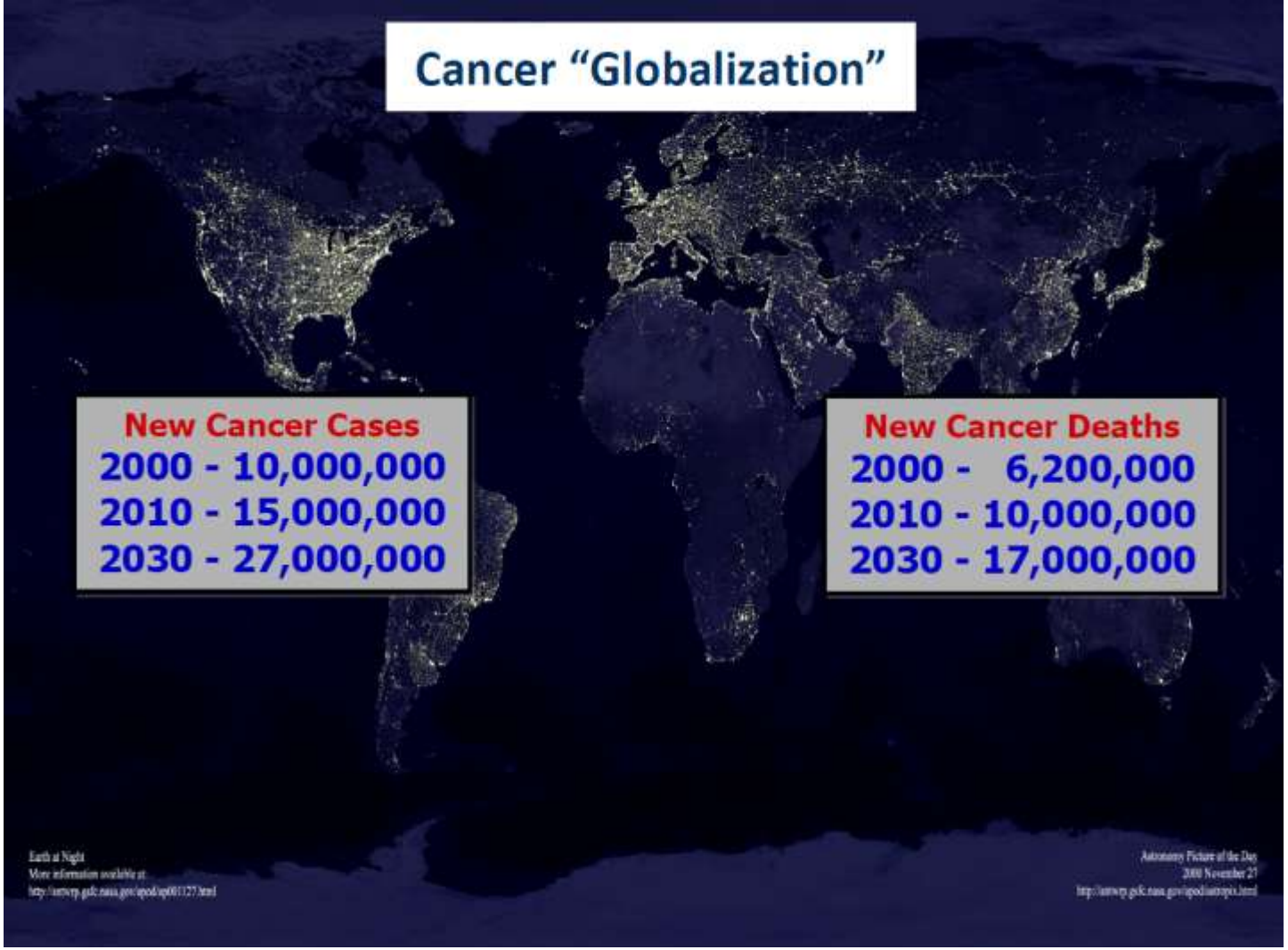
«L'oncologo di fronte al nuovo scenario dei tumori: Innovazione, valori clinici e sostenibilita'»

Francesco Cognetti


Michele Maio
Giovanni Minoli
IL CANCRO HA GIÀ PERSO
La rivoluzione da Nobel dell'IMMUNOTERAPIA dei tumori
PIEMME

insieme contro il cancro

- La realtà oncologica, mondiale e italiana, è radicalmente cambiata nel corso degli ultimi anni

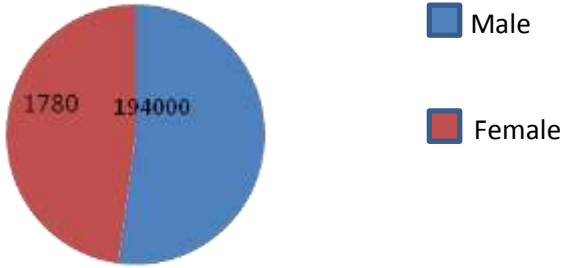

Cancer "Globalization"
New Cancer Cases
2000 - 10,000,000
2010 - 15,000,000
2030 - 27,000,000
New Cancer Deaths
2000 - 6,200,000
2010 - 10,000,000
2030 - 17,000,000
Earth at Night
More information available at:
Astronomy Picture of the Day
2000 November 27

By Conte PF

Do we have arguments to believe that cancer cure is around the corner?

- Epidemiological data
- Considerations

What's the situation in Italy?

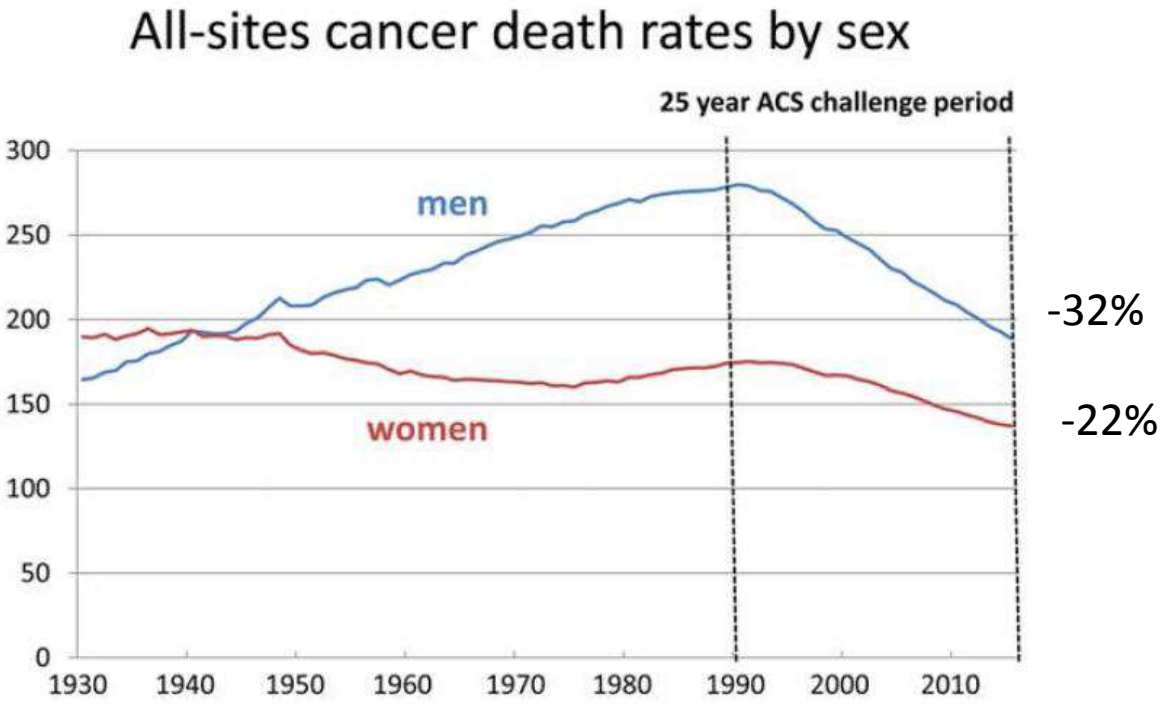


- 2018: 373,000 new cancer diagnosis

- ISTAT 2015: 178.323 death for cancer
- Cancer is the second cause of death (29%) after cardiovascular disease

