## Cosa si aspetta il clinico dal mondo reale?

# Il valore dell' innovazione terapeutica

Marina Chiara Garassino
Responsabile Oncologia Toracica
Fondazione IRCCS Istituto Nazionale dei Tumori
Milano

**Non esiste la parola innovazione sul dizionario filosofico (Abbagnano) o sull’ enciclopedia filosofica (Gallarate)!**

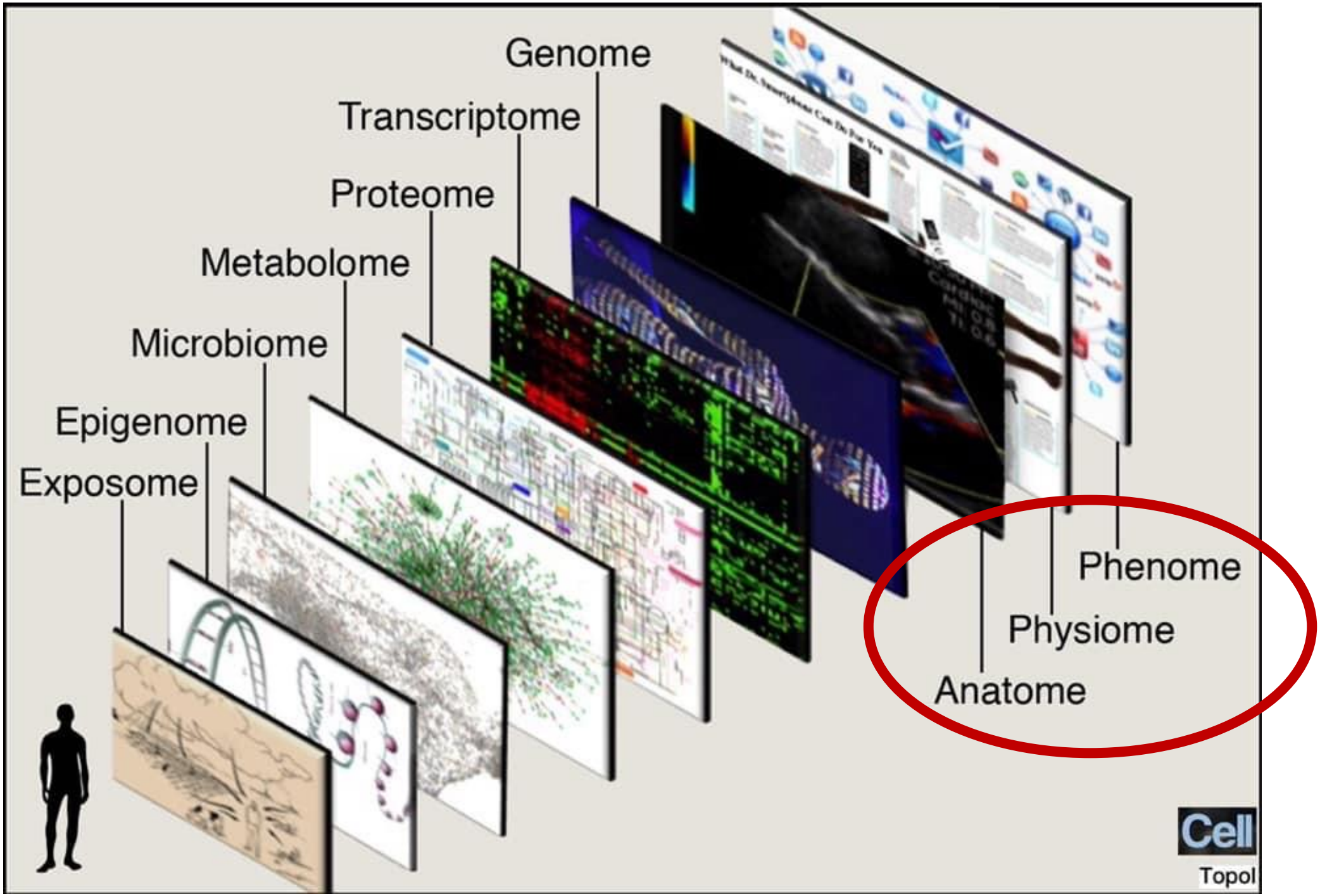
L'**Innovazione** è la **dimensione applicativa di un'invenzione o di una scoperta**. L'innovazione riguarda un processo o un prodotto che garantisce risultati o benefici maggiori apportando quindi un **progresso sociale**, anche se a volte non sempre efficaci e migliorativi rispetto a ciò che va ad innovare.

# Declinazione di innovazione

- Scoperta
- Prevede che la applichiamo
- Prevede che porti una progresso sociale

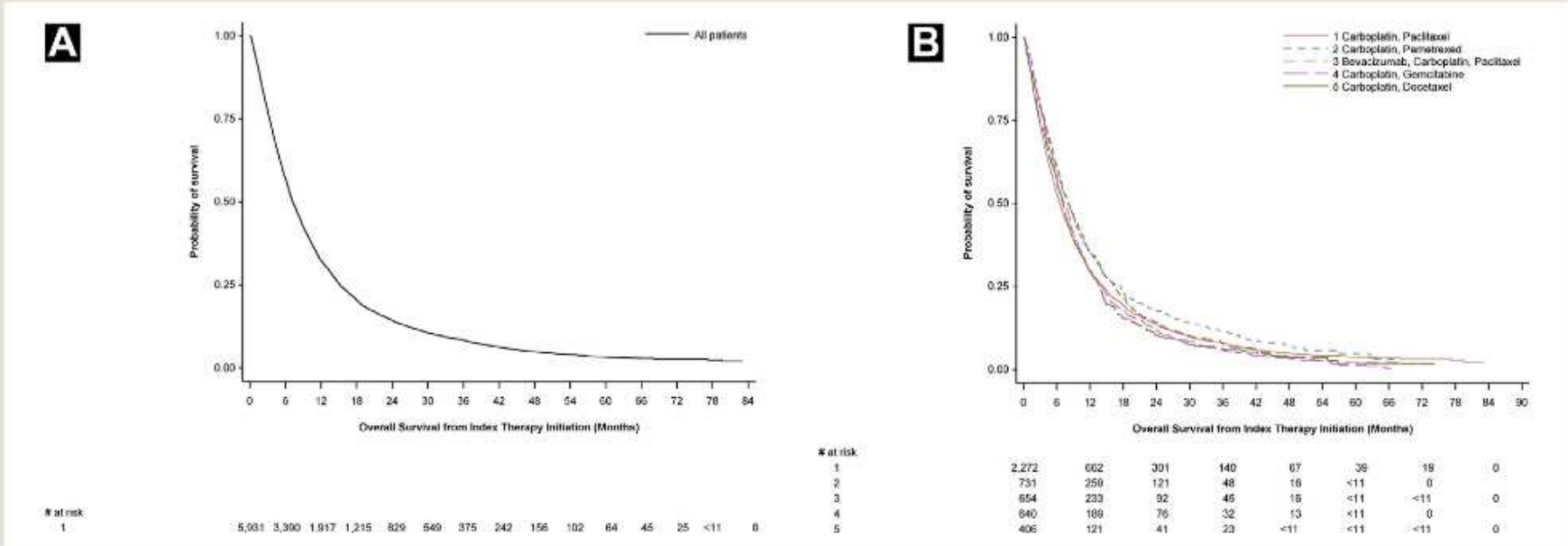
# Declinazione di innovazione

- **Scoperta: tantissime scoperte poche sono diventate innovazione**
- Prevede che la applichiamo
- Prevede che porti una processo sociale (deve essere per tanti)


Genome
Transcriptome
Proteome
Metabolome
Microbiome
Epigenome
Exposome
Phenome
Physiome
Anatome
Cell
Topol

# 1L NSCLC Real World Patterns of Care

**Figure 2** Kaplan-Meier Plots Depicting Overall Survival From Initiation of First-line Therapy for all Patients (A) and for Patients Who Received the 5 Most Common First-line Regimens (B)




Real-World Treatment Patterns, Overall Survival, and Occurrence and Costs of Adverse Events Associated With First-line Therapies for Medicare Patients 65 Years and Older With Advanced Non–small-cell Lung Cancer: A Retrospective Study

Marisa A. Bittoni,[1] Ashwini Arunachalam,[2] Haojie Li,[2] Ramon Camacho,[2] Jinghua He,[2] Yichen Zhong,[2] Gregory M. Lubiniecki,[2] David P. Carbone[1]

# La politica dei piccoli passi

Cancer Treatment Reviews 40 (2014) 485–494

Contents lists available at ScienceDirect

Cancer Treatment Reviews

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

Hot Topic

## The impact of personalized medicine on survival: Comparisons of results in metastatic breast, colorectal and non-small-cell lung cancers

Antonio Rossi [a], Valter Torri [b,*], Marina Chiara Garassino [c], Luca Porcu [b], Domenico Galetta [d]

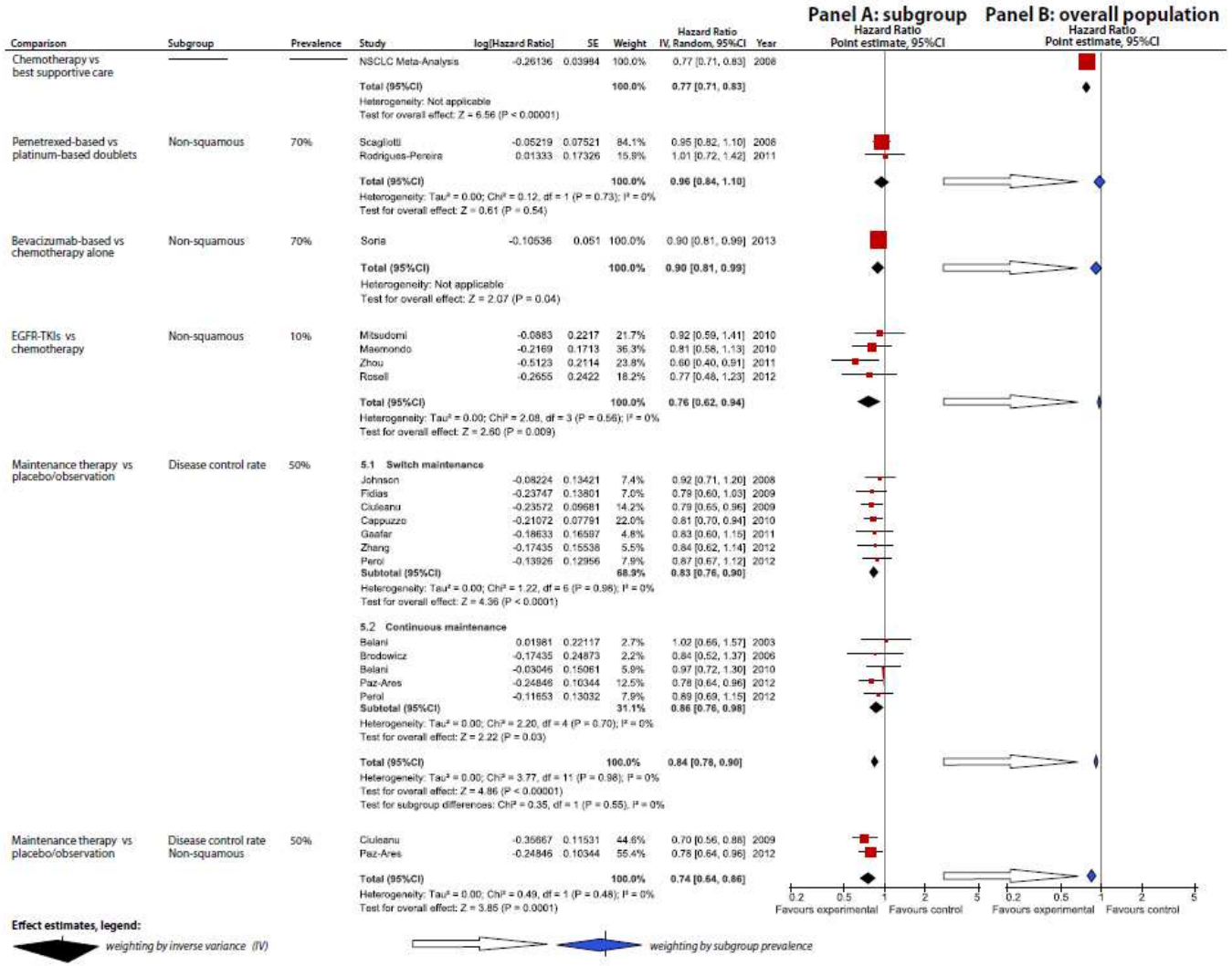
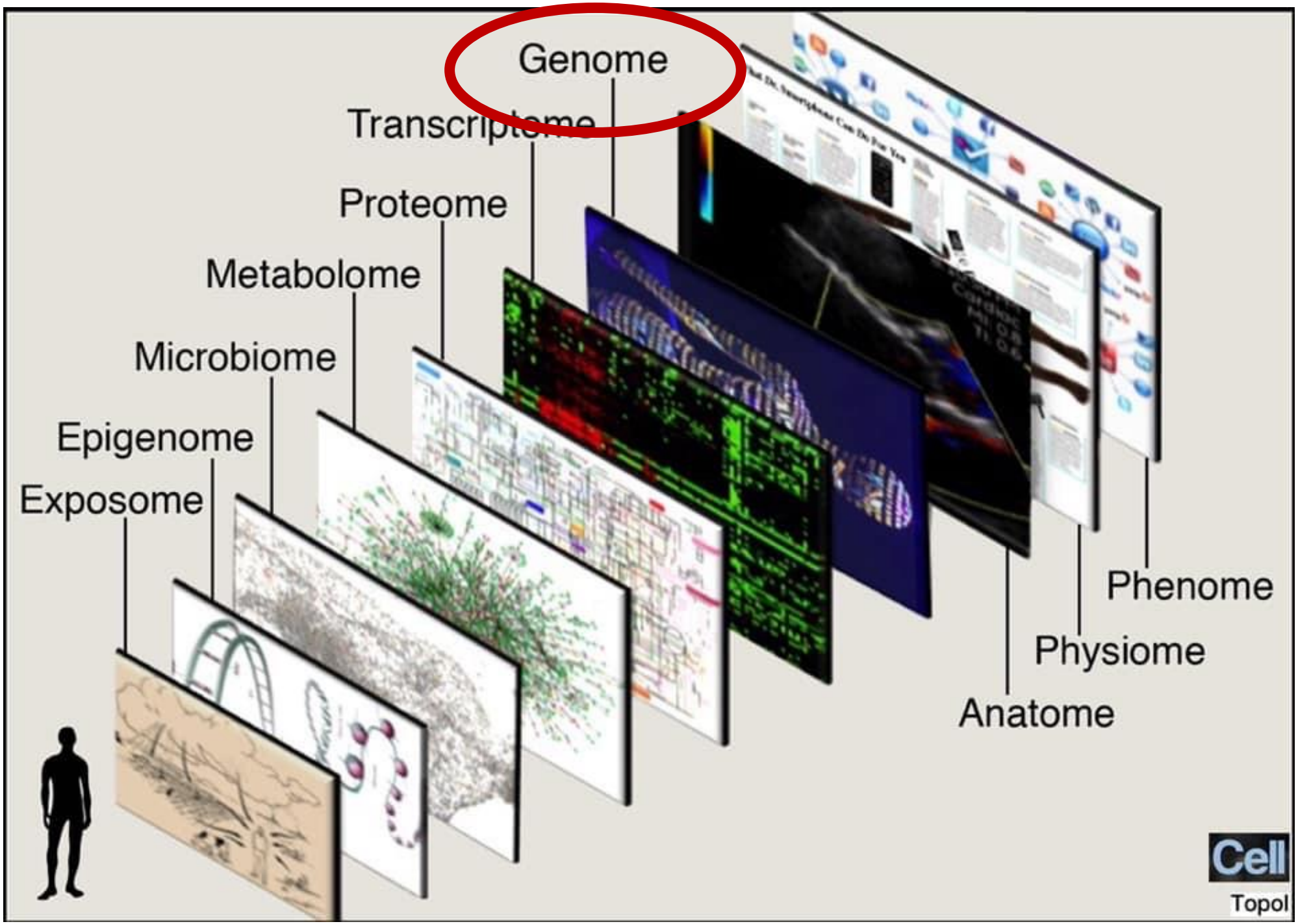



**Fig. 4.** Relative improvements derived by current therapies in metastatic NSCLC.


Genome
Transcriptome
Proteome
Metabolome
Microbiome
Epigenome
Exposome
Phenome
Physiome
Anatome
Cell
Topol

