AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

Nuovi paradigmi per lo sviluppo del farmaco in oncologia

Federica Cuppone

26/09/18

LA PERSONALIZZAZIONE DEL PERCORSO DI CURA:

SANITÀ DIGITALE E MULTIDISCIPLINARIETÀ NELLA GESTIONE DELLA PATOLOGIA ONCOLOGICA FEMMINILE

CREMONA

SALA MAFFEI - CAMERA DI COMMERCIO

VIA DEI LANAIOLI

Dichiarazione di trasparenza/interessi*

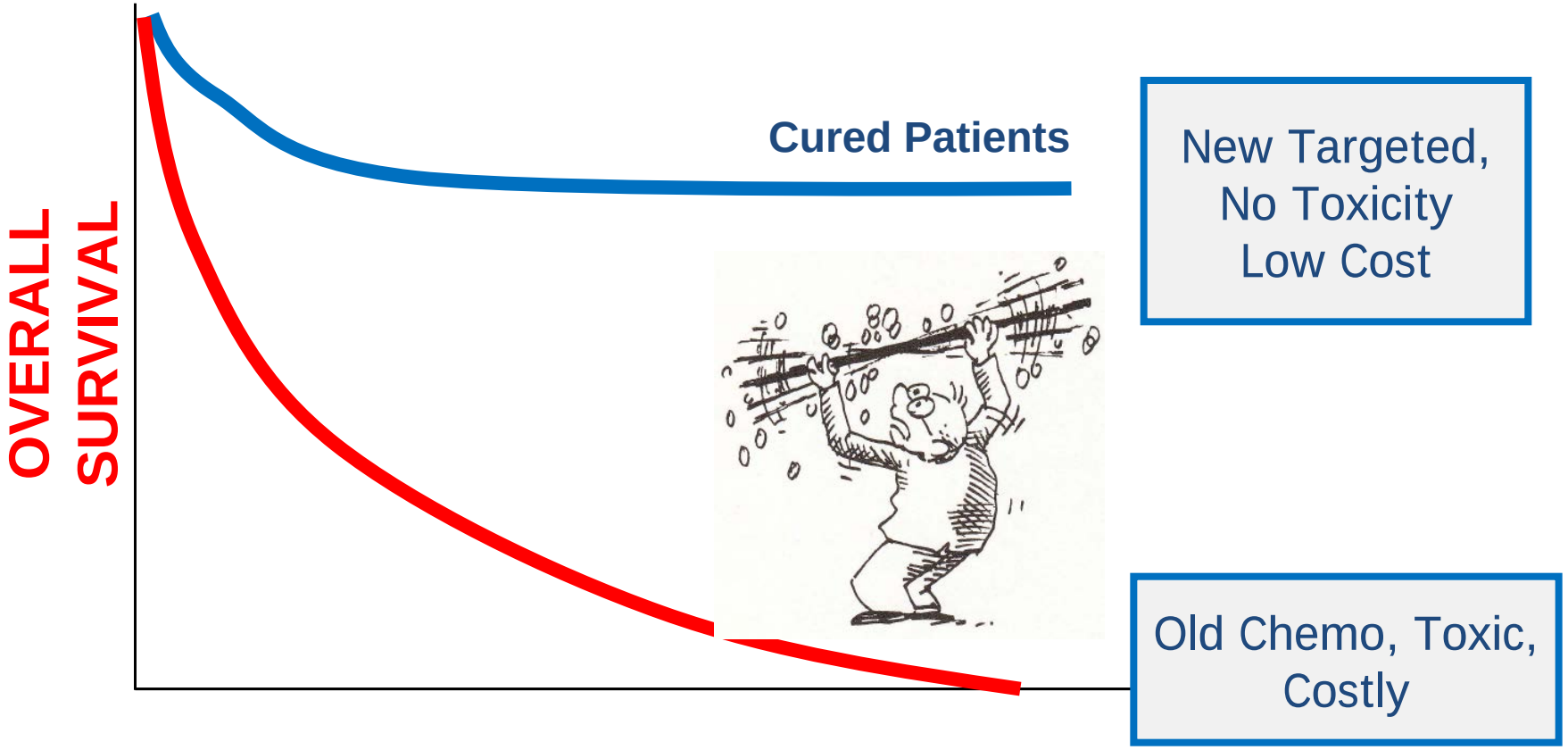
Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	NO	Attualmente	Da 0 a 3 anni precedenti	oltre 3 anni precedenti
INTERESSI DIRETTI:				
1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica	X	☐	☐	☐ obbligatorio
1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico	X	☐	☐	☐ obbligatorio
1.3 Impiego per una società: altre attività	X	☐	☐	☐ facoltativo
2. Consulenza per una società	X	☐	☐	☐ facoltativo
3. Consulente strategico per una società	X	☐	☐	☐ facoltativo
4. Interessi finanziari	X	☐	☐	☐ facoltativo
5. Titolarità di un brevetto	X	☐	☐	☐ facoltativo
INTERESSI INDIRETTI:				
6. Sperimentatore principale	X	☐	☐	☐ facoltativo
7. Sperimentatore	☐	☐	☐	X facoltativo
8. Sovvenzioni o altri fondi finanziari	X	☐	☐	☐ facoltativo
9. Interessi Familiari	X	☐	☐	☐ facoltativo

* Federica Cuppone, secondo il regolamento sul Conflitto di Interessi approvato dal CdA AIFA in data 25.03.2015 e pubblicato sulla Gazzetta Ufficiale del 15.05.2015 in accordo con la policy EMA /626261/2014 sulla gestione del conflitto di interessi dei membri dei Comitati Scientifici e degli esperti.

N.B. <Per questo intervento non ricevo alcun compenso>

What Physicians want to see! 'The Ideal' Curve



Patients affected by [X-tumor] with [Y] signature

Physicians want to impact on Disease Natural History!

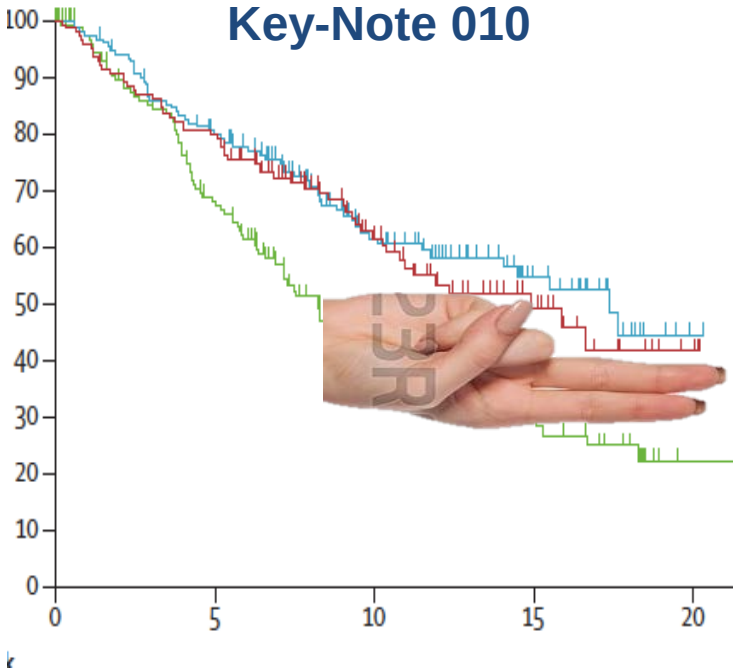
Biomarker-Driven Oncology <2018

- TARGET '***well***' defined:
  - **NSCLC**
    - EGFR sensitizing mutations for EGFR-TKIs
    - EML4-ALK traslocation for Crizotinib (& Ceritinib, Alectinib…)
  - **Breast**
    - HER-2 overexpression for Trastuzumab (& Pertuzumab, TDM1…)
  - **GIST** (85% carry c-KIT mutation…)
    - Imatinib (& Sunitinib, Regorafenib)
  - **Melanoma**
    - B-RAF mutation for Vemurafenib (& Dabrafenib….) and doublets
- TARGET '***approximately***' defined:
  - **RCC**
    - Angiogenesis for Targeted Agents
  - **PD-L1 (>50% positivity) - NSCLC**
    - 'Un-lock' Immune Response

NEJM (‘90s): The ‘Two-Fingers’ Rule

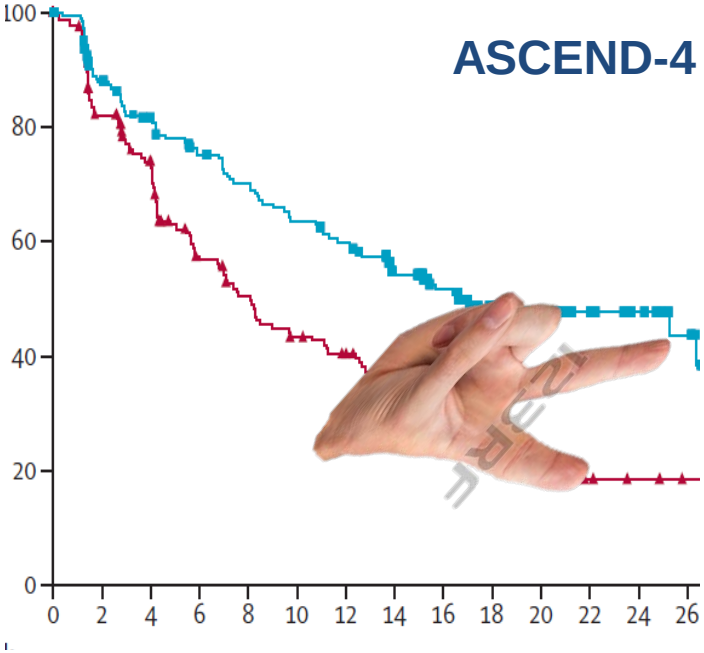
Clinically Data should be considered Meaningful if ‘*at least*’ two fingers separates curves!