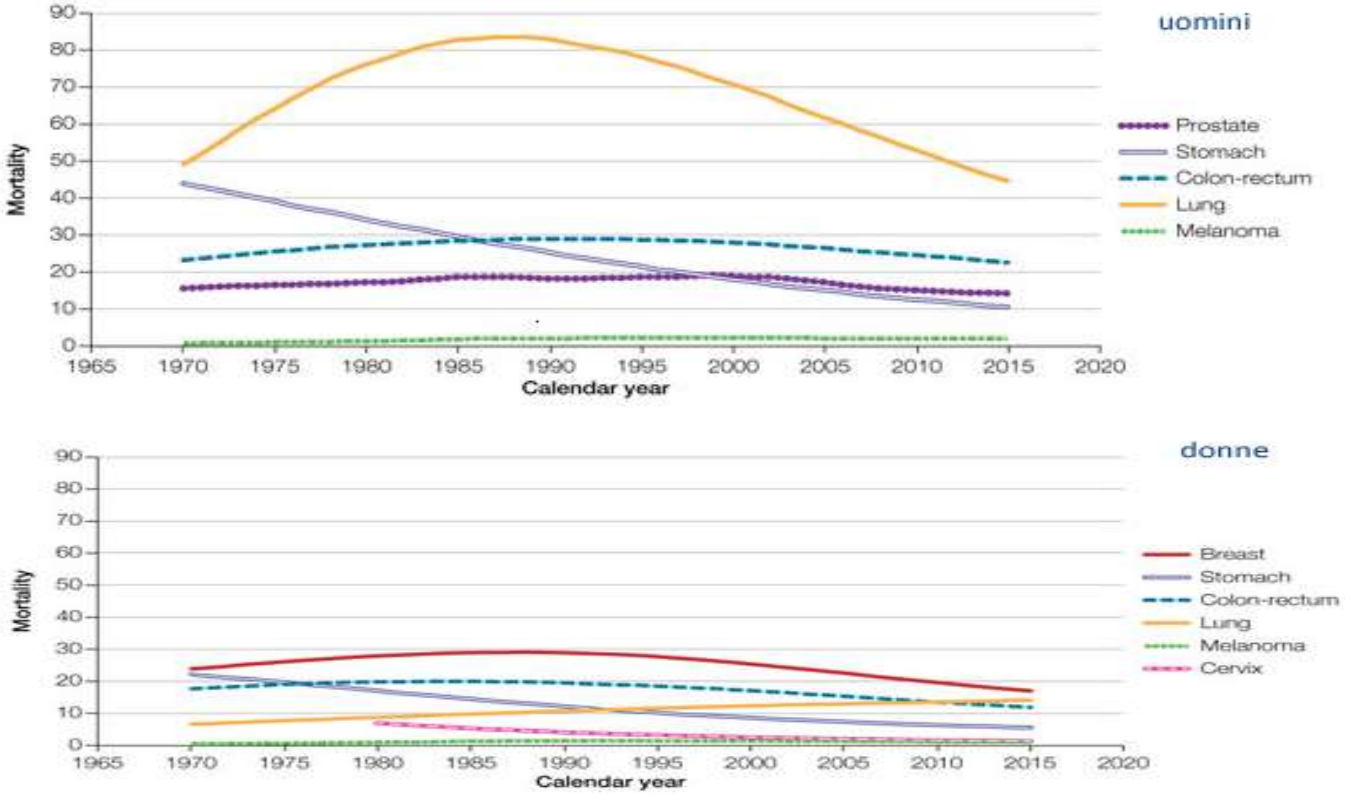
- Prevalence 2017:
  - **Total 3.368.569** **> 2020: 4.500.000**
  - male 1.531.157
  - female 1.837.412

Cancer mortality in the USA



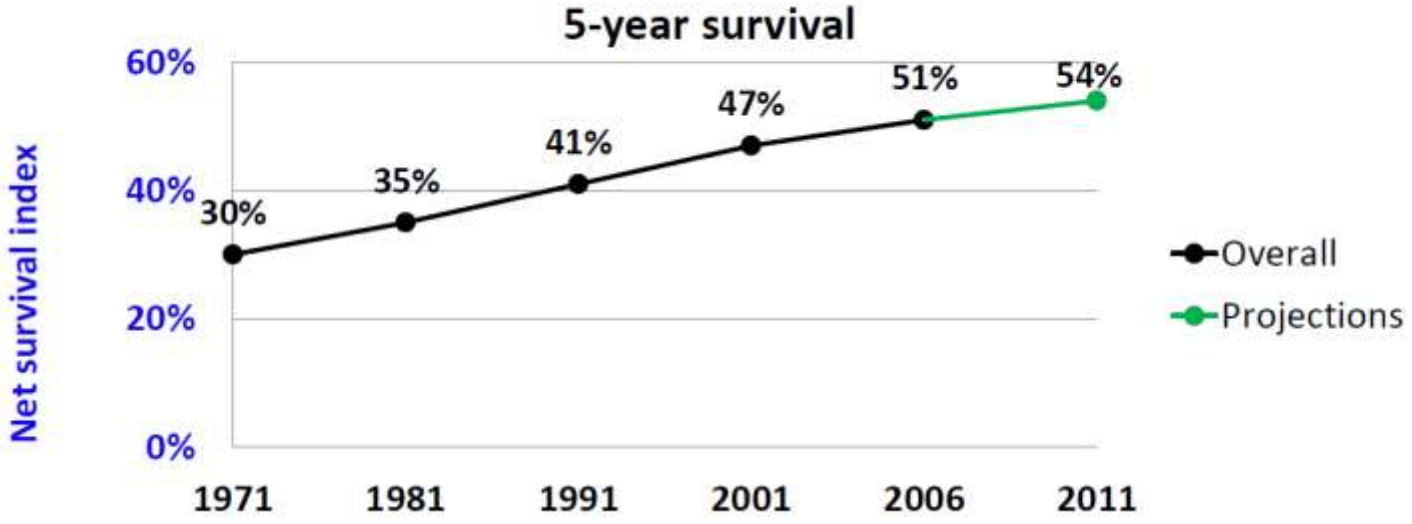
Byers T, et al. CA Cancer J Clin 2016

Cancer mortality in the Italy



- ✓ A cancer is cured when the risk of death of the survivor becomes quasi equal to the risk of death from other causes (background mortality) in the general population of the same age and sex.
- ✓ To take into account the risk of death from other causes, one computes a **net survival**
- ✓ The net survival function is usually estimated 1 year, 5-years, or 10 years after diagnosis

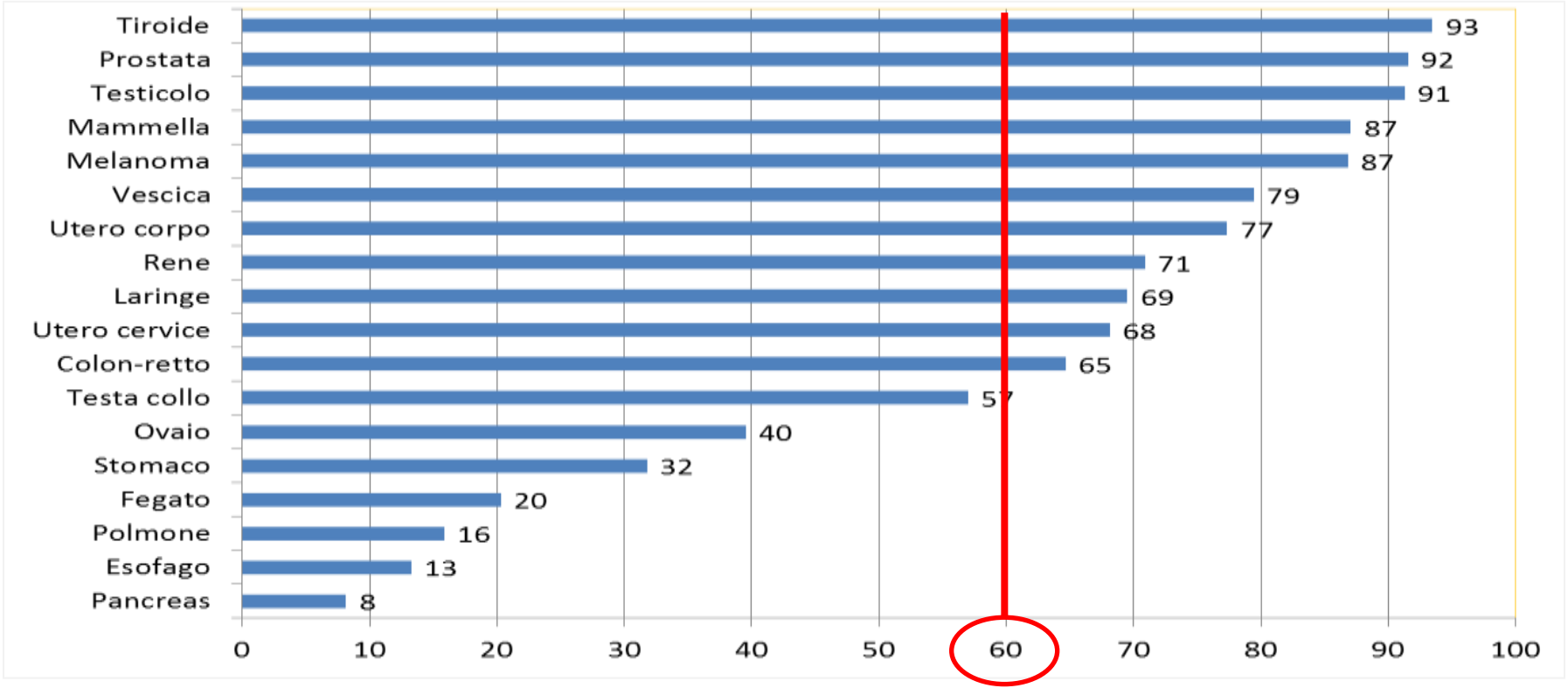
Trends in cancer survival in England, all adults



- > Index designed to be independent of changes in the age distribution of patients with cancer and of changes in the proportion of lethal cancers in each sex.

