SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori
Istituto di Ricovero e Cura a Carattere Scientifico

ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

# Biomarcatori predittivi nella pratica clinica: realtà e prospettive nei tumori solidi

**Paola Ulivi**
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IRST-IRCCS Meldola (FC)

Istituto Superiore di Sanità
22 Febbraio 2019

# Predictive biomarkers

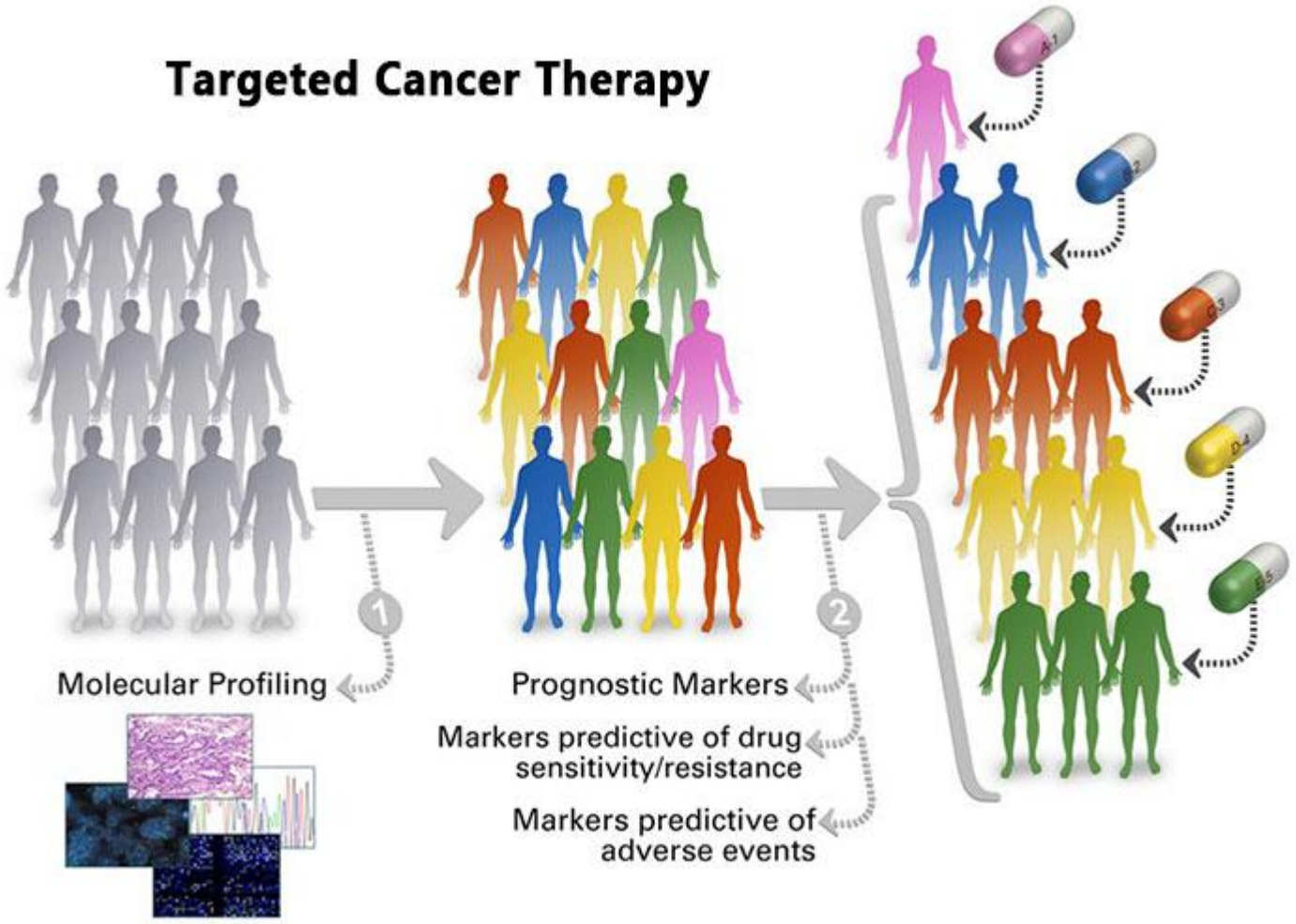
- Patients with malignancies of the same organ respond very differently to a specific drug

- Response rate in unselected patients with different types of advanced cancer vary from <10% to > 90%

- Many of the newer biological or molecular therapies have efficacy in only a minority of unselected patients, and have a high cost

**Need for predictive biomarkers to select patients with higher probability to respond**

# Precision Oncology


Targeted Cancer Therapy
1
Molecular Profiling
2
Prognostic Markers
Markers predictive of drug sensitivity/resistance
Markers predictive of adverse events

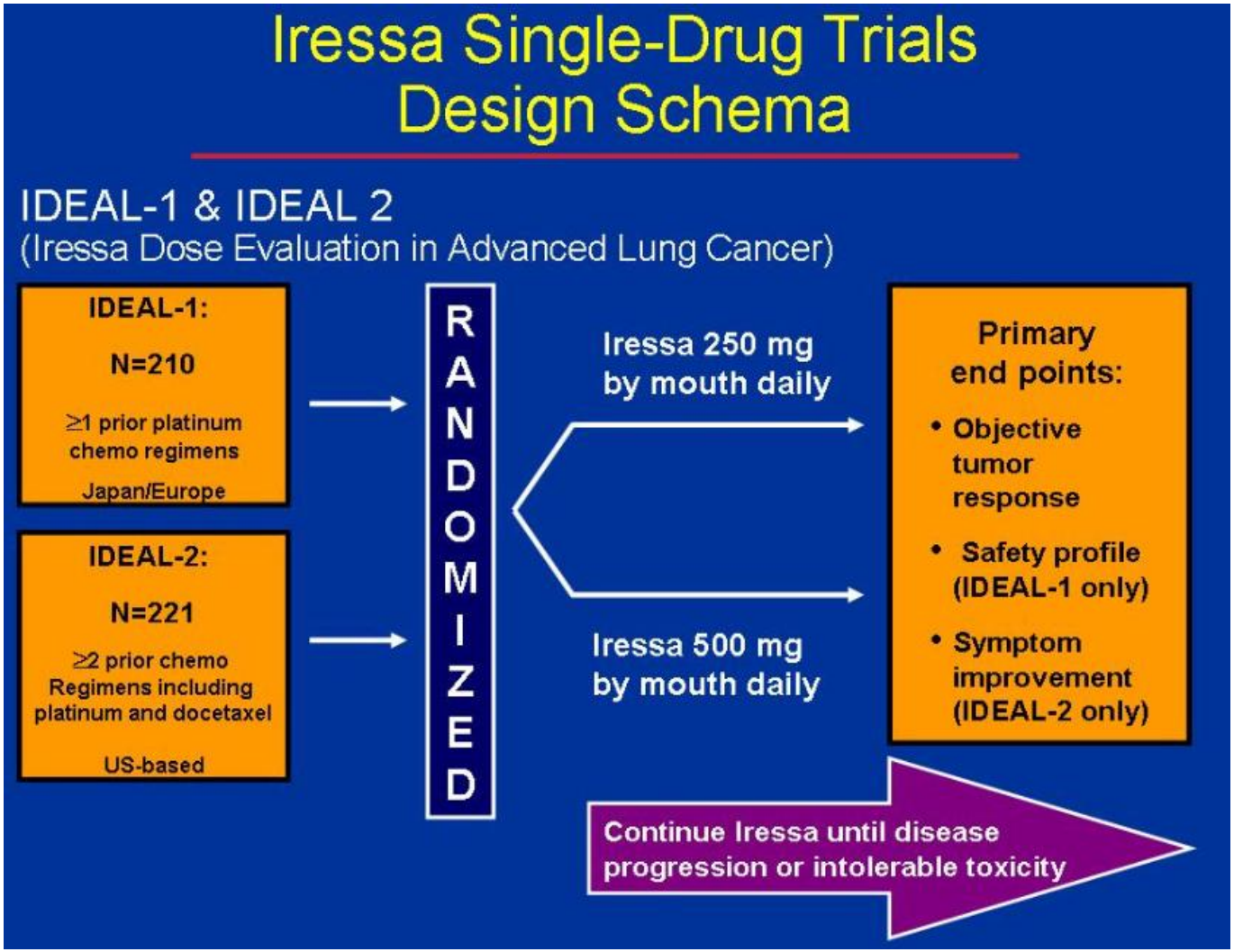
# Approved predictive biomarkers in clinical practice
## (requiring a companion diagnostic test)

| Disease | Drug | Therapeutic target | Predictive marker | Predictive marker frequency |
|---|---|---|---|---|
| **NSCLC** | Gefitinib (IRESSA | EGFR | EGFR mutation | 10-15% |
| | Erlotinib (TARCEVA) | EGFR | EGFR mutation | 10-15% |
| | Afatinib (GILOTRIF) | EGFR | EGFR mutation | 10-15% |
| | Osimertinib (TAGRISSO) | EGFR | EGFR mutation | 10-15% |
| | Crizotinib (XALKORI) | ALK | ALK traslocation | 4% |
| | | ROS1 | ROS1 rearrangements | 2-3% |
| | Pembrolizumab (KEYTRUDA) | PD1 | PD-L1 expression | 30% |
| **Melanoma** | Vemurafenib (ZELBORAF) | BRAF | BRAF mutation | 50% |
| | Dabrafenib | BRAF | BRAF mutation | 50% |
| **GIST** | Imatinib (GLEEVEC) | CKIT | CKIT mutation | 90% |
| **Gastric cancer** | Trastuzumab (HERCEPTIN) | HER2 | HER2 expr/amplif | 10-30% |
| **Breast cancer** | Trastuzumab (HERCEPTIN) | HER2 | HER2 expr/amplif | 20% |
| **Ovarian cancer** | Olaparib | PARP | BRCA1 mutation | 20-30% |
| **Colorectal cancer** | Cetuximab | EGFR | RAS | 50% |
| | Panitumumab | EGFR | RAS | 50% |

# Anti-EGFR drugs story - NSCLC

**……In 2000 first studies with anti-EGFR drugs**

**→ (EGFR overexpression in 50-80% of lung cancer)**




**Response rate: IDEAL 1 ~20%**

**IDEAL 2 ~10%**

by Dr West - http://cancergrace.org/lung/2007/03/03/iressa-tarceva-hx-part-i/

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

# Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

# *EGFR* Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,3*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4†] Bruce E. Johnson,[1,2†] Matthew Meyerson[1,3,4†]