Key-Note 010



Hersbt R et al, Lancet 2015

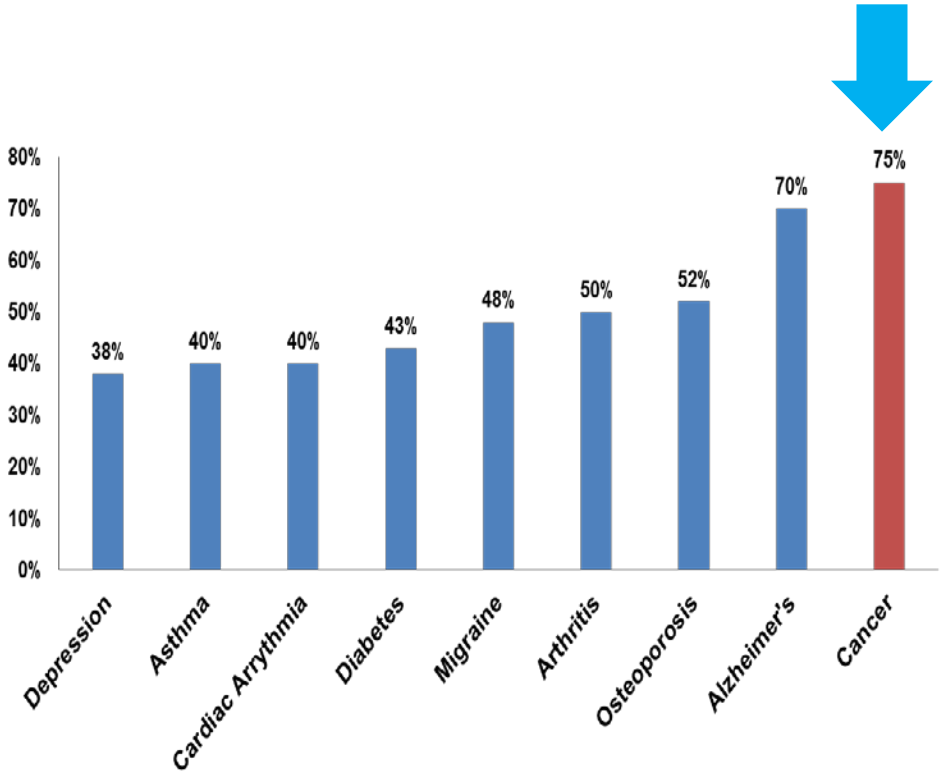
ASCEND-4



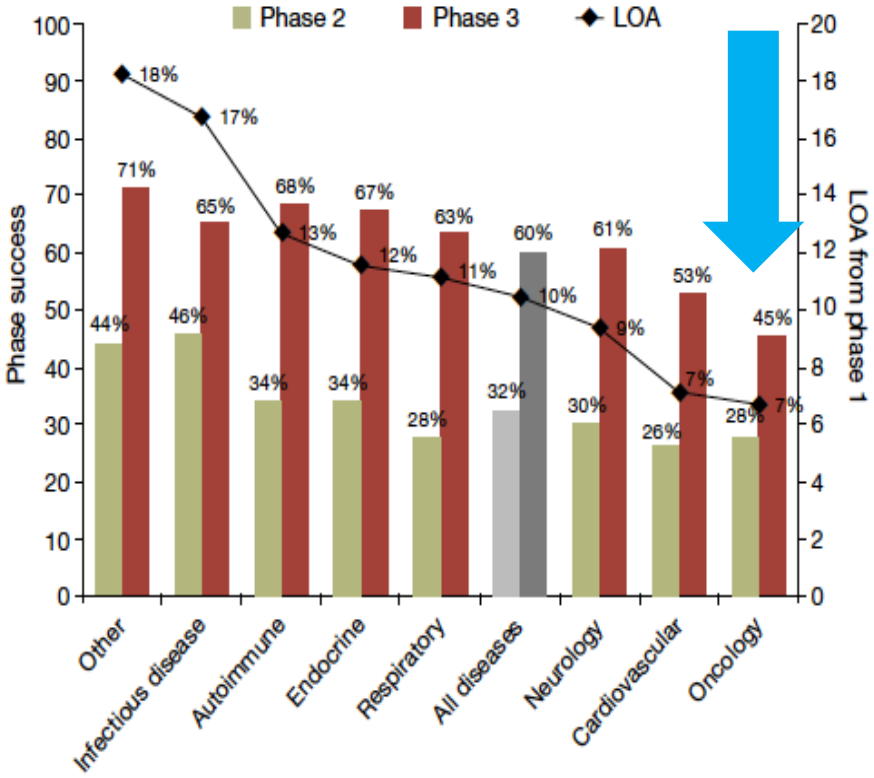
Soria JC et al, Lancet 2017

Why Cancer Research needs ‘to evolve’

Percentage of patients for whom drugs are ineffective

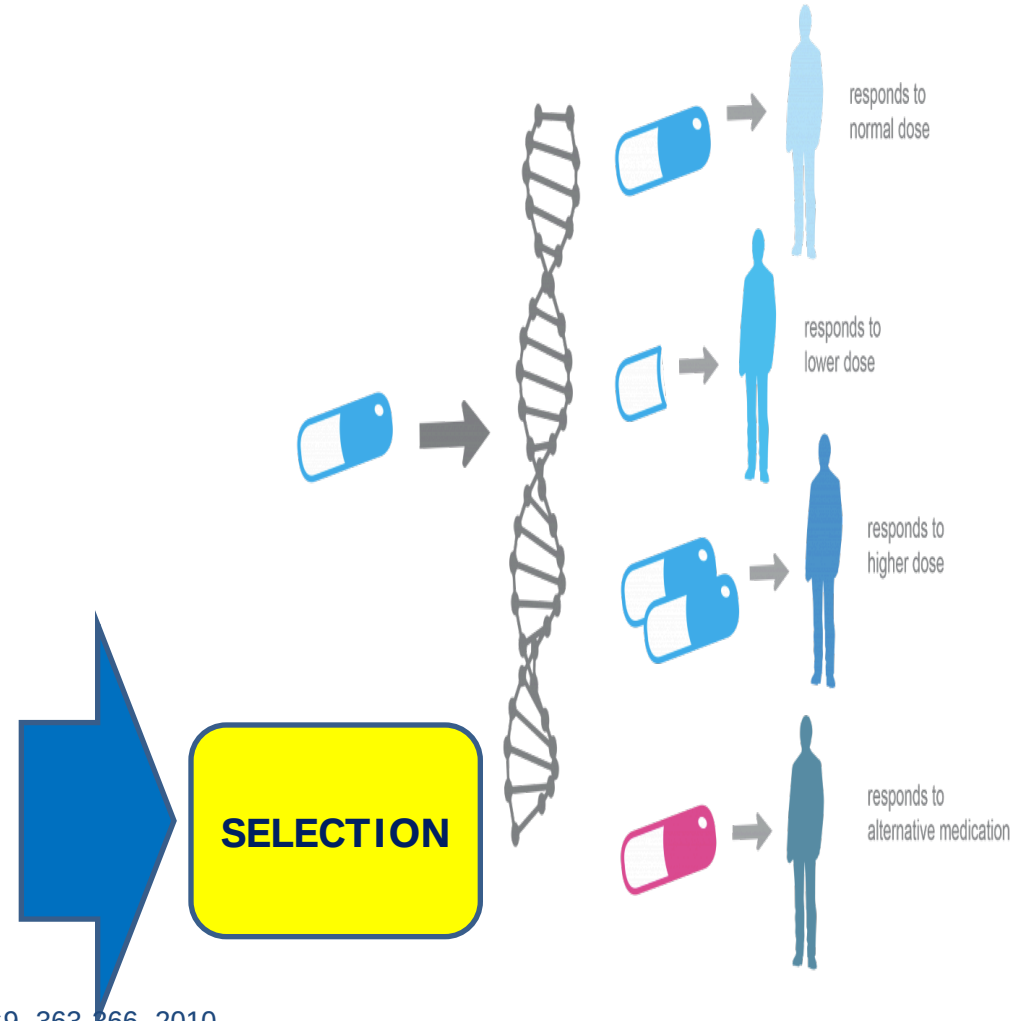


Phase success and LOA [Likelyhood of Approval]



Evolution of anticancer treatment during the years

Therapy	*Era of application*
Locoregional treatments	**1940 - 50**
Chemotherapeutic - based systemic treatments	**1960 - 80**
Targeted treatments	**Latest 6-7 years**
Genomic-based treatments	**Going to start**



Modificato da Tortora GP &Schilsky RL. *Nature Rev. Drug Discovery* 9, 363-366, 2010

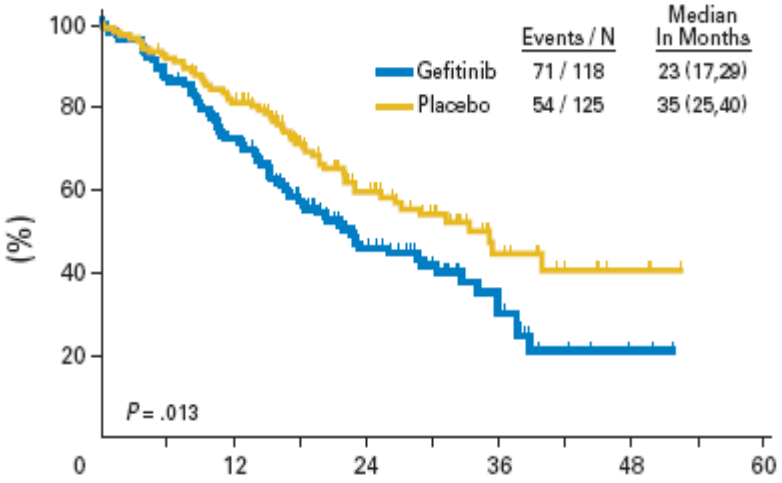
How Biomarkers entered the clinic?

