: ICI-DISCOVER, Protocol Version: 1.0

STUDY PROTOCOL

Title:	**Incidence, clinical management and molecular factors associated with the development of immune-related adverse events in cancer patients receiving PD-1 and PD-L1 inhibitors: a prospective observational study**
Short Title:	Immune-related adverse events in patients receiving immune checkpoint inhibitors
Study ID:	ICI-DISCOVER
Protocol Date:	November 14, 2018
Protocol Version:	1.0
Funding:	Departmental funds
Roles and responsibilities:	*Principal Investigators:* Prof. Rossana Berardi *Clinica Oncologica, Dipartimento di Scienze Cliniche e Molecolari, Università Politecnica delle Marche, Via Tronto 10/A, 60126, Ancona, Italy* Prof. Armando Gabrielli *Clinica Medica, Dipartimento di Scienze Cliniche e Molecolari, Università Politecnica delle Marche, Via Tronto 10/A, 60126, Ancona, Italy*

PROSPETTIVE: SELEZIONE DEL PAZIENTE

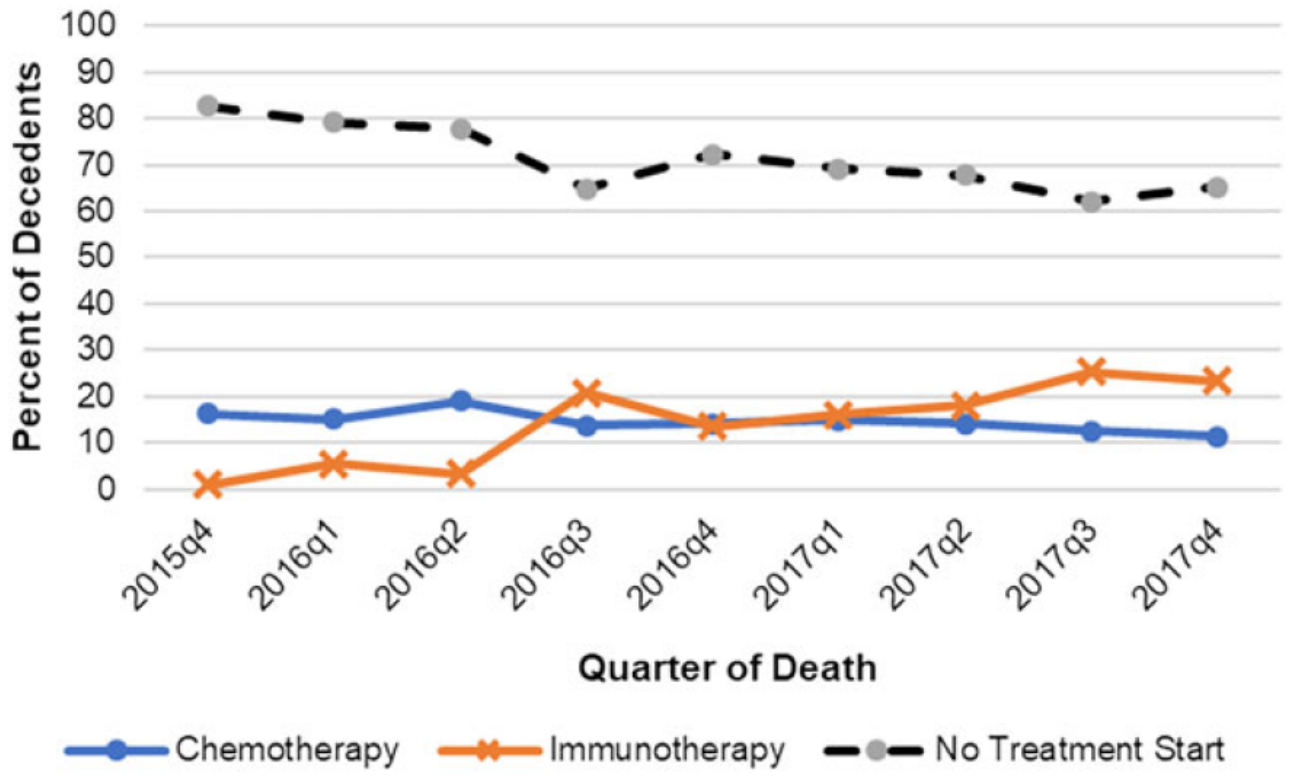
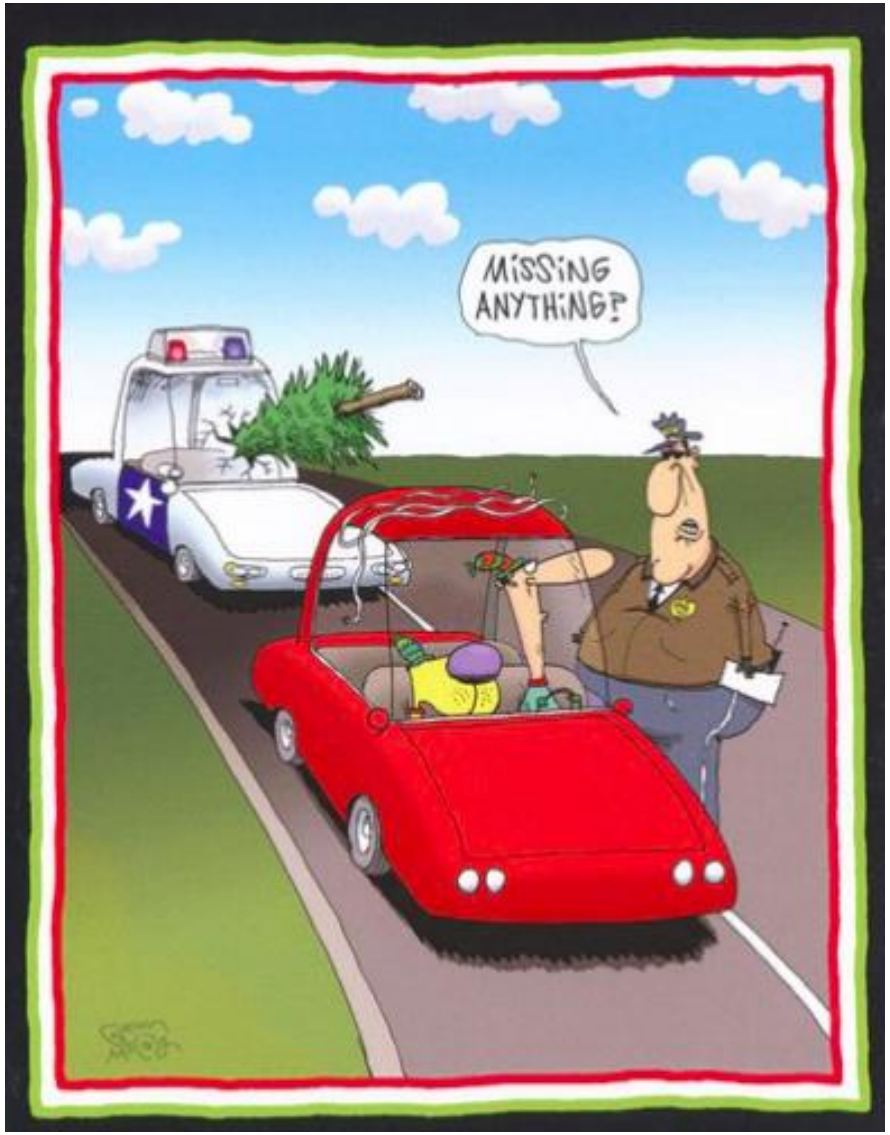