# Two different worlds and approaches

**“MUTATED”MAINLY NEVER SMOKERS**

TARGET THERAPIES

TARGET THERAPIES

CHEMOTHERAPY

**“WILD TYPE” MAINLY SMOKERS**

IMMUNOTHERAPY

CHEMOTHERAPY

# Two different worlds and approaches

**“MUTATED”MAINLY NEVER SMOKERS**

TARGET THERAPIES

TARGET THERAPIES

CHEMOTHERAPY

**“WILD TYPE” MAINLY SMOKERS**

IMMUNOTHERAPY

CHEMOTHERAPY

# 2004: the identification of EGFR mutations in lung cancers

*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]†

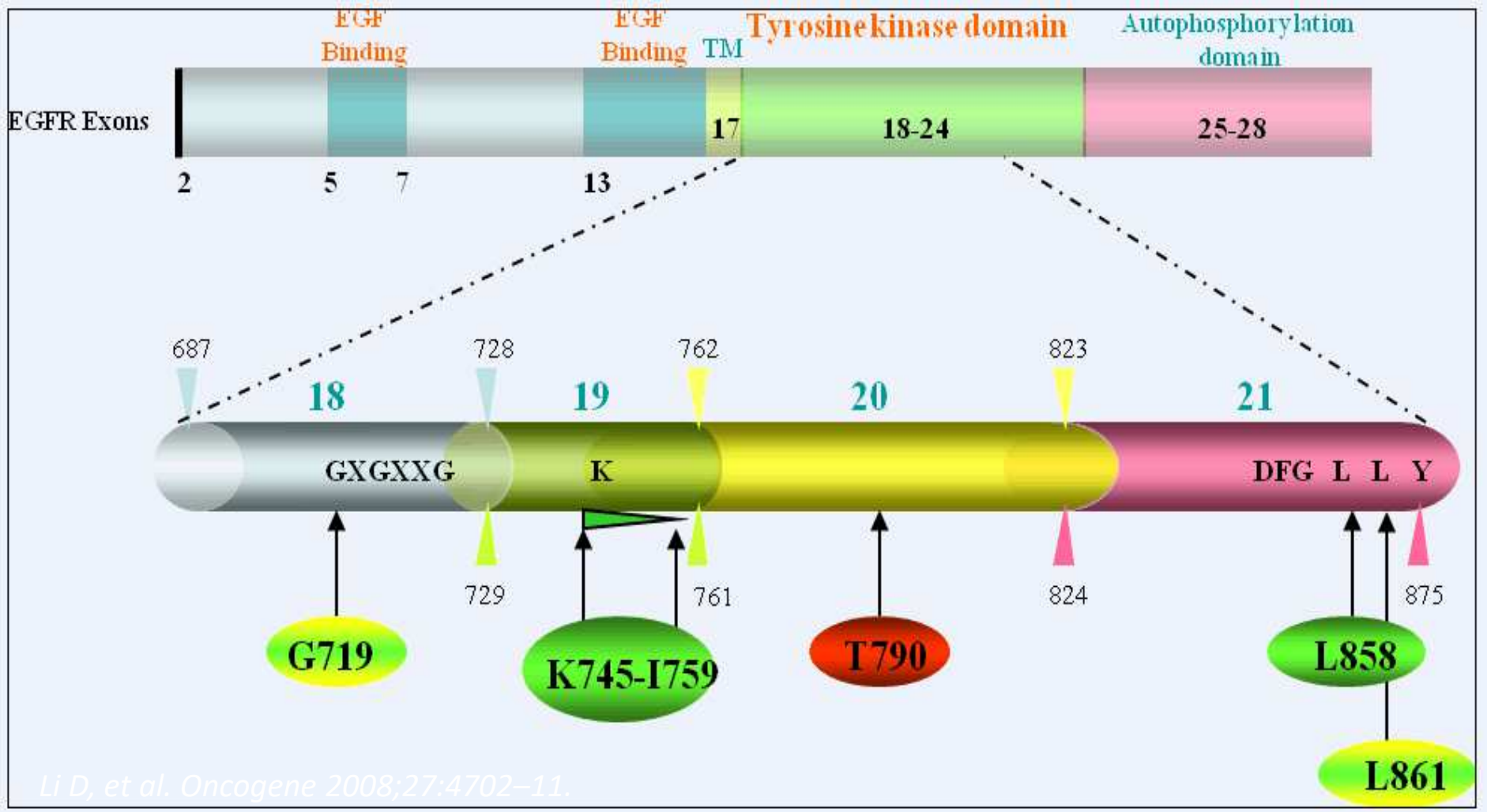
Science 2004

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.

N Engl J Med 2004

# EGFR

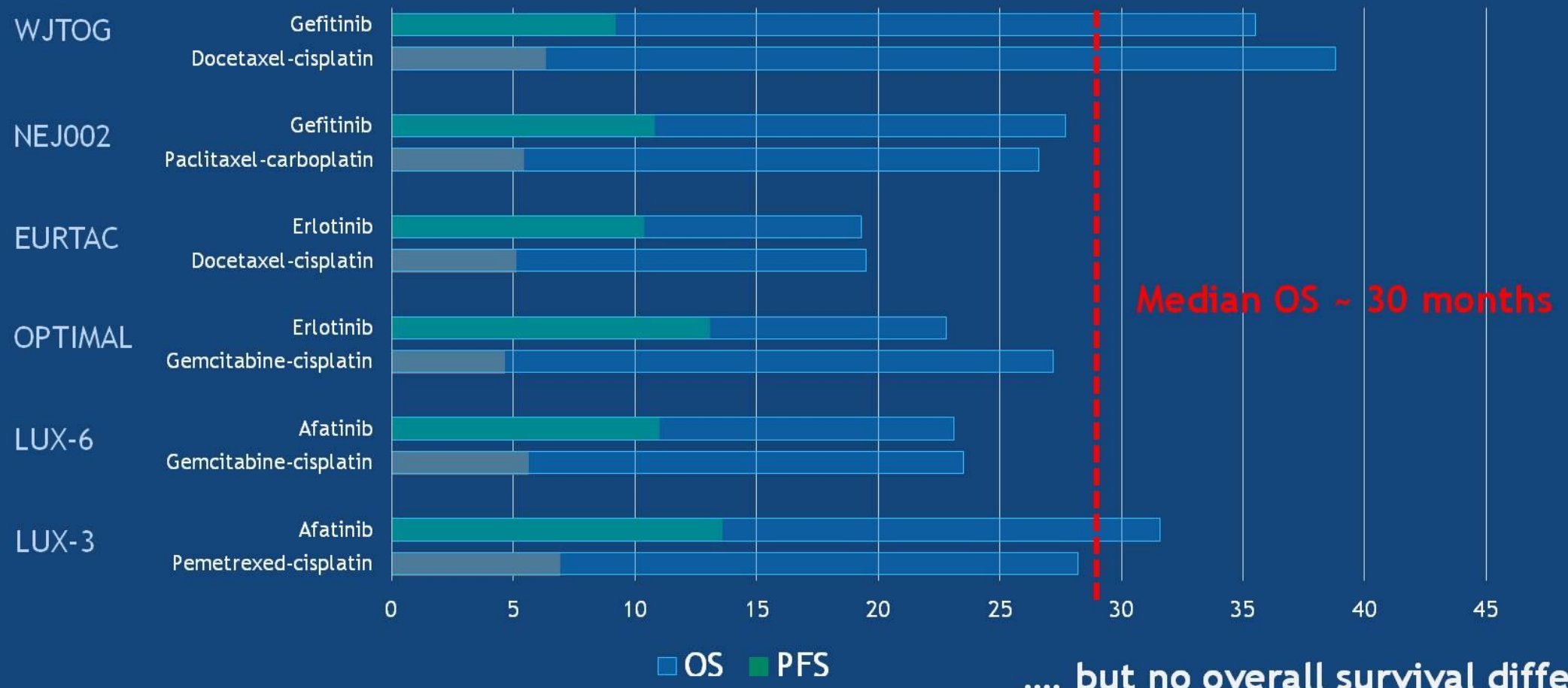



*Li D, et al. Oncogene 2008;27:4702–11.*

# EGFR TKIs in First Line (PFS)

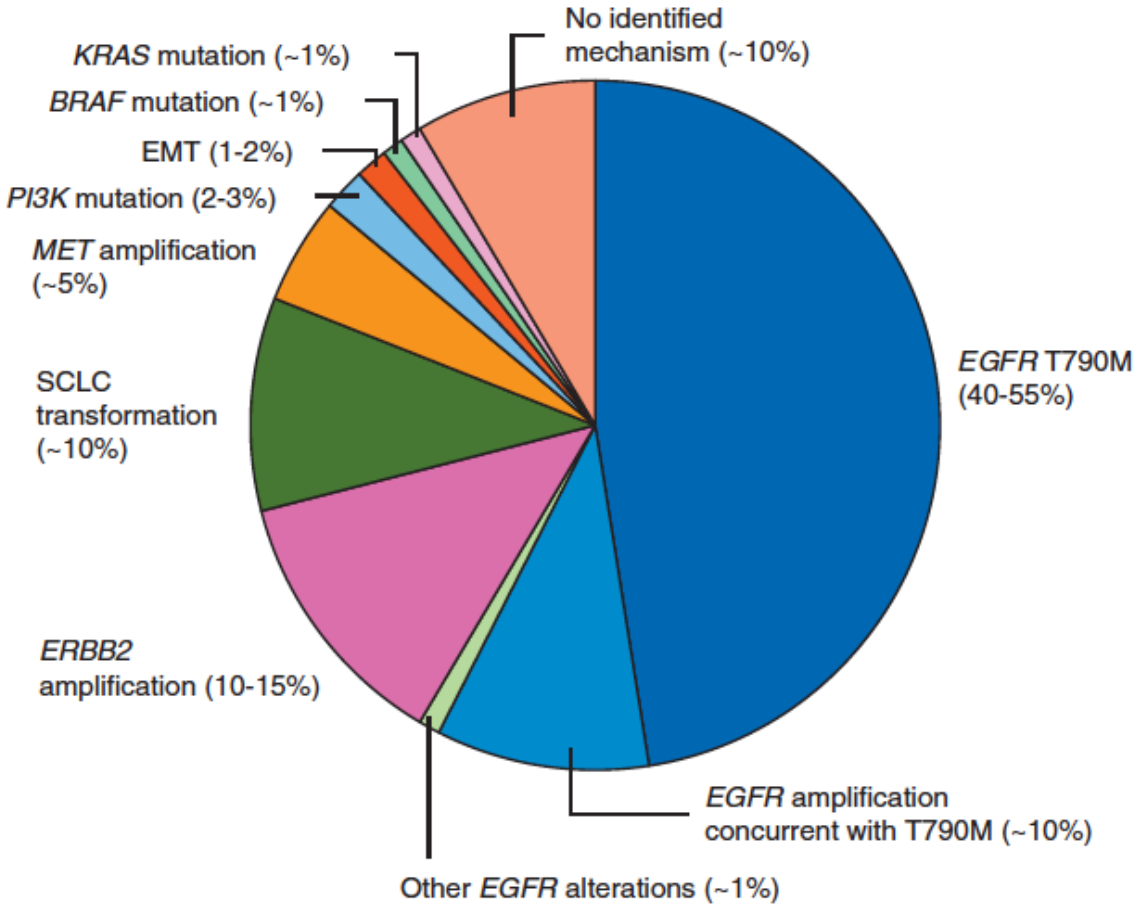
| | EGFR TKIs | Chemio | N° mutati | HR-PFS | 95%CI |
|---|---|---|---|---|---|
| IPASS | gefitinib | Carbo/taxol | 261 | 0.48 | 0.36-0.64 |
| First-SIGNAL | gefitinib | Cis/gem | 309 | 0.54 | 0.26-1.10 |
| CALGB 30406 | erlotinib | Carbo/taxol | 181 | 0.81 | 0.68-0.85 |
| WJTOG | gefitinib | Cis/doc | 177 | 0.48 | 0.33-0.71 |
| NEJSG | gefitinib | Carbo/taxol | 230 | 0.30 | 0.22-0.41 |
| OPTIMAL | erlotinib | Carbo/gem | 164 | 0.16 | 0.10-0.26 |
| EURTAC | erlotinib | Every platinum | 174 | 0.37 | 0.25-0.54 |
| TORCH | erlotinib | Cis/gem | 39 | 0.86 | n.a-1.40 |
| LUX-LUNG3 | afatinib | Cis/pem | 308 | 0.47 | 0.34-0.65 |
| LUX-LUNG 6 | afatinib | Cis/gem | 364 | 0.28 | 0.20-0.39 |