*Science 304, 1497 (2004)*

# EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib

William Pao*†‡, Vincent Miller†§, Maureen Zakowski¶, Jennifer Doherty*, Katerina Politi*, Inderpal Sarkaria‖, Bhuvanesh Singh‖, Robert Heelan**, Valerie Rusch‖, Lucinda Fulton††, Elaine Mardis††, Doris Kupfer††, Richard Wilson††, Mark Kris†§, and Harold Varmus*

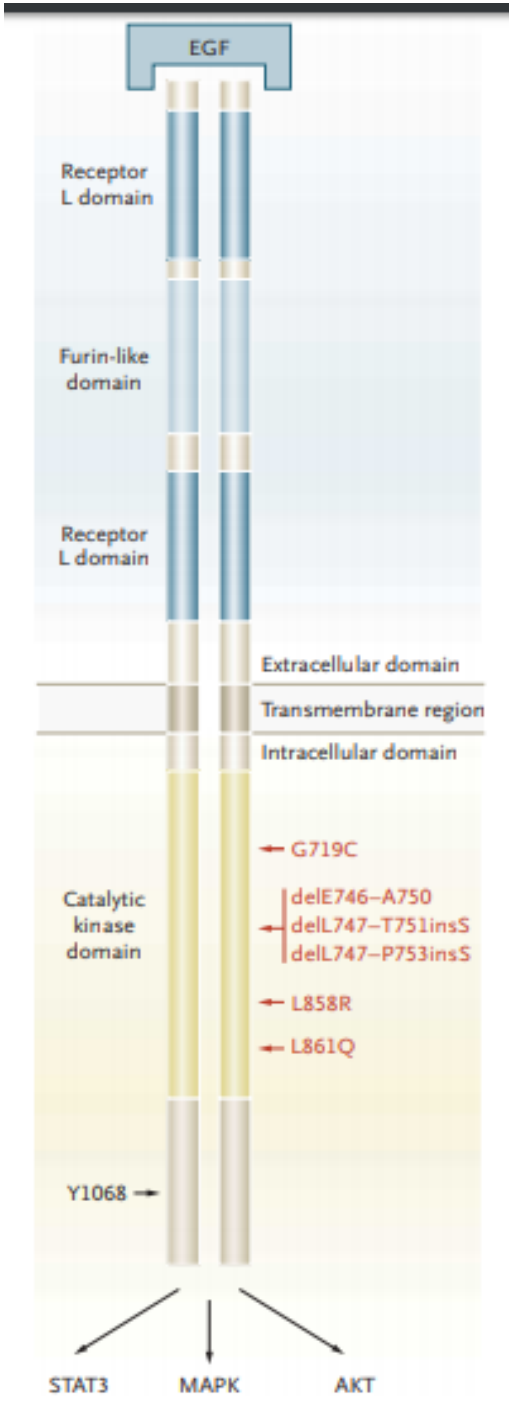
**PNAS September 7, 2004 vol. 101 no. 36**

**Table 1. Characteristics of Nine Patients with Non–Small-Cell Lung Cancer and a Response to Gefitinib.**

| Patient No. | Sex | Age at Beginning of Gefitinib Therapy | Pathological Type* | No. of Prior Regimens | Smoking-Status† | Duration of Therapy | Overall Survival‡ | *EGFR* Mutation§ | Response¶ |
|---|---|---|---|---|---|---|---|---|---|
| | | *yr* | | | | *mo* | | | |
| 1 | F | 70 | BAC | 3 | Never | 15.6 | 18.8 | Yes | Major; improved lung lesions |
| 2 | M | 66 | BAC | 0 | Never | >14.0 | >14.0 | Yes | Major; improved bilateral lung lesions |
| 3 | M | 64 | Adeno | 2 | Never | 9.6 | 12.9 | Yes | Partial; improved lung lesions and soft-tissue mass |
| 4 | F | 81 | Adeno | 1 | Former | >13.3 | >21.4 | Yes | Minor; improved pleural disease |
| 5 | F | 45 | Adeno | 2 | Never | >14.7 | >14.7 | Yes | Partial; improved liver lesions |
| 6 | M | 32 | BAC | 3 | Never | >7.8 | >7.8 | Yes | Major; improved lung lesions |
| 7 | F | 62 | Adeno | 1 | Former | >4.3 | >4.3 | Yes | Partial; improved liver and lung lesions |
| 8 | F | 58 | Adeno | 1 | Former | 11.7 | 17.9 | Yes | Partial; improved liver lesions |
| 9 | F | 42 | BAC | 2 | Never | >33.5 | >33.5 | No | Partial; improved lung nodules |

- 8/9 responsive patients showe EGFR mutation
- none of non responsive patients showed mutation

**Lynch T, NEJM 2004**




**Mutations involving exons 18-21, codifying for the tyrosine kinase activity portion of the protein, implicate in ATP binding**

**Lynch T, NEJM 2004**

VOLUME 26 · NUMBER 15 · MAY 20 2008
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

# First-Line Gefitinib in Patients With Advanced Non–Small-Cell Lung Cancer Harboring Somatic *EGFR* Mutations

*Lecia V. Sequist, Renato G. Martins, David Spigel, Steven M. Grunberg, Alexander Spira, Pasi A. Jänne, Victoria A. Joshi, David McCollum, Tracey L. Evans, Alona Muzikansky, Georgiana L. Kuhlmann, Moon Han, Jonathan S. Goldberg, Jeffrey Settleman, A. John Iafrate, Jeffrey A. Engelman, Daniel A. Haber, Bruce E. Johnson, and Thomas J. Lynch*

**Phase II study: EGFR mutated patients treated in first line with gefitinib 250mg/d until progression**

98 pt screened for mutation → 34 (35%) mutated

→ **response rate 55% (95% CI, 33 to 70)**
**PFS 9.2 months (95% CI, 6.2 to 11.8)**

VOLUME 24 · NUMBER 21 · JULY 20 2006
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

# Prospective Phase II Study of Gefitinib for Chemotherapy-Naïve Patients With Advanced Non–Small-Cell Lung Cancer With Epidermal Growth Factor Receptor Gene Mutations

*Akira Inoue, Takuji Suzuki, Tatsuro Fukuhara, Makoto Maemondo, Yuichiro Kimura, Naoto Morikawa, Hiroshi Watanabe, Yasuo Saijo, and Toshihiro Nukiwa*

75 pt screened for mutation → *25 (*33%) EGFR mutated

→ **ORR 75% (95% CI,54% to 96%), DCR 88% (95% CI, 71% to 100%)**
**PFS 9.7 months (95% CI, 7.4 to 9.9 months)**

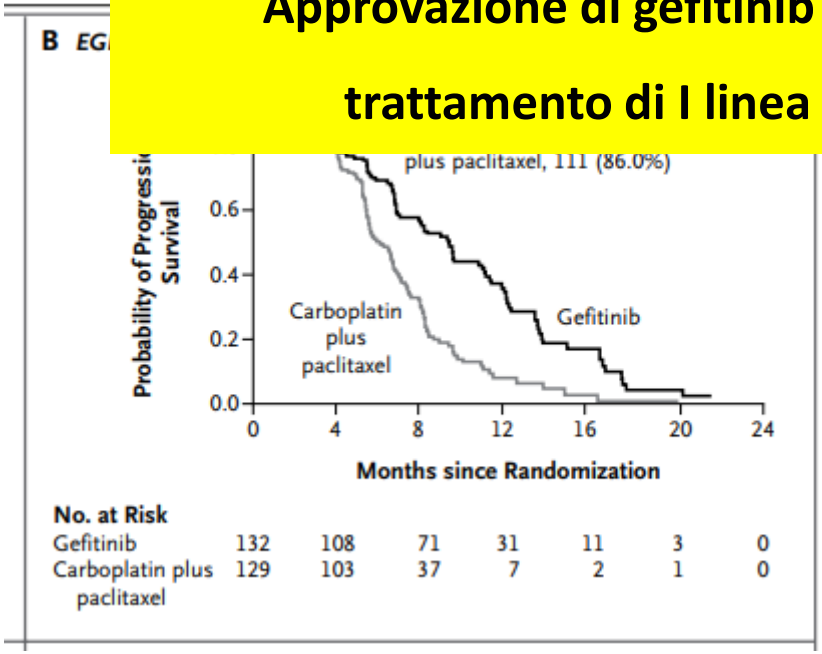
The NEW ENGLAND JOURNAL of MEDICINE

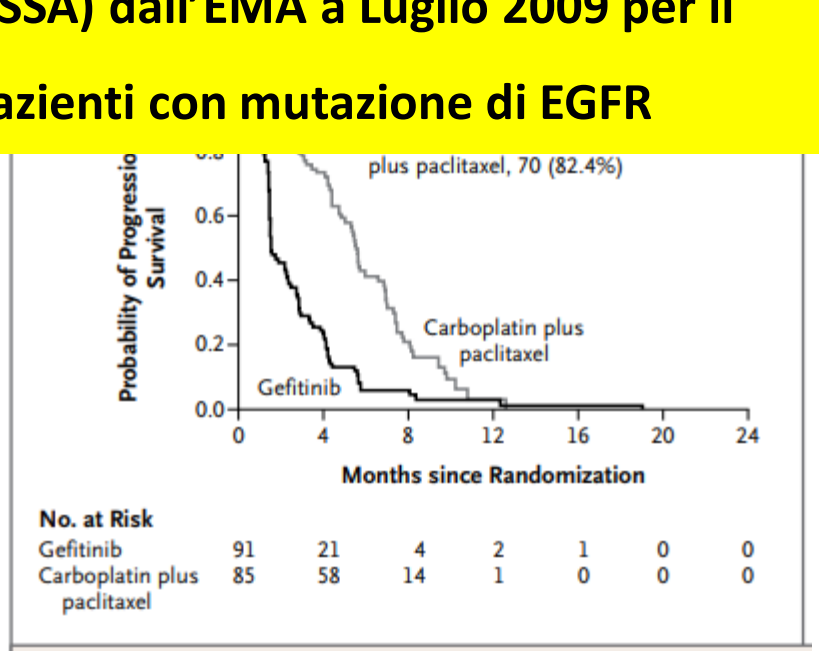
ESTABLISHED IN 1812 SEPTEMBER 3, 2009 VOL. 361 NO. 10

# Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

Tony S. Mok, M.D., Yi-Long Wu, M.D., F.A.C.S., Sumitra Thongprasert, M.D., Chih-Hsin Yang, M.D., Ph.D., Da-Tong Chu, M.D., Nagahiro Saijo, M.D., Ph.D., Patrapim Sunpaweravong, M.D., Baohui Han, M.D., Benjamin Margono, M.D., Ph.D., F.C.C.P., Yukito Ichinose, M.D., Yutaka Nishiwaki, M.D., Ph.D., Yuichiro Ohe, M.D., Ph.D., Jin-Ji Yang, M.D., Busyamas Chewaskulyong, M.D., Haiyi Jiang, M.D., Emma L. Duffield, M.Sc., Claire L. Watkins, M.Sc., Alison A. Armour, F.R.C.R., and Masahiro Fukuoka, M.D., Ph.D.