- **EGFR mutations**
  - Time to ‘Drug discovery’ to ‘best result’: 10-15 yrs
  - Big failure after approval
  - The Academy ‘saved’ the Pharma
- EML4-ALK traslocation
- HER-2 overexpression

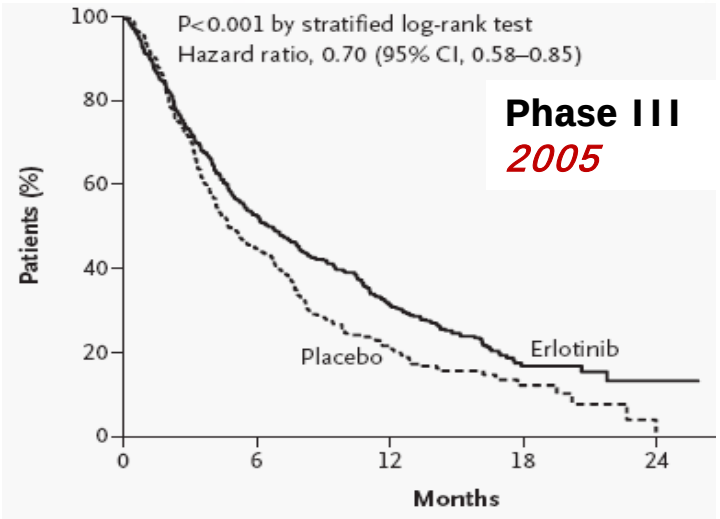
The sentence *'Wait a minute: we are wrong!'* was pronouced after the drug enter the market!

EGFR TKIs Before the Predictor
(EGFR mutation)

Phase III
2005

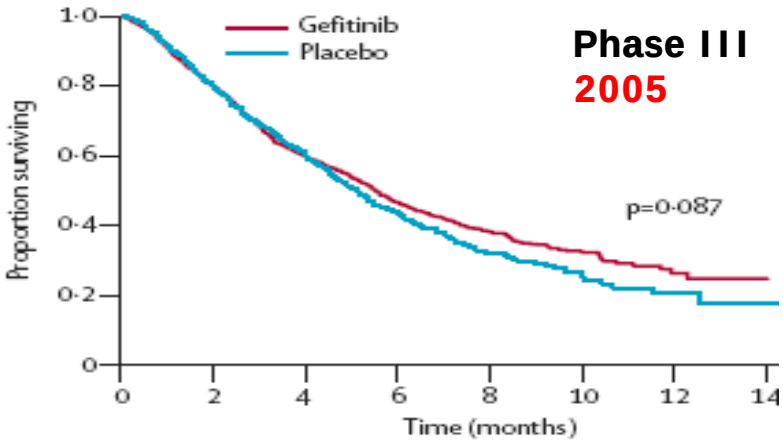


Sign. detrimental



Phase III
2005

Small benefit

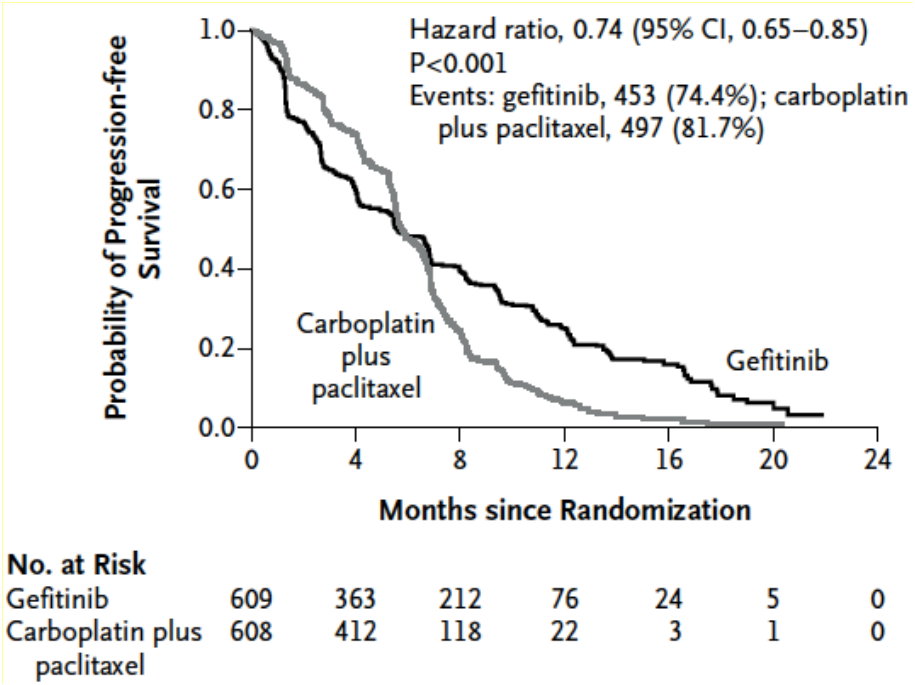


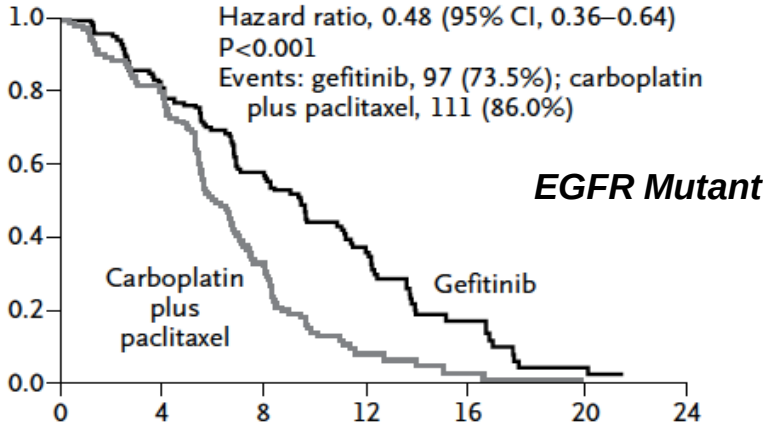
Phase III
2005

No difference

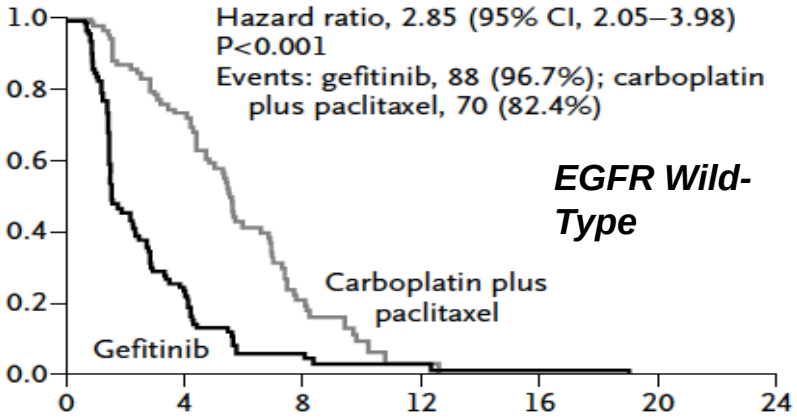
IPASS trial: Gefitinib vs. Carbo-Paclitaxel, Clinically Enriched Population

- '*Clinically Enriched*' Population (non-smokers, adeno)
- 55% of patients with tissue available: EGFR mutant





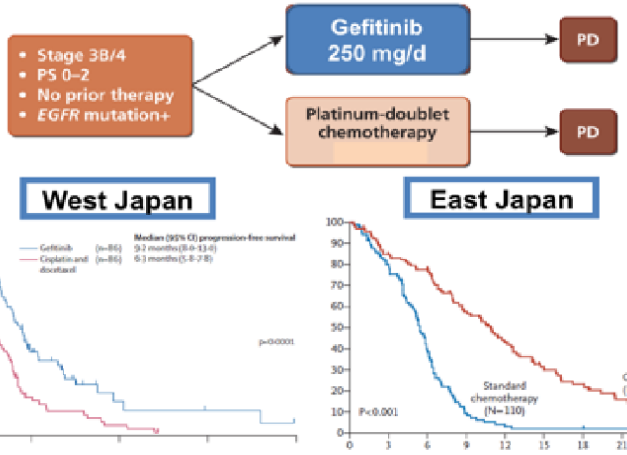
Significant Qualitative Interaction accoding to EGFR



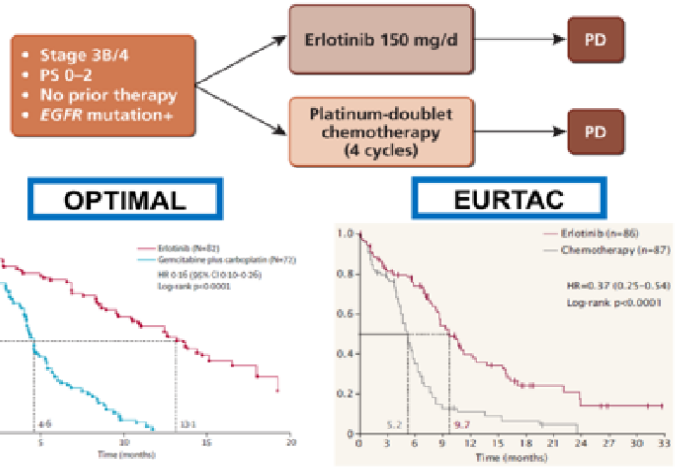
The EGFR mutation makes the difference!