# EGFR TKIs approved in 1L: PFS benefit



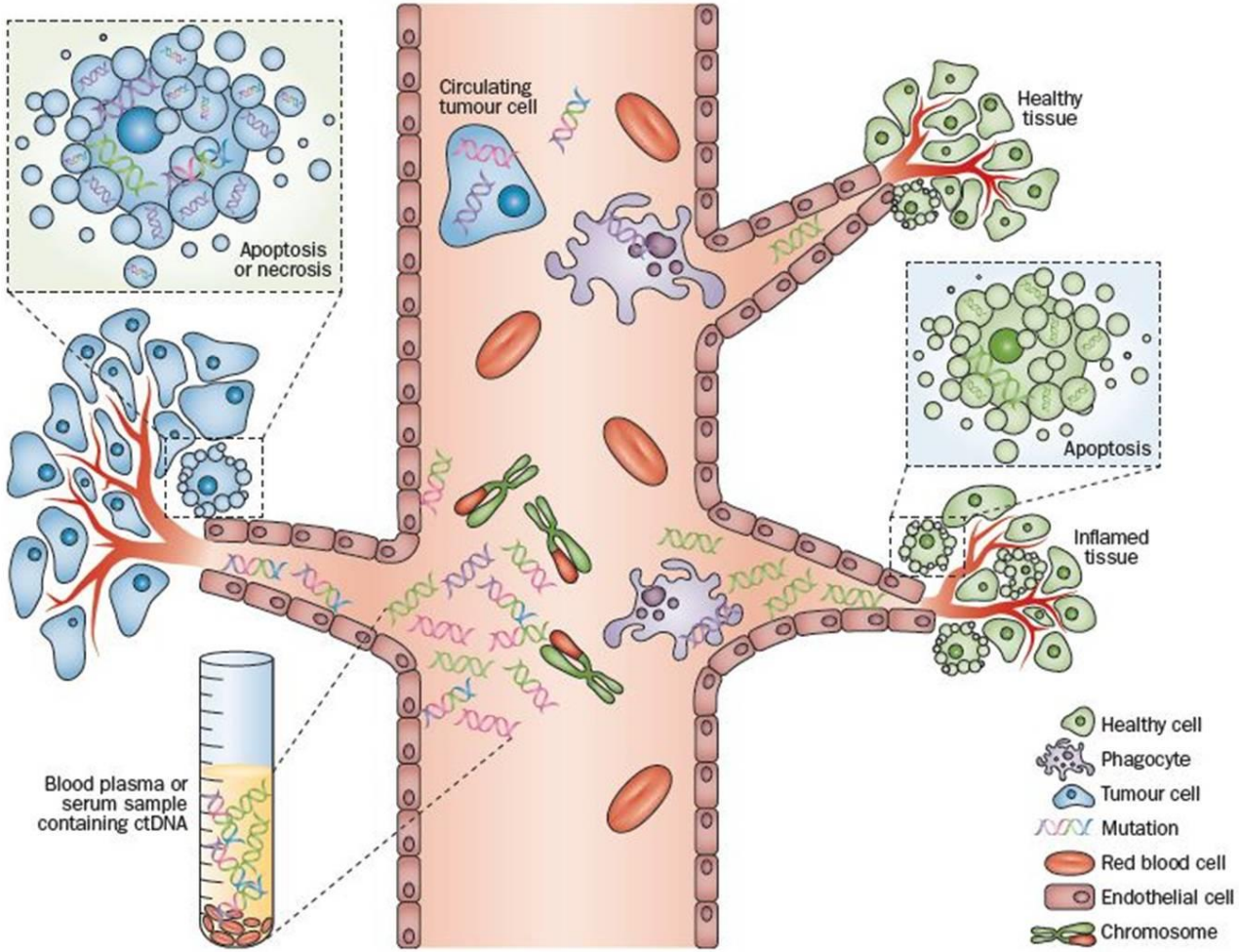

.... but no overall survival difference

# EGFR mutati
# meccanismi di resistenza a TKI di I-II gen




***Westover et al, Ann Oncol 2018***

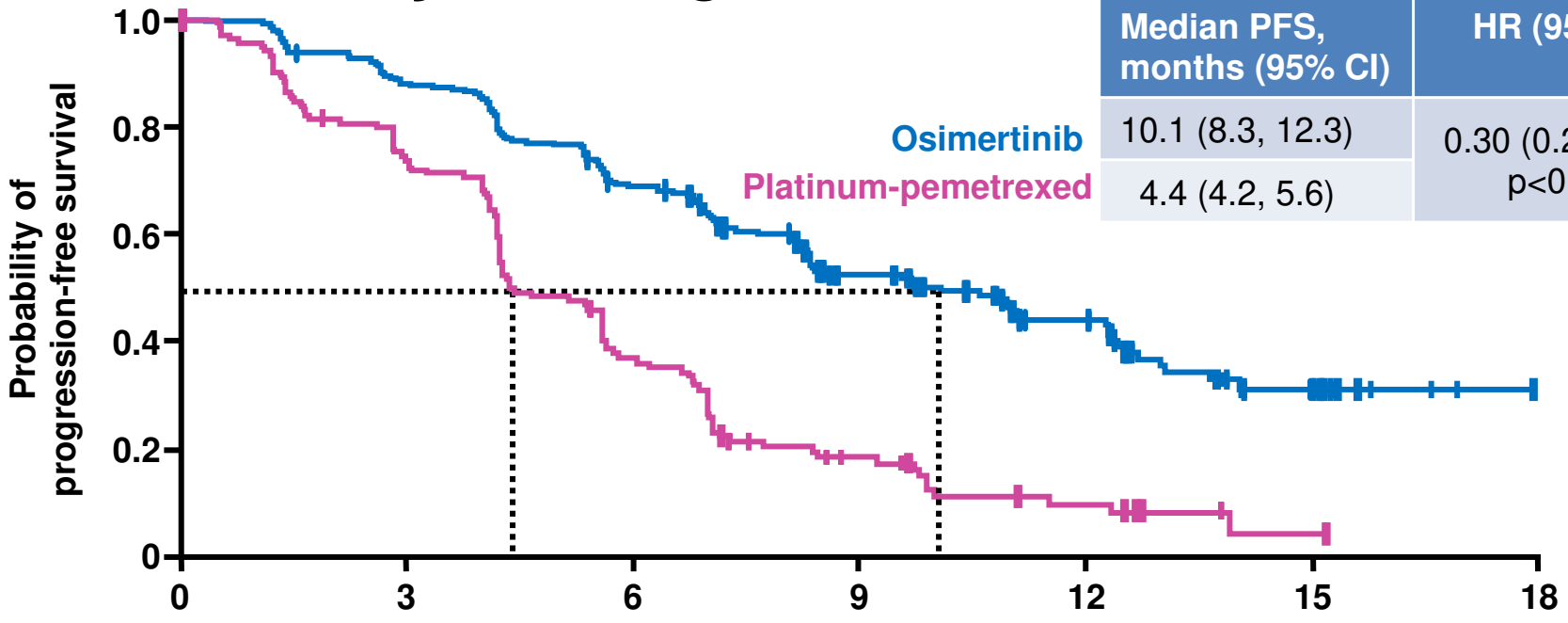
# Can we find EGFR T790M from the blood ?




Crowley E et al. Nat Rev Clin Oncol. 2013;10(8):472-84.

# Osimertinib alla progressione

## AURA3 primary endpoint: PFS by investigator assessment




| | Median PFS, months (95% CI) | HR (95% CI) |
|---|---|---|
| Osimertinib | 10.1 (8.3, 12.3) | 0.30 (0.23, 0.41) p<0.001 |
| Platinum-pemetrexed | 4.4 (4.2, 5.6) | |

| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Osimertinib | 279 | 240 | 162 | 88 | 50 | 13 | 0 |
| Platinum-pemetrexed | 140 | 93 | 44 | 17 | 7 | 1 | 0 |

- Analysis of PFS by BICR was consistent with the investigator-based analysis: **HR 0.28** (95% CI 0.20, 0.38), p<0.001; median PFS 11.0 vs 4.2 months.

Population: intent-to-treat
Progression-free survival defined as time from randomisation until date of objective disease progression or death; calculated using the Kaplan-Meier approach. Progression included deaths in the absence of RECIST progression.
Tick marks indicate censored data; CI, confidence interval

# Real-life efficacy of osimertinib in pretreated patients with advanced non-small cell lung cancer harboring EGFR T790M mutation

Jean Bernard Auliac[a,*], Maurice Pérol[b], David Planchard[c], Isabelle Monnet[d], Marie Wislez[e], Hélène Doubre[f], Florian Guisier[g], Eric Pichon[h], Laurent Greillier[i], Bénédicte Mastroianni[j], Chantal Decroisette[k], Roland Schott[l], Sylvestre Le Moulec[m], Jennifer Arrondeau[n], Alexis B. Cortot[o], Laurence Gerinière[j], Aldo Renault[p], Catherine Daniel[q], Lionel Falchero[r], Christos Chouaid[d]



Lung Cancer 127 (2019) 96–102

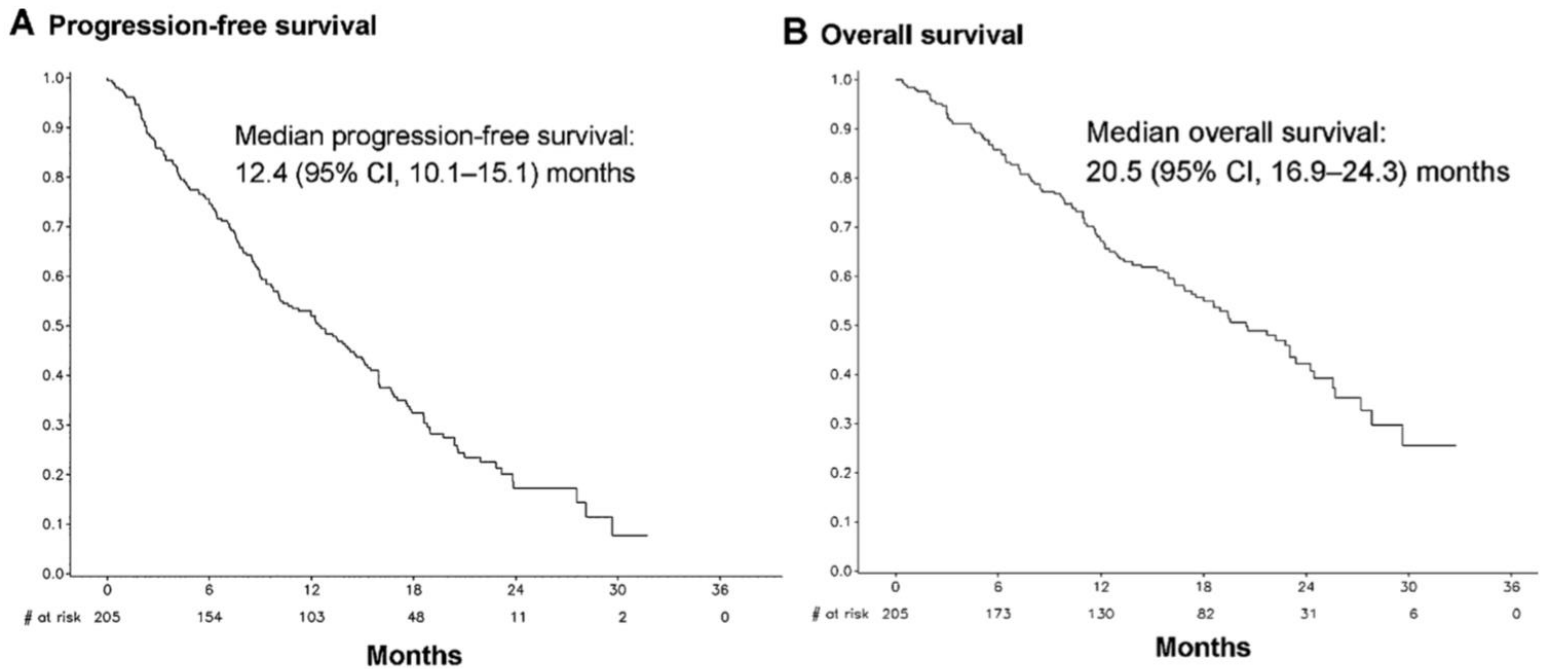
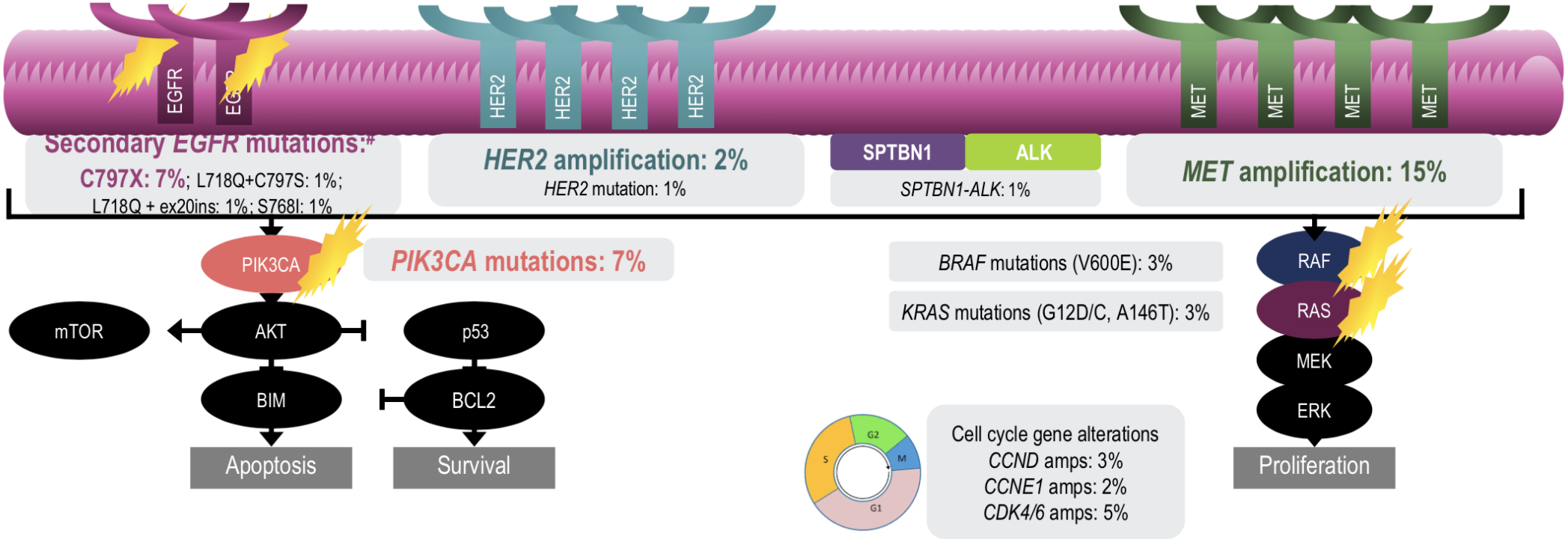



**Fig. 1.** Progression-free survival (A) and overall survival (B) of the entire cohort from osimertinib initiation.

# Results: Candidate acquired resistance mechanisms with osimertinib (n=91)*

- No evidence of acquired EGFR T790M
- The most common resistance mechanisms were *MET* amplification and EGFR C797S mutation
  - Other mechanisms included *HER2* amplification, *PIK3CA* and *RAS* mutations



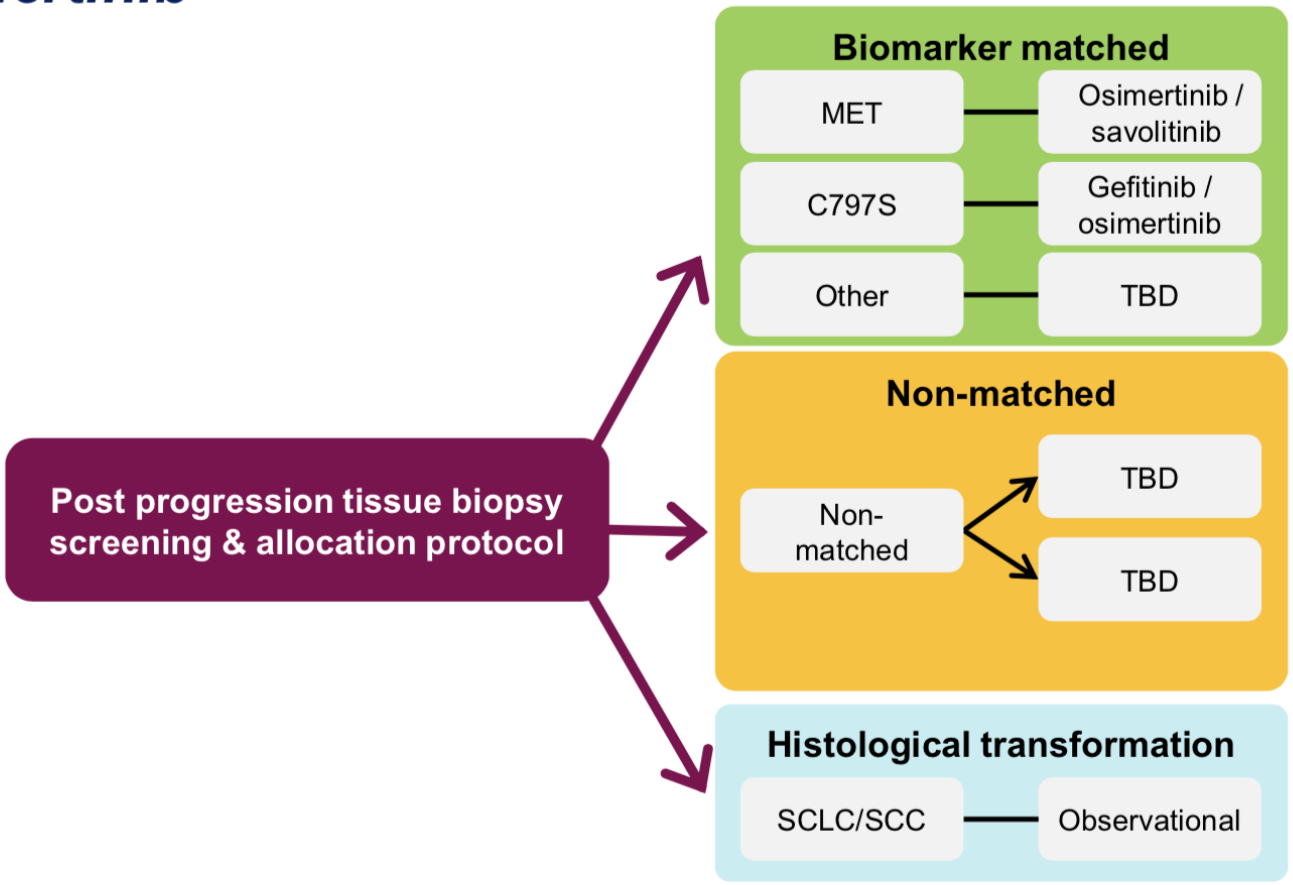

*Resistance mechanism reported may overlap with another; #Two patients had de novo T790M mutations at baseline of whom one acquired C797S at progression



Ramalingam SS, et al. Presented at: ESMO 2018; October 19-23, 2018; Munich, Germany. Abs LBA50.