**Approvazione di gefitinib (IRESSA) dall'EMA a Luglio 2009 per il trattamento di I linea di pazienti con mutazione di EGFR**



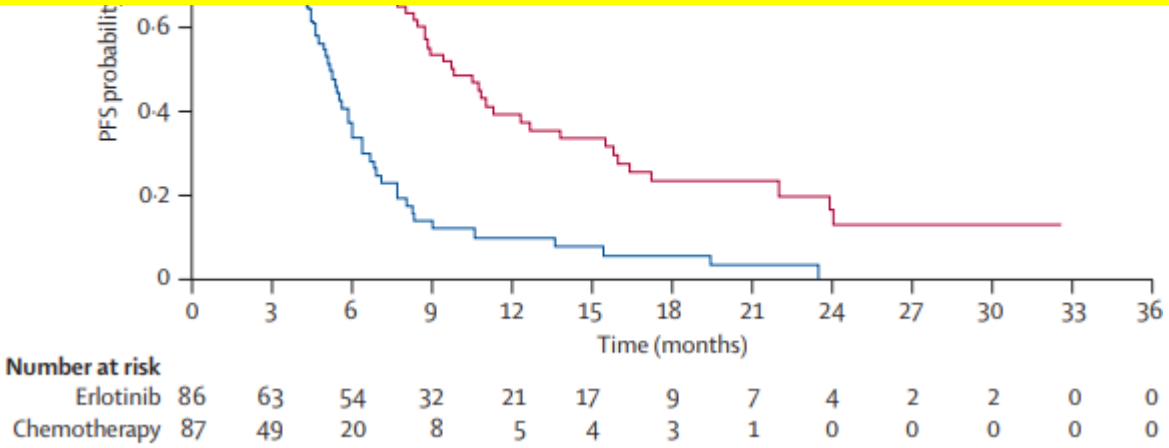



# Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial

*Rafael Rosell, Enric Carcereny, Radj Gervais, Alain Vergnenegre, Bartomeu Massuti, Enriqueta Felip, Ramon Palmero, Ramon Garcia-Gomez, Cinta Pallares, Jose Miguel Sanchez, Rut Porta, Manuel Cobo, Pilar Garrido, Flavia Longo, Teresa Moran, Amelia Insa, Filippo De Marinis, Romain Corre, Isabel Bover, Alfonso Illiano, Eric Dansin, Javier de Castro, Michele Milella, Noemi Reguart, Giuseppe Altavilla, Ulpiano Jimenez, Mariano Provencio, Miguel Angel Moreno, Josefa Terrasa, Jose Muñoz-Langa, Javier Valdivia, Dolores Isla, Manuel Domine, Olivier Molinier, Julien Mazieres, Nathalie Baize, Rosario Garcia-Campelo, Gilles Robinet, Delvys Rodriguez-Abreu, Guillermo Lopez-Vivanco, Vittorio Gebbia, Lioba Ferrera-Delgado, Pierre Bombaron, Reyes Bernabe, Alessandra Bearz, Angel Artal, Enrico Cortesi, Christian Rolfo, Maria Sanchez-Ronco, Ana Drozdowskyj, Cristina Queralt, Itziar de Aguirre, Jose Luis Ramirez, Jose Javier Sanchez, Miguel Angel Molina, Miquel Taron, Luis Paz-Ares, on behalf of the Spanish Lung Cancer Group in collaboration with the Groupe Français de Pneumo-Cancérologie and the Associazione Italiana Oncologia Toracica*

Lancet Oncol 2012; 13: 239–46

**Approvazione di erlotinib (TARCEVA) dall'EMA a Settembre 2011 per il trattamento di I linea di pazienti con mutazione di EGFR**



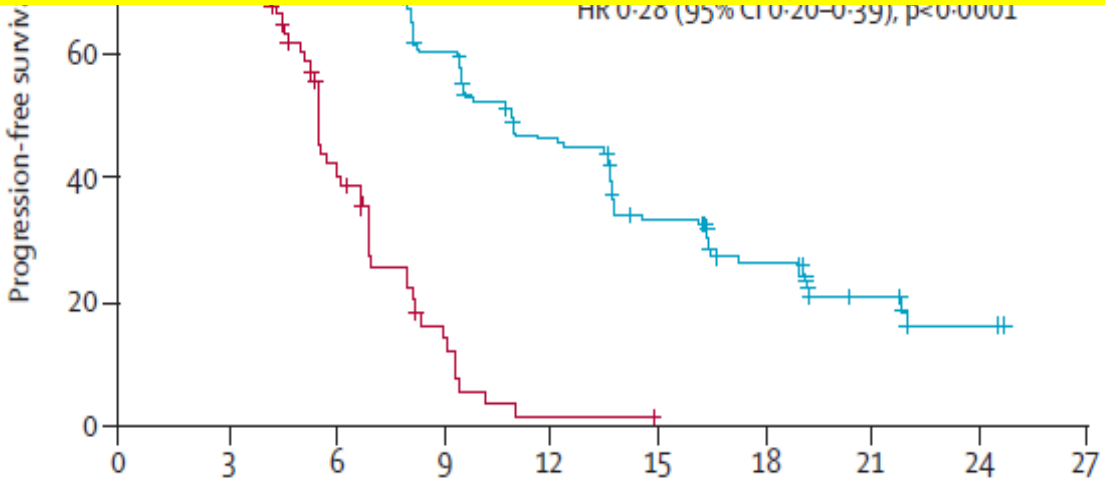
# Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring *EGFR* mutations (LUX-Lung 6): an open-label, randomised phase 3 trial

*Yi-Long Wu, Caicun Zhou, Cheng-Ping Hu, Jifeng Feng, Shun Lu, Yunchao Huang, Wei Li, Mei Hou, Jian Hua Shi, Kye Young Lee, Chong-Rui Xu, Dan Massey, Miyoung Kim, Yang Shi, Sarayut L Geater*

**Lancet Oncol 2014; 15: 213–22**

A

**Approvazione di afatinib (GELOTRIF) dall'EMA a Settembre 2013 per il trattamento di I linea di pazienti con mutazione di EGFR**



**Since 2010, all patients with a diagnosis of advanced lung adenocarcinoma MUST be characterized for EGFR before any treatment decision**

# Different methodologies

| Methodologies | Sensitivity |
|---|---|
| Direct Sequencing (Sanger) | 15-20% |
| Pyrosequencing | 3-5% |
| Mass Array (Sequenom) | 3% |
| Cobas® | 5% |
| Chip Hibridization | 5% |
| ARMS | 1-5% |
| PNA/LNA/CLAMP | 0.1% |
| Digital PCR | 0.01% |
| **Next Generation sequencing** | **0.01-5%** |

# Approved predictive biomarkers in clinical practice
## (requiring a companion diagnostic test)

| Disease | Drug | Therapeutic target | Predictive marker | Predictive marker frequency |
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| **NSCLC** | Gefitinib (IRESSA | EGFR | EGFR mutation | 10-15% |
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| | Osimertinib (TAGRISSO) | EGFR | EGFR mutation | 10-15% |
| | Crizotinib (XALKORI) | ALK | ALK traslocation | 4% |
| | | ROS1 | ROS1 rearrangements | 2-3% |
| | Pembrolizumab (KEYTRUDA) | PD1 | PD-L1 expression | 30% |
| **Melanoma** | Vemurafenib (ZELBORAF) | BRAF | BRAF mutation | 50% |
| | Dabrafenib | BRAF | BRAF mutation | 50% |
| **GIST** | Imatinib (GLEEVEC) | CKIT | CKIT mutation | 90% |
| **Gastric cancer** | Trastuzumab (HERCEPTIN) | HER2 | HER2 expr/amplif | 10-30% |
| **Breast cancer** | Trastuzumab (HERCEPTIN) | HER2 | HER2 expr/amplif | 20% |
| **Ovarian cancer** | Olaparib | PARP | BRCA1 mutation | 20-30% |
| **Colorectal cancer** | Cetuximab | EGFR | RAS mutation | 50% |
| | Panitumumab | EGFR | RAS mutation | 50% |

# The majority of predictive biomarkers approved in clinical practice are gene mutation

- Results in terms of presence/absence (without cut off, reference curve, etc…)
- Objective interpretation of data
- Less variability among the different laboratories
- Methodologies easy for Molecular Biology  Laboratories
- Analysis on DNA more stable respect to analysis on RNA, proteins….