Figure 1. Initiation of new therapy in the last 60 days of life in patients with metastatic urothelial carcinoma, by treatment type. Abbreviations: q1, first quarter; q2, second quarter; q3, third quarter; q4, fourth quarter.

Parikh RB, et al. Oncologist. 2019 Jun;24(6):e397-e399.


IS ANYTHING MISSING?
¿¿¿


MISSING ANYTHING?

HOW FAR WILL WE GO?

FINANCIAL SUSTAINABILITY

laduraverità

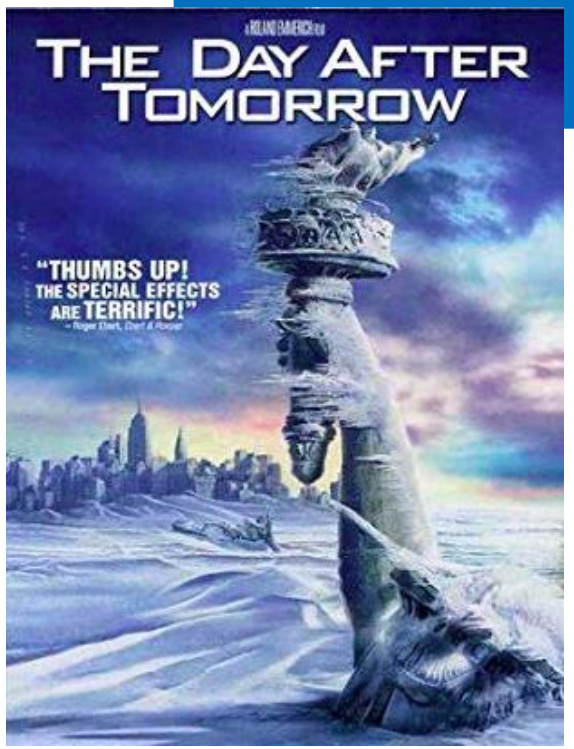
IMMUNOTERAPIA

- EFFICACE
- TUTTI LA VOGLIONO, TUTTI LA CERCANO
- MIGLIORE TOLLERANZA vs CHEMIOTERAPIA

IMMUNOTERAPIA

-PRESTAZIONI ELEVATE A COSTI ELEVATI
-DIVERSE TOSSICITÀ non ZERO TOSSICITÀ
-NON SEMPRE, QUANDO È GIUSTO

THE DAY AFTER TOMORROW
ECONOMIC SCENARIO



"Instead of moving forward, this approach promotes the most therapy as soon as possible until the money runs out."