Mok t et al, NEJM 2009

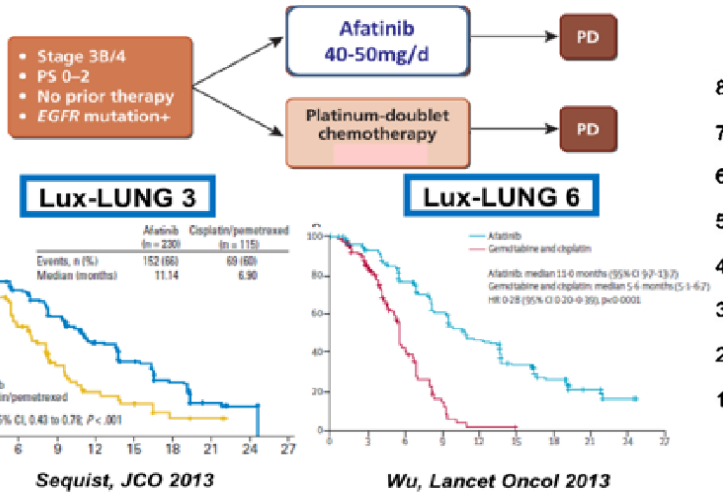
EGFR Mutant: TKIs *vs.* Chemo



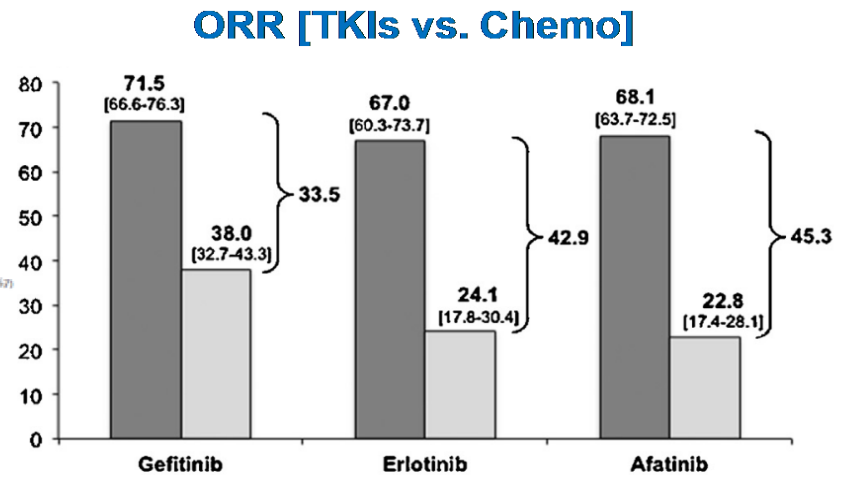
Mitsudomi, Lancet Oncol 2011 *Maemondo, NEJM 2010*



Zhou, Lancet Oncol 2011 *Rosell, Lancet Oncol 2012*



Sequist, JCO 2013 *Wu, Lancet Oncol 2013*



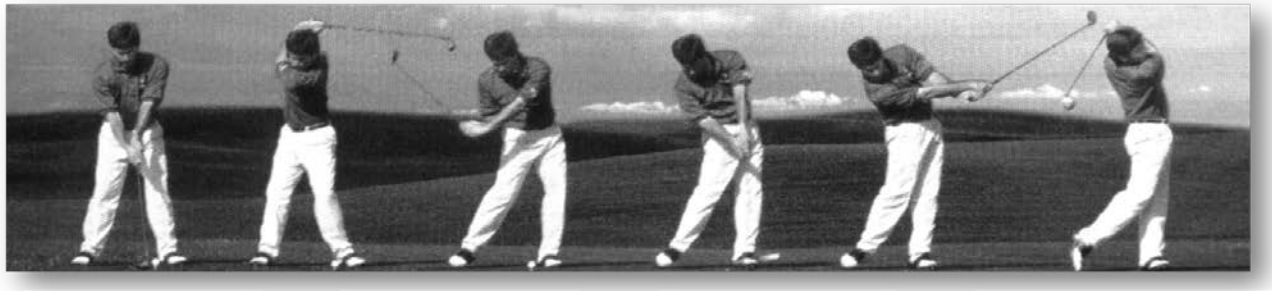
Pilotto S, CROH 2014

Time of Biomarker Discovery: *EGFR* mutation

Preclinical

Traditional Drug Development according to Phases and Aims

Phase 1 → **Phase 2** → **Phase 3** → **Phase 4**



MTD	Safety Activity	Efficacy	Effectiveness Other

EGFR Mutation

How Biomarkers entered the clinic?

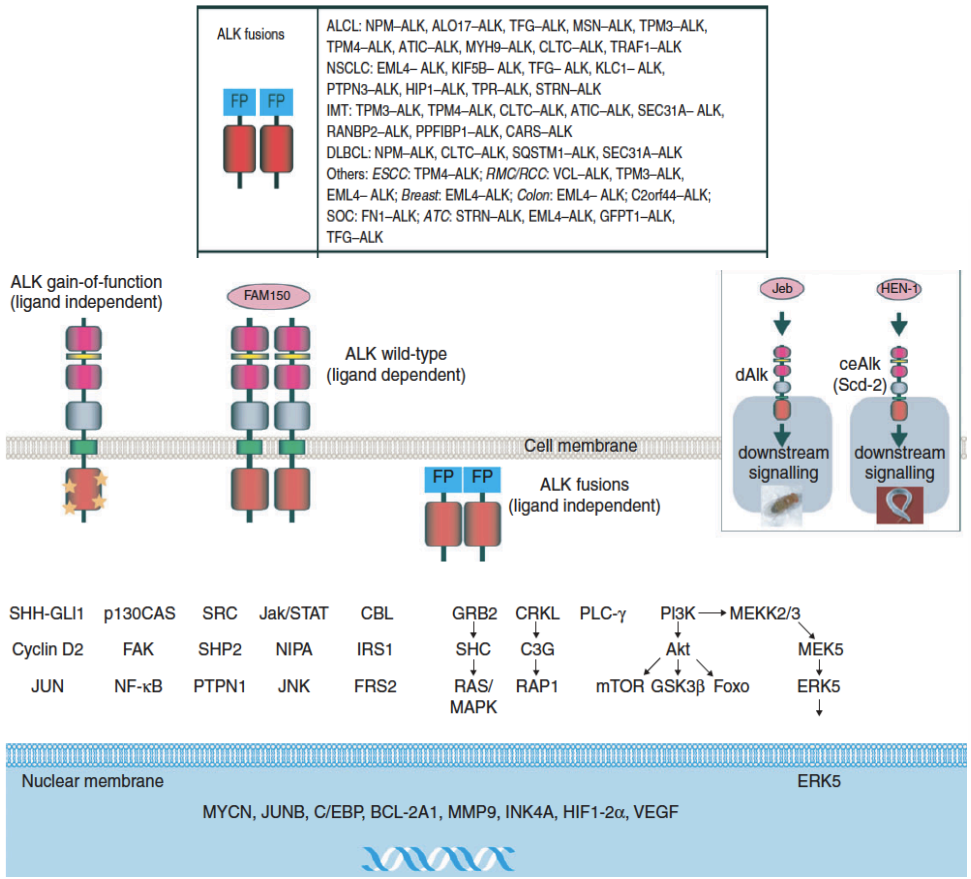
- EGFR mutations

- **EML4-ALK traslocation**
  - **Time to 'Drug discovery' to 'best result': 5-7 yrs**
  - **'Change-the-target' early**
  - **Newest upcoming drugs have similar efficacy**

- HER-2 overexpression, T790M mutation

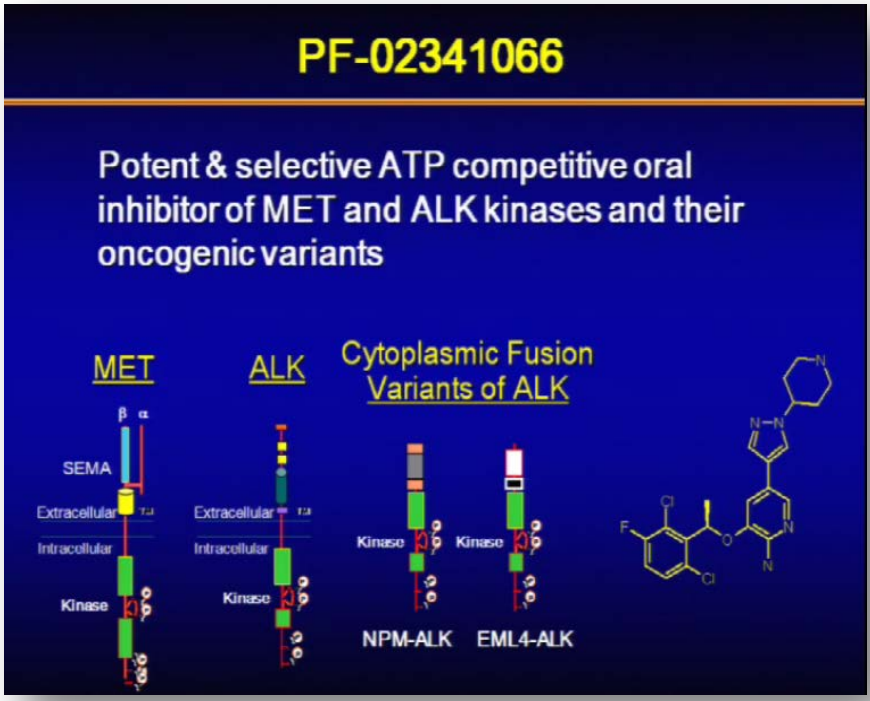
The sentence 'Wait a minute: we are wrong!' was pronouced DURING the early phases!