# ORCHARD

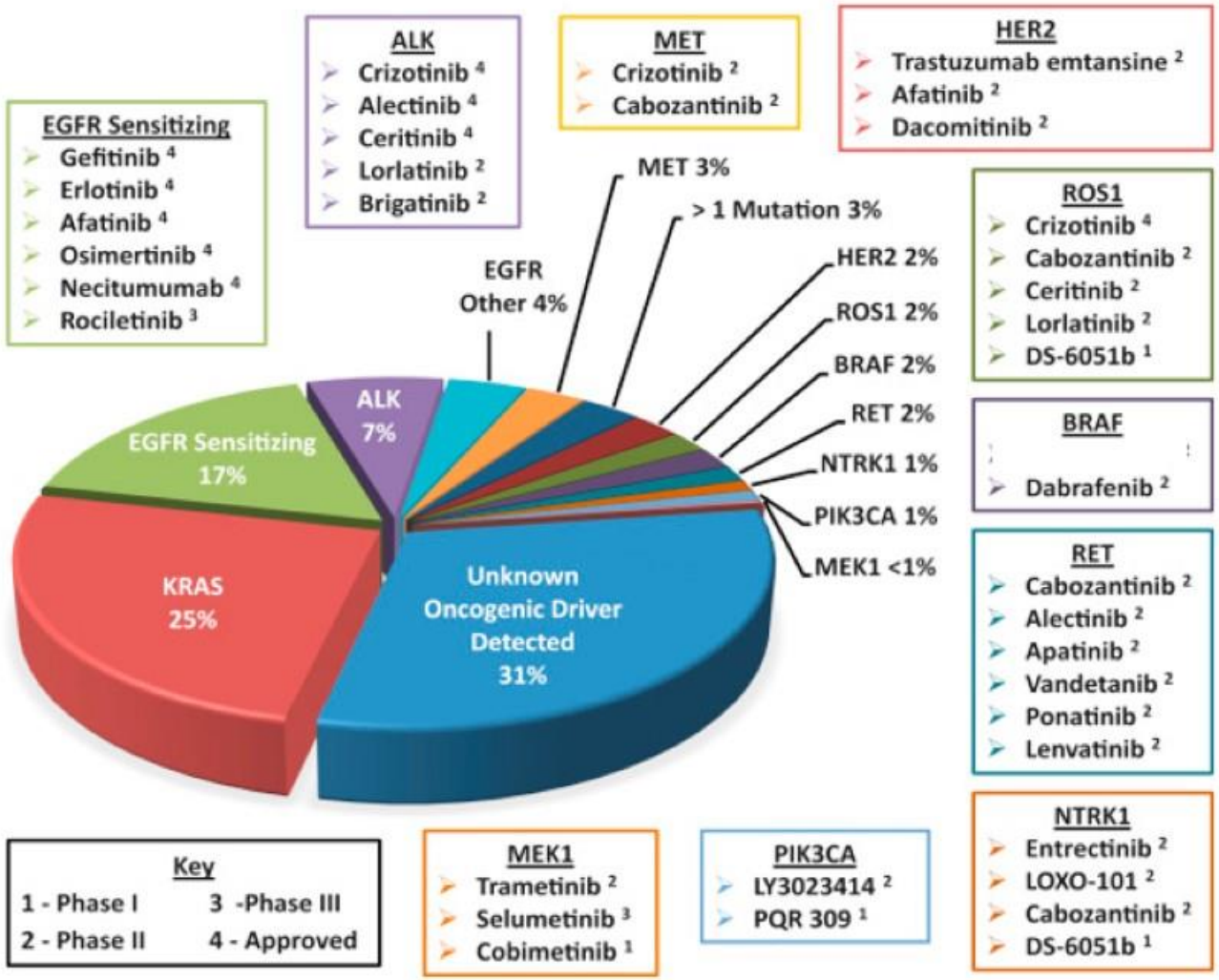
## *Open-label, global multicentre, multidrug Phase II platform study in 1L EGFRm advanced NSCLC patients whose disease has progressed on osimertinib*




- Designed to have appropriate treatment option for all 1L progressor who enrol
- Additional treatment Arms to be added as resistance mechanisms are identified
- Supported with strong translational genomic and non-genomic biomarker exploration studies

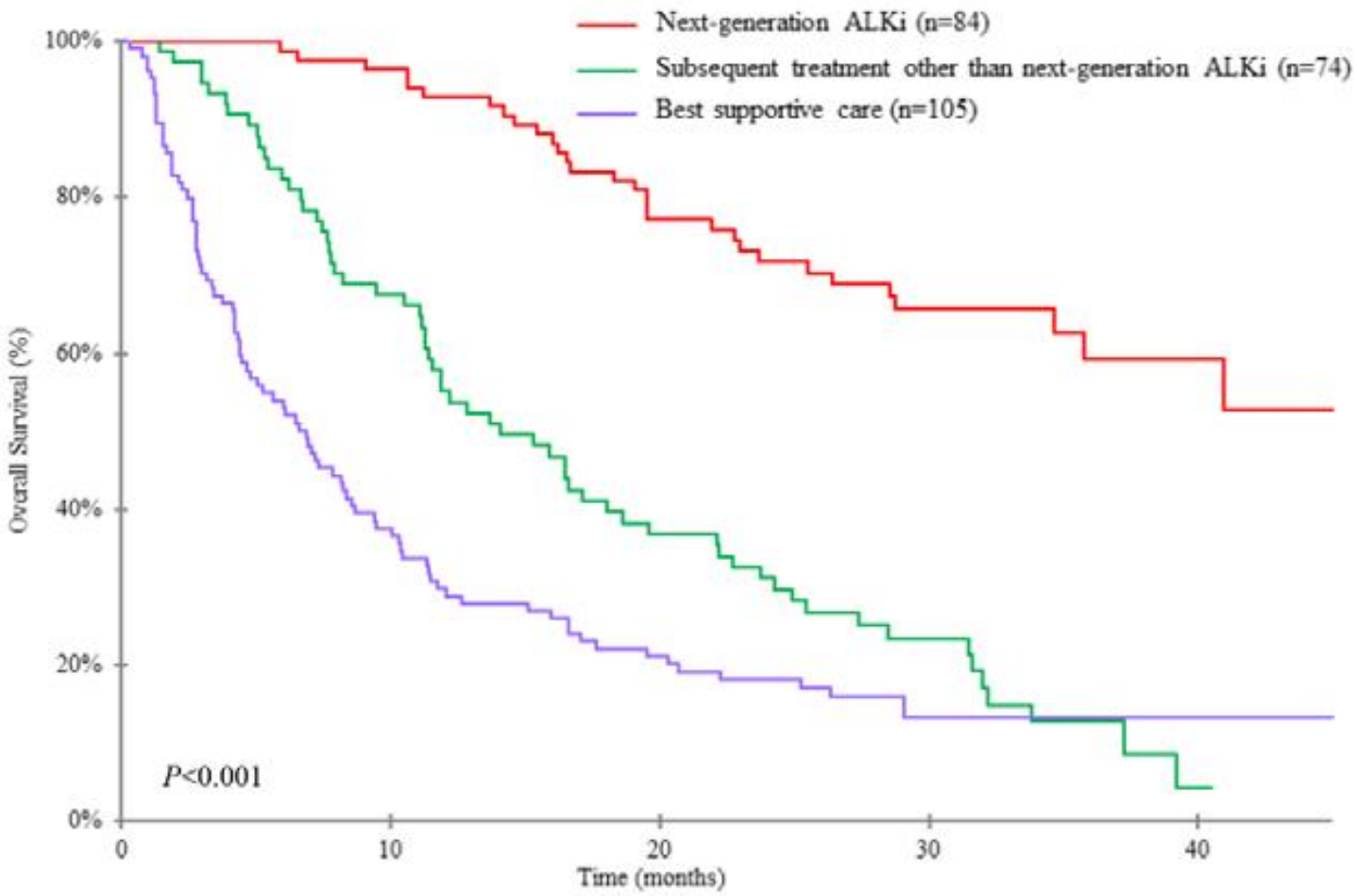
MET, MET proto-oncogene; SCC, squamous cell carcinoma

# Lung Adenocarcinoma Molecular Properties and Personalized Therapy




Tsao AS, et al. *J Thorac Oncol.* 2016;11:613-638.

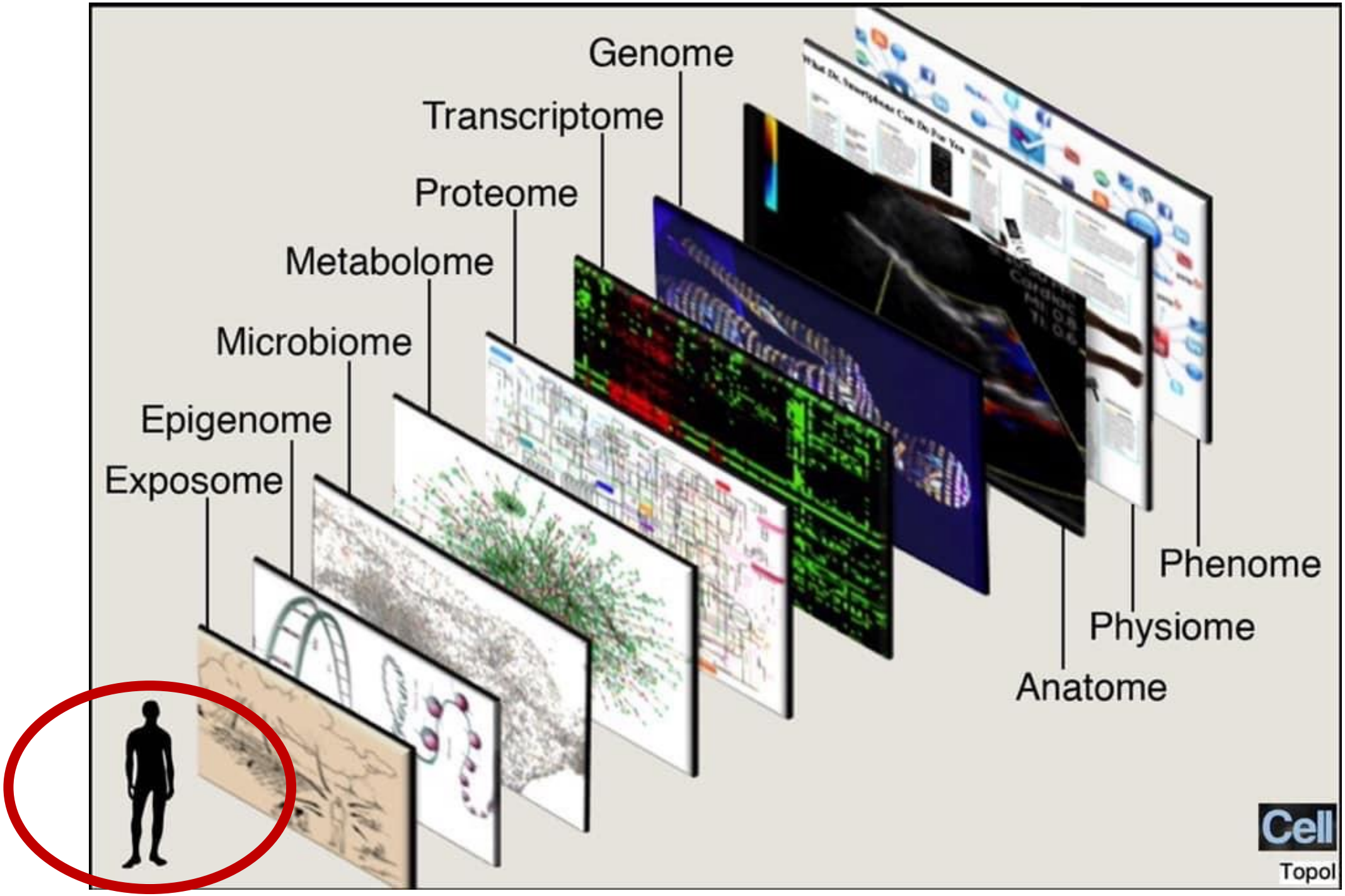
# I pazienti con la traslocazione di ALK (4%) vivono anni




**Number at risk**

| | | | | | |
|---|---|---|---|---|---|
| Next-generation ALKi | 84 | 81 | 62 | 36 | 11 |
| Subsequent treatment other than next-generation ALKi | 74 | 49 | 26 | 12 | 1 |
| Best supportive care | 105 | 39 | 22 | 9 | 3 |

***Duruisseaux M et al, Oncotarget 2017***


Genome
Transcriptome
Proteome
Metabolome
Microbiome
Epigenome
Exposome
Phenome
Physiome
Anatome
Cell
Topol

# STORIA MOLTO BELLA E LUNGA….

## William Coley (1862-1936)

1891: William Coley (Memorial Sloan Kettering Cancer Center-MSKCC, NY). Used the Coley toxin containing live or inactivated bacteria like Serratia Marcescens and Streptococcus pyogenes to treat over 1000 sarcoma patients by intratumor injections. Reproducibility was limited but some patients showed a benefit

## Albert Calmette (1863-1933) and Camille Guèrin (1872-1961)

BCG is a vaccine used to prevent tuberculosis (TB). Is composed of mycobacterium Bovis that causes inflammation-dependen immunotherapy of superficial bladder cancer; it has been used for over 30 years. The most effective immunotherapy against a human tumor (ladder)

## Paul Ehrlich (1854-1905)

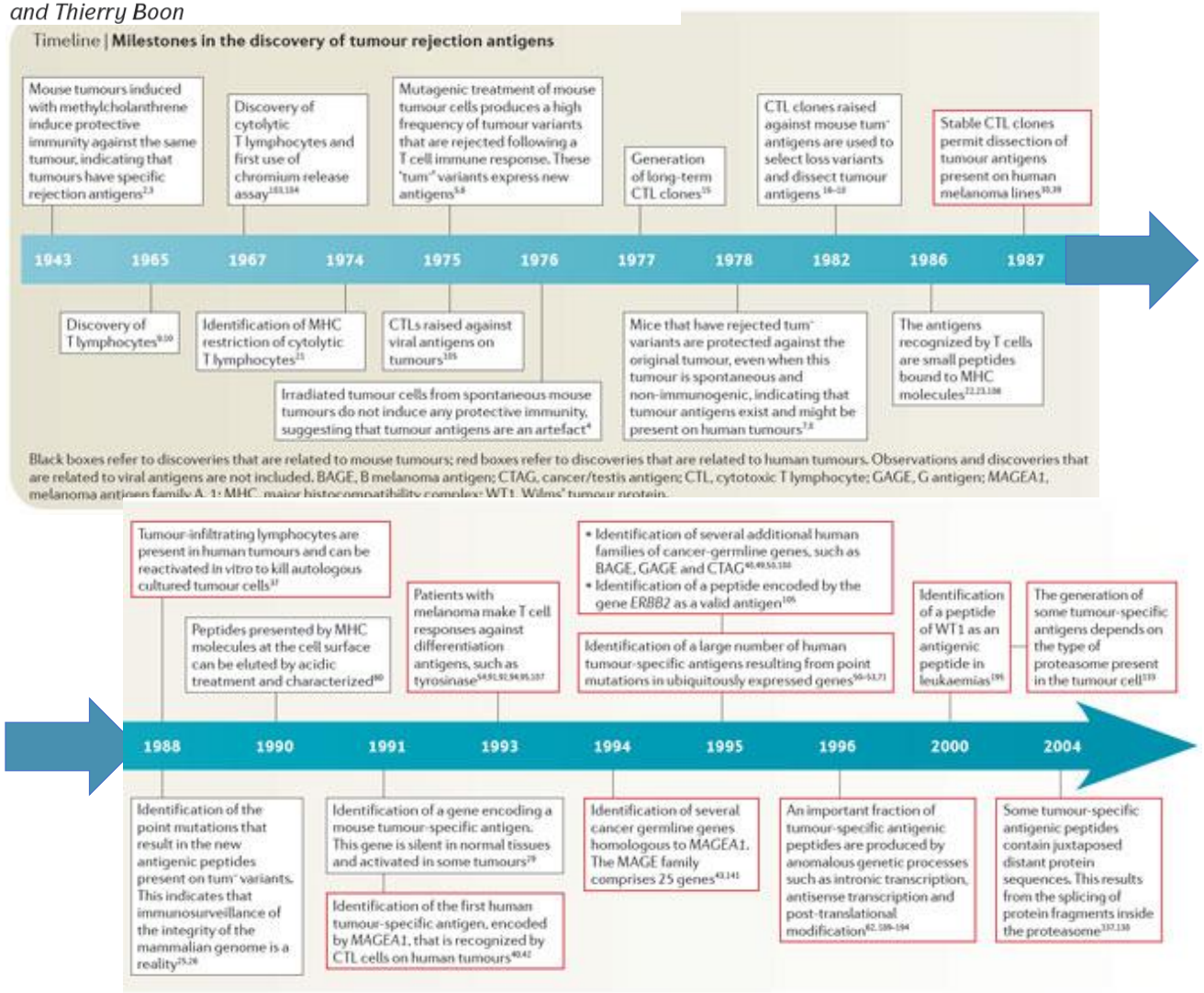
Microbiologo tedesco (fondatore della chemioterapia) 1900: suggerisce che alcune molecole all'interno dell'organismo possono essere in grado di combattere i tumori

## Frank Macfarlane Burnet (1899-1989)

Suggerisce che le cellule tumorali possono causare una risposta immunitaria in grado di distruggere il tumore senza alcuna manifestazione clinica (1957: teoria dell'Immunosorveglianza)