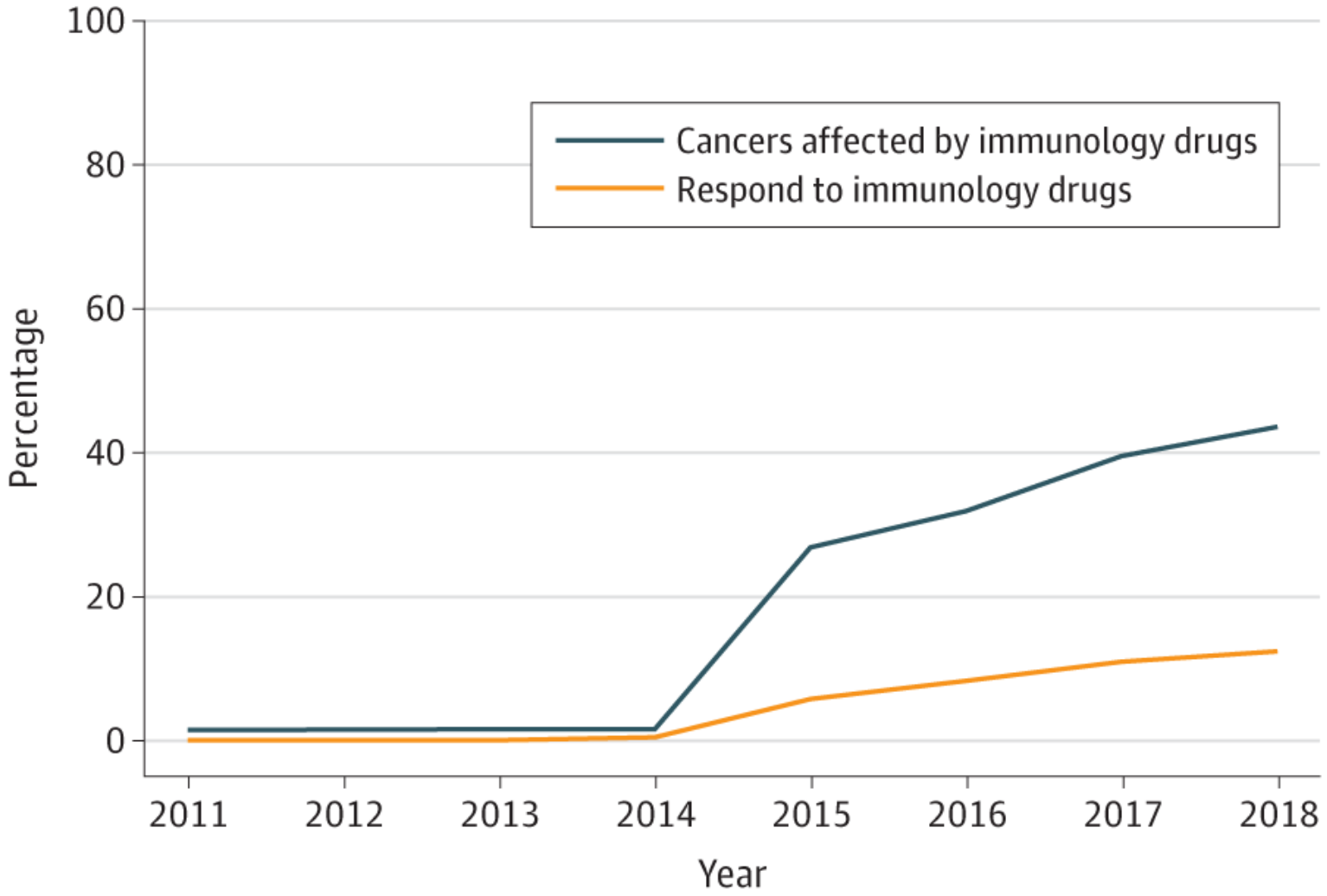
Howard Jack West

Immunoterapia per tutti?

Movie: "The DAY AFTER TOMORROW " by

Roland Emmerich 2004

Percentage of US Patients With Cancer Who May Benefit and Respond to Checkpoint Inhibitors (2011-2018)



Haslam A, Prasad V. *JAMA Netw Open.* 2019;2(5):e192535.