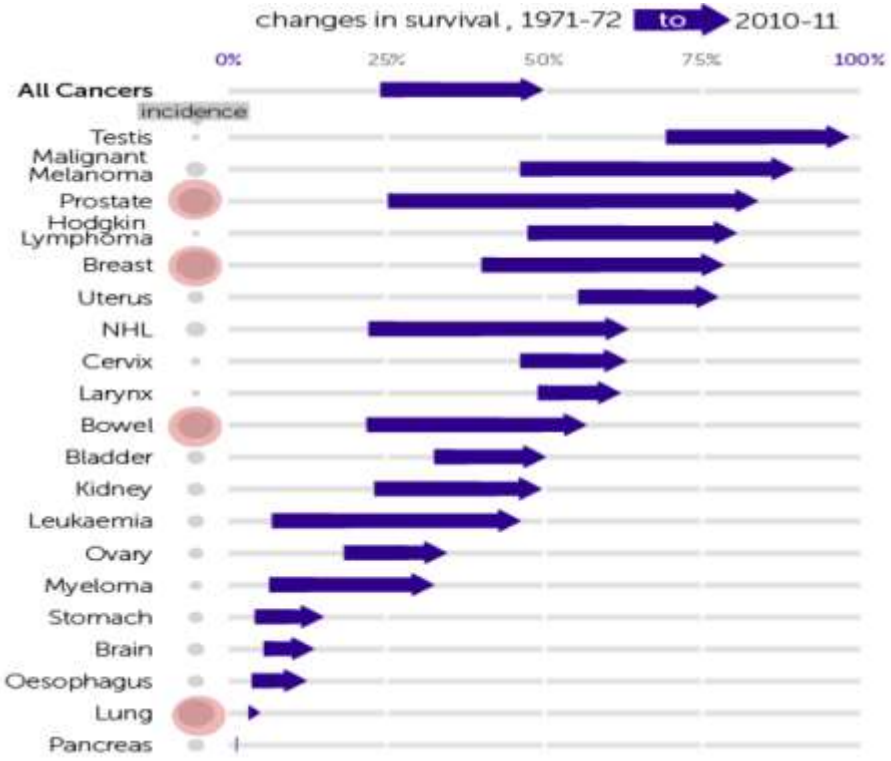
Quaresma M, et al. Lancet 2015

Sopravvivenza per sede



Coviello, 2017

England 10-year net survival changes in ~ 40 years



Source: cruk.org/cancerstats

Why cancer cure could be around the corner?

- ✓ New knowledge
- ✓ New tools
  - ✓ Liquid biopsies
  - ✓ The advent of precision medicine and molecular targeted agents
  - ✓ The raise of immuno-oncology

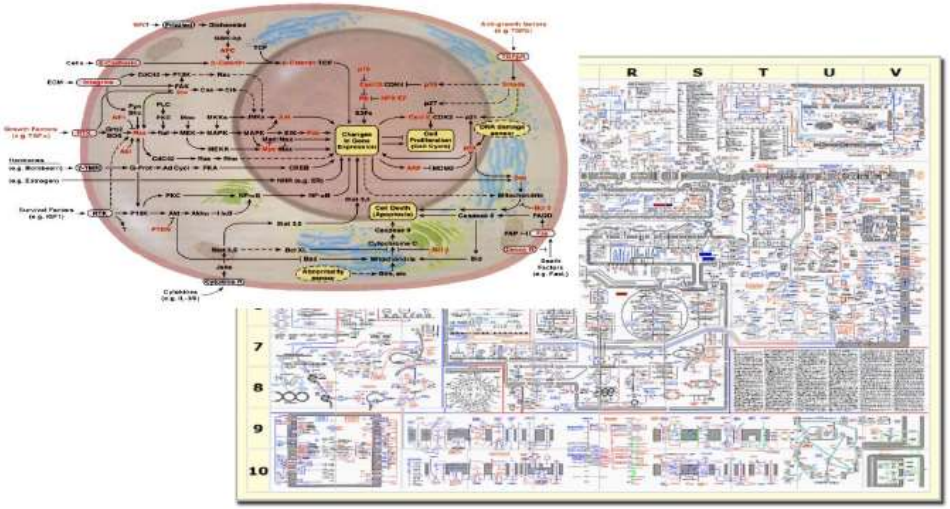
New knowledge

- New scientific insights and a spur of technological innovations, make prospects for success greater than ever
- There is dramatic shift in our fundamental understanding of cancer
- Although each tumor is molecularly unique, certain pathways are repeatedly affected

→ The revised « hallmarks of cancer »

Lowy D & Collins F, N Engl J Med 2016

The molecular circuitry of cancer cells is better understood….



Some pathways are repeatedly affected

Hallmarks of Cancer: The Next Generation. Hanahan D and Weinberg R, Cell 2011

Innovation and clinical value

- New drugs are not always innovative
- Clinical values of innovative drugs is not always granted
- Costs of new drugs are not related to their clinical value
- Delayed access to innovation in an issue

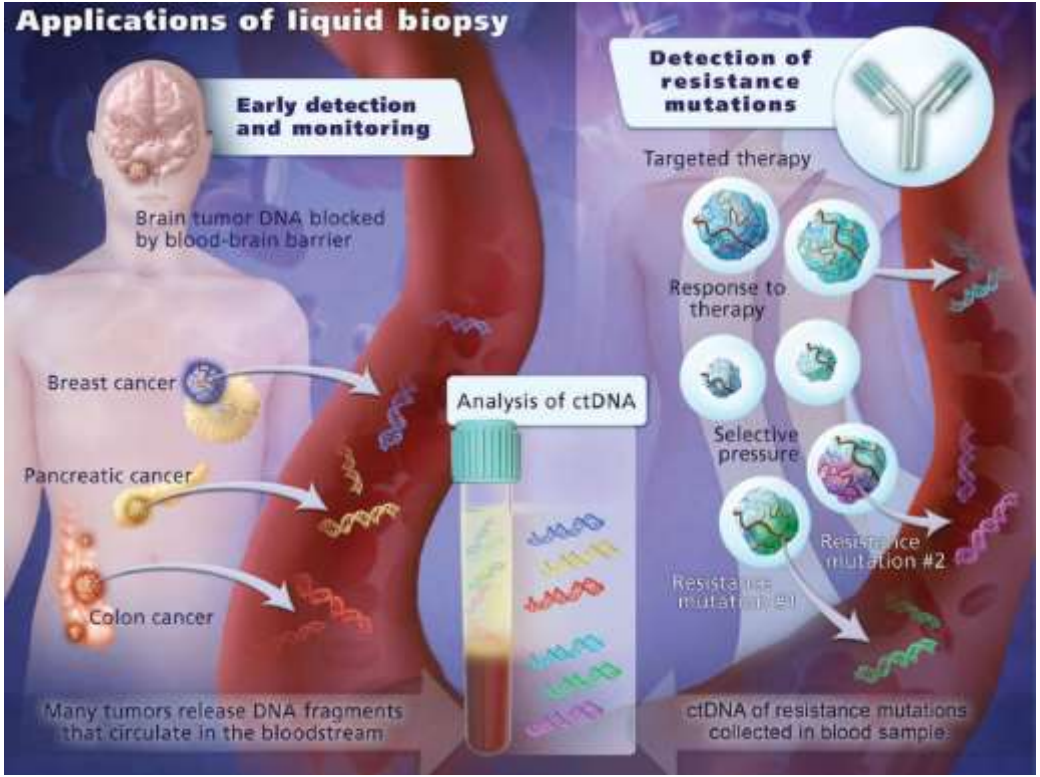
- What is «true» innovation?
- Is a new agent innovative only because is new?
- Are innovations always useful for the patients?
- Is «true» innovation affordable?
- True Innovation is for limited numbers of patients only
- Overtreatment is unaffordable

New tools

- *Liquid biopsies*
  - Can allow earlier detection of the disease
  - Earlier identification of treatable genomic alterations
  - Potential monitoring of residual disease
- New anti-cancer therapies: MTA and immunomodulators
- Recurrent altered pathways in cancer cells
  - Have fostered the development of MTA
  - And their use in metastatic and sometimes adjuvant setting
- The advent of immuno-oncology
  - A new paradigm
  - A large spectrum of activity
  - A wave beyond T-cell modulation

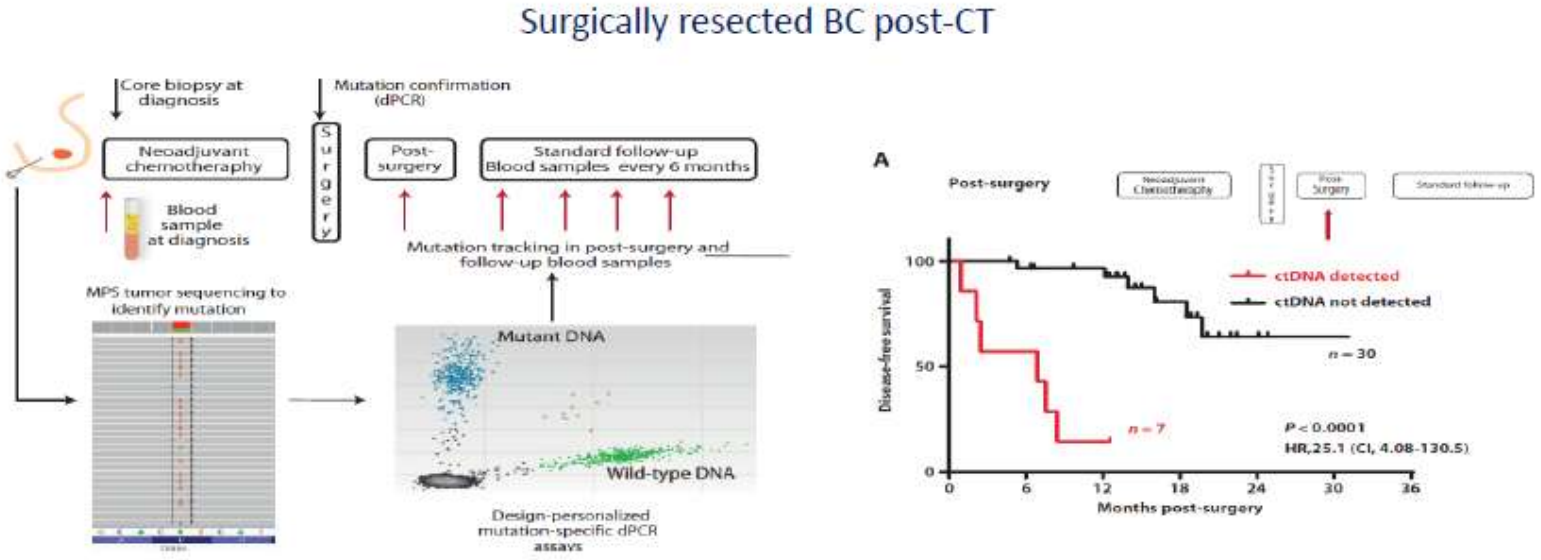
Liquid biopsies open a complete new perspective