ALK-signaling and De-addiction in NSCLC: Early Phases



Hallberg B & Palmer RH, Ann Oncol 2016

CRIZOTINIB (PROFILE 1001): Rationale of ALK/MET/ROS1 inhibition



Kwak E et al, ASCO 2009

ALK-De-addiction in NSCLC: Crucial Role of Early phases

Study Dosing and Objectives

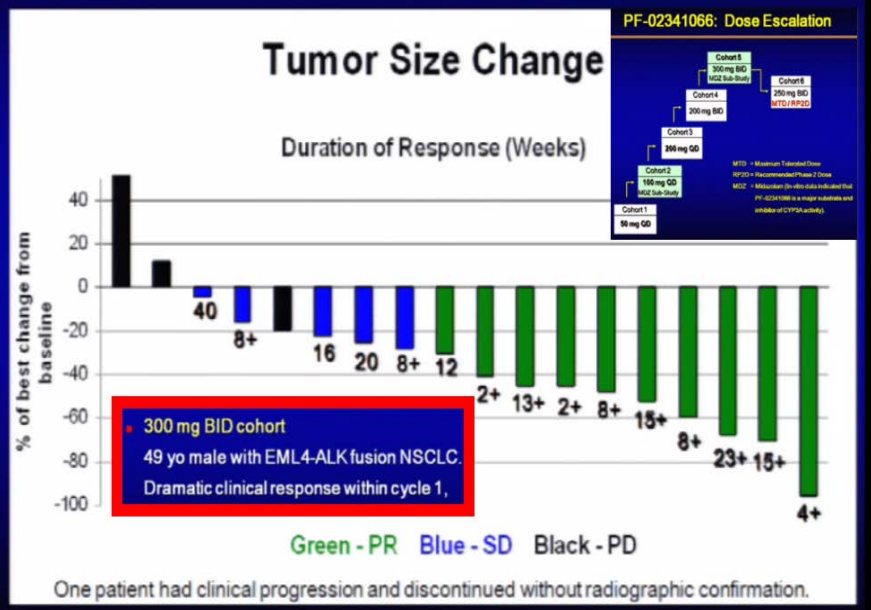
PF-02341066 dosing schedule:

Continuous oral administration for 28 days per cycle.
A single Day -7 dose was administered to establish PK.

1. **Phase I dose escalation**
   - Determine the safety profile of PF-02341066.
   - Determine recommended phase 2 dose (RP2D).
   - Determine the PK profile after oral dosing.

2. **Recommended Phase 2 Dose Cohort (RP2D)**
   - Enroll patients with MET or ALK activation into a Molecular Cohort.
   - Focused study on patients with ALK fusion after observing preliminary evidence of dramatic activity.

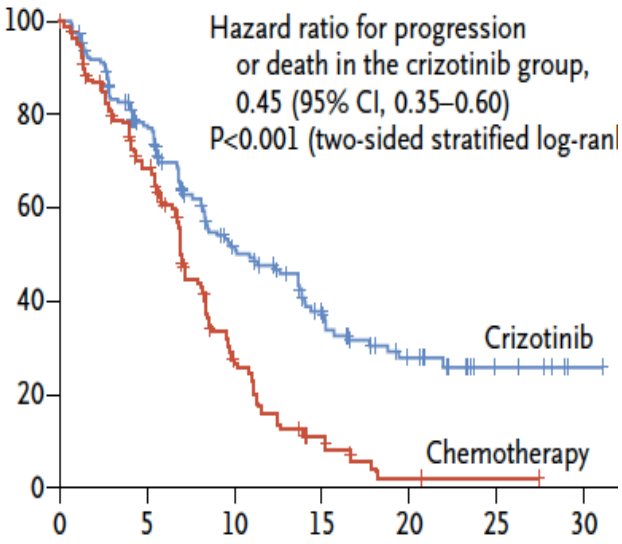
Tumor Responses to PF-02341066 for NSCLC Evaluable Patients with ALK Fusions



Kwak E et al, ASCO 2009

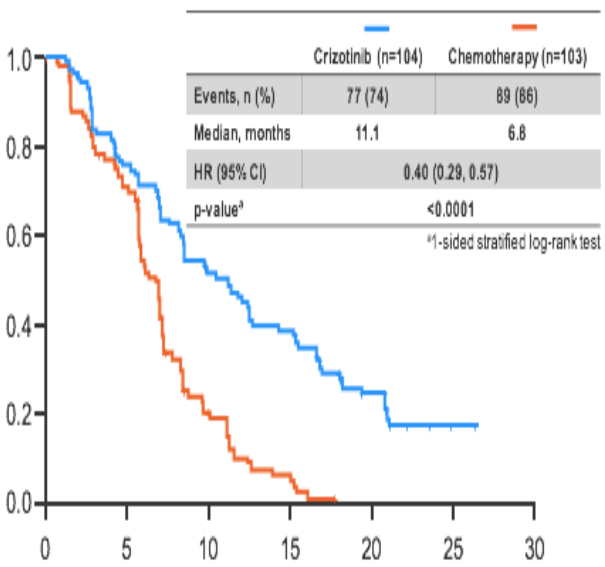
Why do we need ALK-TKIs UPFRONT? First Line Data *vs.* Chemo

PROFILE 1014 [CRIZOTINIB *vs.* Chemo]



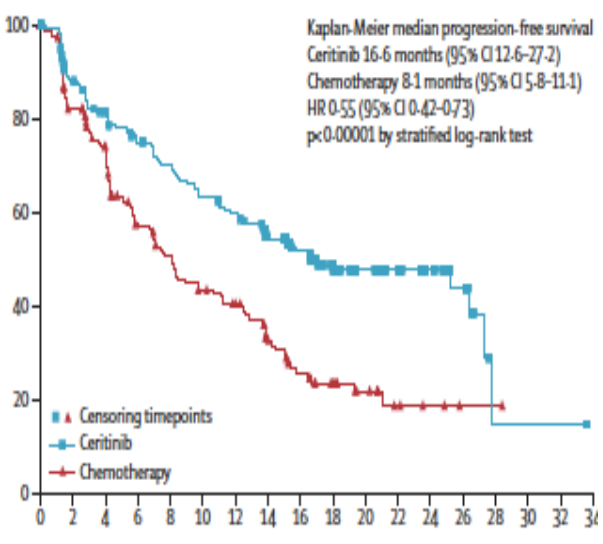
Solomon B et al, NEJM 2014

PROFILE 1029 [CRIZOTINIB *vs.* Chemo]



Lu S et al, ASCO 2016

ASCEND 4 [CERITINIB vs. Chemo]

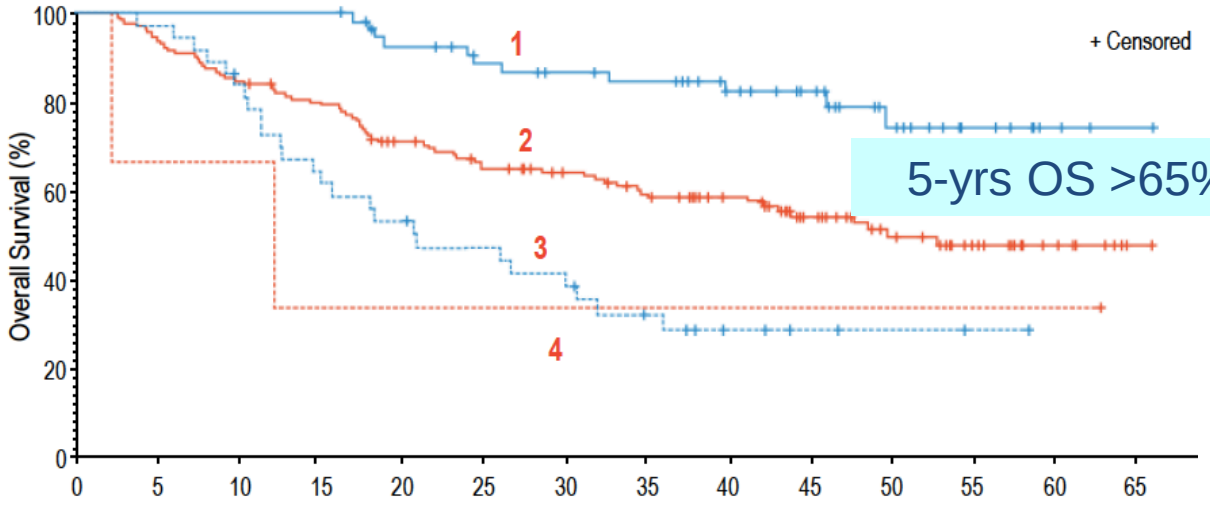


Soria JC et al, Lancet 2017

UPFRONT ALK-TKIs significantly delay disease progression *vs.* First-Line Chemo

Why do we need a ALK-TKIs SEQUENCE? Retrospective Data from RCTs

Impact of Subsequent Therapy on OS: ALK TKI *vs.* Treatment Other Than ALK TKI



5-yrs OS >65%!!!