Cancer Treatment Reviews 48 (2016) 20–24

Contents lists available at ScienceDirect

Cancer Treatment Reviews

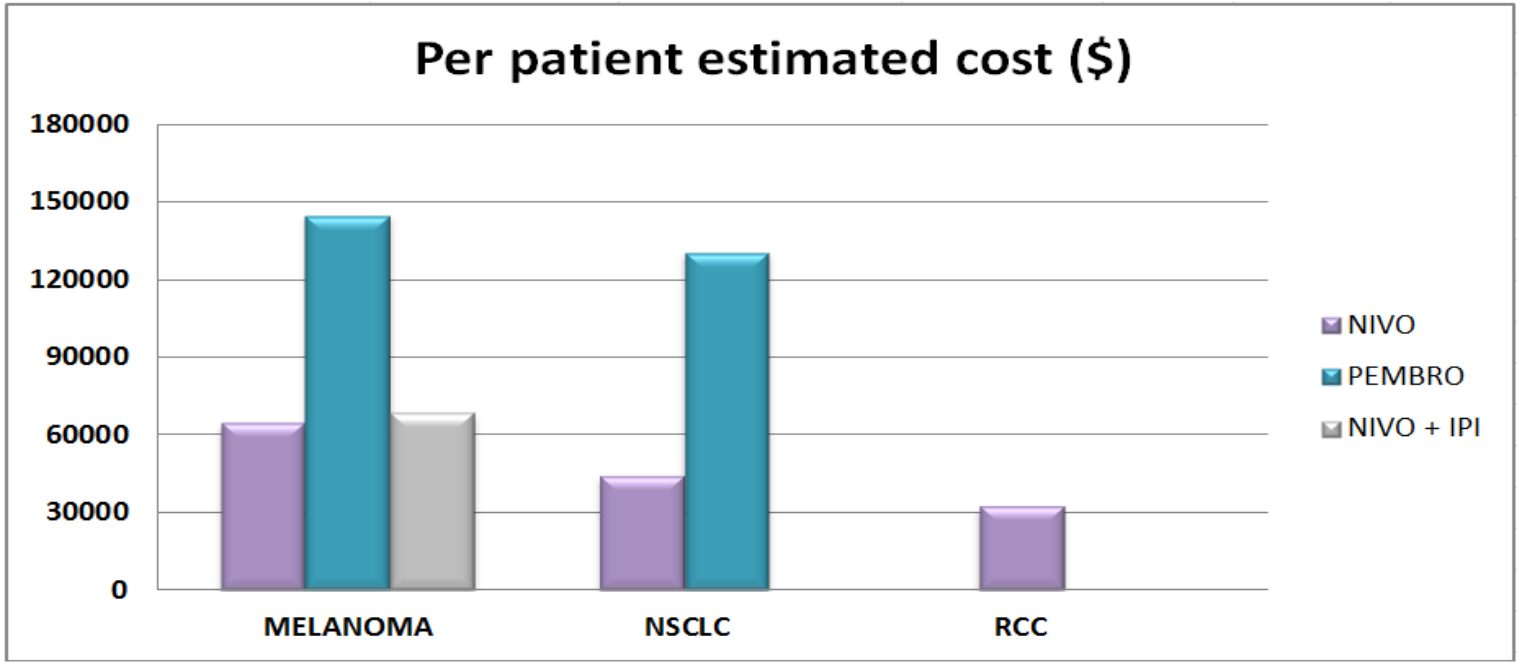
journal homepage: www.elsevierhealth.com/journals/ctrv