# All are no perfect biomarkers

- **Objective response rate in patients carrying the specific alteration: 70-80%**

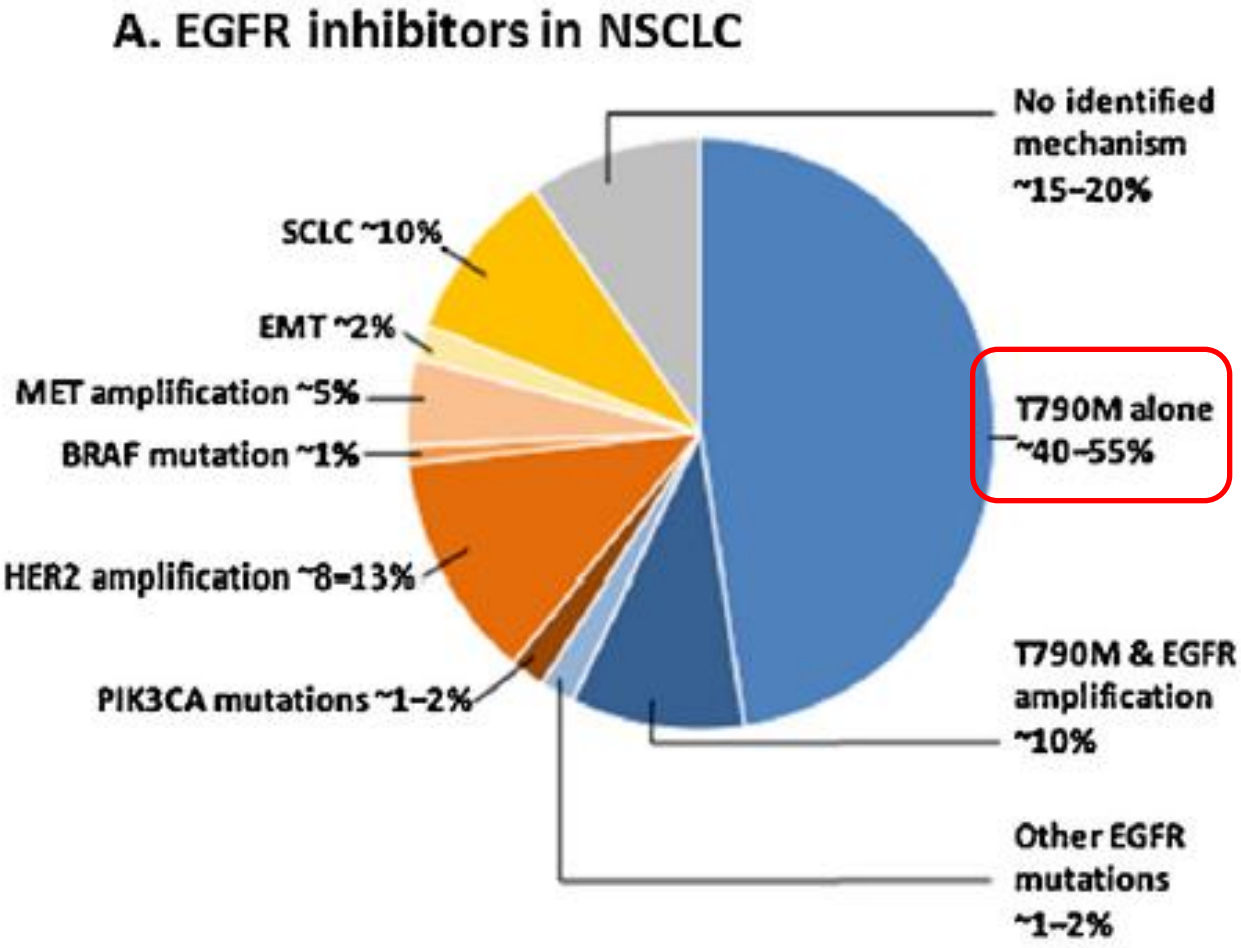
  ↳ Unknown primary resistance mechanisms

- **Some patients without the target alteration could respond to therapy**

- **Median durable clinical response: about 10-12 months**

  ↳ Acquired resistance mechanisms

# Principal resistance mechanisms to EGFR-TKIs in NSCLC

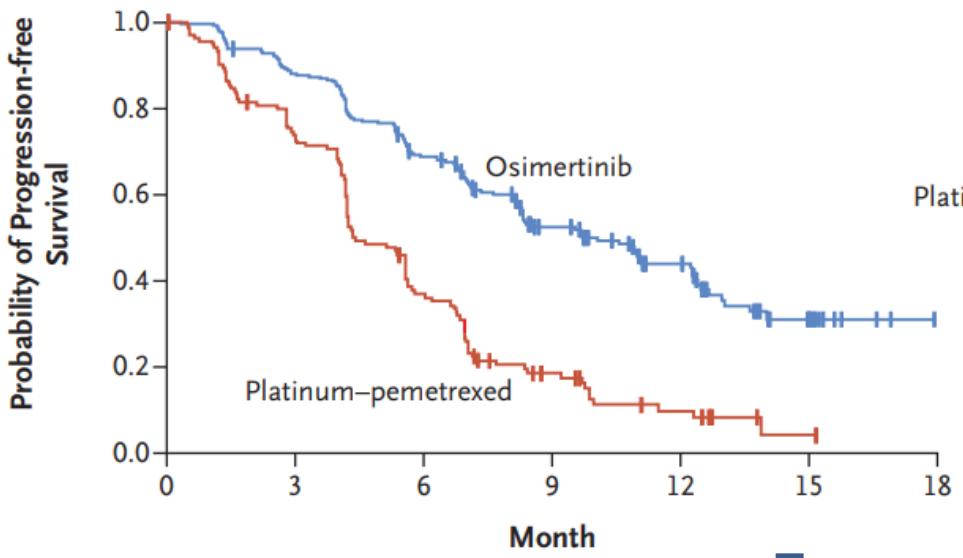



Gillis NK et al, drug Res Update 2016

n engl j med February 16, 2017

# Osimertinib or Platinum–Pemetrexed in *EGFR* T790M–Positive Lung Cancer

T.S. Mok, Y.-L. Wu, M.-J. Ahn, M.C. Garassino, H.R. Kim, S.S. Ramalingam, F.A. Shepherd, Y. He, H. Akamatsu, W.S.M.E. Theelen, C.K. Lee, M. Sebastian, A. Templeton, H. Mann, M. Marotti, S. Ghiorghiu, and V.A. Papadimitrakopoulou, for the AURA3 Investigators*




| | No. of Patients | Median Progression-free Survival *mo (95% CI)* |
|---|---|---|
| Osimertinib | 279 | 10.1 (8.3–12.3) |
| Platinum–pemetrexed | 140 | 4.4 (4.2–5.6) |

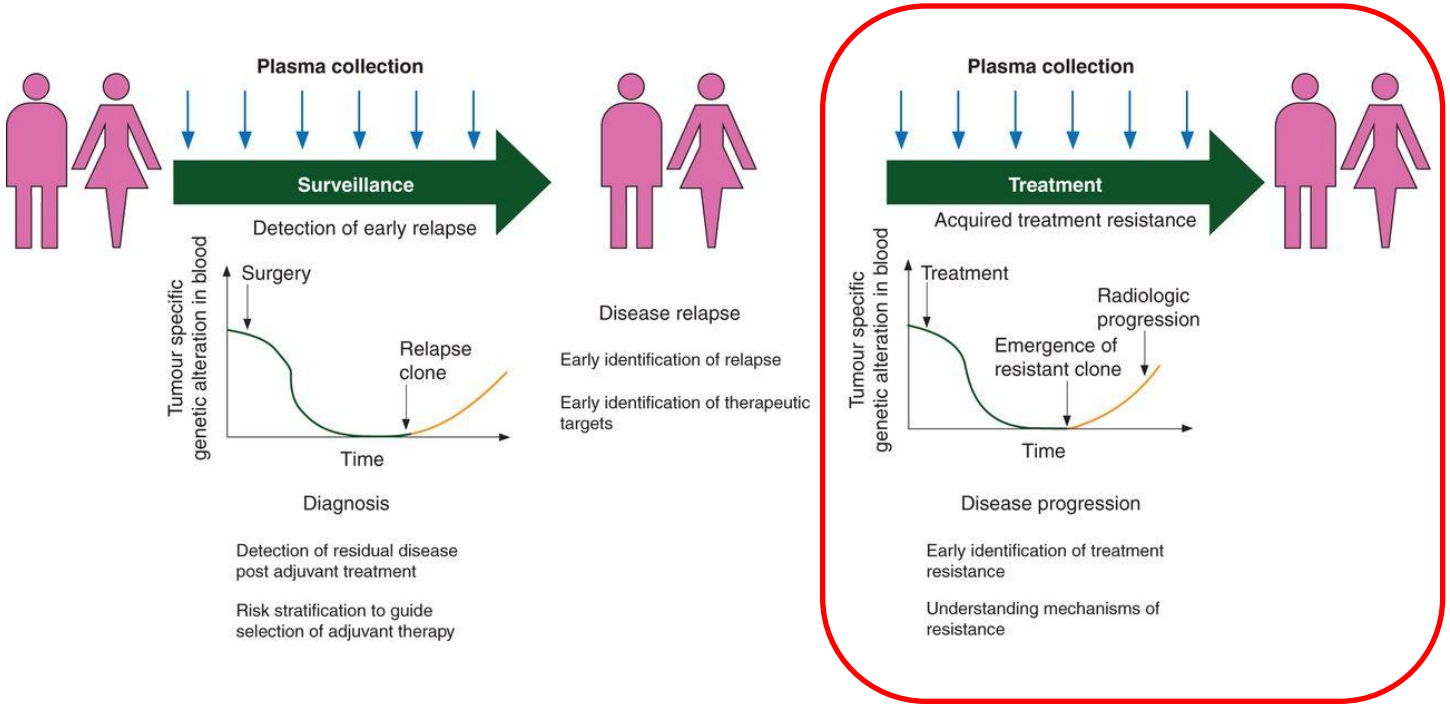
Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

**Approval of Osimertinib in patients developing a T790M mutation at progression with a EGFR-TKI**

# Necessity to characterize the tumor tissue after progression to decide the subsequent treatment

- Molecular characterization of tumor tissue of relapsed lesion (re-biopsy)

- Use of liquid biopsy (free circulating DNA)



# Other biomarkers under evaluation for targeted therapy

| Disease | Drug | Therapeutic target | Predictive marker | Predictive marker frequency |
|---|---|---|---|---|
| **NSCLC** | Vemurafenib/Dabrafenib | BRAF | BRAF mutation | 2-3% |
| | Trastuzumab | HER2 | HER2 mutation | 2-4% |
| | Cabozantinib | MET | MET mutation/amplification | 4% |
| | Cabozantinib | RET | RET rearrangements | 1% |
| | | | | |
| **Multiple tumors** | Entrectinib<br>Larotrectinib | NTRK1/2/3 | NTRK rearrangements | 0.3-20% |
| | | | | |