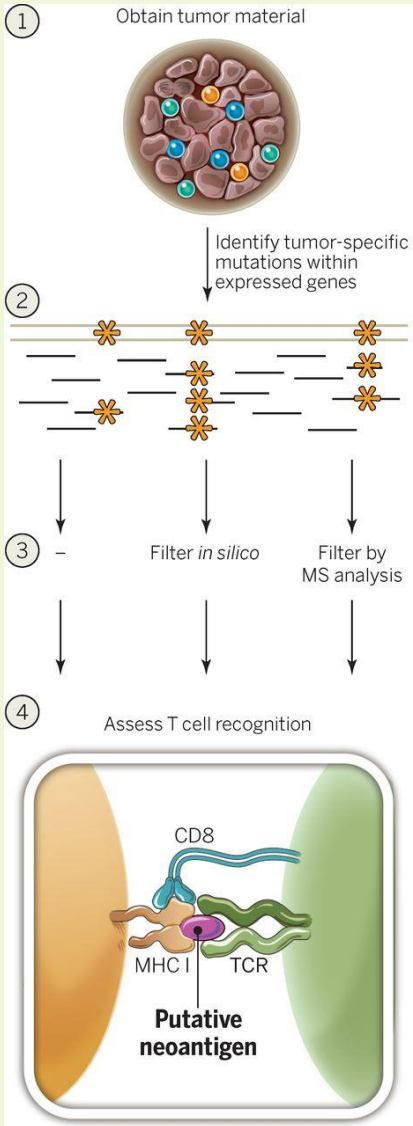
# Tumour antigens recognized by T lymphocytes: at the core of cancer immunotherapy

*Pierre G. Coulie, Benoît J. Van den Eynde, Pierre van der Bruggen and Thierry Boon*




NATURE REVIEWS | CANCER 14:135,2014

## Cancer exome–based identification of neoantigens




**Ton N. Schumacher, and Robert D. Schreiber**
**Science 2015;348:69-74**

Science
AAAS

# Escape from immune control is a hallmark of cancer

## Elimination

*Cancer immunosurveillance*

- **Effective antigen processing/presentation**
- **Effective activation and function of effector cells**
  - e.g. T cell activation without co-inhibitory signals

## Equilibrium

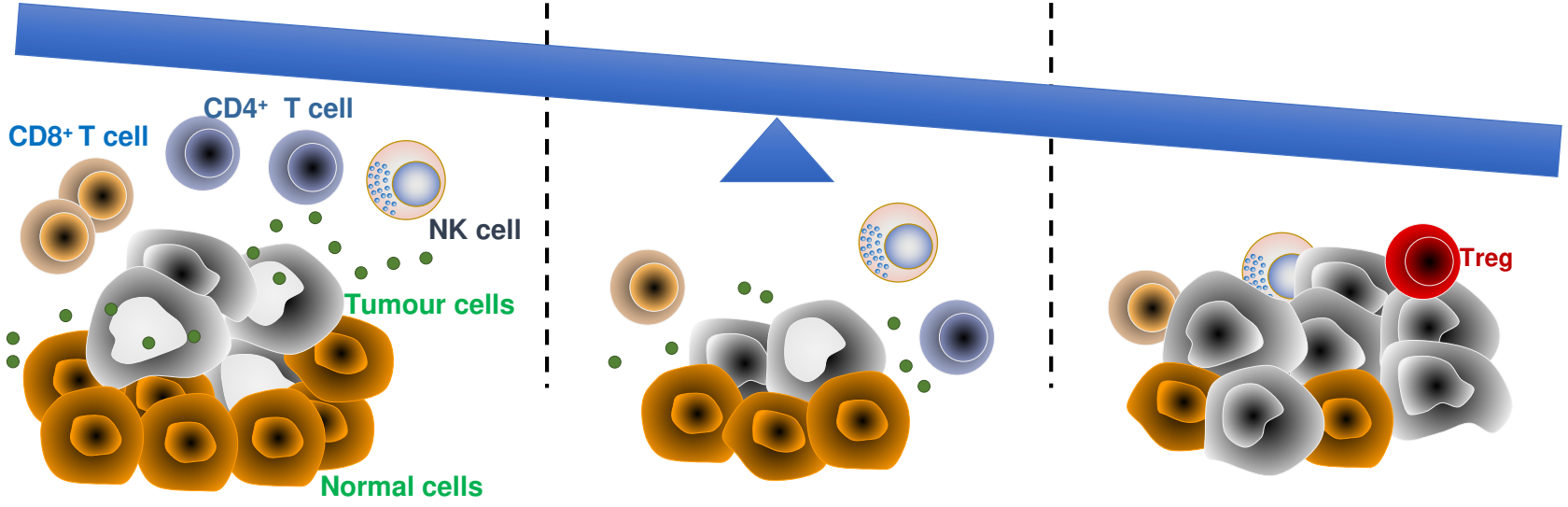
*Cancer dormancy*

- **Genetic instability**
- **Tumour heterogeneity**
- **Immune selection**

## Escape

*Cancer progression*

- **Tumours avoid elimination through the outgrowth of tumour cells that can suppress, disrupt or 'escape' the immune system**
- **Reduced immunogenicity**



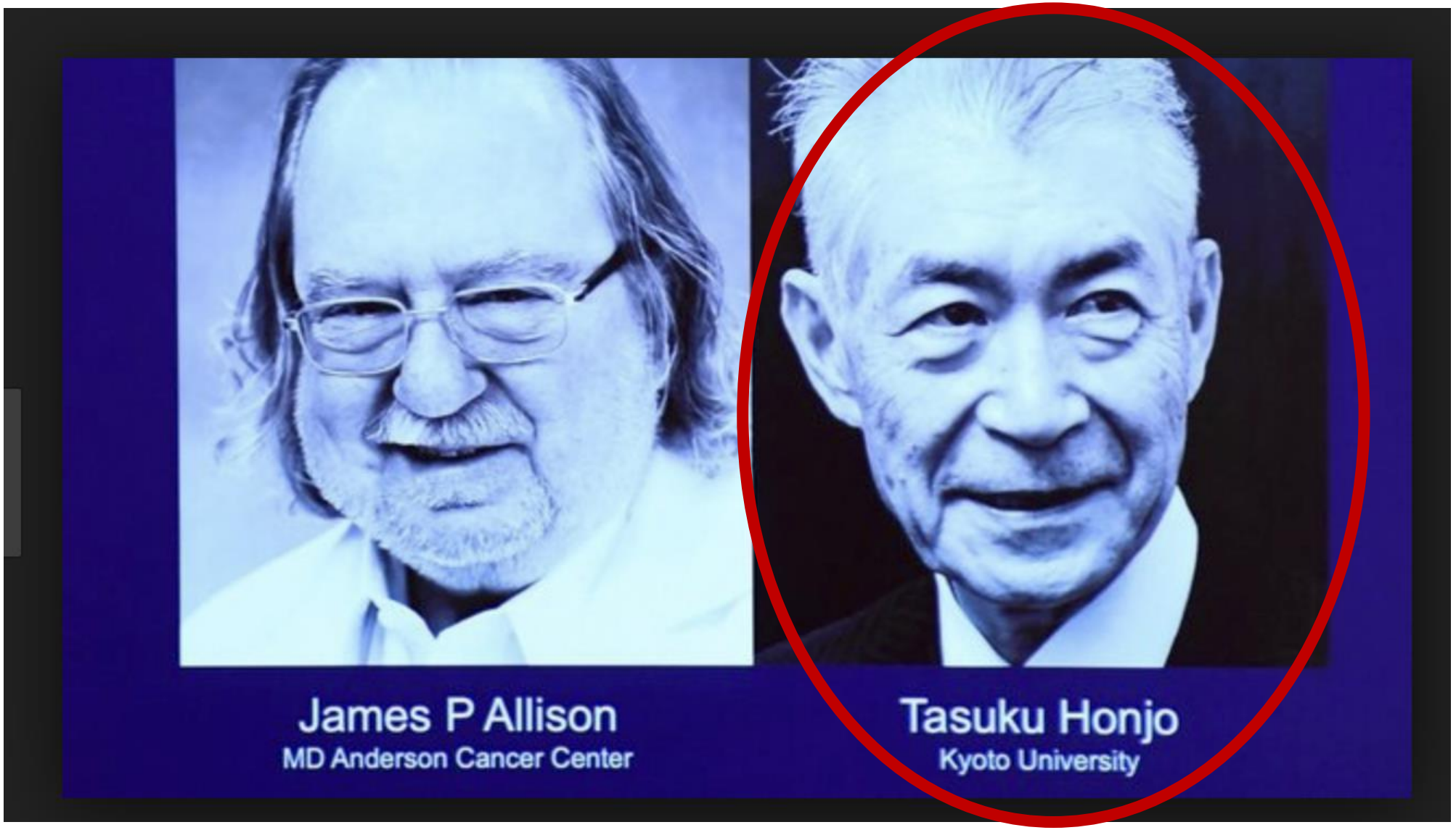

NK = natural killer; Treg = regulatory T cells.

Vesely M and Schreiber R. *Ann N Y Acad Sci.* 2013;1284:1–5.

# Premio Nobel 2018

# Premio Nobel 2018

# PD-1



# +26 anni

# The Rapid Pace of Cancer Immunotherapy Research

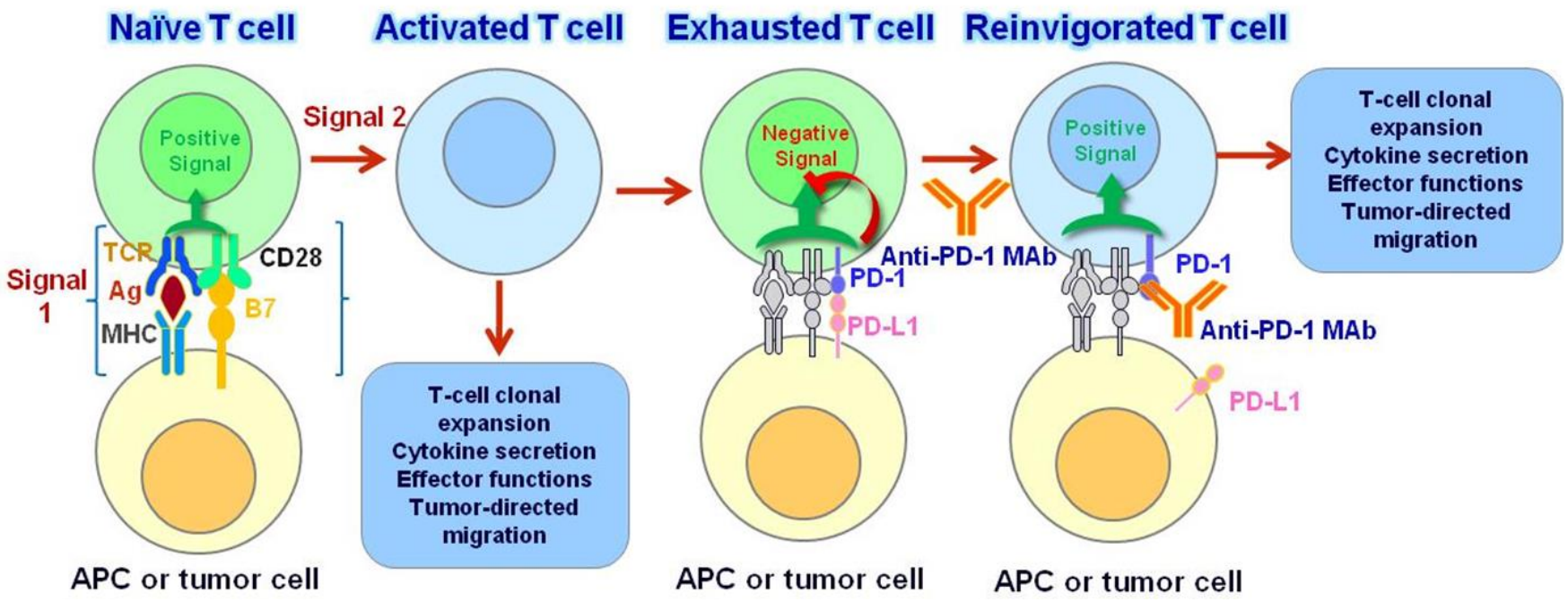







**From the breakthrough of year 2013 for *Nature* and *Science* to the inspiration of the moonshot project for next generation immunotherapy**