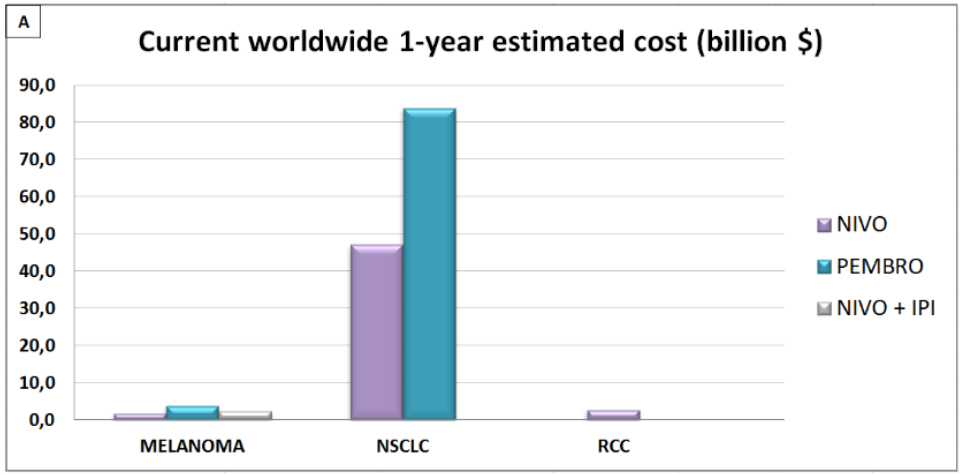
Anti-Tumour Treatment

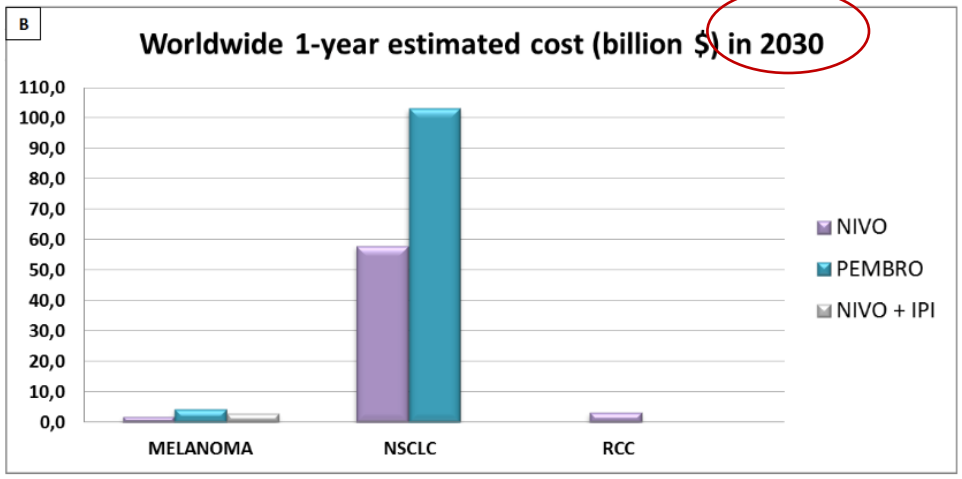
Economic sustainability of anti-PD-1 agents nivolumab and pembrolizumab in cancer patients: Recent insights and future challenges

Francesca Tartari [a,1], Matteo Santoni [b,*,1], Luciano Burattini [b], Paola Mazzanti [b], Azzurra Onofri [b], Rossana Berardi [b]

PER PATIENT ESTIMATED COST ($) OF NIVOLUMAB AND PEMBROLIZUMAB FOR THE TREATMENT OF CANCER

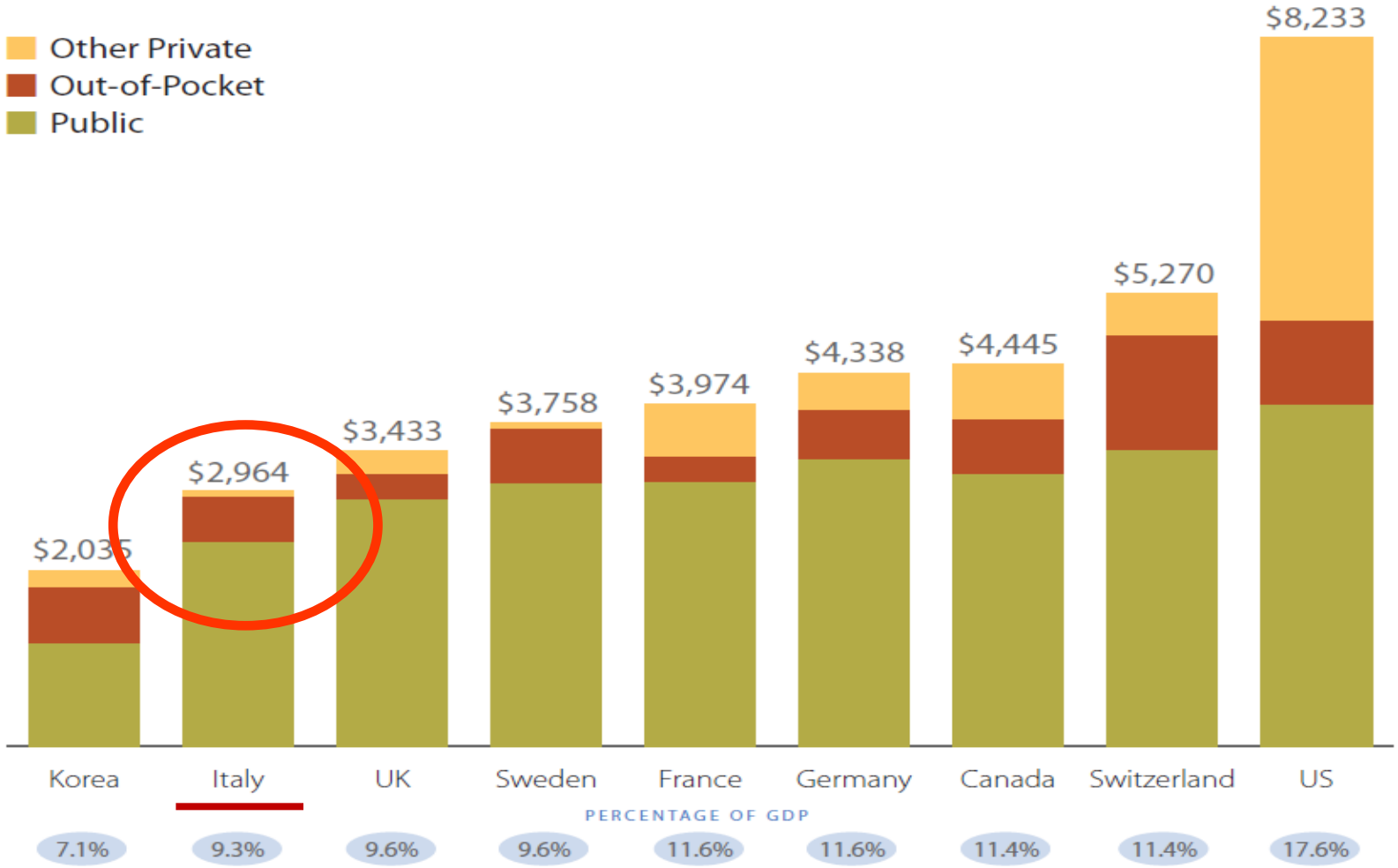






Health Spending Per Capita and as a Share of GDP

Selected Developed Countries, 2010



Notes: US spending per capita as reported by OECD differs from CMS figures reported elsewhere in this report. Health spending refers to National Health Expenditures.