# Immune checkpoint inhibitors (ICIs) therapies

*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

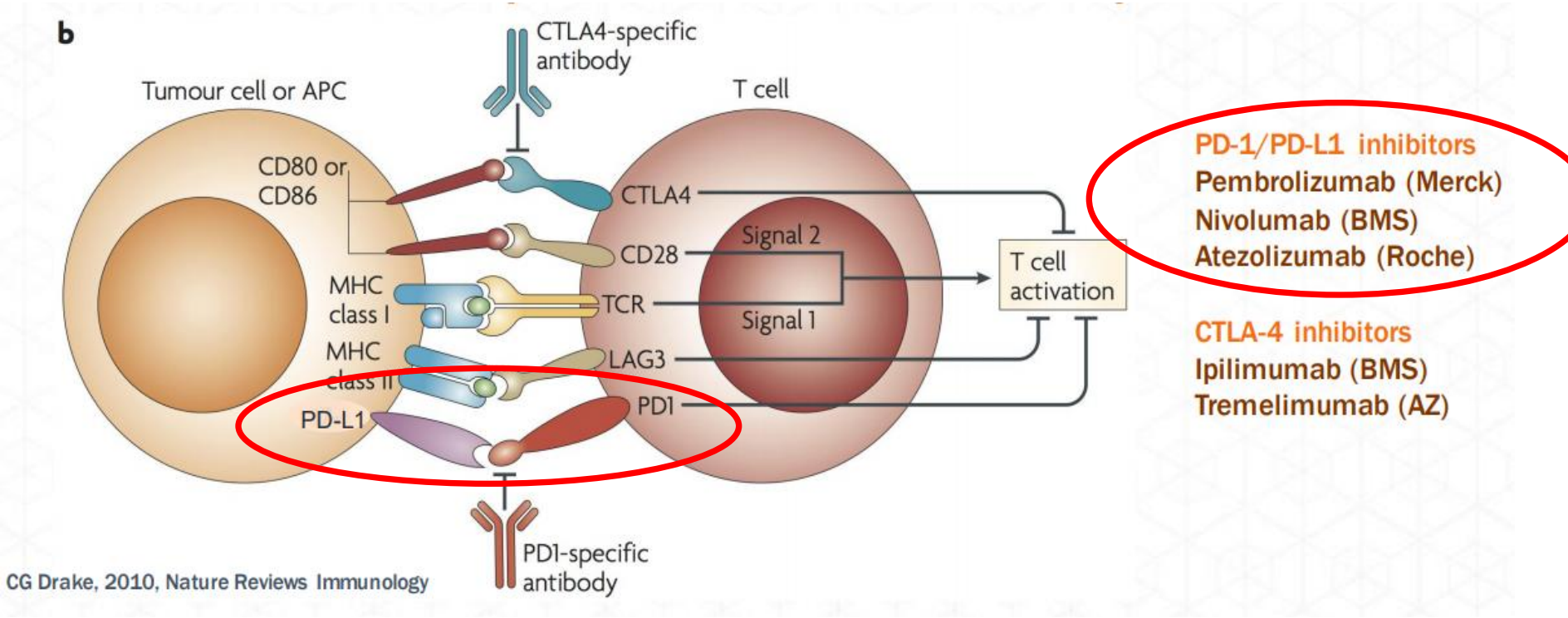
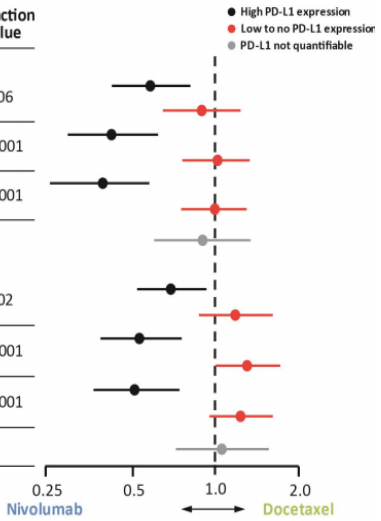
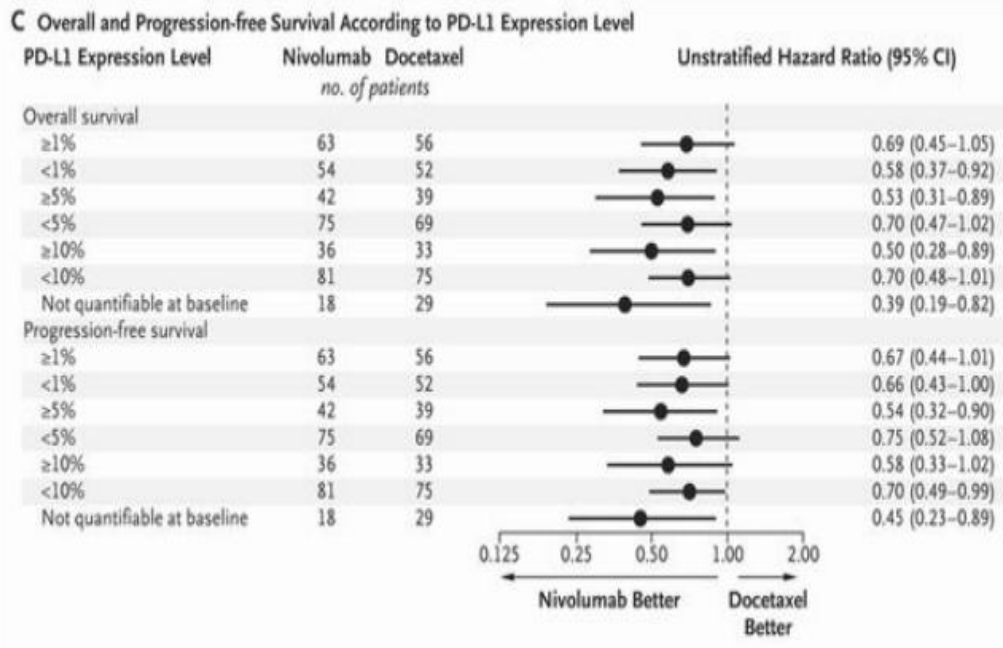


**Figure S7. Plot of Overall Survival and Progression-free Survival Hazard Ratios by PD-L1 Expression at Baseline.**

| PD-L1 expression level | Nivolumab n | Docetaxel n | Unstratified HR (95% CI) | Interaction *P*-value |
|---|---|---|---|---|
| **OS** | | | | |
| ≥1% | 123 | 123 | 0.59 (0.43, 0.82) | 0.06 |
| <1% | 108 | 101 | 0.90 (0.66, 1.24) | |
| ≥5% | 95 | 86 | 0.43 (0.30, 0.63) | <0.001 |
| <5% | 136 | 138 | 1.01 (0.77, 1.34) | |
| ≥10% | 86 | 79 | 0.40 (0.26, 0.59) | <0.001 |
| <10% | 145 | 145 | 1.00 (0.76, 1.31) | |
| Not quantifiable at baseline | 61 | 66 | 0.91 (0.61, 1.35) | |
| **PFS** | | | | |
| ≥1% | 123 | 123 | 0.70 (0.53, 0.94) | 0.02 |
| <1% | 108 | 101 | 1.19 (0.88, 1.61) | |
| ≥5% | 95 | 86 | 0.54 (0.39, 0.76) | <0.001 |
| <5% | 136 | 138 | 1.31 (1.01, 1.71) | |
| ≥10% | 86 | 79 | 0.52 (0.37, 0.75) | <0.001 |
| <10% | 145 | 145 | 1.24 (0.96, 1.61) | |
| Not quantifiable at baseline | 61 | 66 | 1.06 (0.73, 1.56) | |



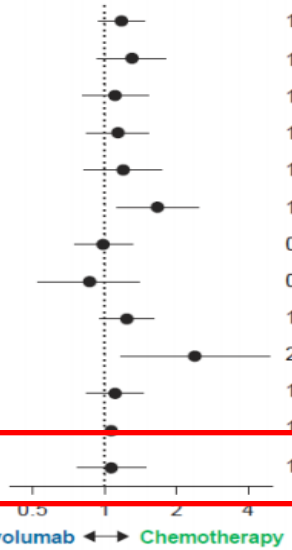

**Check Mate -057 Borgheai H et al, NEJM 2015 2° line of treatment ADC**




**Check Mate 017 Brahmer JR et al, NEJM 2015 2° line of treatment SCC**

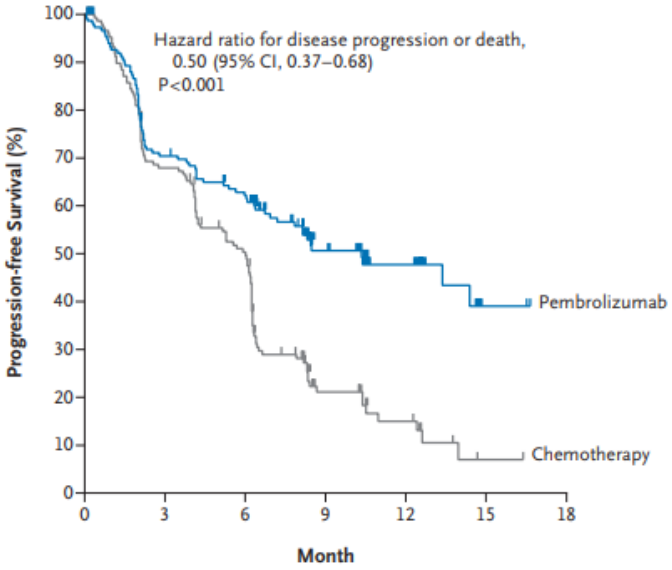
**Figure S4A. Progression-free Survival in Subgroups of Patients with ≥5% PD-L1 Expression.**

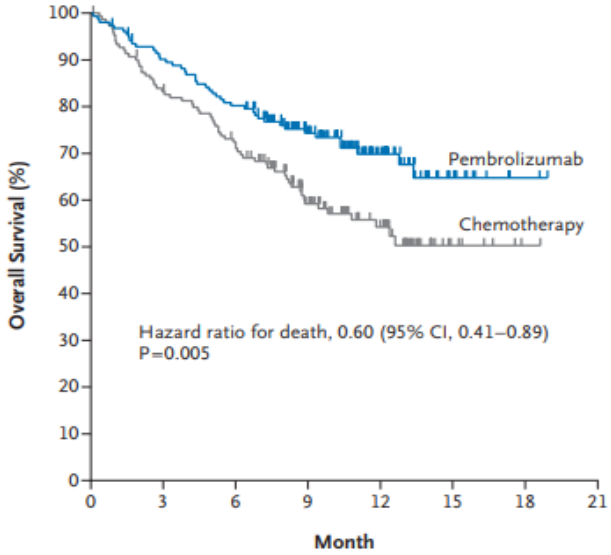
| Subgroup | Nivolumab n | Nivolumab Median Progression-free Survival, mo | Chemotherapy n | Chemotherapy Median Progression-free Survival, mo | Unstratified Hazard Ratio (95% CI) |
|---|---|---|---|---|---|
| Overall | 211 | 4.2 | 212 | 5.9 | 1.18 (0.94, 1.49) |
| ≥65 yr | 92 | 4.2 | 104 | 5.7 | 1.30 (0.93, 1.82) |
| <65 yr | 119 | 5.4 | 108 | 6.5 | 1.11 (0.81, 1.54) |
| Male | 143 | 4.2 | 118 | 5.8 | 1.14 (0.84, 1.53) |
| Female | 68 | 4.1 | 94 | 6.0 | 1.20 (0.82, 1.74) |
| ECOG PS = 0 | 66 | 4.5 | 77 | 7.2 | 1.67 (1.12, 2.49) |
| ECOG PS ≥1 | 144 | 4.1 | 135 | 5.4 | 0.99 (0.75, 1.32) |
| Squamous | 48 | 3.3 | 48 | 4.7 | 0.87 (0.53, 1.41) |
| Nonsquamous | 163 | 4.2 | 164 | 6.8 | 1.24 (0.95, 1.62) |
| Never smoker | 22 | 2.9 | 24 | 6.8 | 2.39 (1.16, 4.93) |
| Former smoker | 145 | 4.2 | 145 | 5.7 | 1.11 (0.84, 1.47) |
| Current smoker | 42 | 5.4 | 39 | 6.9 | 1.07 (0.63, 1.79) |
| ≥50% PD-L1+ | 88 | 5.4 | 126 | 5.8 | 1.07 (0.77, 1.49) |