No. at risk													
Crizotinib followed by any ALK TKI	57	57	57	57	50	45	42	40	33	25	16	8	3	1
Crizotinib followed by any follow-up therapy other than ALK TKI	37	36	30	22	19	16	13	9	5	3	2	1	0	0
Chemotherapy followed by any ALK TKI	145	136	123	113	97	86	79	70	60	43	30	20	10	1
Chemotherapy followed by any follow-up therapy other than ALK TKI	3	2	2	1	1	1	1	1	1	1	1	1	1	0

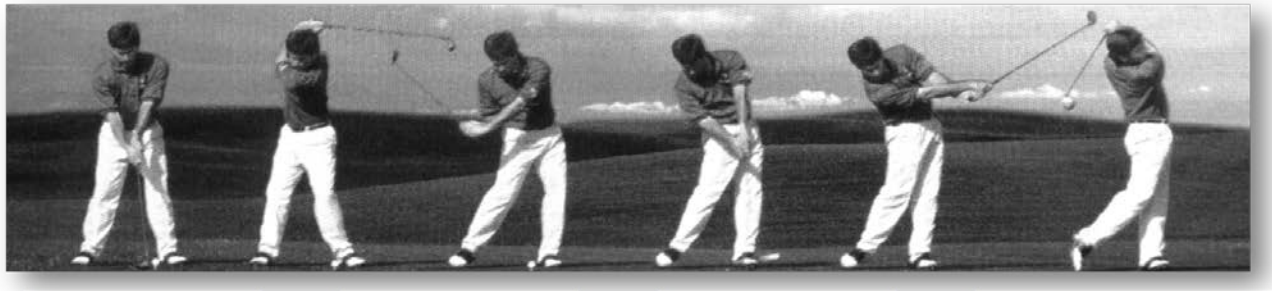
Mok T et al, ESMO 2017

Time of Biomarker Discovery: *ALK rearrangement*

Preclinical

Traditional Drug Development according to Phases and Aims

Phase 1 → **Phase 2** → **Phase 3** → **Phase 4**



MTD	Safety Activity	Efficacy	Effectiveness Other

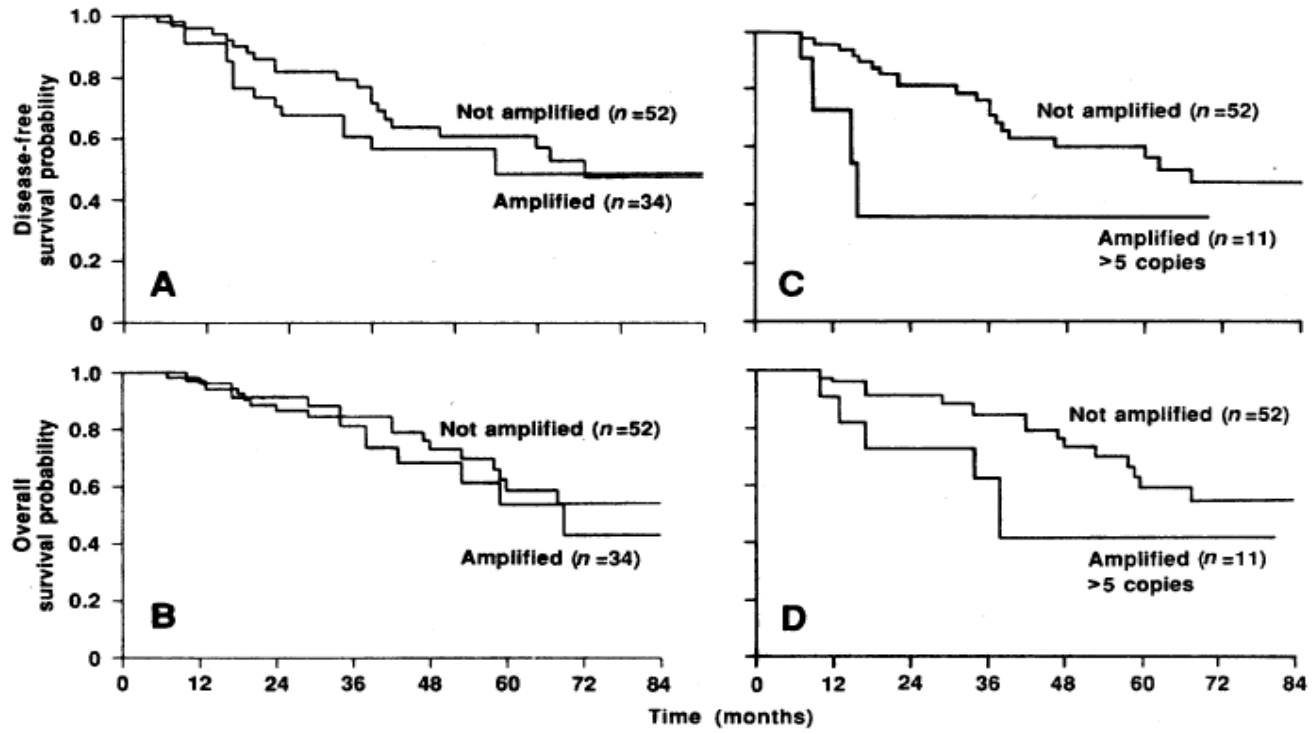
EML4-ALK Trasl.

How Biomarkers entered the clinic? HER2 and T790M

- EGFR mutations
- EML4-ALK traslocation
- HER-2 overexpression, T790M mutation
  - Time to ‘Drug discovery’ to ‘best result’: 3-7 yrs
  - Strong ‘Rationale’ and ‘Science’ behind from different Academies & Pharma
  - ‘Brave’ Investigators, sinergy with Pharma

The sentence *'Wait a minute: we are wrong!'* was NEVER pronouced

HER2-addicted tumors as a 'Distinct Prognostic Entity'

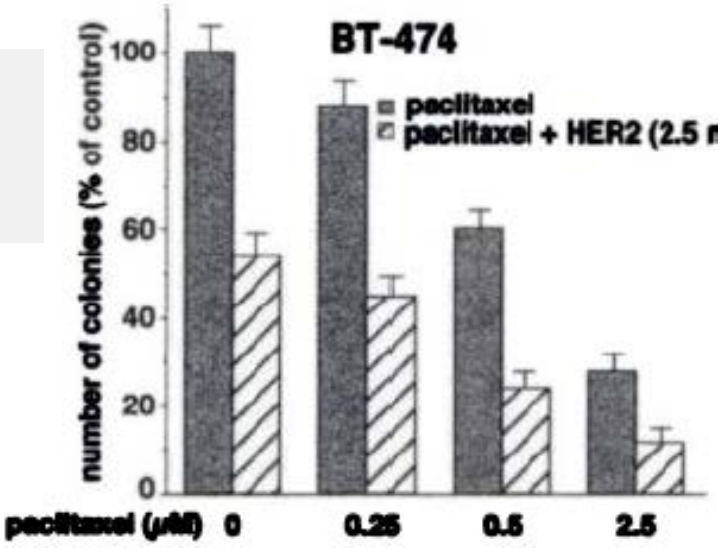


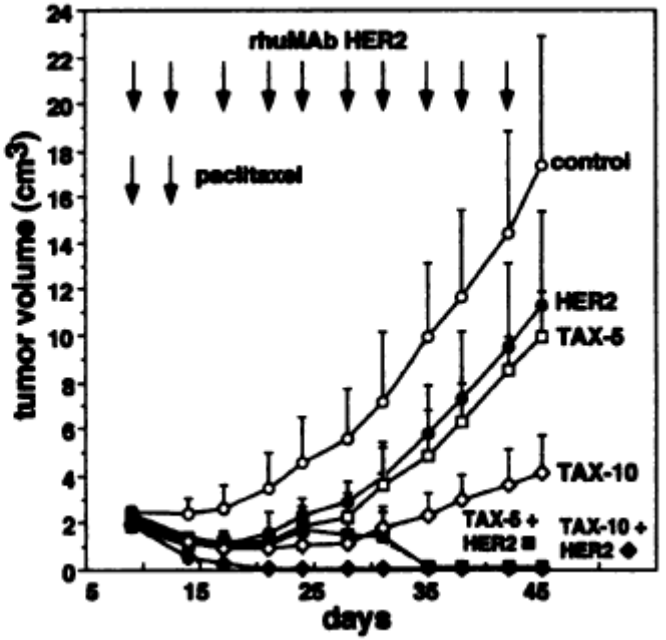
Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/*neu* Oncogene

Slamon D et al, Science 1998

Trastuzumab enhances DOXO and Paclitaxel efficacy in HER2-addicted xenografts

Strong Preclinical Evidence



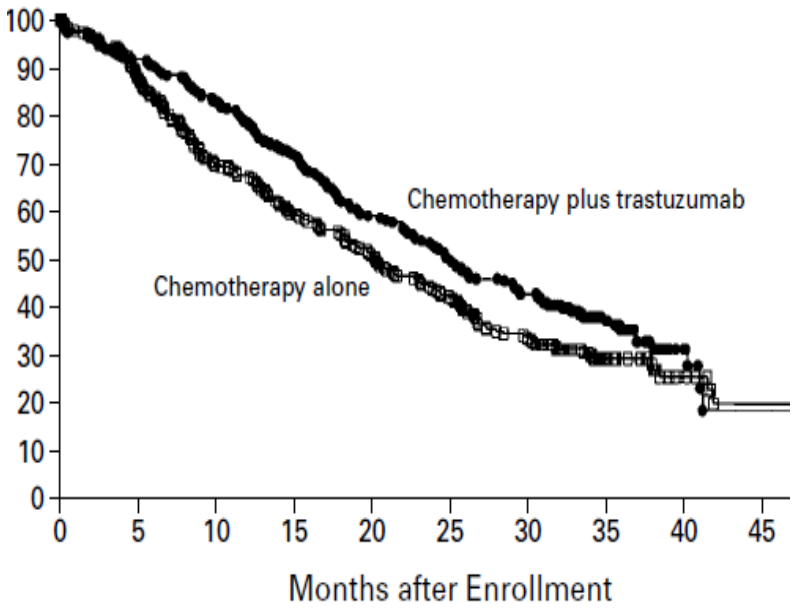


Recombinant Humanized Anti-HER2 Antibody (Herceptin™) Enhances the Antitumor Activity of Paclitaxel and Doxorubicin against HER2/*neu* Overexpressing Human Breast Cancer Xenografts[1]