Source: Organization for Economic Cooperation and Development, *OECD Health Data 2012*, June 2012, www.oecd.org.

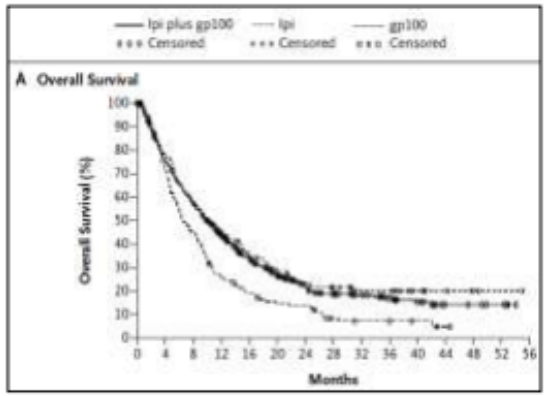
California HealthCare Foundation. *Health Care Costs 101: Slow But Steady*. California Health Care Almanac. Aug 2012

THE ONCOLOGIST DREAM
PRACTICE CHANGING SCENARIO

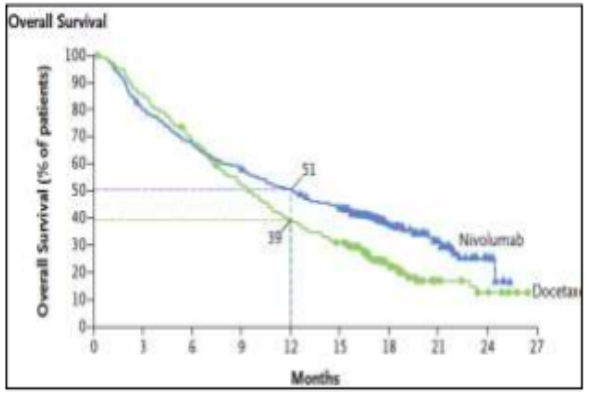
Movie: «A week from God»

by Tom Shadyac with Jim Carrey, 2003

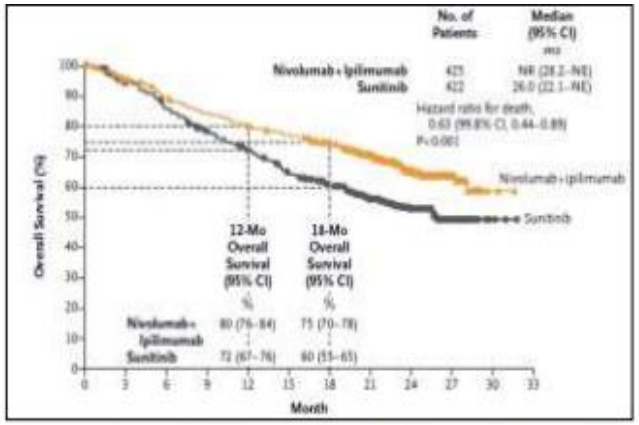
Ruolo della immunoterapia nel paziente oncologico: incremento di sopravvivenza in varie patologie