# Segnali co-attivatori e co-inibitori

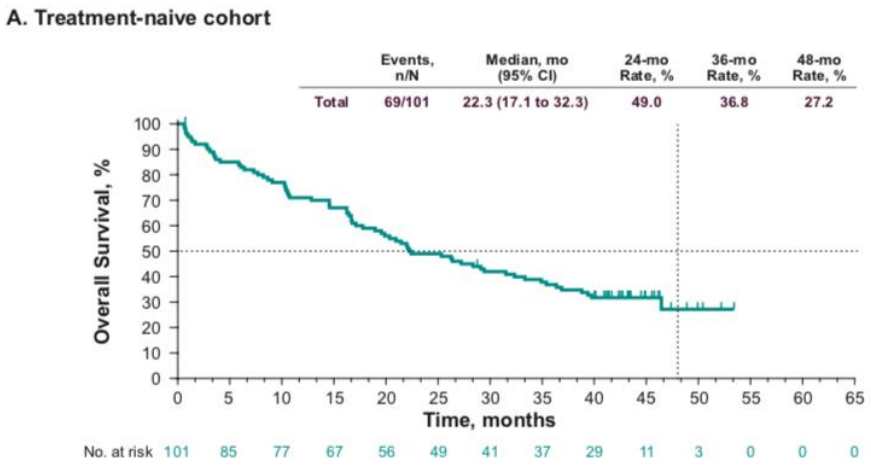



*Topalian and Brahmer NEJM 2012*

# Cosa otteniamo a 4 anni (pembro KEYNOTE-001)

## Naive

27.2%

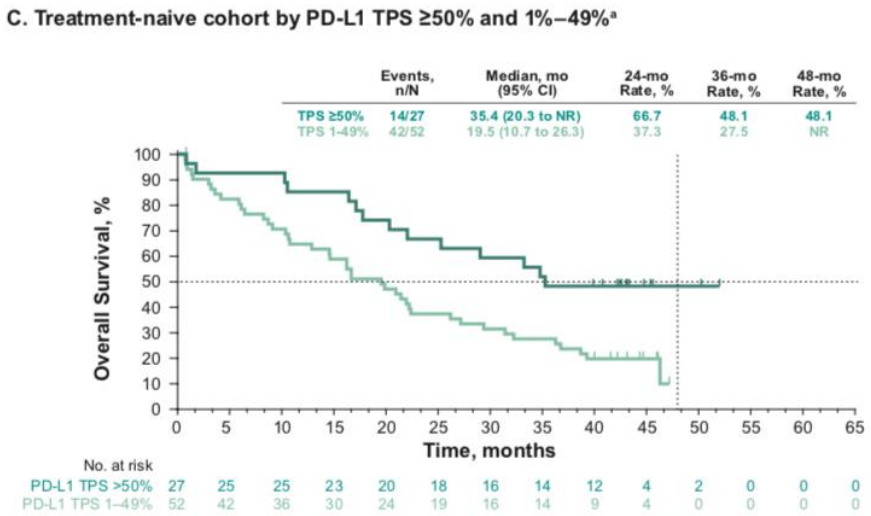



PD-L1>50%

48.1%

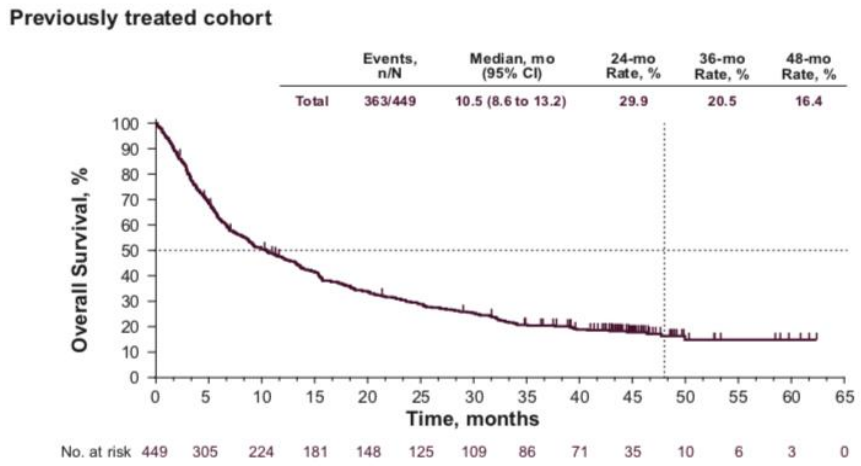
PD-L1>1%

10%




## Pretreated

16.4%




PD-L1>50%

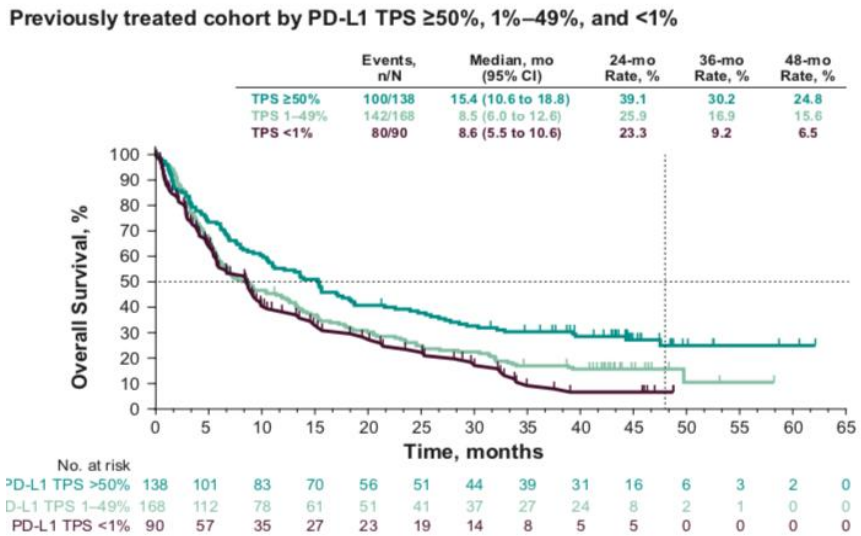
24.8%

PD-L1 1-49%

15.6%

PD-L1 50%

6.5%



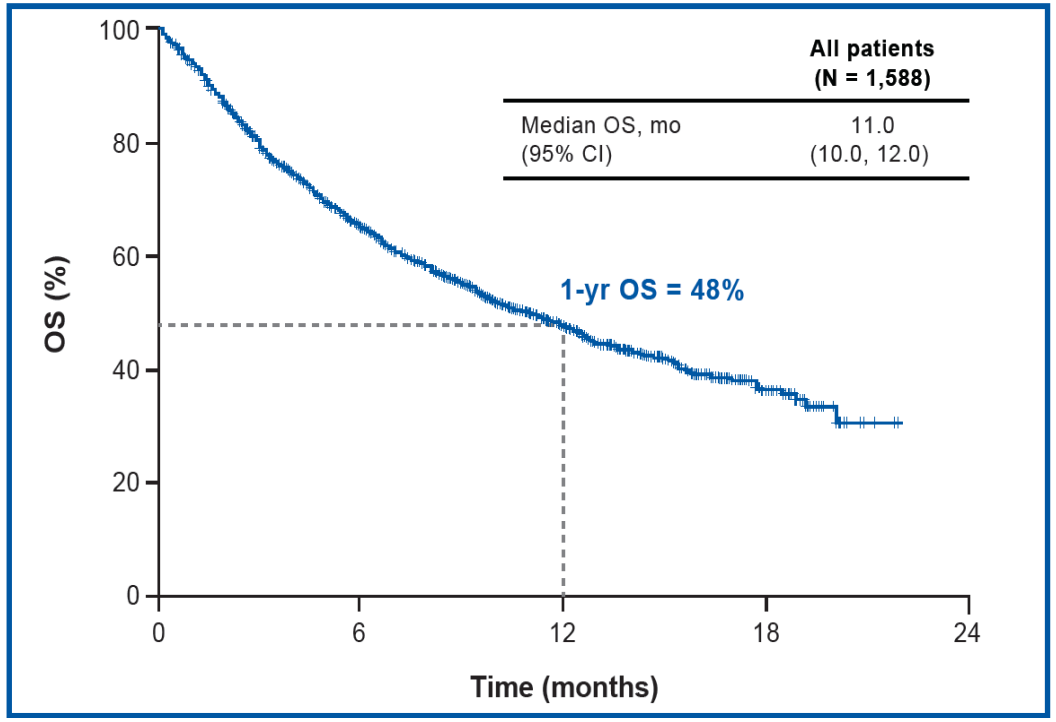

Dr. Mark A. Socinski

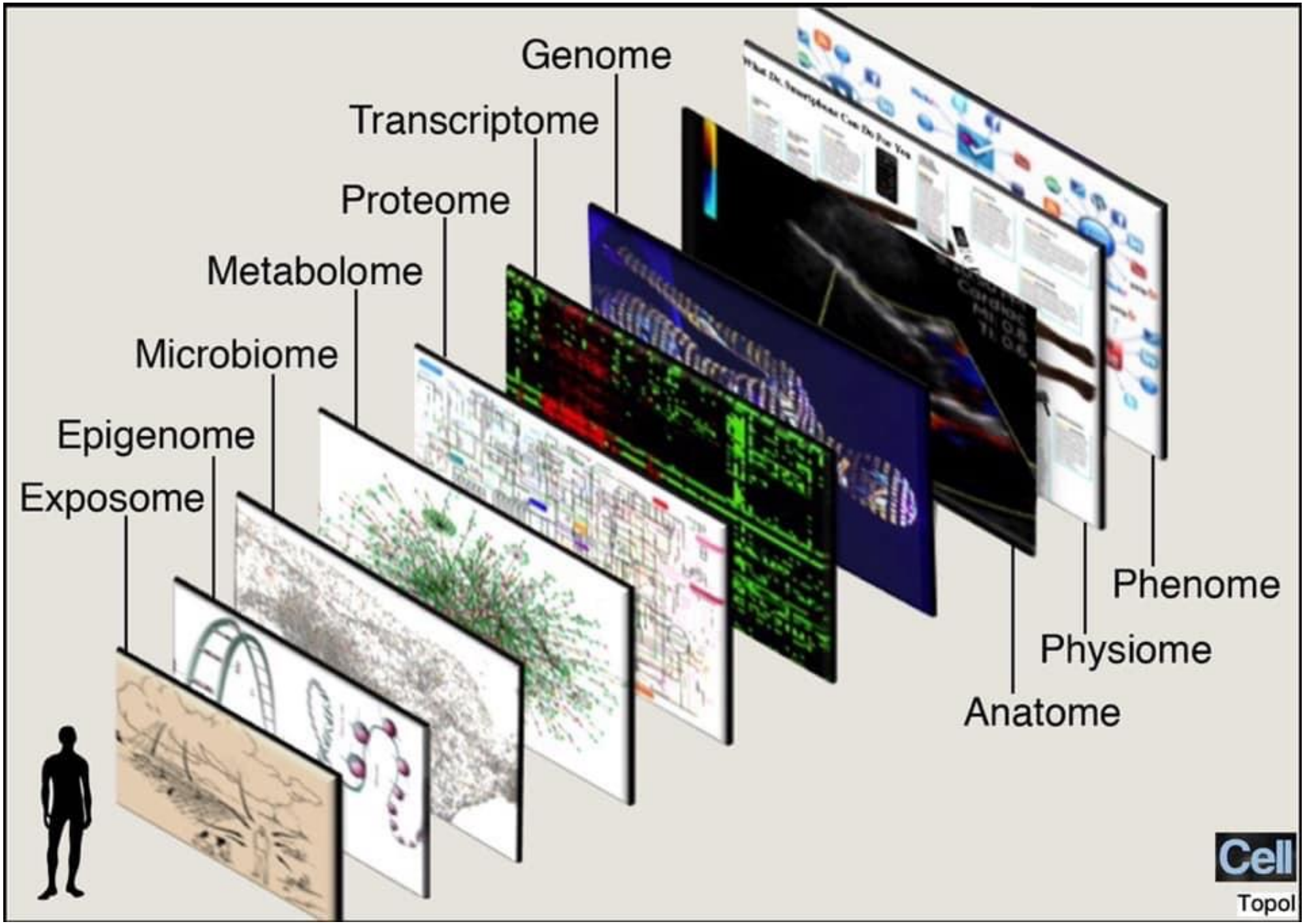
# EAP nivolumab su 1500 pazienti = trial clinici

## Survival

- Median OS was 11.0 months (95% CI: 10.0, 12.0), and the OS rate at 1 year was 48% (Figure 1)
- Median PFS was 3.0 months (95% CI: 2.9, 3.1), and the PFS rate at 1 year was 22% (Figure 2)

**Figure 1.** Kaplan–Meier estimate of OS




Genome
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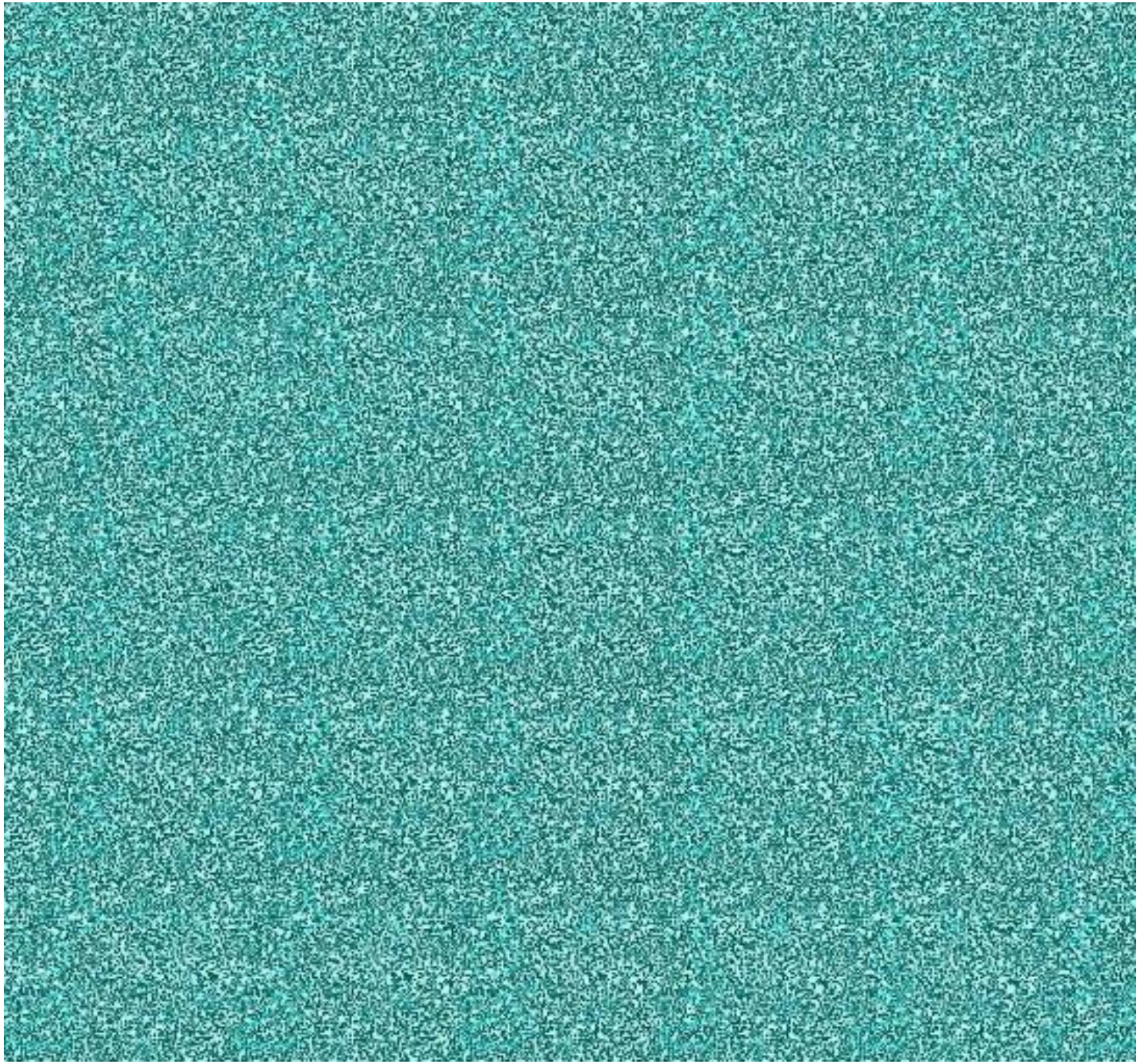
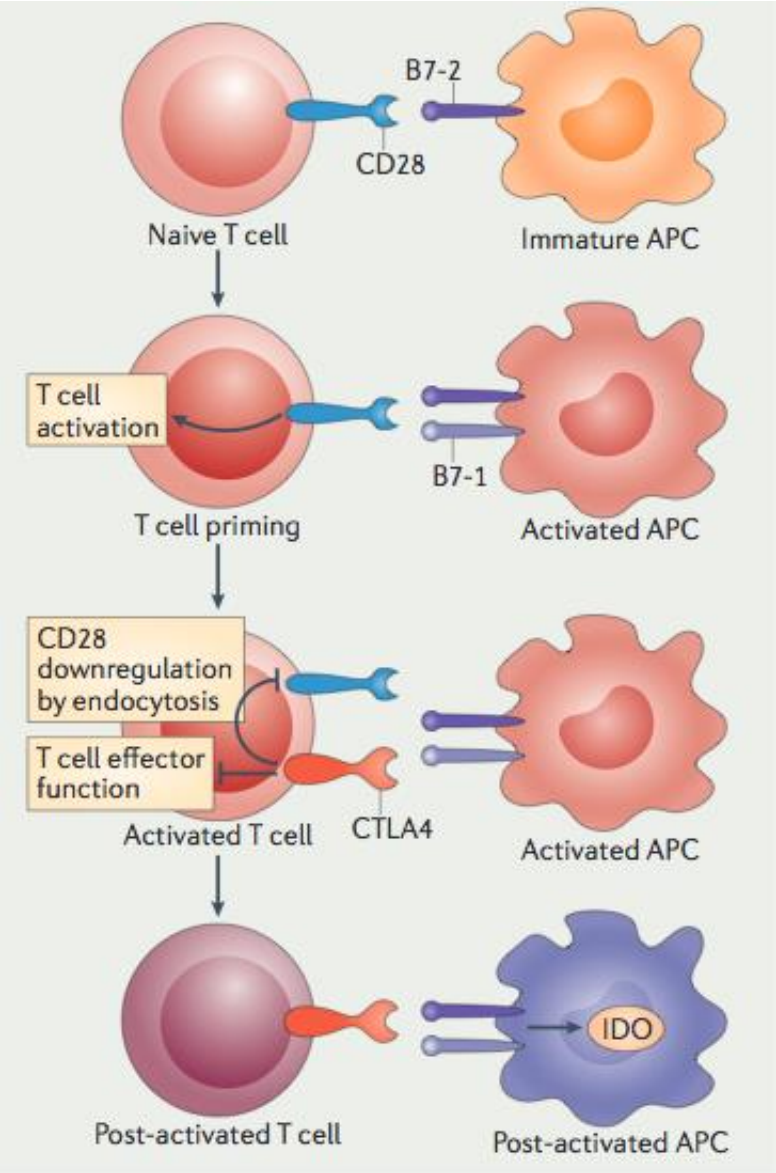
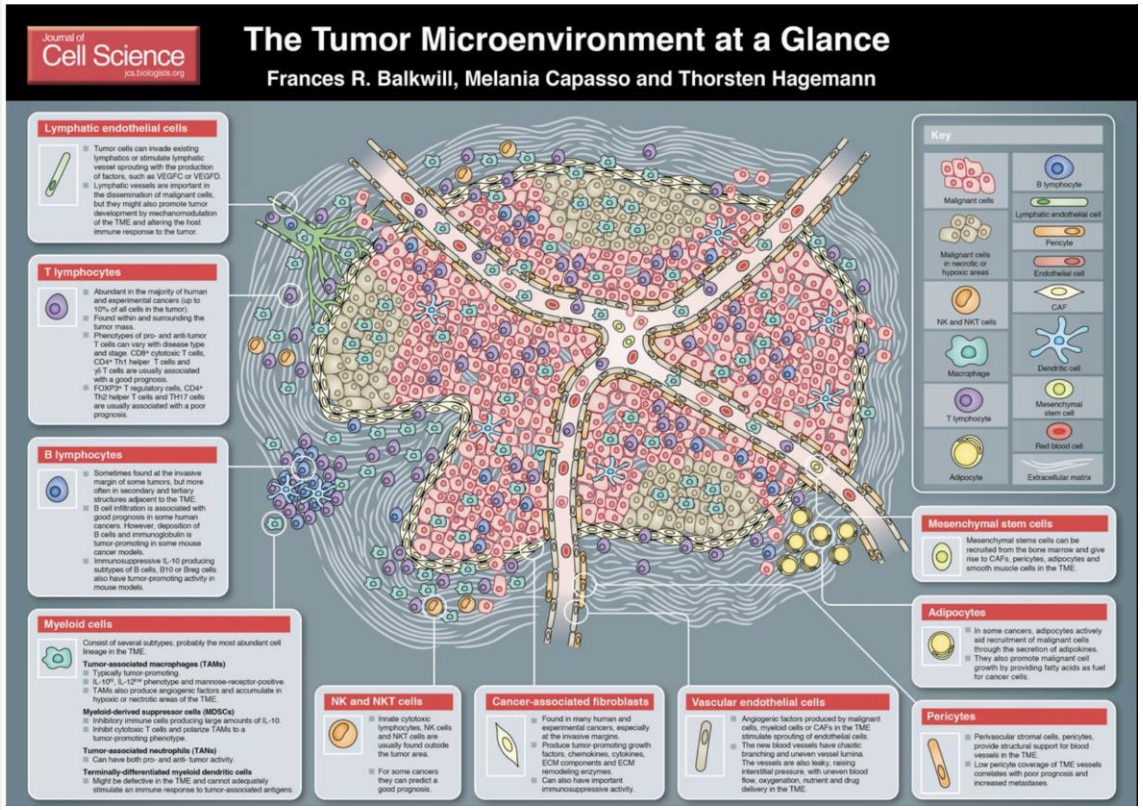
Cell
Topol