**Check Mate 026 Carbone DP et al, NEJM 2017 1°line of treatment NSCLC**

## KEYNOTE 024- Reck M et al, NEJM 2016- 1° line treatment in pt with PD-L1 >50%



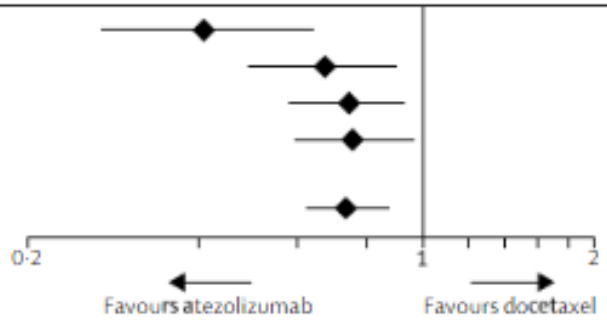




**Pembrolizumab approval in first line treatment in patients with PD-L1 expression >=50%**

## OAK: Rittmeyer A et al, Lancet 2017; phase III in 2° line NSCLC

F

| | n (%) | Median overall survival (months) | | HR (95% CI) |
|---|---|---|---|---|
| | | Atezolizumab | Docetaxel | |
| TC3 or IC3 | 137 (16) | 20·5 | 8·9 | 0·41 (0·27–0·64) |
| TC2/3 or IC2/3 | 265 (31) | 16·3 | 10·8 | 0·67 (0·49–0·90) |
| TC1/2/3 or IC1/2/3 | 463 (54) | 15·7 | 10·3 | 0·74 (0·58–0·93) |
| TC0 and IC0 | 379 (45) | 12·6 | 8·9 | 0·75 (0·59–0·96) |
| ITT | 850 (100) | 13·8 | 9·6 | 0·73 (0·62–0·87) |

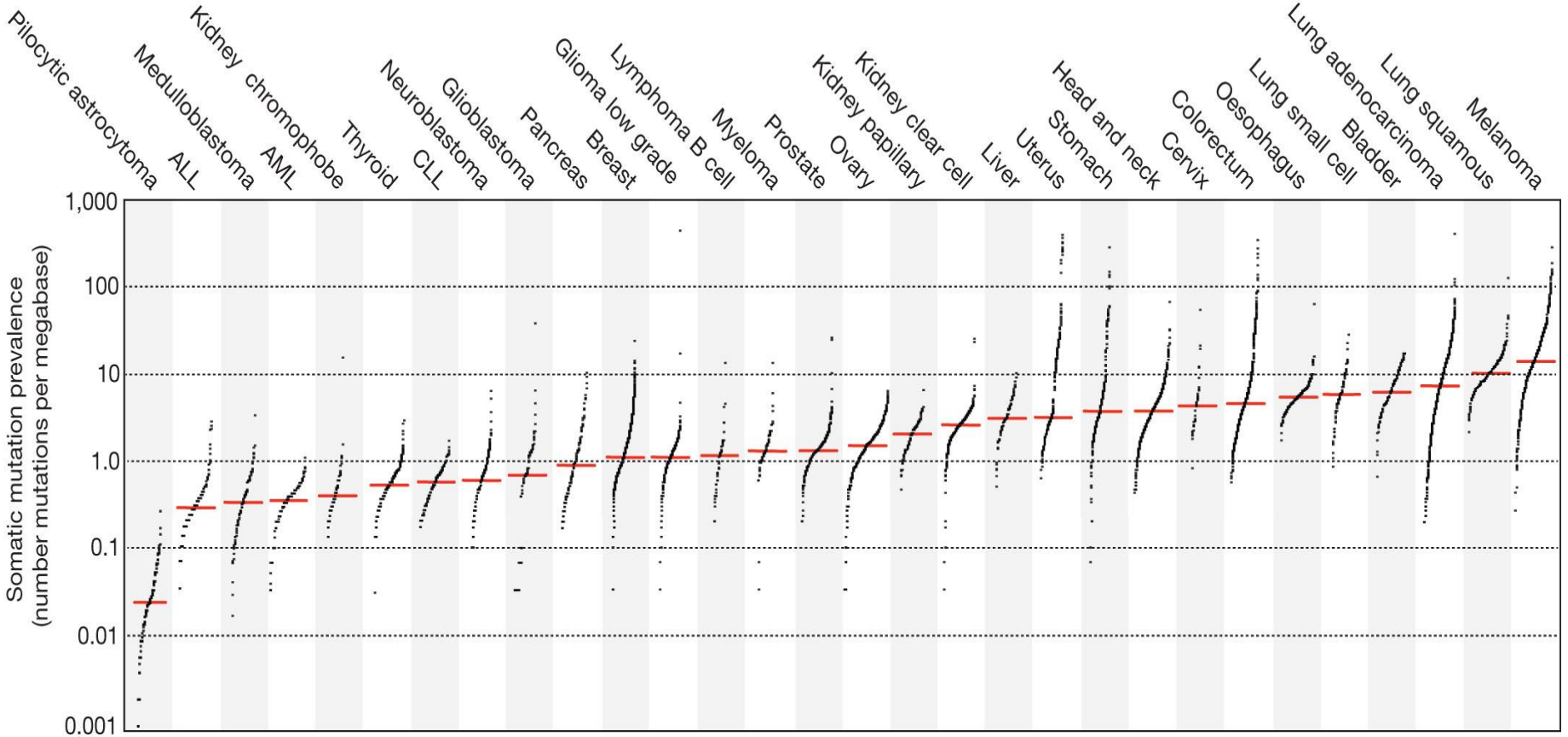


## Different anti-PD-L1 Ab clones in the different studies

| | BMS | Merck | Genentech | AstraZeneca |
|---|---|---|---|---|
| **Therapy** | Nivolumab | Pembrolizumab | Atezolizumab | Durvalumab |
| **Target** | PD-1 | PD-1 | PD-L1 | PD-L1 |
| **Clone** | 28-8 | 22C3 | SP142 | SP263 |
| **Positivity** | 1-10% tumor | 1-50% tumor | 1-50%, IC, TC | >25% tumor |
| **Commercial** | No | No | Yes | Yes |
| **Platform** | Auto (DAKO) | Auto (DAKO) | Auto (Ventana) | Auto (Ventana) |

**High variability of results**

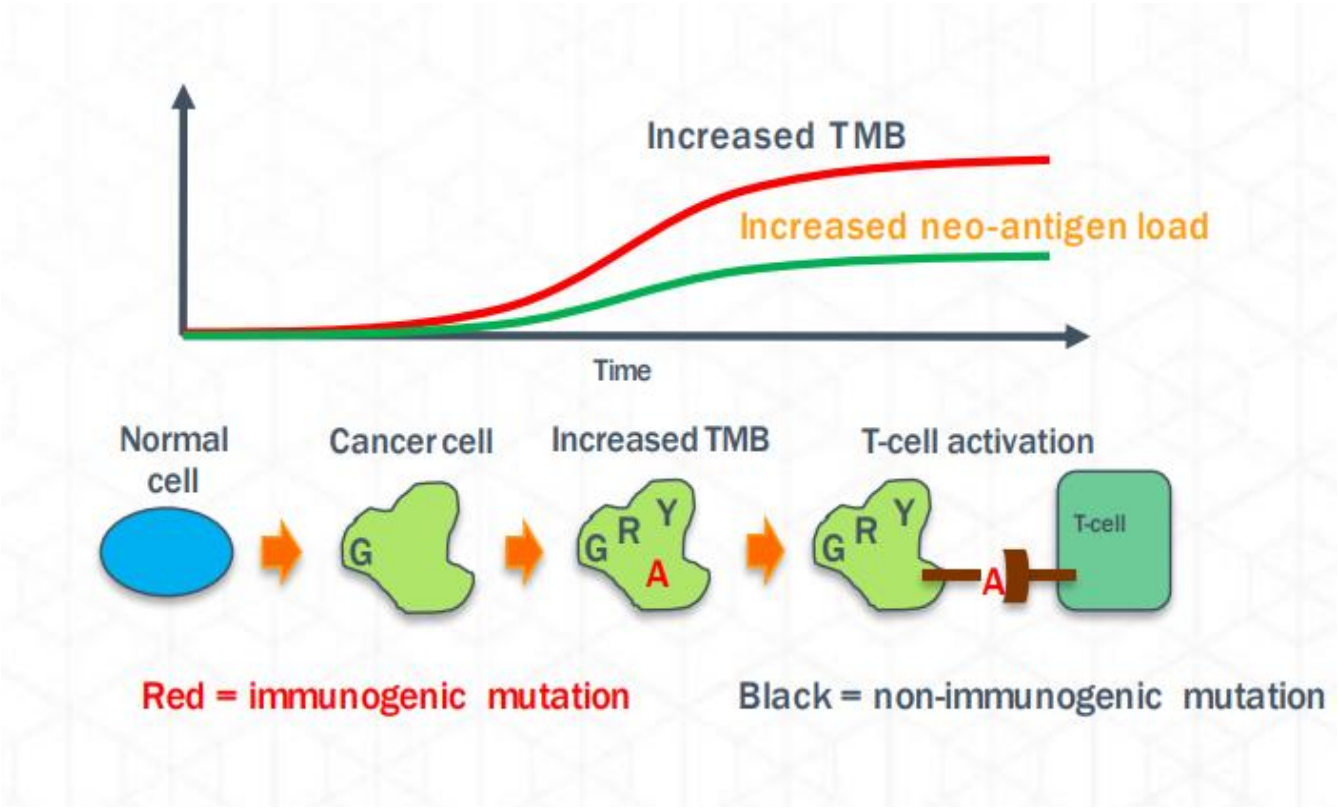
# Prevalence of somatic mutations across human cancer types