- Screening and diagnosis??
- Prognostic evaluation
- Monitoring of minimal residual disease
- Monitoring of response/resistance
- Assesment of molecular heterogeneity
- Molecular evolution



Bettegowda C, et al. STM 2014

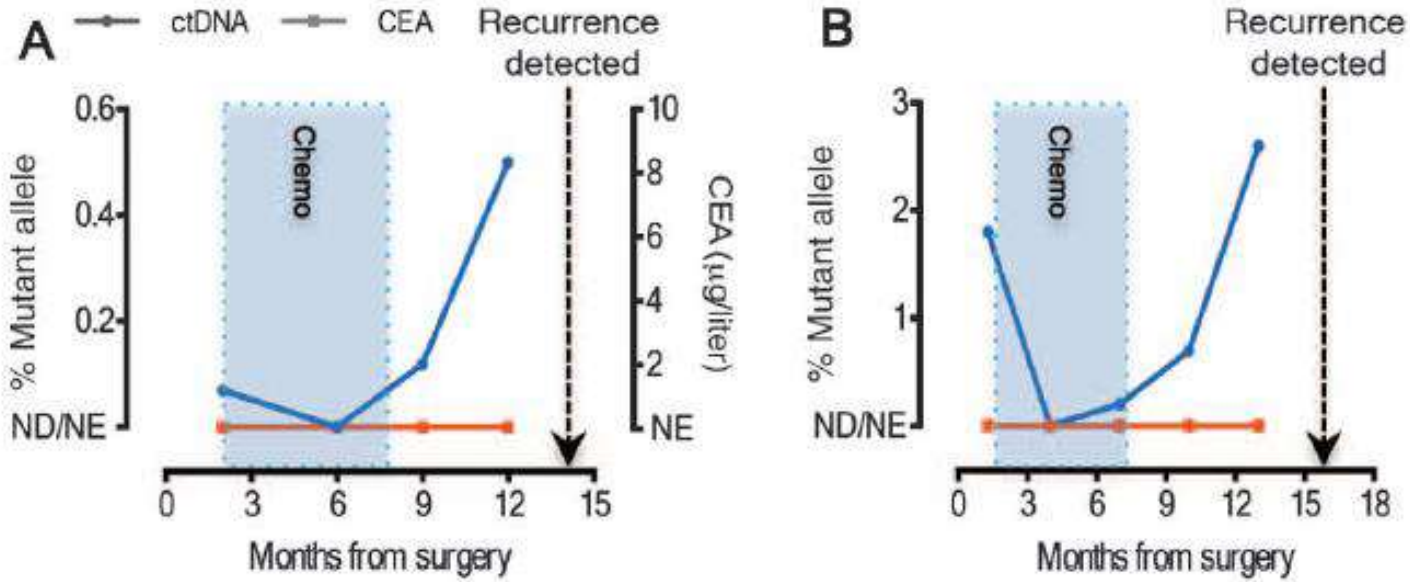
Liquid biopsies in resectable disease (breast cancer)



Garcia-Murillas I, STM 2015

Liquid biopsies in resectable disease (colorectal cancer)

Stage II colorectal cancer



Tie J, et al. STM 2016

Anti-cancer therapy in 70’s to 90’s

More sophisticated XRT

Less mutilating and organ-spearing approaches

Systemic anti-cancer therapies after 2010's

TARGETED THERAPIES

The blue-print
from
Hallmarks of cancer

CHEMOTHERAPY

Combination CT

Adjuvant CT

IMMUNOTHERAPIES

Innovation in oncology: la strada da percorrere

A «Patient-Centric» Health Care must guarantee three essential elements:

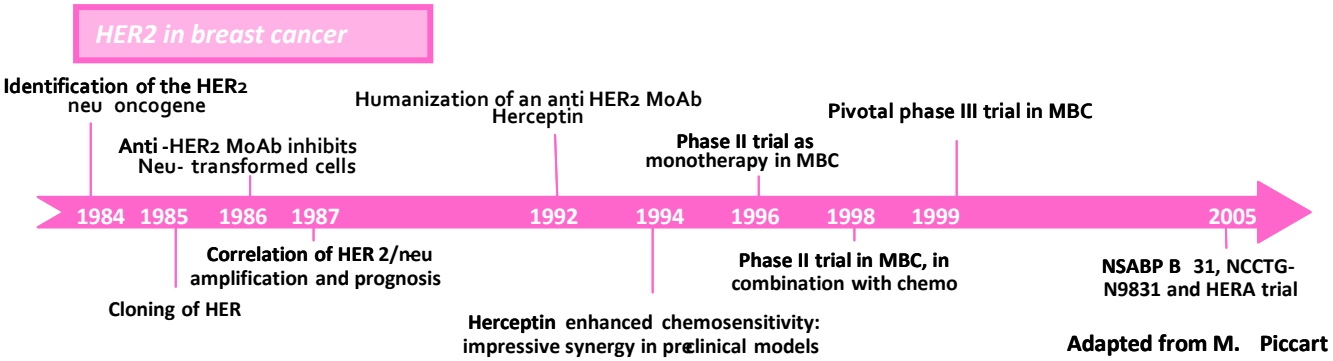
- availability – disponibilita’

- affordability - accessibilita’, sostenibilita’

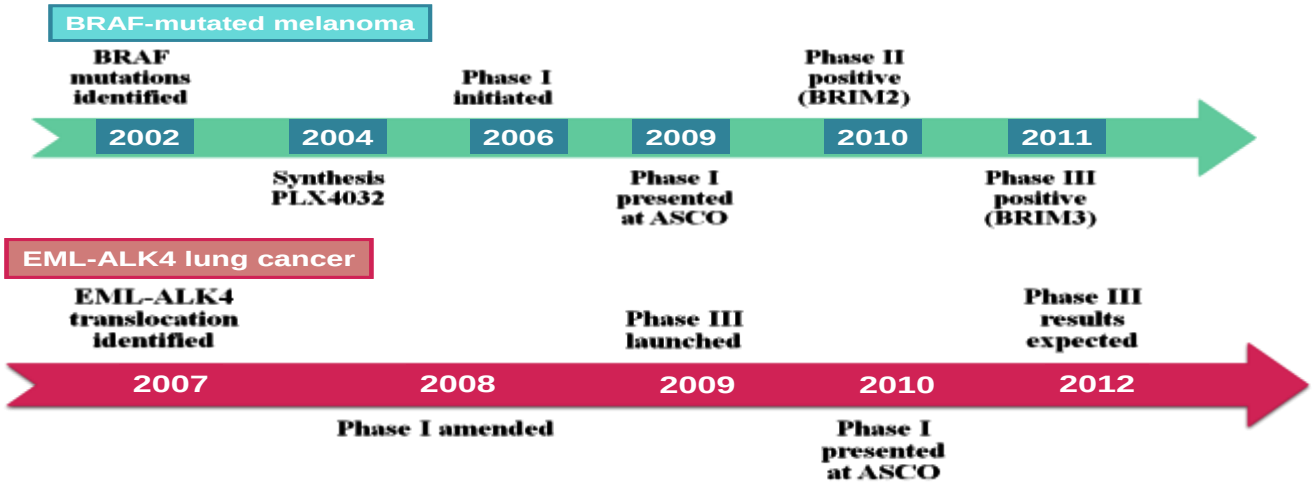
- appropriateness - appropriatezza

AVAILABILITY

Targeted agents and Companion Diagnostics



Accelerated Clinical Translation



AVAILABILITY
NeoAdjuvant vs Adjuvant Trials

	Adjuvant	Neo-adjuvant
Number of Patients	thousands	hundreds
Efficacy Endpoint	DFS	pCR
Primary analysis	years after end of recruitment	months after end of recruitment
Biological Window	No	Yes
Functional Imaging	No	Yes
Sample Collection	baseline	multiple time points
Cost	+++++	++

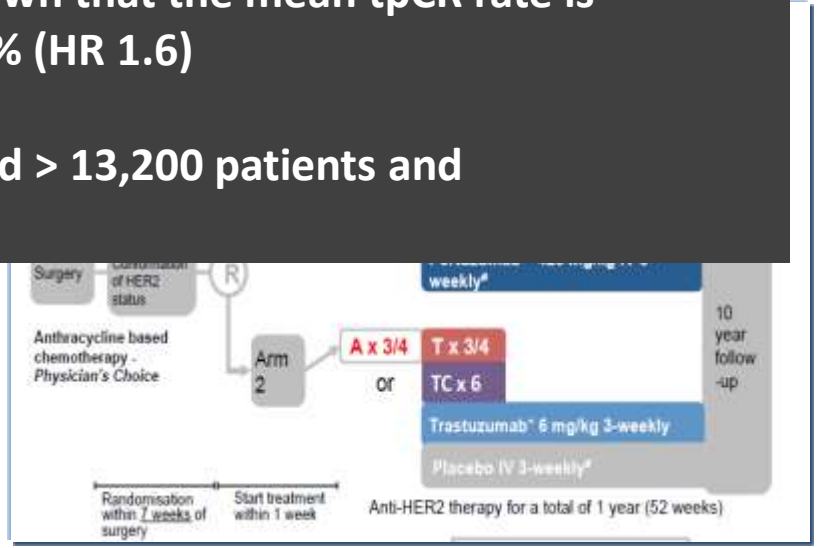
Ongoing Adjuvant Trials of Dual HER2 blockade in HER2-Positive Primary Breast Cancer