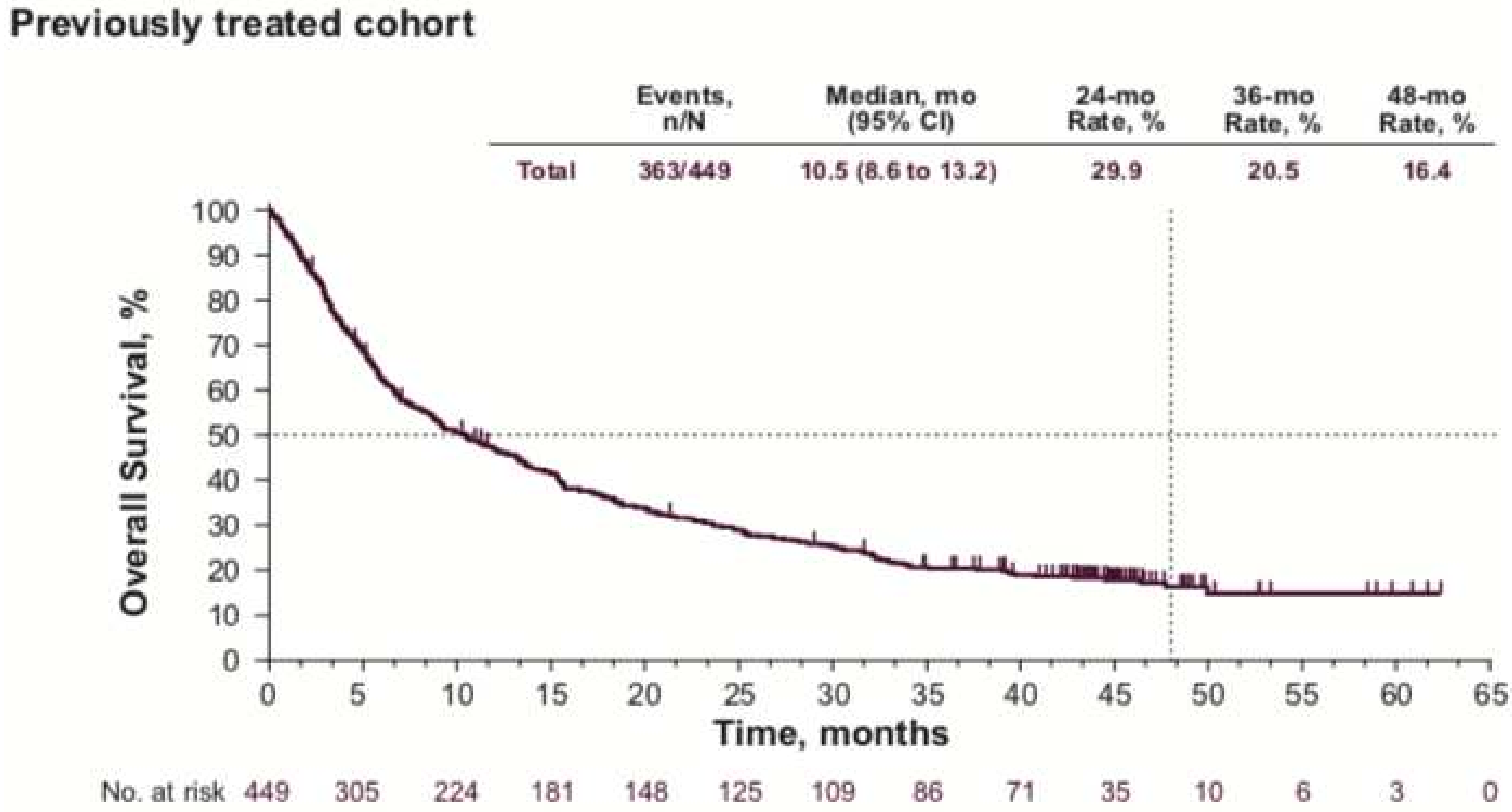
# La complessita del microambiente rende “utopistico” che un solo farmaco guarisca tutti



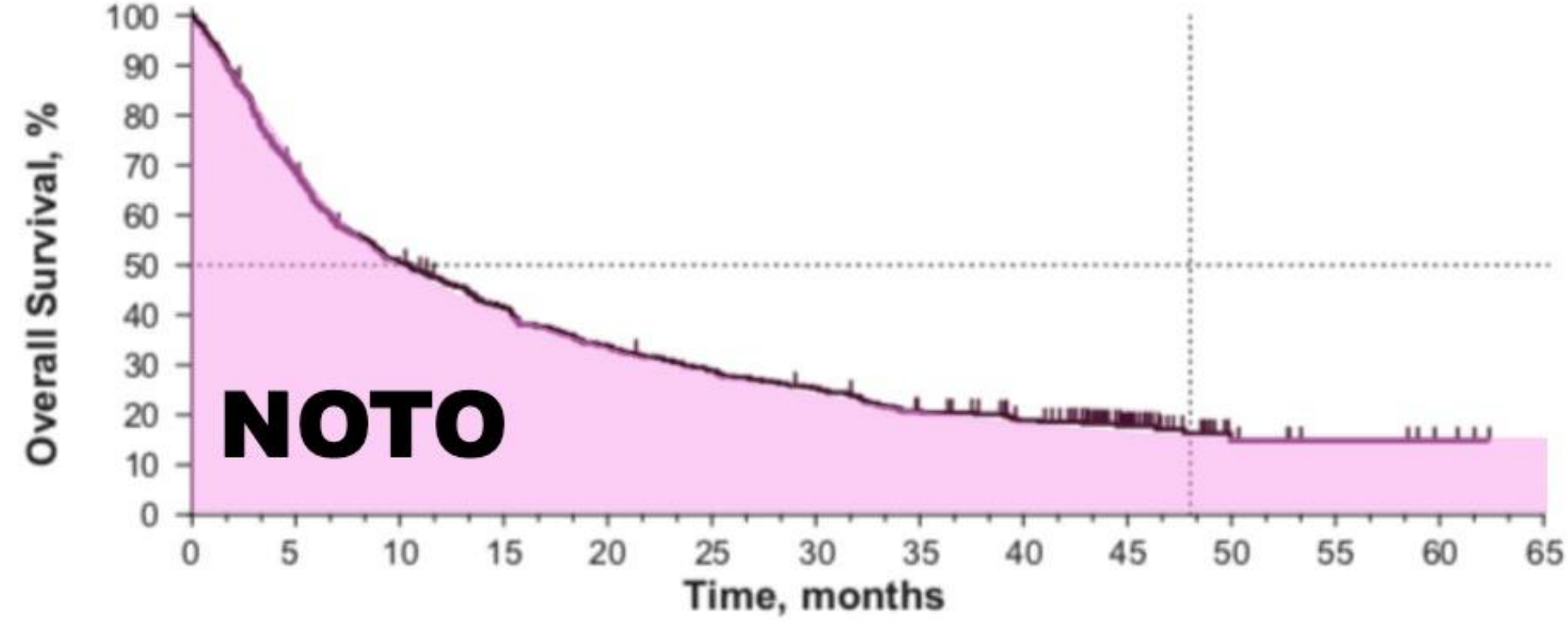

Chen L, et al. *Nat Rev Immunol.* 2013;13(4):227-242.

# Cosa otteniamo a 4 anni (pembro KEYNOTE-001)



## Previously treated cohort

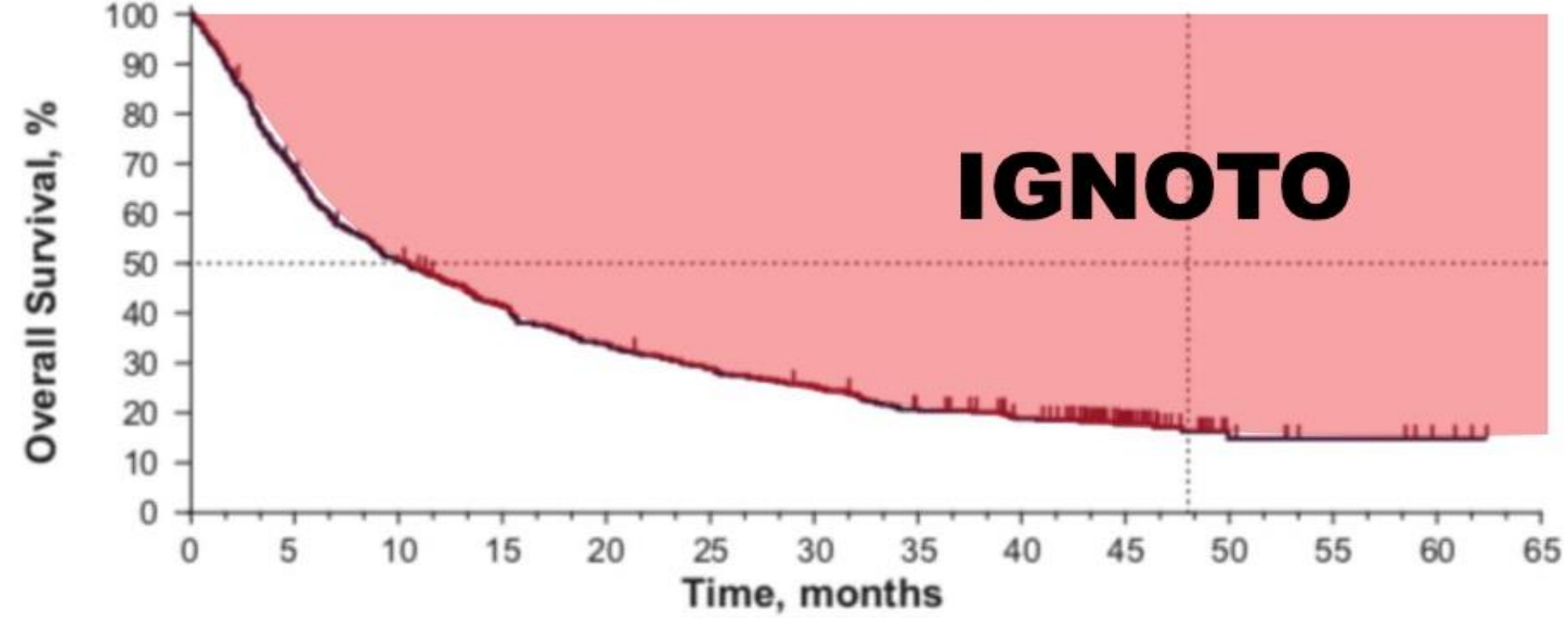
| | Events, n/N | Median, mo (95% CI) | 24-mo Rate, % | 36-mo Rate, % | 48-mo Rate, % |
|---|---|---|---|---|---|
| Total | 363/449 | 10.5 (8.6 to 13.2) | 29.9 | 20.5 | 16.4 |




| No. at risk | 449 | 305 | 224 | 181 | 148 | 125 | 109 | 86 | 71 | 35 | 10 | 6 | 3 | 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

## Previously treated cohort

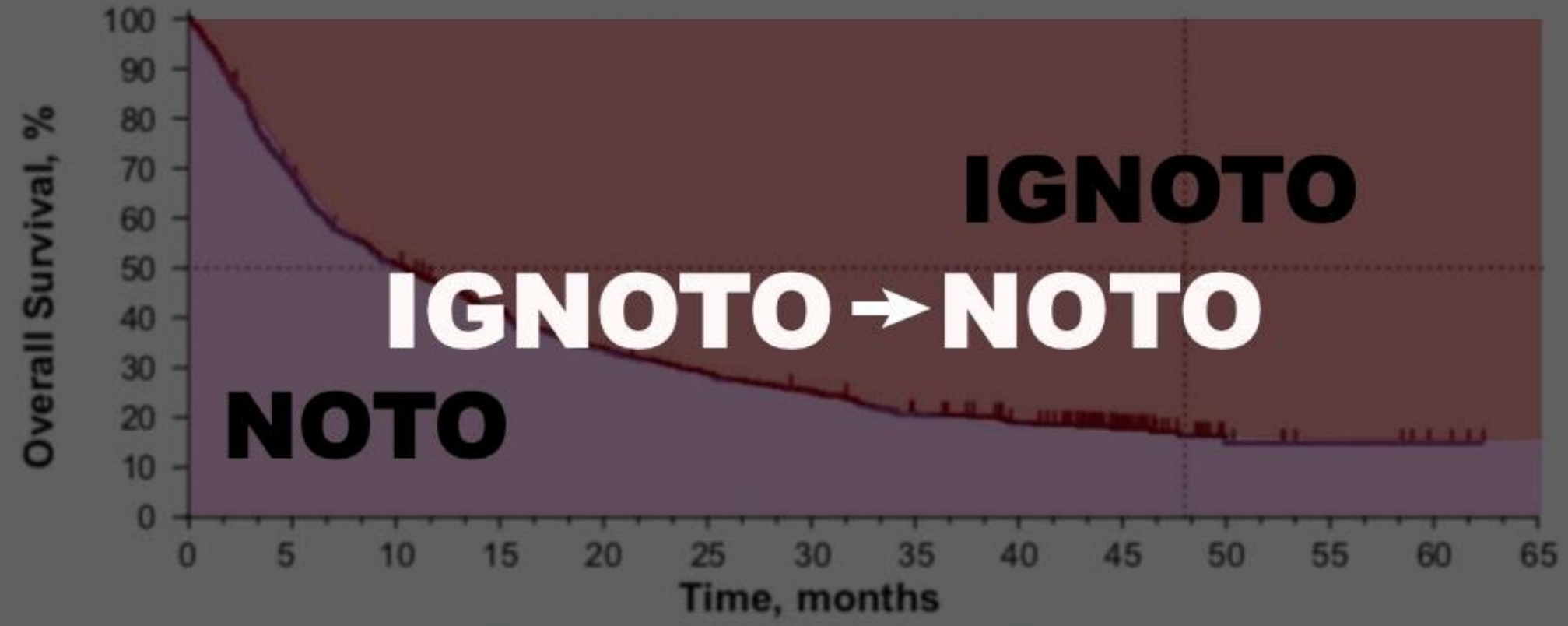
| | Events, n/N | Median, mo (95% CI) | 24-mo Rate, % | 36-mo Rate, % | 48-mo Rate, % |
|---|---|---|---|---|---|
| Total | 363/449 | 10.5 (8.6 to 13.2) | 29.9 | 20.5 | 16.4 |




| No. at risk | 449 | 305 | 224 | 181 | 148 | 125 | 109 | 86 | 71 | 35 | 10 | 6 | 3 | 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