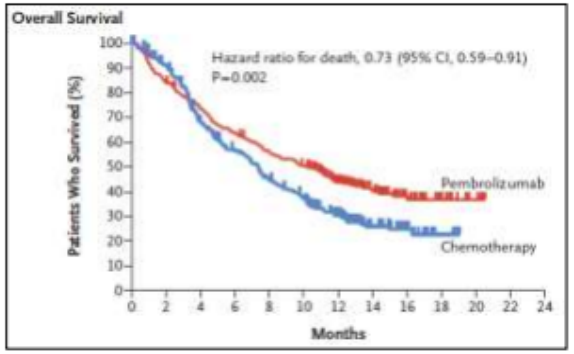
Metastatic Melanoma
Hodi NEJM 2010



Advanced NSCLC
Borghaei NEJM 2015

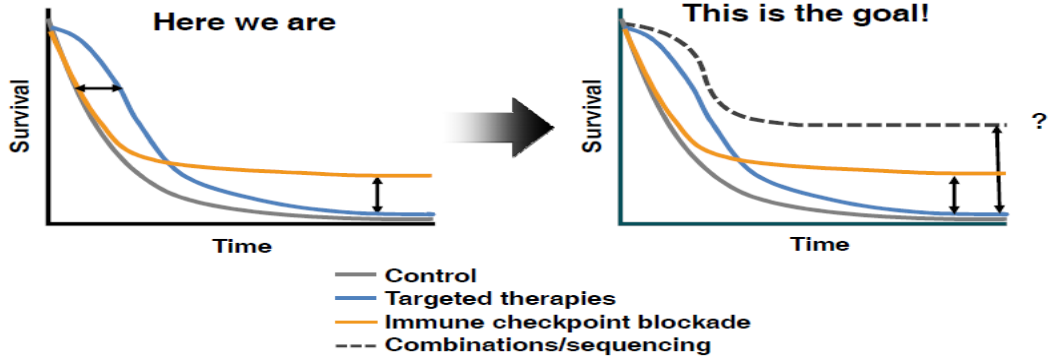


Advanced Renal Cell Carcinoma
Motzer NEJM 2018



Advanced Urothelial Carcinoma
Bellmunt NEJM 2017

Gli immunocheck-point inhibitors hanno portato ad un netto miglioramento in termini di sopravvivenza, con un quota di circa 20% di lungo sopravviventi



FINANCIAL TOXICITY

JOURNAL OF ONCOLOGY PRACTICE
The Authoritative Resource for Oncology Practices
SEPTEMBER 2014

Impact of Financial Burden of Cancer on Survivors' Quality of Life

By Kathleen M. Fenn, Suzanne B. Evans, MD, MPH, Ruth McCorkle, PhD, Michael P. DiGiovanna, MD, PhD, Lajos Pusztai, MD, DPhil, Tara Sanft, MD, Erin W. Hofstatter, MD, Brigid K. Killelea, MD, MPH, M. Tish Knobf, PhD, Donald R. Lannin, MD, Maysa Abu-Khalaf, MD, MBBS, Nina R. Horowitz, MD, and Anees B. Chagpar, MD, MSc, MPH, MA, FRCS(C), FACS

Yale School of Medicine; and Yale School of Nursing, New Haven, CT

Cancer
Month 00, 2016

Measuring Financial Toxicity as a Clinically Relevant Patient-Reported Outcome: The Validation of the COmprehensive Score for financial Toxicity

Jonas A. de Souza, MD, MBA[1]; Bonnie J. Yap, MS[1]; Kristen Wroblewski, MS[2]; Victoria Blinder, MD, MSc[3]; Fabiana S. Araújo, PhD[4]; Fay J. Hlubocky, PhD[1]; Lauren H. Nicholas, PhD[5]; Jeremy M. O'Connor, MD[1]; Bruce Brockstein, MD[6]; Mark J. Ratain, MD[1]; Christopher K. Daugherty, MD[1]; and David Cella, PhD[7]

Published in final edited form as:
Oncology (Williston Park). 2013 February ; 27(2): 80–149.

Financial Toxicity, Part I: A New Name for a Growing Problem

S. Yousuf Zafar, MD, MHS[1] and **Amy P. Abernethy, MD**[1]

[1]Center for Learning Health Care, Duke Clinical Research Institute, Duke Cancer Institute, Durham, North Carolina

THE RIGHT DRUG FOR THE RIGHT PATIENT AT THE RIGHT TIME

TAILORED MEDICINE

ALIAS

Offrire al paziente il miglior trattamento a disposizione in base alle sue condizioni e alle caratteristiche della neoplasia

COMPLIANCE - COUNSULING - FARMACOSOSTENIBILITA'

APPROPRIATEZZA

FARMACOVIGILANZA

ADERENZA

Una goccia nell'oceano?

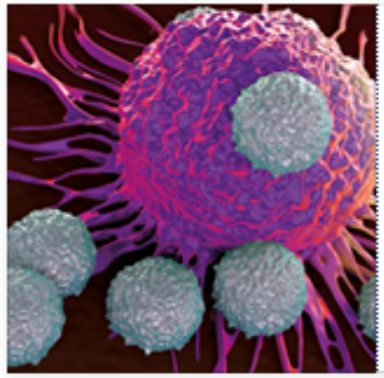
r i farmaci
ci innovativi

Con la legge di bilancio del 2017 (legge 11 dicembre 2016 n. 232. comma 401) è stato istituito il "**Fondo per il concorso al rimborso alle regioni per l'acquisto dei medicinali oncologici innovativi**".

Analogamente al fondo per i farmaci innovativi istituito nel 2015 e rinnovato nel 2016 e poi nel 2017, questo nuovo Fondo, che si riferisce ai soli farmaci oncologici innovativi, ha un valore di 500 mln che saranno assegnati a decorrere dal 1 gennaio del 2017. Il miliardo di euro dei due Fondi è ricavato dal fabbisogno sanitario nazionale standard.

Con determina del direttore generale di AIFA, da adottarsi entro il 31 marzo 2017, sono stabiliti i criteri che definiscono l'innovatività dei farmaci. Questa determina è stata poi aggiornata con quella del 18 settembre (n. 1535/2017).

AIOM ha condiviso un link.
18 ottobre alle ore 14:39 ·



Il governo stanzia 500 milioni per i farmaci oncologici. Aiom: 'Un primo passo per il 'Patto contro il cancro'' - AIOM

L'Associazione ha lo scopo di promuovere il...