Baselga J et al, Cancer Res 1998

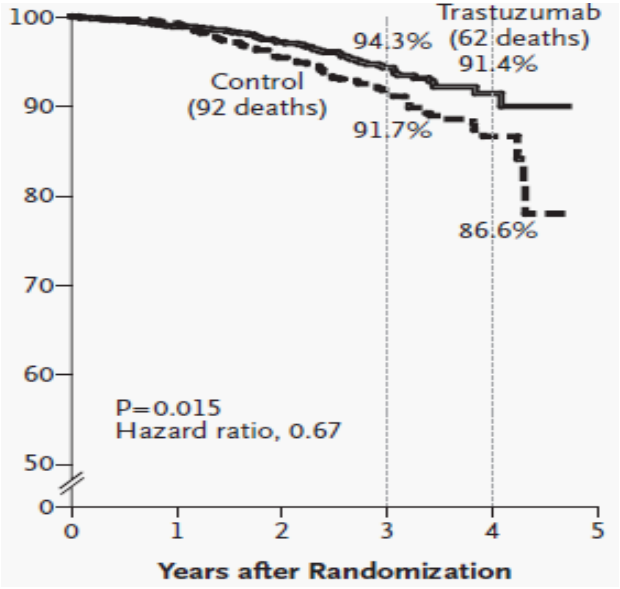
Trastuzumab improves Survival in HER2 positive Advanced and Early Breast Cancer

Dramatic Clinical Evidence



USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

Slamon D et al, NEJM 2001



Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

Robert et al, NEJM 2005

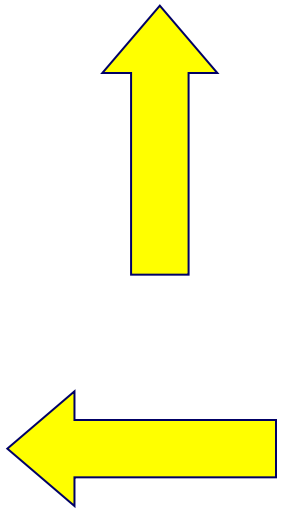
What if Trastuzumab as Untargeted?

Marker	Prevalence	Treatment Effect (1yr)	Targeted Design	Untargeted Design
HER2+	25-30%	+10%	469	23,586

	ACTUAL TARGETED TRIAL	HYPOTHETICAL NON-TARGETED TRIAL
N = 469	HER-2 ++ or +++	All patients
Response rate	50% vs 32% P < 0.001	37% vs 32% P = 0.27
One-year mortality	22% vs 33% P=0.008	30% vs 33% P = 0.45

Slamon et al., New Engl. J Med, 2001

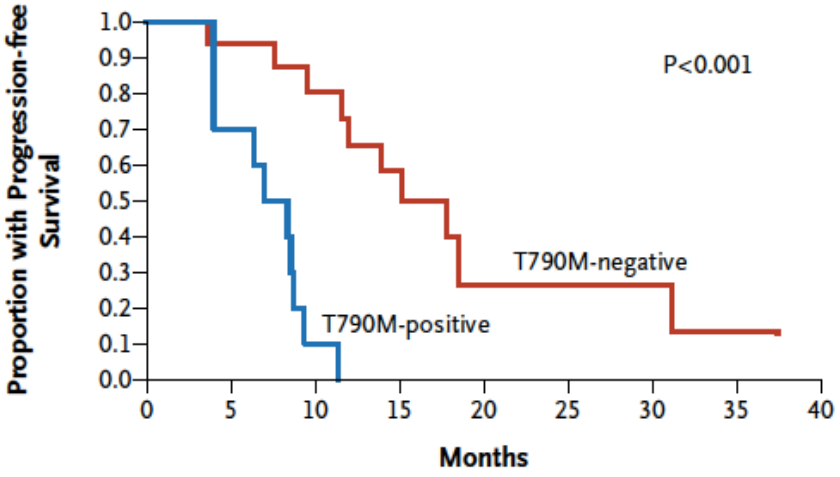
Drug killed !



Buyse, ASCO 2005

‘Switching’ the prognosis of Patients resistant to First Line TKIs carrying the T790M mutation