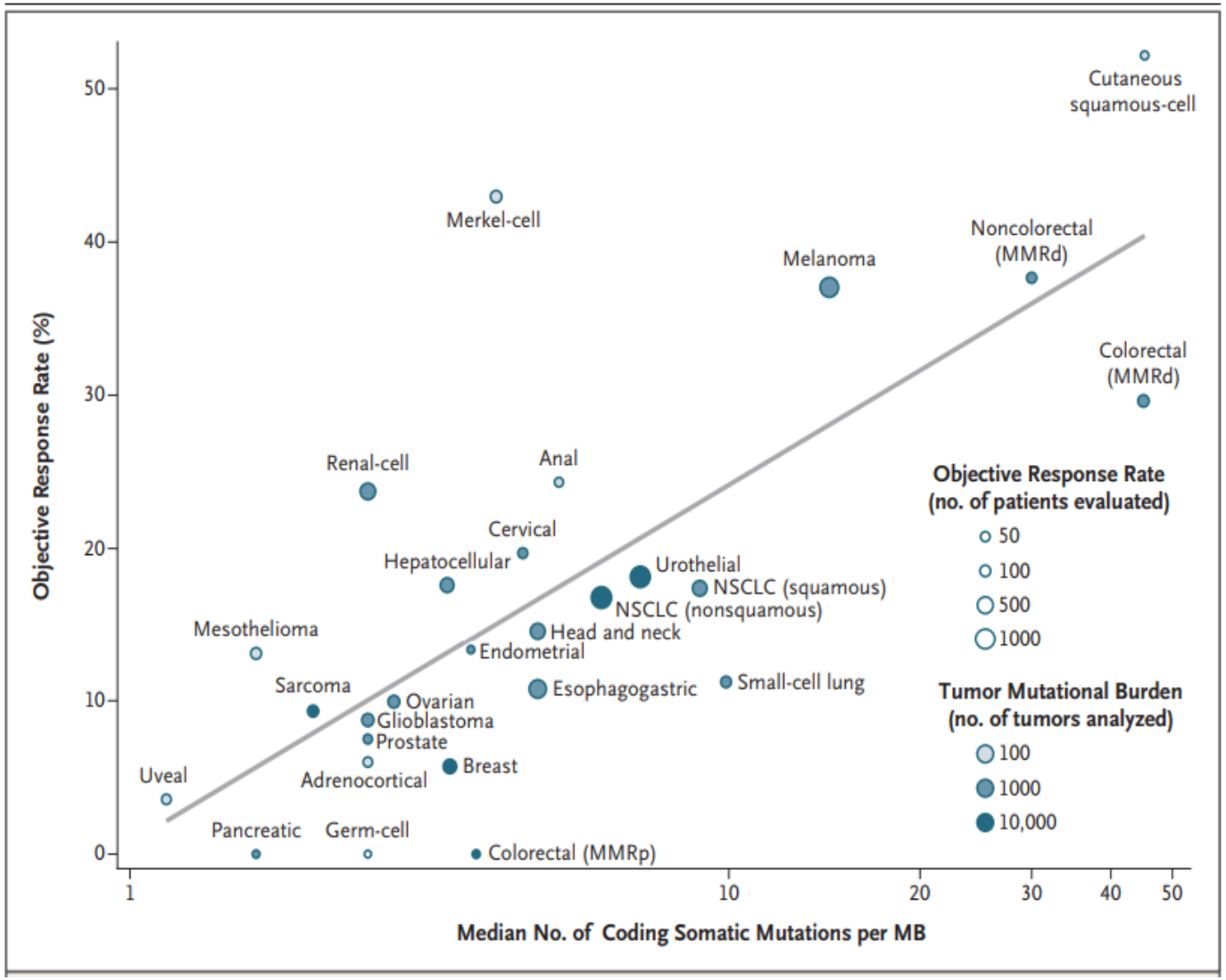



**Tumor mutational burden (TMB) measures the quantity of somatic mutations found in a tumor**

LB Alexandrov *et al. Nature* 1-7 (2013)

# Measuring the total number of somatic mutations (TMB) acts as a proxy for neo-antigen burden



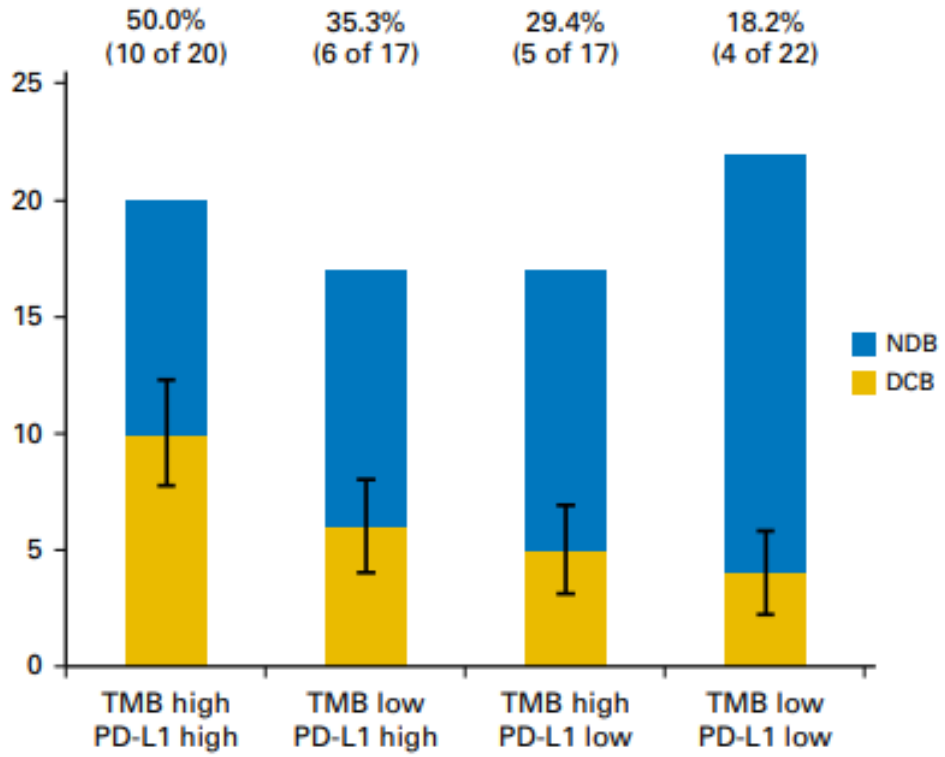



- Some cancers have a response to therapy that is better than that predicted by TMB (i.e. Merkel-cell carcinoma)
- Other have a response worse than that predicted (i.e. colorectal cancer MMRd)

**Yarchoan M et al, NEJM 2017**

- TMB and PD-L1 expression were independent variables,

- Composite of TMB plus PD-L1 further enriched for benefit to ICIs




Rizvi H et al, JCO 2018

# Issues relative to TMB analysis

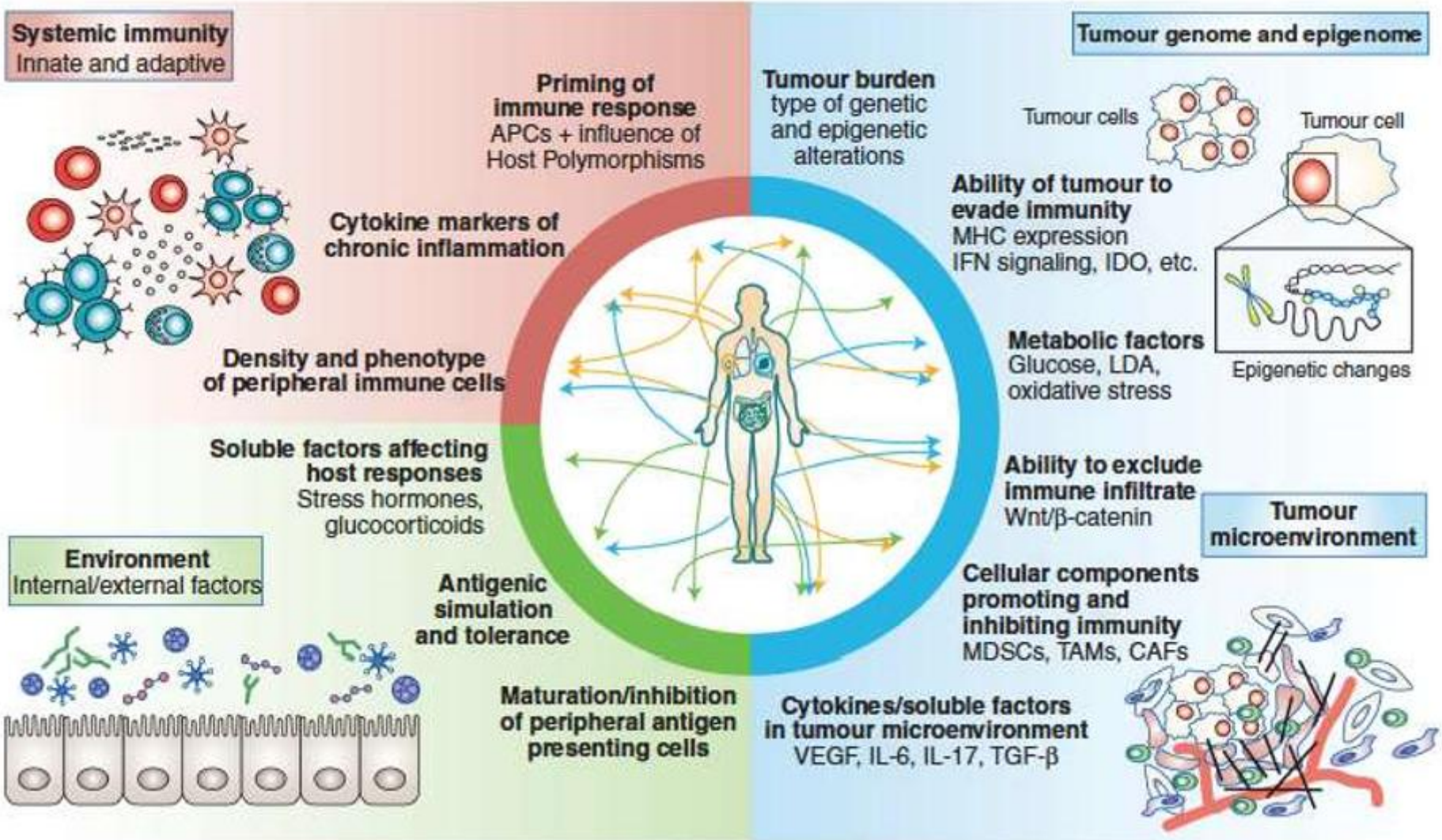
-Exome analysis is expensive, time consuming, and requires expert bioinformatics for results interpretation