ALTTO 8,400 pts

Neoadjuvant trials of dual block have included a total 1,810 patients and have shown that the mean tpCR rate is increased from 29.6% to 48% (HR 1.6)

Adjuvant trials have included > 13,200 patients and results are still pending

Aphinity 4,800 pts



TRIAL CLINICI FASE PRECOCE: FASE I

- ✓ Determinazione della dose
- ✓ Analisi delle tossicita’
- ✓ Validare e verificare l’attivita’ dei farmaci in relazione alla loro azione verso markers biologici

FASE I : nuove procedure

- ✓ Master protocols:
  - ✓ Avvio contemporaneo di piu' studi paralleli :
    - ✓ Basket trials
    - ✓ Umbrella trials
    - ✓ Platform trials

AFFORDABILITY
NICE Statement

"We support the general principle that the NHS should pay a price which reflects the additional therapeutic benefit of new drugs. We also share the Government's ambition to ensure that the opinion exists for all new licensed drugs to be offered to those patients who can benefit for them"

provided that the price is a fair reflection of their value

Oncology pathway and outcome: time to RT for Head and neck patients

Country	Population and Nb	Primary endpoint
NCDB USA	25216 patients with stage III/IV H and N tumors	Median OS according to time to RT after surgery

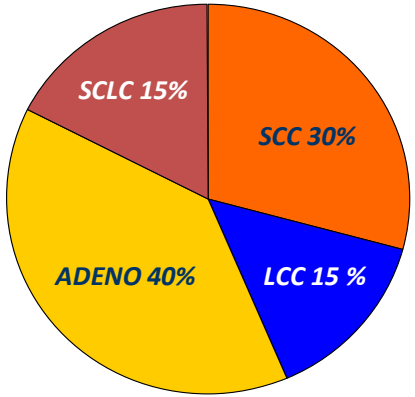
Time to radiotherapy			
	<42 days	43-49 days	>50 days
patients	9765	4735	10716
Median OS yrs	10.5	8.2	6.5

Harris LP et al. JAMA Otolaryngol Head and Neck Surg, 2018

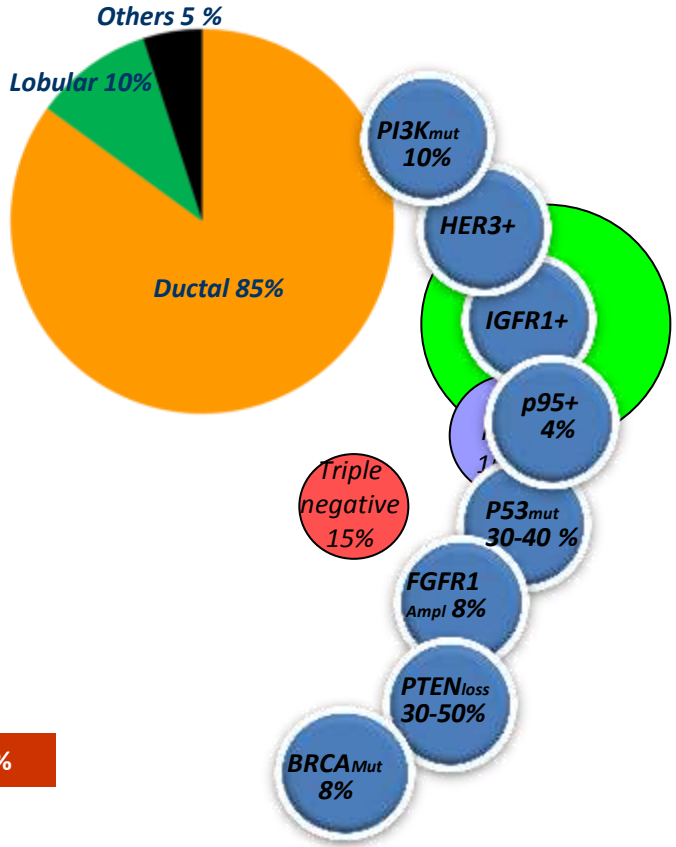
APPROPRIATENESS

Lung and Breast Cancer: from Histology to molecularly characterized diseases

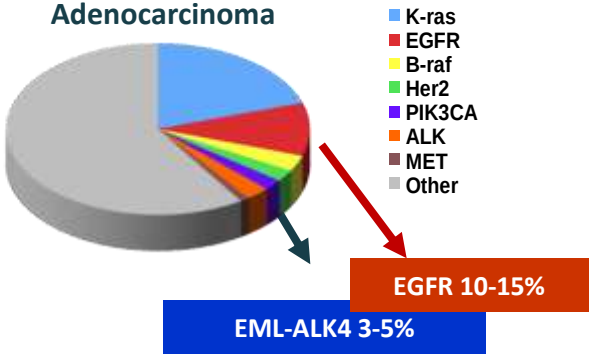
Lung Cancers



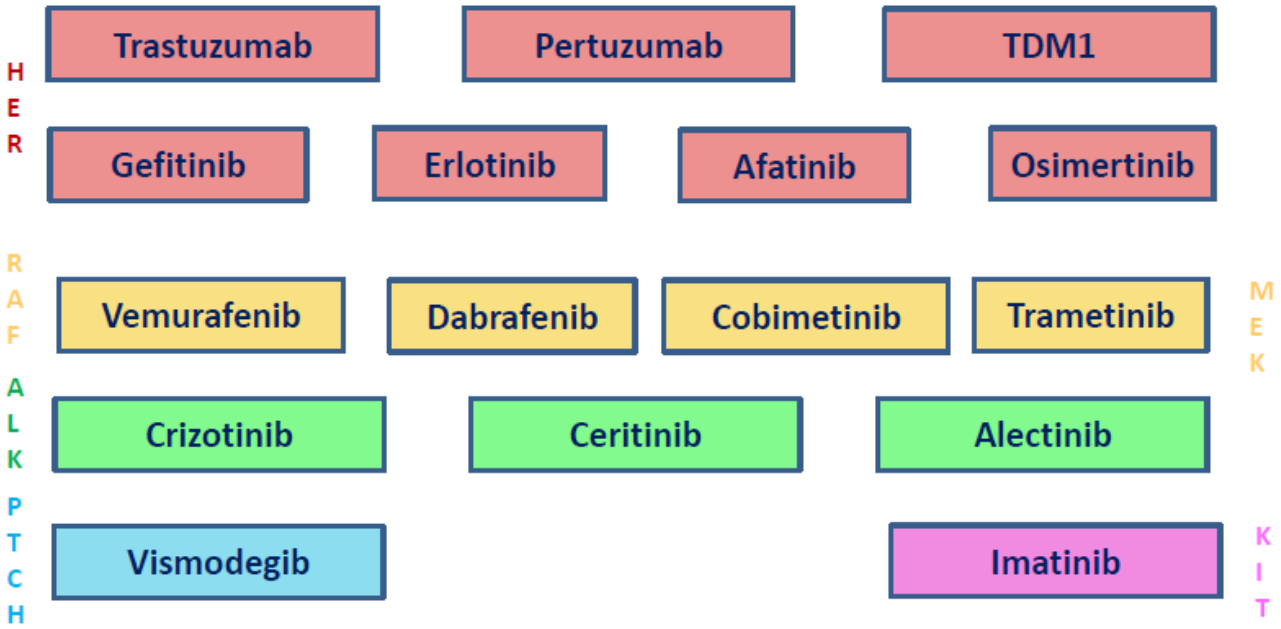
Breast Cancers



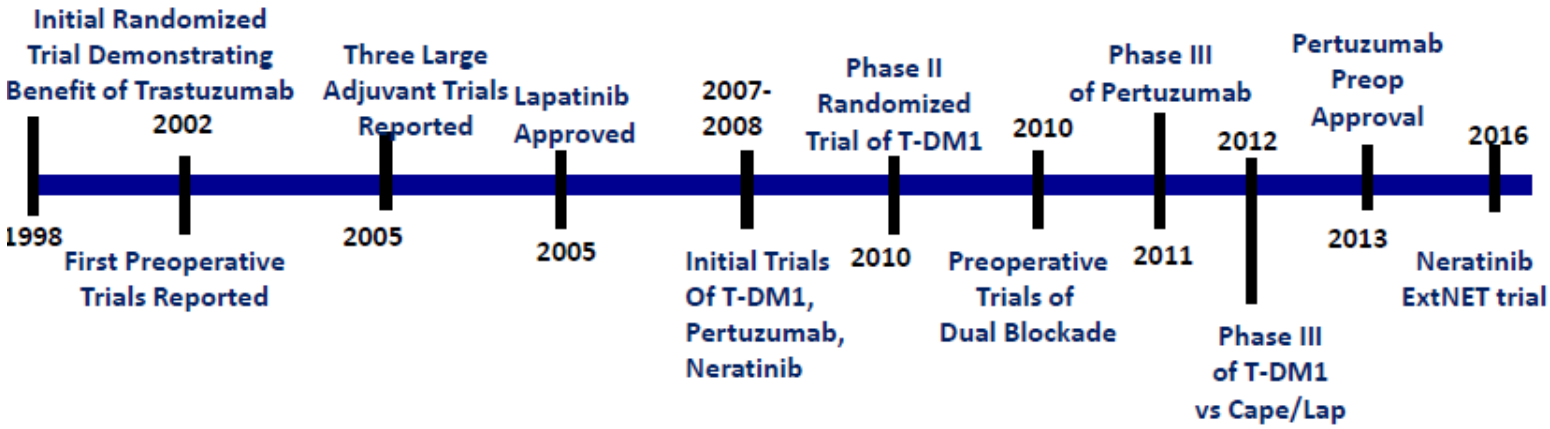
Somatic Mutations in Adenocarcinoma



Examples of marketed targeted therapies



In 2016, ≈90% of women diagnosed with early (operable) HER2+ breast cancer are potentially cured