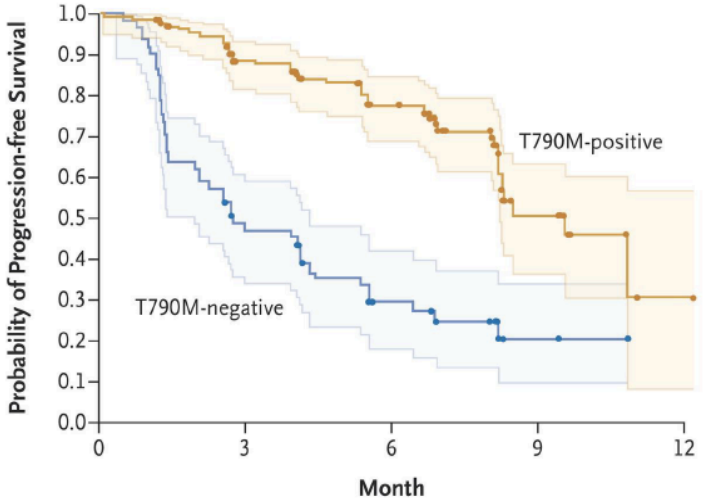
Chemo/BSC



No. at Risk								
T790M-negative	16	15	11	7	2	2	2	1
T790M-positive	10	7	1	0				

Maheswaran S et al, NEJM 2008

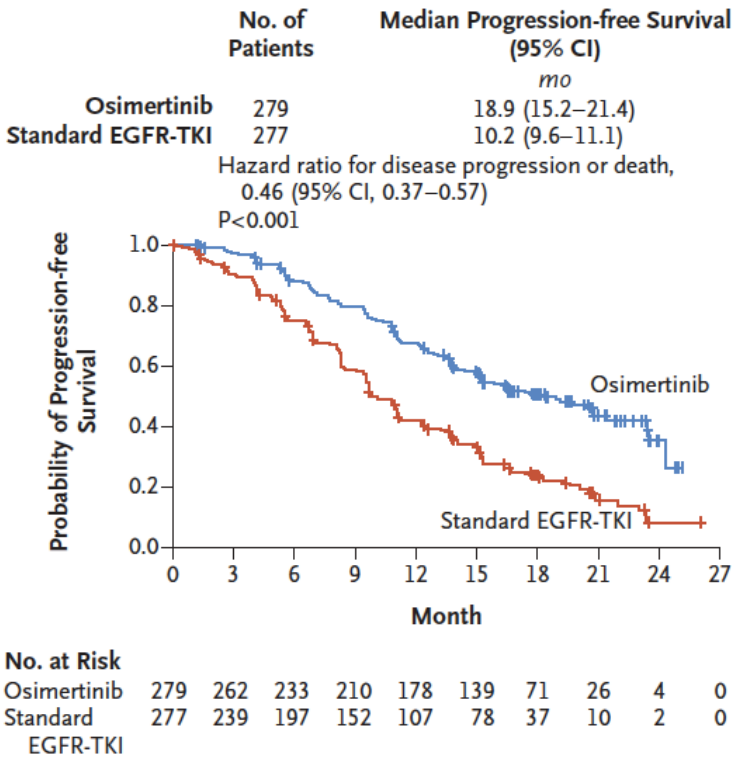
Osimertinib

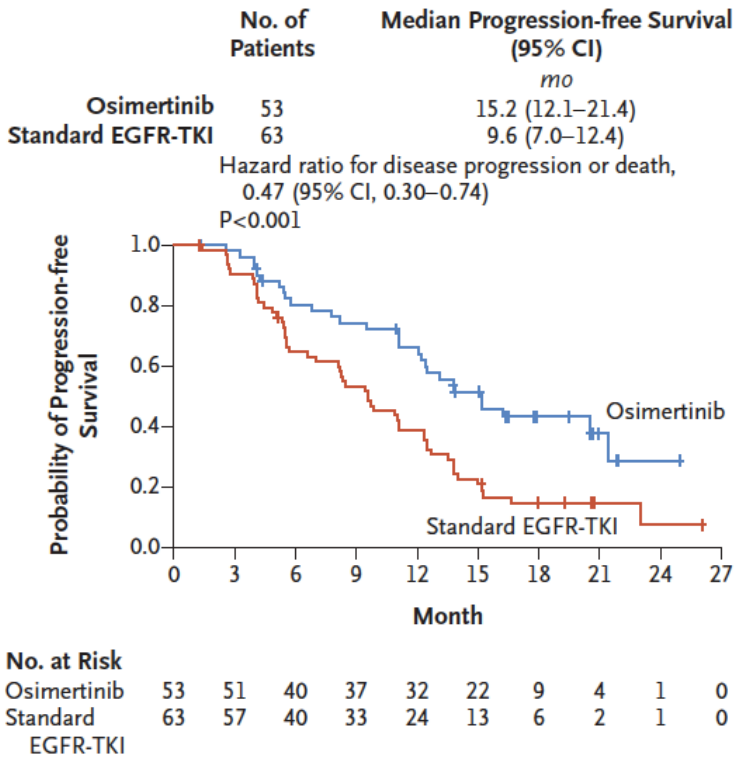


No. at Risk					
T790M-positive	138	100	70	14	1
T790M-negative	62	27	13	3	0

Janne P et al, NEJM 2015

Osimertinib not only for T790M EGFR mutation at resistance

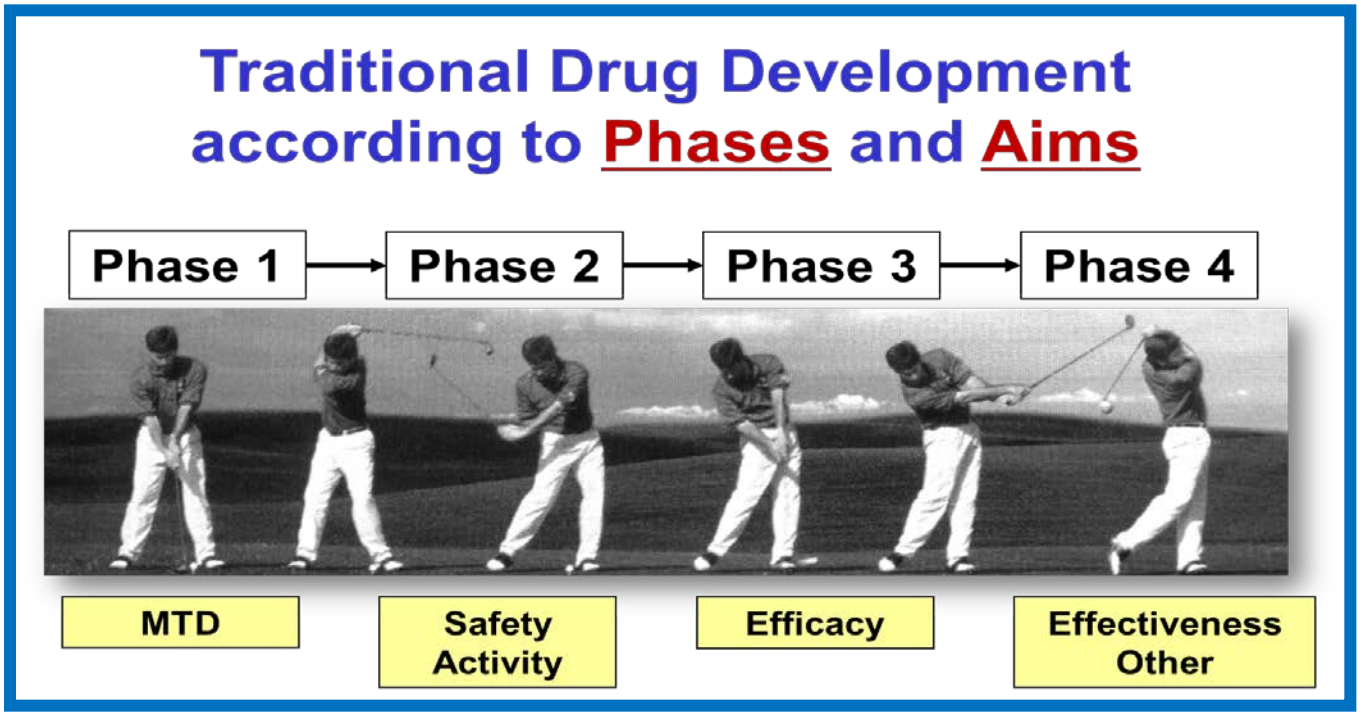




Soria JC et al, NEJM 2017

Time of Biomarker Discovery: HER2 / T790M

Preclinical



HER2 overexpr.
T790M mutation

Biomarker Driven Clinical Trials

Basket

Test the effect of targeted agents on same genomic alterations across a variety of cancer types

Umbrella

Test the effect of targeted agents on different genomic alterations in a single cancer type

Why new design ?

- Classical phase I,II, and III models require enormous resources
- Time to bring a new oncology drug to market 8-12 years
- Cost to bring a new drug to market can exceed $1 billion
- 70% of oncology drugs fail in phase II
- 59% of oncology drugs fail in phase III
- Have focused on histology-dependent strategies
- Limited collaboration between sponsors, academia, and funding sources
- Traditional models not designed to address “niche” agents with very small populations expected to benefit

Regulatory perspectives

- May introduce *operational bias*.

- May not be able to preserve *type I error rate*.
- *P-values* may not be correct.

- *Confidence intervals* may not be reliable.

- May result in *a totally different trial* that is unable to address the medical questions the original study intended to answer.

- *Validity* and *integrity* may be in doubt.

Protocol amendments

- **Rationale for changes**
  - -Clinical
  - -Statistical
- **Review process**
  - -Internal protocol review
  - -IRB
  - -Regulatory agencies

First FDA Approval Agnostic of Cancer Site

Does oncology change its paradigm? The challenge of agnostic approval of new therapies.

• In May 23, 2017, the Food and Drug Administration (FDA) approved pembrolizumab, a programmed death (PD-1) inhibitor, for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite-instability–high (MSI-H) or mismatch-repair–deficient (dMMR) solid tumors, regardless of tumor site or histology.

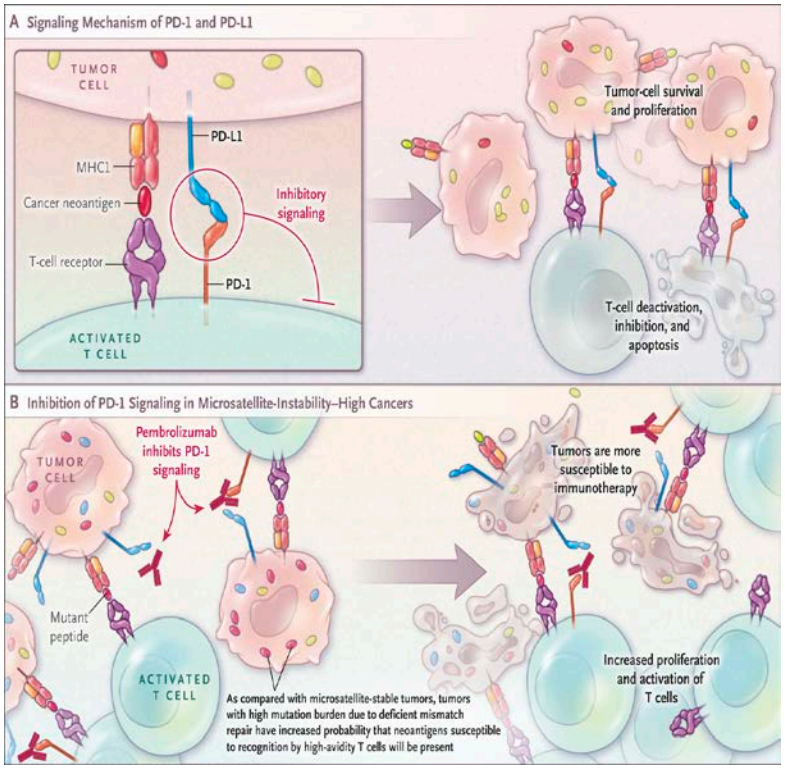
•The indication statement listed specific prior therapies for MSI-H or dMMR colorectal cancer on the basis of the patient population studied and in the context of multiple approved drugs for metastatic colorectal cancer. Rather than requiring separate development programs for each disease site, this approval was based on biomarkers irrespective of organ site or histology.

•The FDA granted accelerated approval to pembrolizumab for the MSI-H–dMMR indication, requiring the sponsor to conduct trials to further evaluate overall response rate and duration in additional patients with different tumor types in a nonrandomized setting. Most accelerated approvals require sponsors to perform randomized trials after approval.

•The FDA approved this indication without approved companion diagnostic tests for MSI-H or dMMR because of the high unmet medical need (with most patients having few therapeutic options), the high response rate, and the known safety profile.

When a Biomarker Defines the Indication: the MSI-H case

MSI-H tumors share common histopathologic characteristics, including lymphocytic infiltration, somatic hypermutation, and increased neoantigen formation. These neoantigens may serve as targets for the immune system, rendering a tumor susceptible to immunotherapy. In addition, MSI-H tumors can up-regulate immunologic checkpoints, such as PD-1 or programmed death ligand 1 (PD-L1), in infiltrating lymphocytes.



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When a Biomarker Defines the Indication: the MSI-H case

- The FDA's approval of pembrolizumab was based on data from 149 patients with MSI-H or dMMR cancer who were enrolled in five multicenter, single-group clinical trials.
- Most patients (84% for colorectal cancer and 53% for other tumors) had received two or more therapies for metastatic or unresectable disease.
- ORR was 39.6% (95% confidence interval [CI], 31.7 to 47.9). Responses lasted 6 months or more in 78% of patients who had a response.
- ORR was similar irrespective of whether the patients were diagnosed with colorectal cancer (36%; 95% CI, 26 to 46) or other cancers (46%; 95% CI, 33 to 59).

Pembrolizumab Response Rate by Tumor Type.*

Tumor Type	No. of Tumors	Patients with a Response	Range of Response Duration
		no. (%)	*mo*
Colorectal cancer	90	32 (36)	1.6+ to 22.7+
Endometrial cancer	14	5 (36)	4.2+ to 17.3+
Biliary cancer	11	3 (27)	11.6+ to 19.6+
Gastric or gastroesophageal junction	9	5 (56)	5.8+ to 22.1+
Pancreatic cancer	6	5 (83)	2.6+ to 9.2+
Small-intestine cancer	8	3 (38)	1.9+ to 9.1+
Breast cancer	2	2 (100)	7.6 to 15.9
Prostate cancer	2	1 (50)	9.8+
Other cancers	7	3 (43)	7.5+ to 18.2+

* Response was as defined by RECIST. "Other cancers" includes one patient each with the following tumor types: bladder, esophageal, sarcoma, thyroid, retroperitoneal, small-cell lung cancer, and renal cell cancer (includes two patients who could not be evaluated and were considered not to have had a response). A + sign indicates that the response was ongoing at the time of data cutoff.

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The “mutational model”

•A drug is approved and put on the market because it is active on a certain driver mutation and is approved regardless of the primary disease site, age, or gender.

•The healthcare system should be able to anticipate these changes, so as to put in place regulatory procedures aimed at guaranteeing appropriateness and economic sustainability.

•The answer to this challenge should be obtained through multidisciplinary networks of health professionals (oncologists, pathologists, epidemiologists, health decision makers, etc.) supported by updated disease registries. In this way, it would be possible to gather data and evidence in real time, guaranteeing the needed governance of the system.