## Previously treated cohort

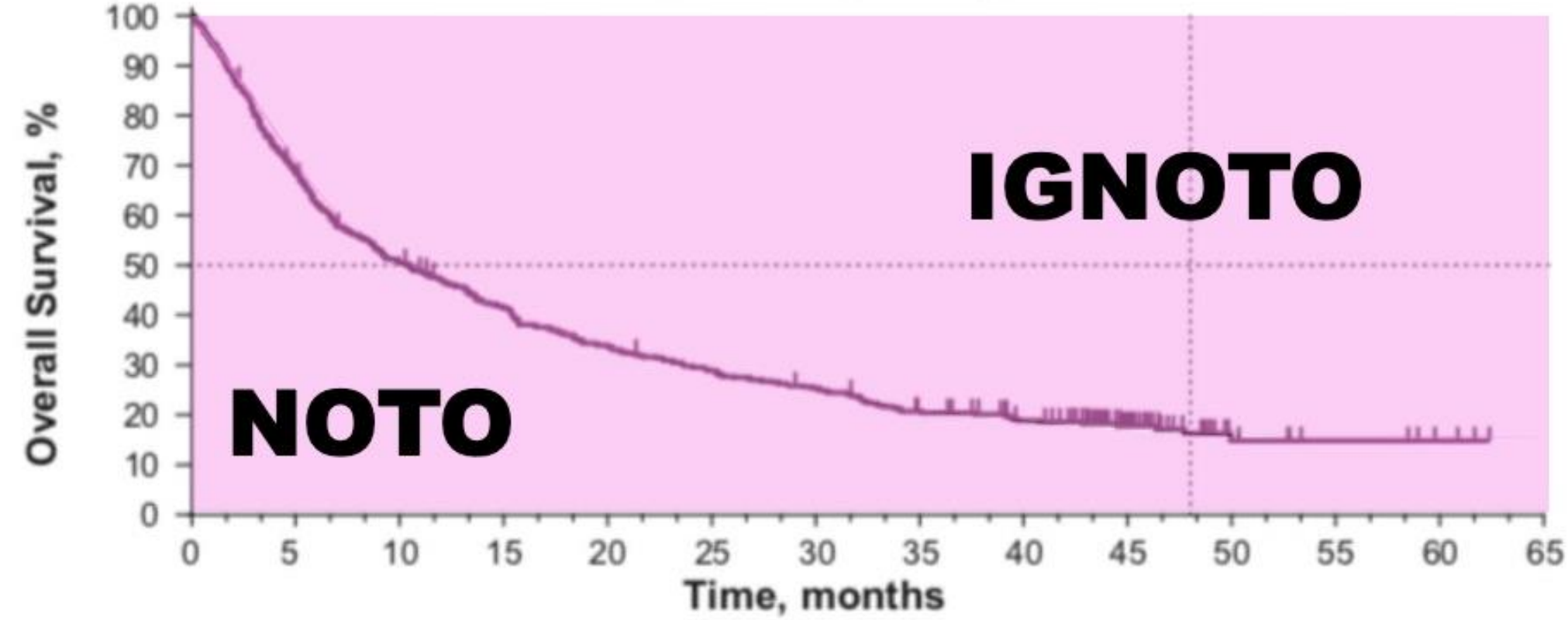
| | Events, n/N | Median, mo (95% CI) | 24-mo Rate, % | 36-mo Rate, % | 48-mo Rate, % |
|---|---|---|---|---|---|
| Total | 363/449 | 10.5 (8.6 to 13.2) | 29.9 | 20.5 | 16.4 |




| No. at risk | 449 | 305 | 224 | 181 | 148 | 125 | 109 | 86 | 71 | 35 | 10 | 6 | 3 | 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

## Previously treated cohort

| | Events, n/N | Median, mo (95% CI) | 24-mo Rate, % | 36-mo Rate, % | 48-mo Rate, % |
|---|---|---|---|---|---|
| Total | 363/449 | 10.5 (8.6 to 13.2) | 29.9 | 20.5 | 16.4 |




| No. at risk | 449 | 305 | 224 | 181 | 148 | 125 | 109 | 86 | 71 | 35 | 10 | 6 | 3 | 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

## Previously treated cohort

| | Events, n/N | Median, mo (95% CI) | 24-mo Rate, % | 36-mo Rate, % |
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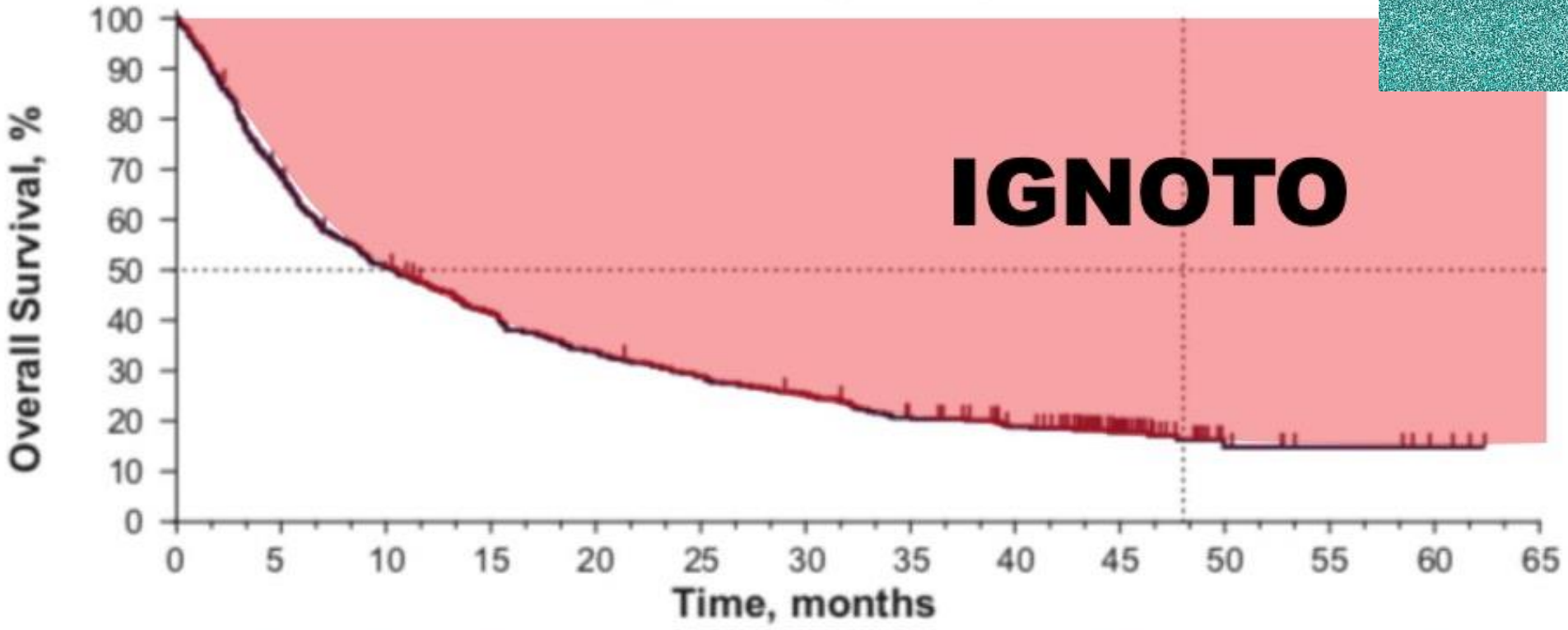
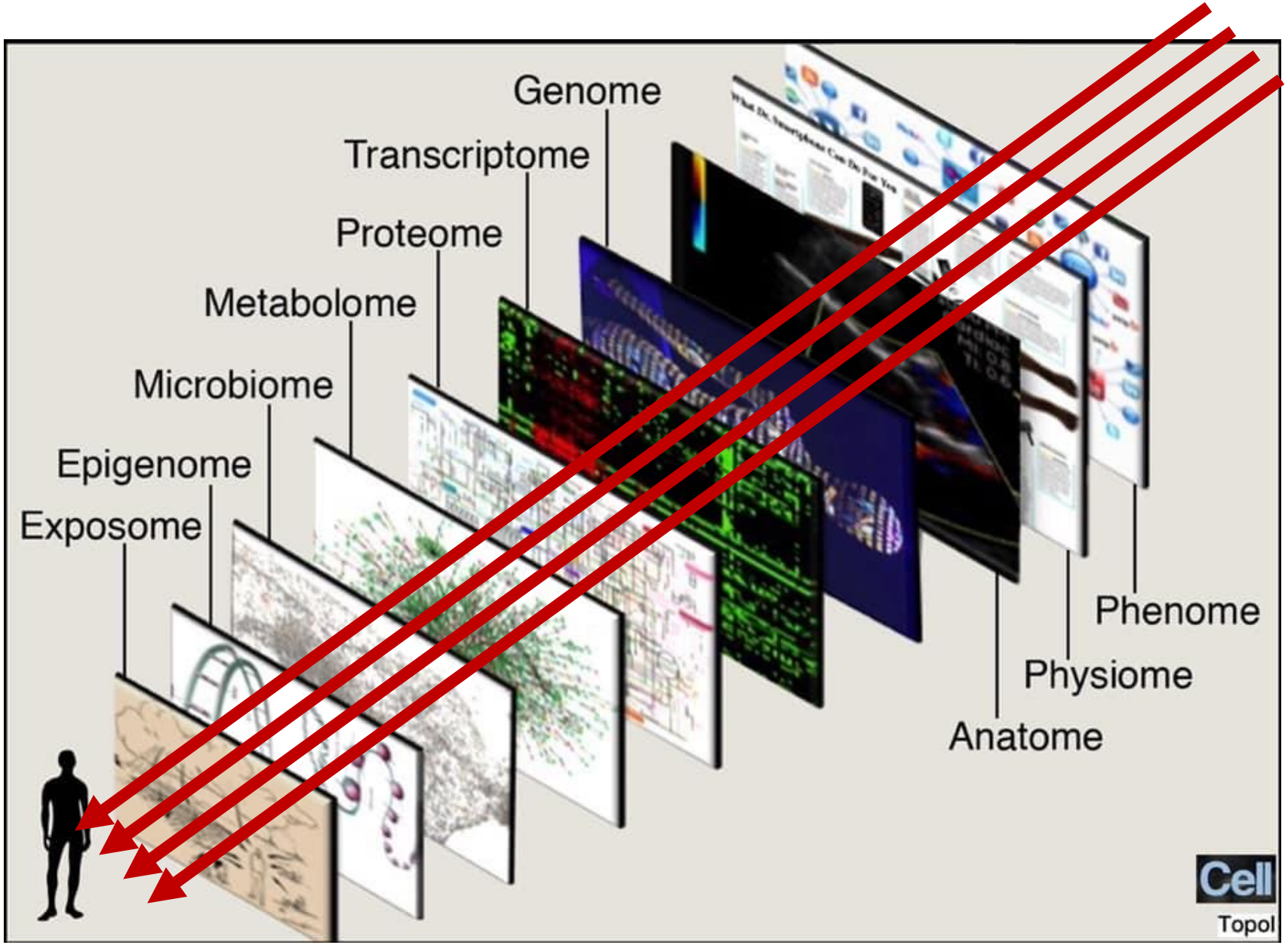
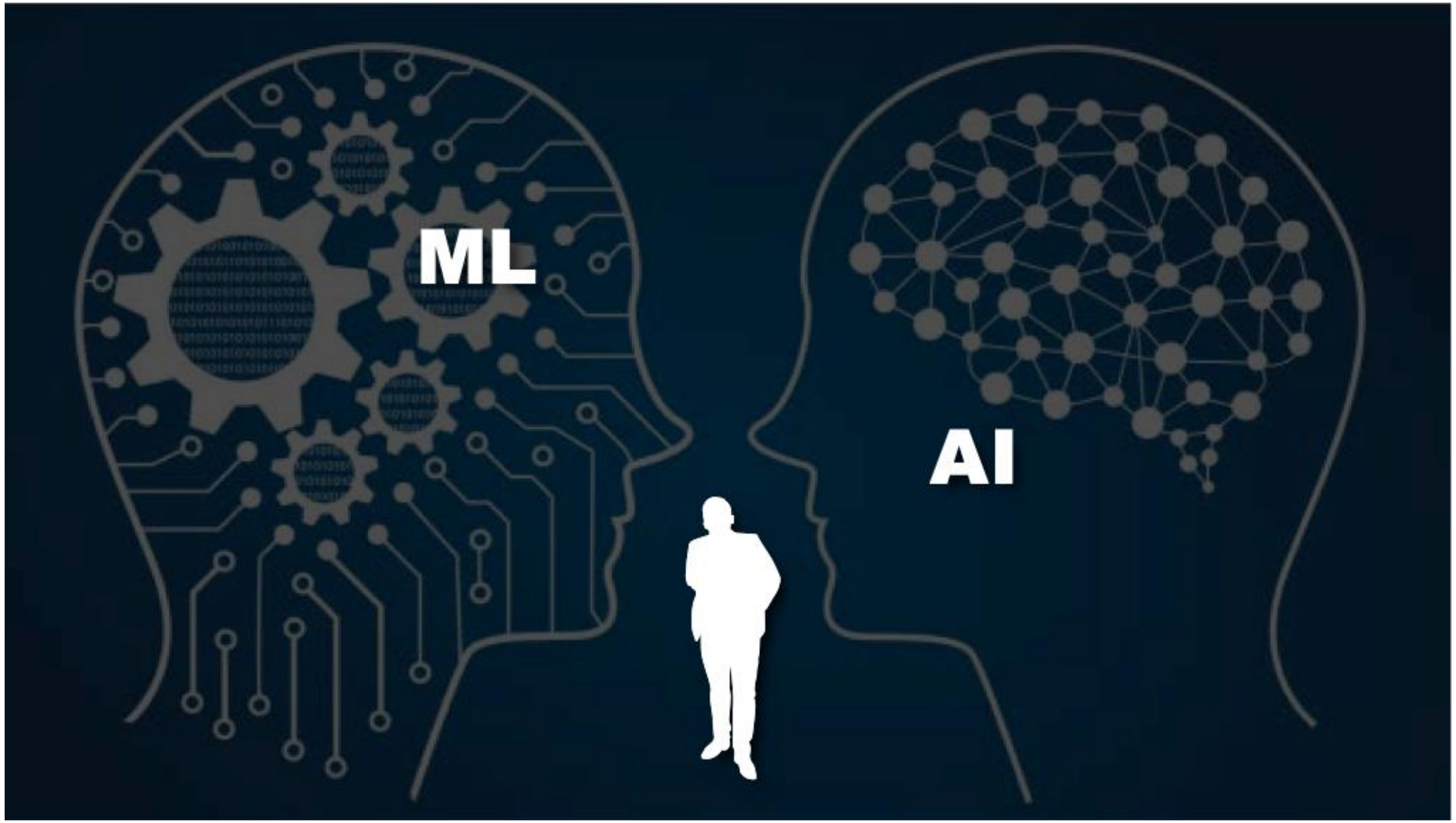



IGNOTO

| No. at risk | 449 | 305 | 224 | 181 | 148 | 125 | 109 | 86 | 71 | 35 | 10 | 6 | 3 | 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

# La Parola individuo vuole dire indivisibile




ML
AI

Uno di questi modelli è l'***Innovation Value Chain*** presentato da Hansen e Birkinsham[17], che si focalizza sugli anelli deboli della catena per far sì che vengano

**Figura 6 - The Innovation Value Chain**

| | IDEA GENERATION | | | CONVERSION | | DIFFUSION |
|---|---|---|---|---|---|---|
| | IN-HOUSE<br>Creation within a unit | CROSS-POLLINATION<br>Collaboration across units | EXTERNAL<br>Collaboration with parties outside the firm | SELECTION<br>Screening and initial funding | DEVELOPMENT<br>Movement from idea to first result | SPREAD<br>Dissemination across the organization |
| KEY QUESTIONS | Do people in our unit create good ideas on their own? | Do we create good ideas by working across the company? | Do we source enough good ideas from outside the firm? | Are we good at screening and funding new ideas? | Are we good at turning ideas into viable products, busi-nesses, and best practices? | Are we good at diffusing developed ideas across the company? |
| KEY PERFORMANCE INDICATORS | Number of high-quality ideas gener-ated within a unit. | Number of high-quality ideas generated across units. | Number of high-quality ideas gener-ated from outside the firm. | Percentage of all ideas generated that end up being selected and funded. | Percentage of funded ideas that lead to rev-enues; number of months to first sale. | Percentage of penetra-tion in desired markets, chan-nels, customer groups; number of months to full diffusion. |

**Fonte: Hansen M. T., Birkinshaw J., "The Innovation Value Chain", *Harvard Business Review*, p. 124, June 2007**

messe in atto solo le attività realmente utili. Gli autori propongono una visione

# Declinazione di innovazione

- Scoperta non sempre porta innovazione
  - ✓Tutte le scoperte hanno avuto un pensiero traversale dietro
  - ✓Va favorita la comunicazione tra livelli di persone anche negli ambienti di lavoro (dissociazione tra la scienza e il luogo di lavoro e la politica/società)
  - ✓Forse introduzione di figure non mediche
  - ✓Comunicazione tra «cose» (AI, ML)
  - ✓Fine dei trial clinici?

Il valore dell' innovazione

- Prevede che la applichiamo
- Prevede che porti una progresso sociale

# Grazie per l’ attenzione