Modified from Carlos Artega

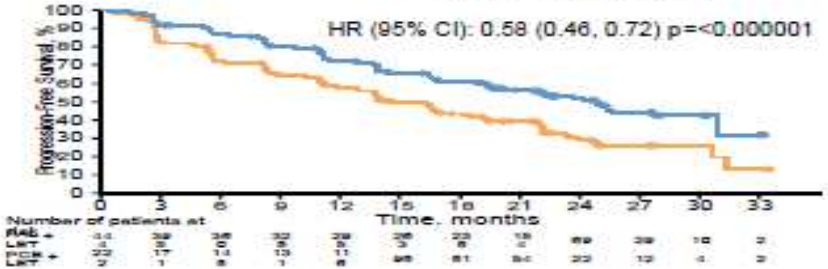
ER+ endocrine sensitive

PFS benefit in 1st Line AI + CDK4/6 inhibitor Phase III Trials

PALOMA 2 (2:1)

Median PFS
Palbociclib + NSAI: 24.8 m
placebo + NSAI: 14.5 m

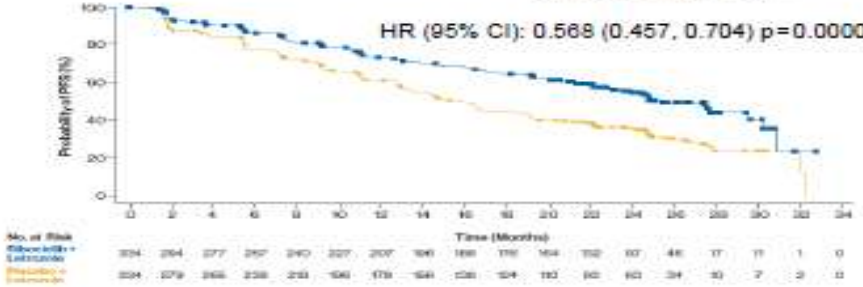
HR (95% CI): 0.58 (0.46, 0.72) p=<0.000001

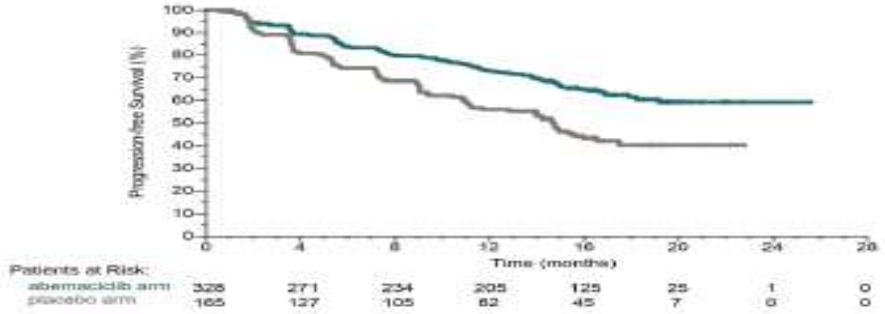


MONALEESA 2 (1:1)

Median PFS
Ribociclib + NSAI: 25.3 m
placebo + NSAI: 16 m

HR (95% CI): 0.568 (0.457, 0.704) p=0.000000096





MONARCH 3 (2:1)

Median PFS
abemaciclib + NSAI: not reached
placebo + NSAI: 14.7 m

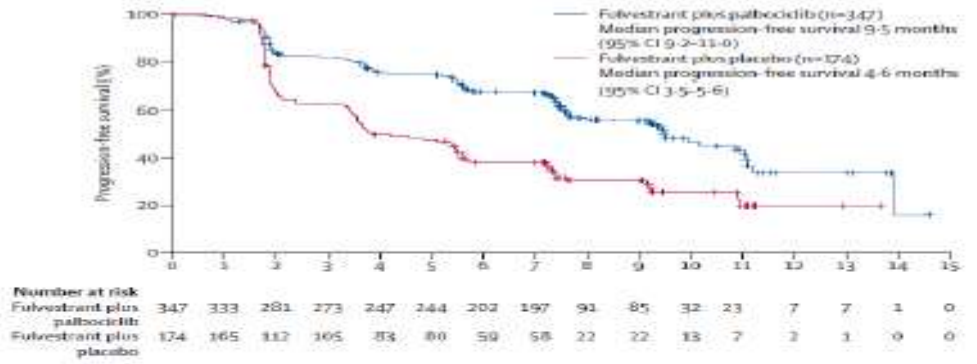
HR (95% CI): 0.543 (0.409, 0.723) p=0.000021

ER+ endocrine resistant

PFS Benefit in 2nd Line Fulvestrant + CDK 4/6 inhibitor Phase III Trials

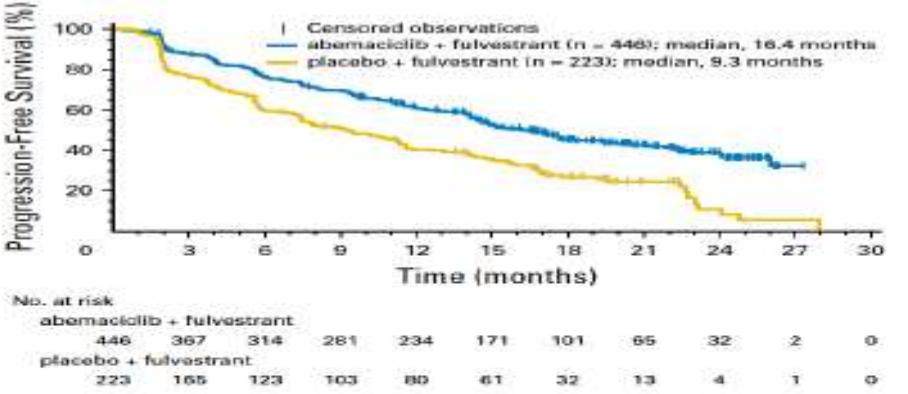
PALOMA3[1,2]

HR (95% CI): 0.46 (0.36, 0.59)
p =<0.0001

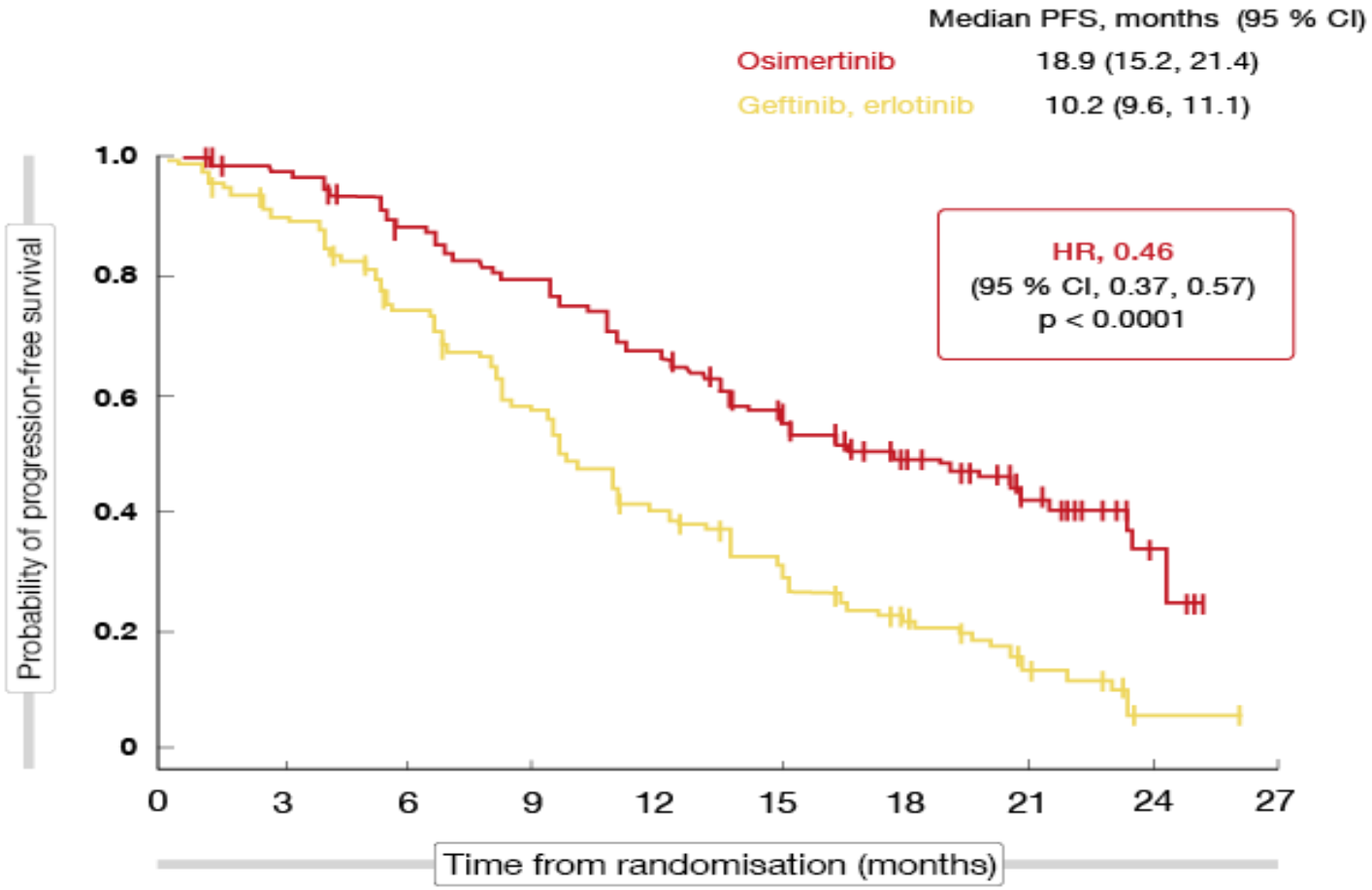


MONARCH2[3]