AIOM.IT | DI EVENTI TELEMATICI - WWW.EVTEL.COM

UNIVERSITÀ POLITECNICA DELLE MARCHE

Sharing risks and costs

Azienda Ospedaliero Universitaria OSPEDALI RIUNITI Umberto I - G.M.Lancisi - G.Salesi Ancona

Agenzia Italiana del Farmaco AIFA

FARMINDUSTRIA
L'INDUSTRIA DEL FARMACO, L'IMPRESA DELLA VITA

MEAs
Managed Entry Agreements

Negotiation agreements between Country Authority (AIFA) and companies sharing the risk

- **Payment by Result**
- **Risk Sharing**
- **Success Fee**
- **Cost Sharing**
- **Capping o Payback**
- **Cost/Volume**
- **Flat Rate**

UNIVERSITÀ POLITECNICA DELLE MARCHE

Recupero risorse

Azienda Ospedaliero Universitaria OSPEDALI RIUNITI Umberto I - G.M.Lancisi - G.Salesi Ancona

+ di € 700.000,00

+ di € 1.000.000,00

+ di € 2.000.000,00

+ di € 17.000.000,00

+ di € 2.500.000,00

+ di € 1.500.000,00

Courtesy Dr. Marinozzi

MULTIDISCIPLINARY MANAGEMENT

ITALCERT

CERTIFICATO N° 693SGQ01

Si certifica che il

Sistema di Gestione per la Qualità

messo in atto da

Azienda Ospedaliero Universitaria
Ospedali Riuniti UMBERTO I – G.M. LANCISI – G. SALESI
Via Conca, 71 – IT 60126 ANCONA (AN)

nelle Sedi Operative

Via Conca, 71 – IT 60126 ANCONA (AN)
Via Corridoni, 11 – IT 60123 ANCONA (AN)
Via Toti, 4 – IT 60123 ANCONA (AN)

è conforme alla norma

UNI EN ISO 9001:2015 (ISO 9001:2015)

per i seguenti Processi

Progettazione ed erogazione di Percorsi Diagnostico Terapeutico Assistenziali (PDTA)
a garanzia della qualità dell'assistenza sanitaria fornita ai pazienti
dell'Azienda Ospedaliero Universitaria Ospedali Riuniti di Ancona
con specifico riferimento all'attività di degenza ed ambulatoriale
oltre ai processi relativi ai servizi trasversali ai PDTA.

L'AMMINISTRATORE DELEGATO
Dr. Ing. Roberto Cusolito

Data di Prima Emissione	Data di Prima Emissione ITALCERT	Data di Rinnovo	Data di Scadenza
2014-04-02	2018-06-05	2018-09-15	2021-09-14

Settore IAF 38

ACCREDIA

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UNI EN ISO 9001-2015 (ISO 9001-2015)

Sistema di gestione conforme alla Norma ISO 9001:2015 valutato secondo le prescrizioni del documento SINCERT RT-04.

Management system conforming to standard ISO 9001:2015 assessed according to the provisions of SINCERT document RT-04.

per i seguenti Processi

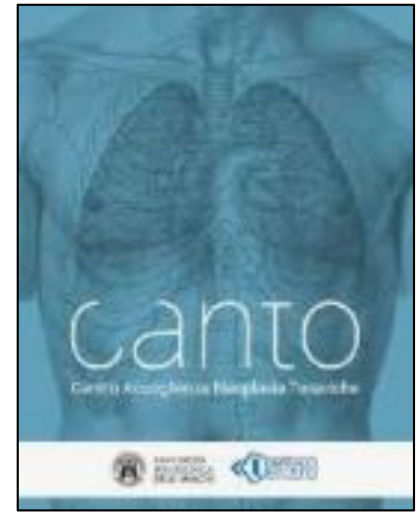
concerning the following kinds of Processes

Progettazione ed erogazione di Percorsi Diagnostico Terapeutico Assistenziali (PDTA)
a garanzia della qualità dell'assistenza sanitaria fornita ai pazienti
dell'Azienda Ospedaliero Universitaria Ospedali Riuniti di Ancona
con specifico riferimento all'attività di degenza ed ambulatoriale
oltre ai processi relativi ai servizi trasversali ai PDTA.

L'Organismo di certificazione in data 14/09/2018 ha emesso il certificato di conformità alla norma UNI EN ISO 9001:2015

DISCUSSIONE MULTIDISCIPLINARE:
come cambia il PDTA del paziente con NSCLC III stadio

Prof. Stefano Gasparini
Dott.ssa Lina Zuccatosta
PNEUMOLOGIA
Prof.ssa Rossana Berardi
Dott.ssa Paola Mazzanti
Dott.ssa Marzia Di Pietro Paolo
ONCOLOGIA
Dott.ssa Giovanna Mantello
Dott. Andra Maucieri
RADIOTERAPIA
Dott. Majed Refai
Dott. Francesco Xiumè
CHIRURGIA TORACICA
Dott.ssa Miriam Badaloni
RADIOLOGIA
Dott.ssa Francesca Barbisan
ANATOMIA PATOLOGICA



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r.berardi@univpm.it
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