- Large panel of genes have been analysed as alternative, but no standardized panel have been established

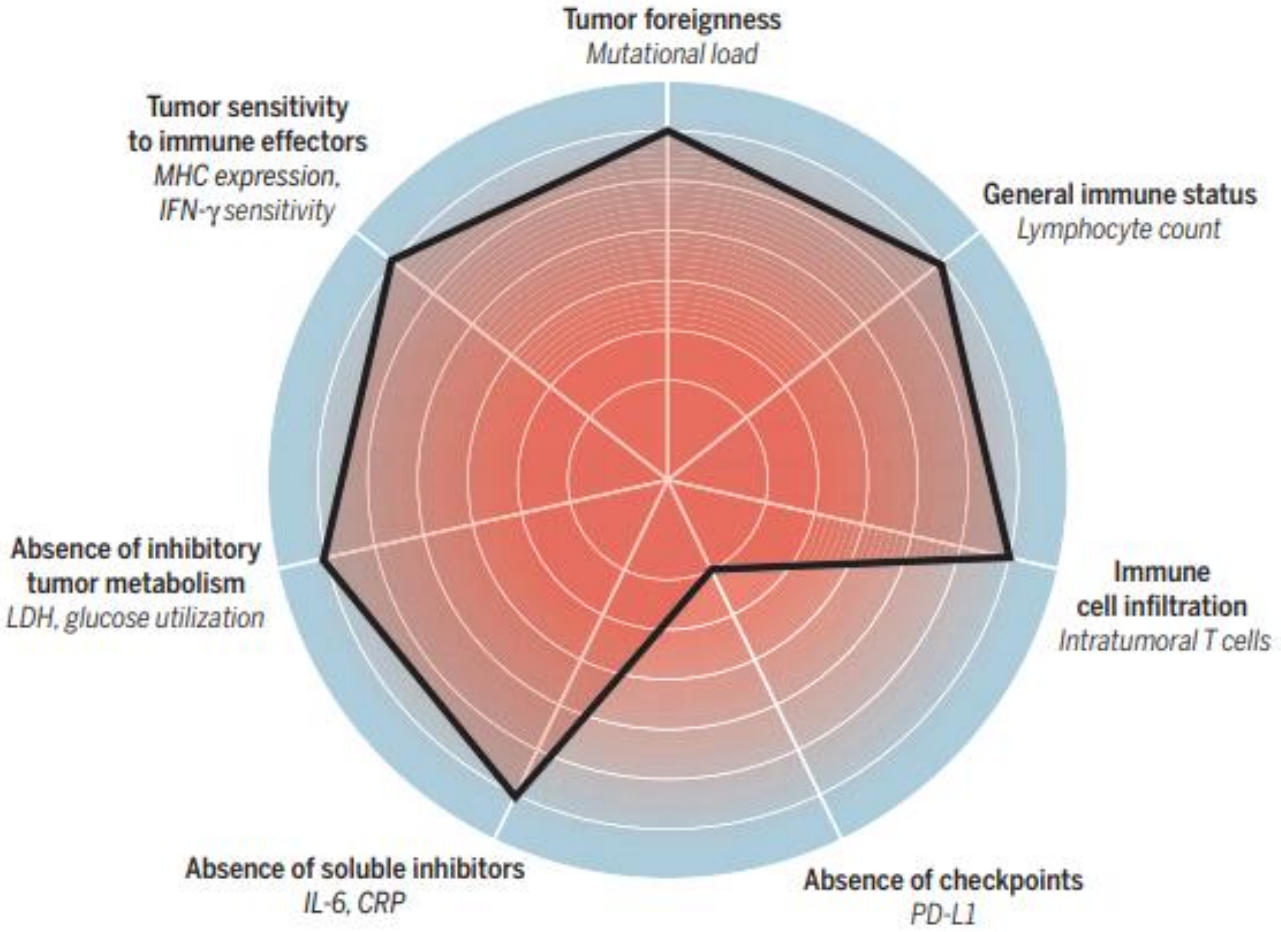
- Difficulties to standardize the determination between different laboratories

- Foundation One is one of the methodologies used in clinical trials and for which a cut off has been established, but it is too expensive ($ 5.800 for each patient) for a routinary use

# Immune parameters influencing response to immunotherapy



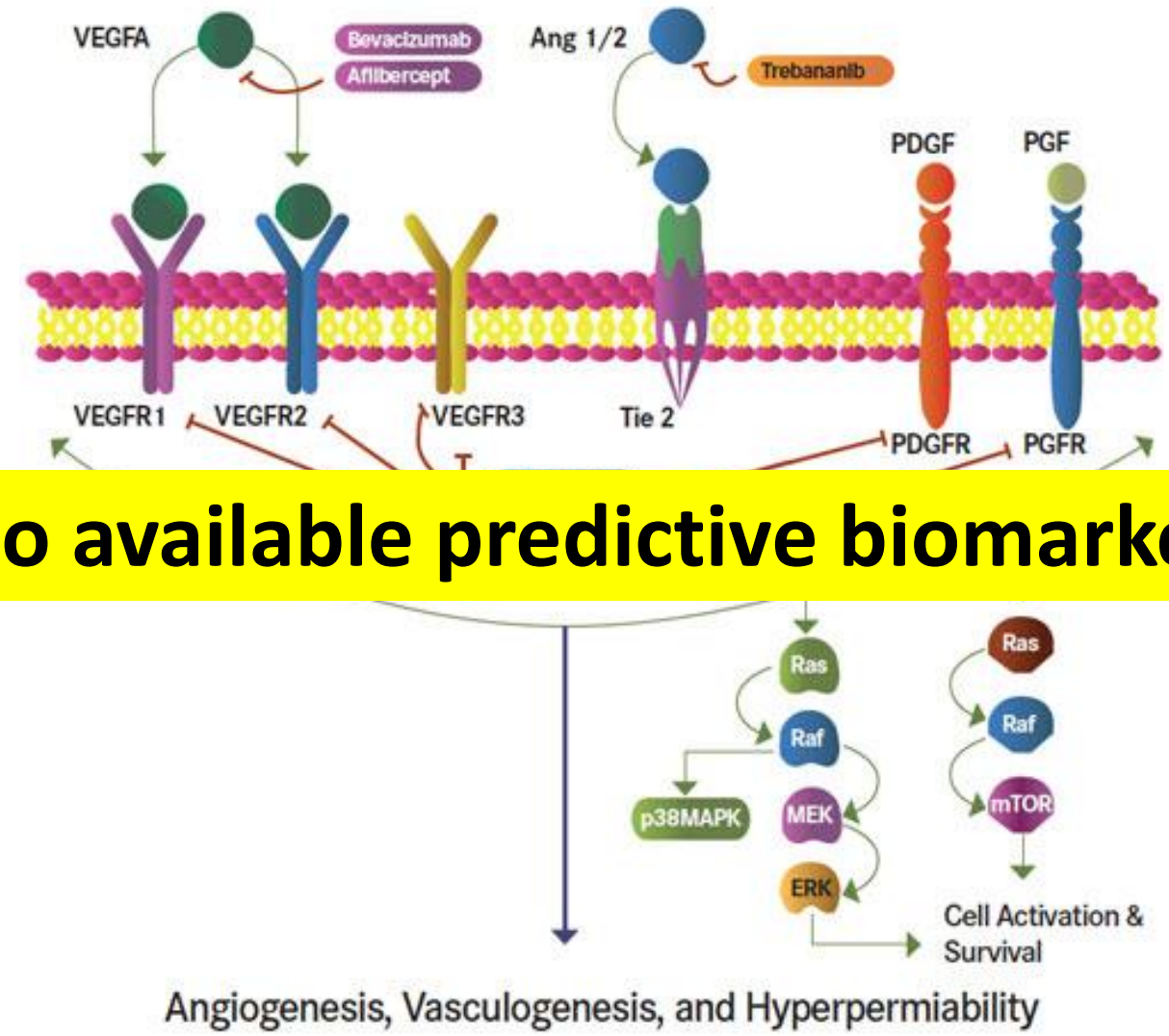

Cogdill A, Brit J Cancer 2017




**The cancer immunogram.** The radar plot depicts the seven parameters that characterize aspects of cancer-immune interactions for which biomarkers have been identified or are plausible. Potential biomarkers for the different parameters are shown in italics. Desirable states are located in blue; progressively undesirable states are shown in the red gradient. The black line connecting the data values for each parameter represents a plot for a single hypothetical patient. In the case shown, it may be argued that single-agent PD-1 blockade, rather than combined PD-1 and CTLA-4 blockade, could be a first treatment of choice. For details on this case and other hypothetical patient cases, see (*2*).

**Blank CU, Science 2016**

# Antiangiogenic treatment




**No available predictive biomarkers**

Martin L, J Clin Oncol 2007

# Conclusions

- A series of predictive biomarkers to targeted therapy are nowaday available and usable in the clinical practice

- The majority of approved predictive biomarkers are gene alterations

- The increasing of molecular knowledge of tumor and drugs available against the specific alterations make mandatory the use of multi panel approaches

- Liquid biopsy is recognized and indicated for NSCLC molecular characterization

- Accurate predictive biomarkers with regard to ICIs are not yet available

- Molecular alghoritm including different parameters will be probably more indicated, but more complex to standardize, as predictors of ICIs sensitivity

- The rapid evolution of increasingly sofisticated and advanced methodologies will help in the search and development of predictive molecular markers


# Thank you for your attention