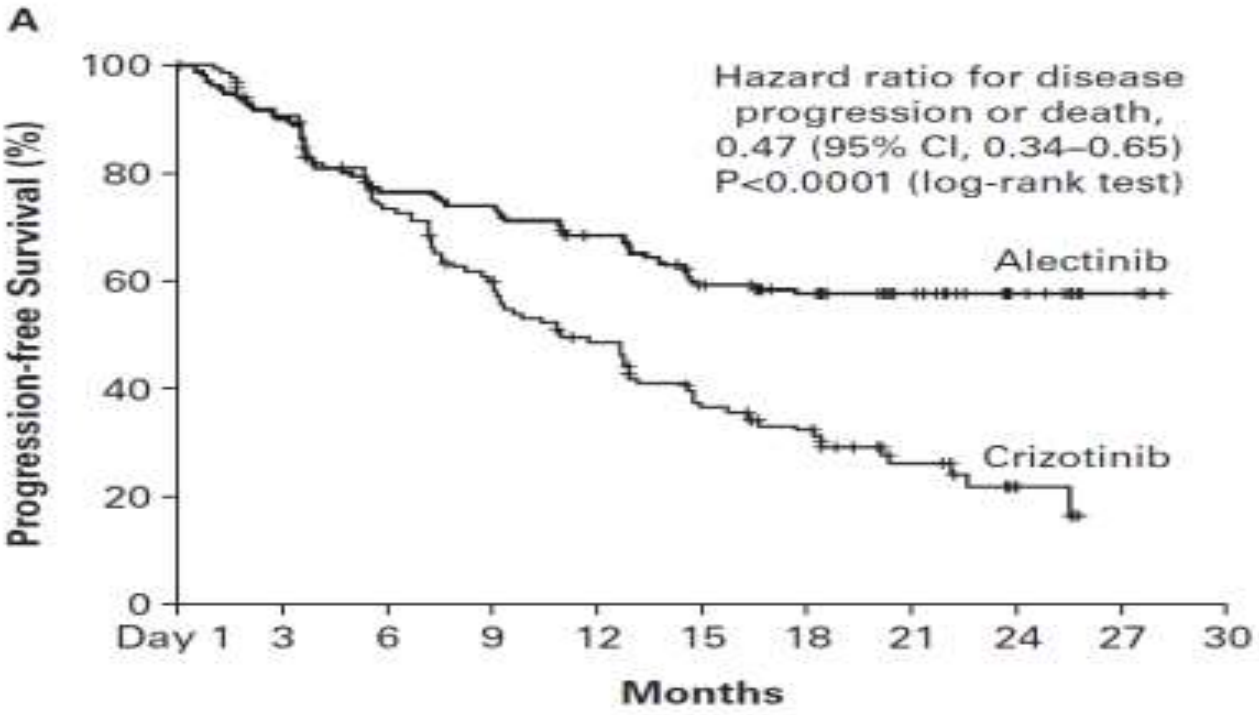
HR (95% CI): 0.55 (0.45, 0.68)
p =<0.001



[1]Turner NC, et al. N Engl J Med 2015; [2]Cristofanilli M, et al. Lancet Oncol 2016; [3]Sledge G, et al. J Clin Oncol 2017



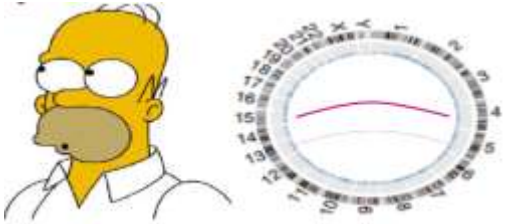
The New England Journal of Medicine November 18, 2017



No. at Risk

Crizotinib	151	132	104	84	65	46	35	16	5	
Alectinib	152	135	113	109	97	81	67	35	15	3

The New England Journal of Medicine. August 31, 2017; 377:829-838



Stupid Cancers

- ❖ Single dominant mutation
- ❖ Small mutational load
- ❖ Monotherapy is effective
- ❖ Resistance rare, late, same pathway

Smart Cancers

- ✓ Multiple mutational drivers
- ✓ Large mutational load
- ✓ Multi-targeted therapy required
- ✓ Resistance common, early
- ✓ High intra tumor heterogeneity

Adapted from G.Sledge & Stephens, PJ, et al. Nature 2009

Added-value of Immune Targeted Therapies

- **Adaptive anti-tumor immunity is polyclonal:**

  better control of tumor heterogeneity

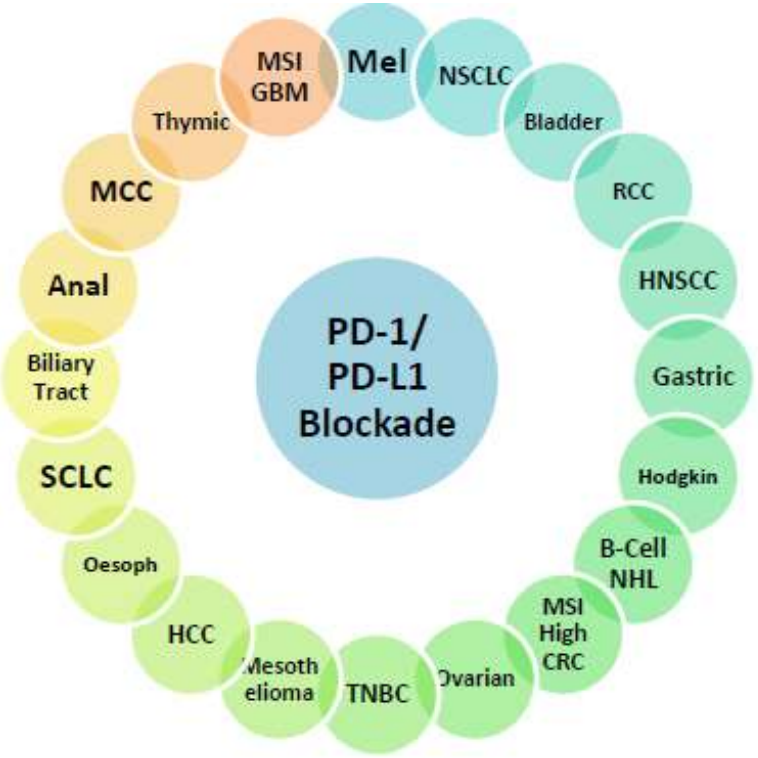
- **Adaptive anti-tumor immunity has memory:**

  durable remissions

- **Adaptive anti-tumor immunity is tumor-antigen specific:**

  less off-target toxicity than conventional therapies

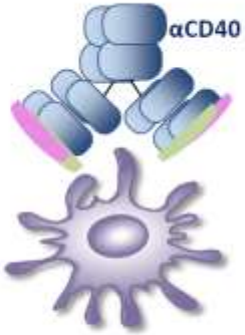
Spectrum of activity of anti PD1/PDL1



Adapted from A Marabelle

Immunomodulation way beyond T-cells

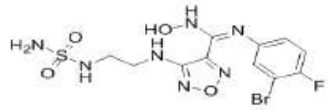
NK Cells

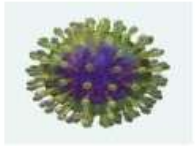


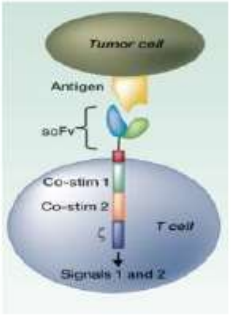
DCs
B-cells

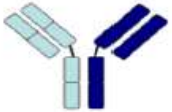
TAMs

Other immunotherapies







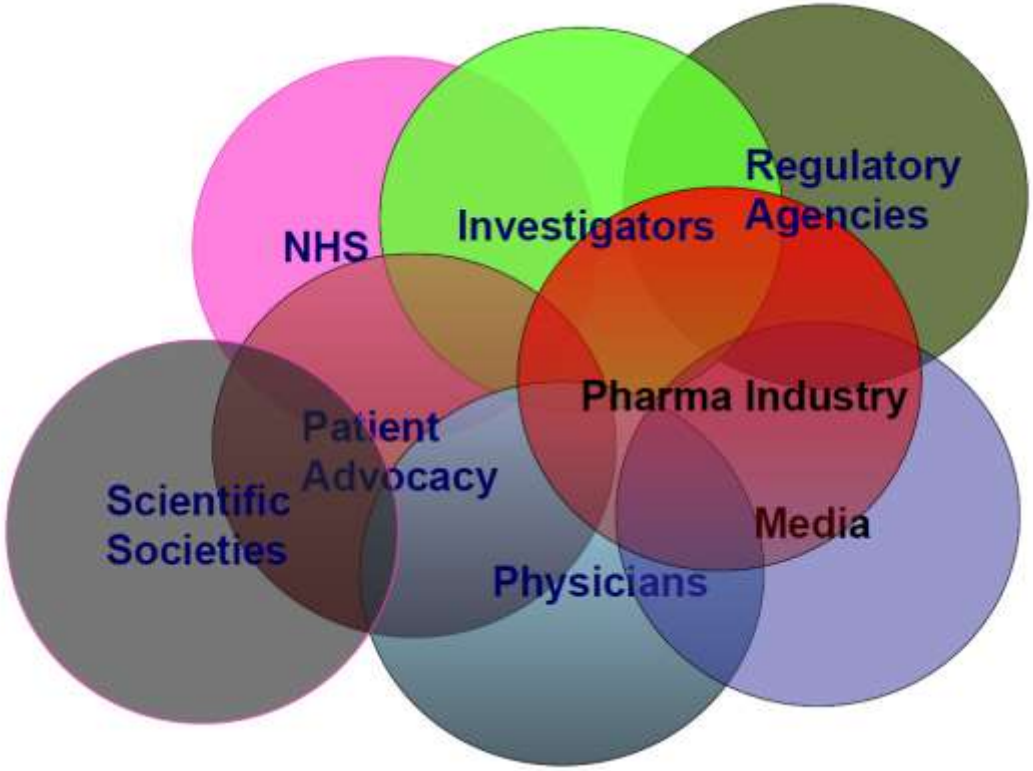


Oral Immuno Modulator	Oncolytic Virus	CAR T-cells	Bi Spe	Cancer Vaccines

Key challenges on that specific road

- ✓ Unite the cancer-care community
- ✓ Modify the regulatory environment

A new alliance against cancer



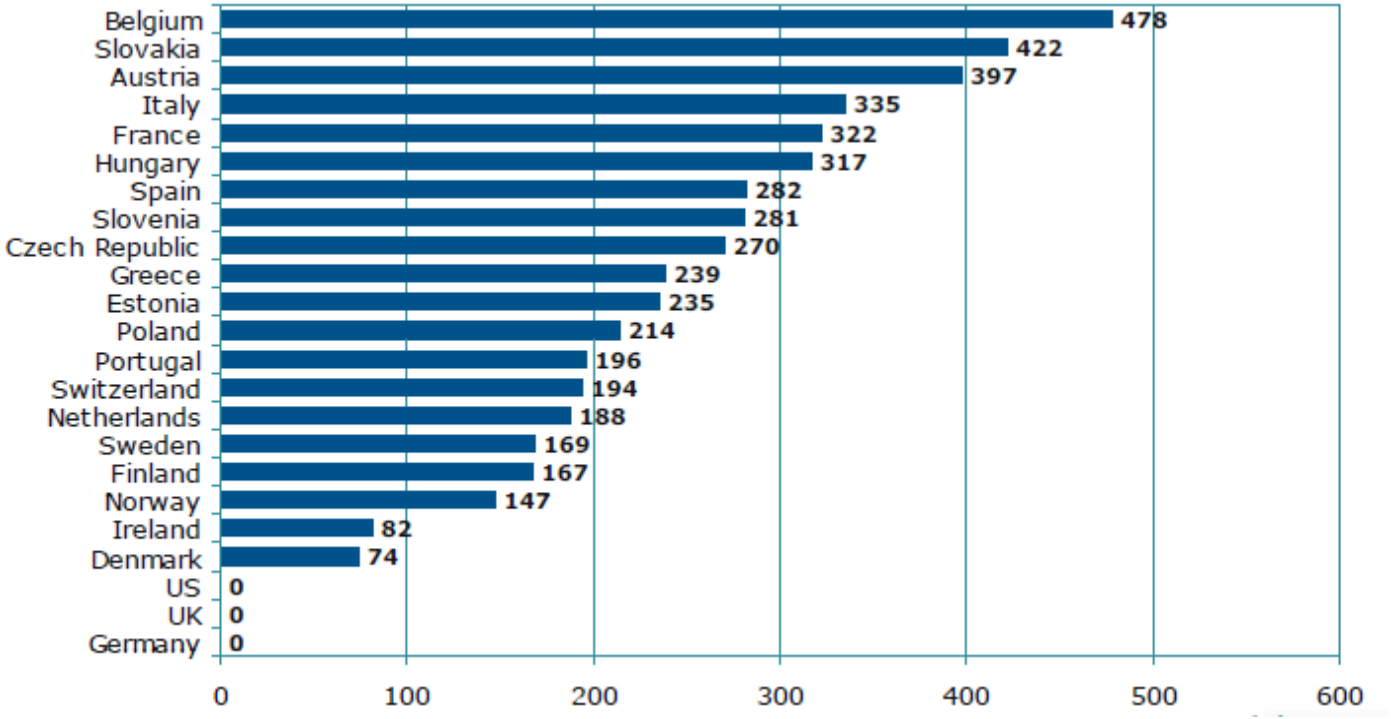
By Conte PF

Modify the regulatory environment

- ✓ Many lives are tragically ended not by cancer but by bureaucracy

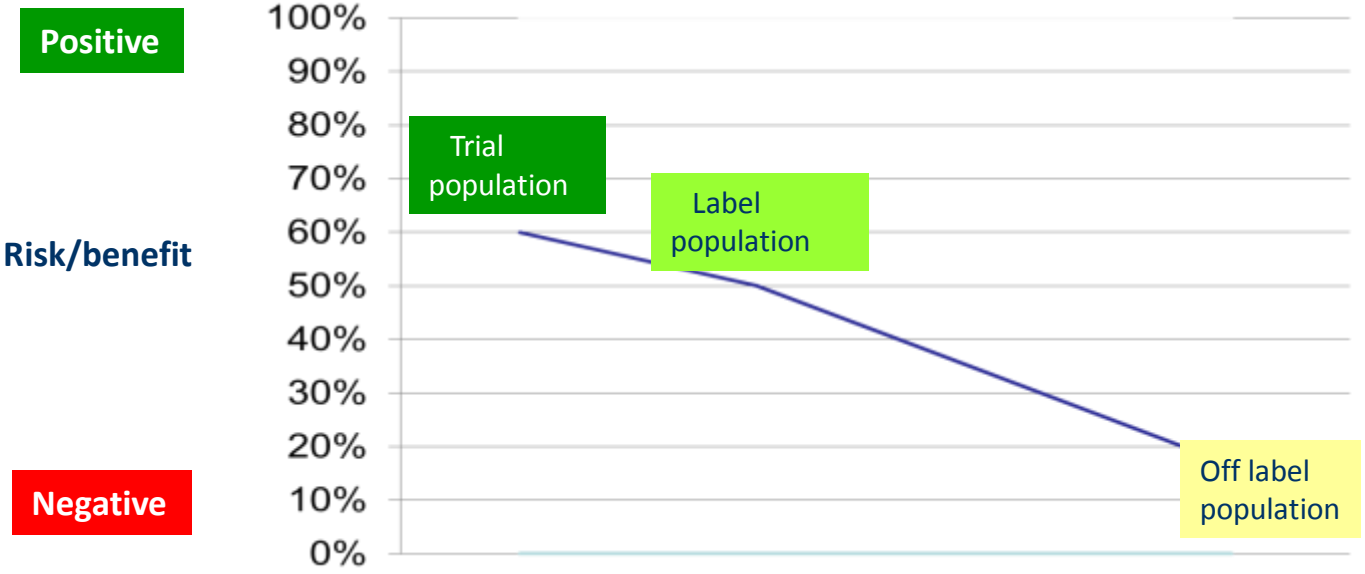
- ✓ To make new cancer drugs available to cancer patients before they are marketed should be a strong focus of the community
- ✓ We are not limited by science but by our ability to make good use of information and treatments we already have (De Vita)

Market access delay in EU (days)



Source Efpia 2007 (www.efpia.org)

The efficacy - effectiveness gap



Conclusion

- There will never be a world without cancer
  - It is in our biology
  - Every day millions of cells divide
  - That represents too many opportunities for harm or mistakes
- But we can probably transform even metastatic cancer into a chronic disease
- While … reinforcing prevention

A grate cure is just to avoid cancer altogether

Avoid the Toast-attitude

No smoking

Moderate drinking

Fight overweigth

Physical activity and healthy diet

Vaccinations,
sex protection

A path to cure is to understand early signs of disease

Detect a lump in the breast

New or persistent coughing

New or modifying naevi

Blood in the sputum or stools...

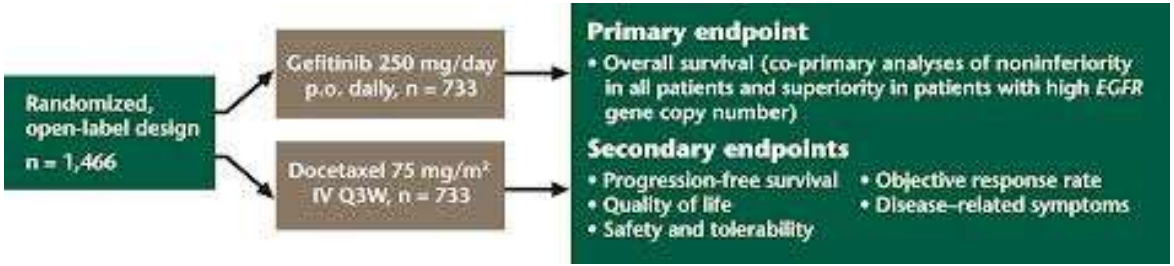
...Awarness can make a huge impact


Michele Maio
Giovanni Minoli
IL CANCRO HA GIÀ PERSO
La rivoluzione da Nobel dell'IMMUNOTERAPIA dei tumori
PIEMME

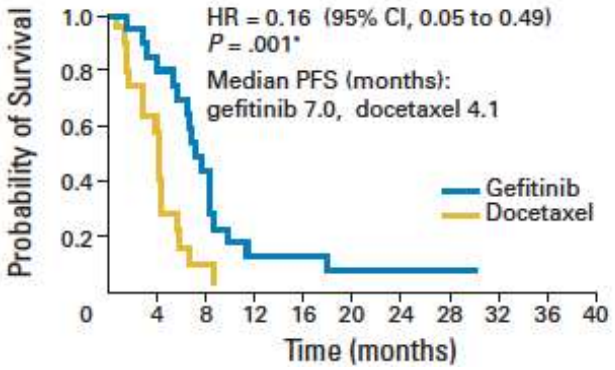
insieme contro il cancro

Grazie per l’attenzione

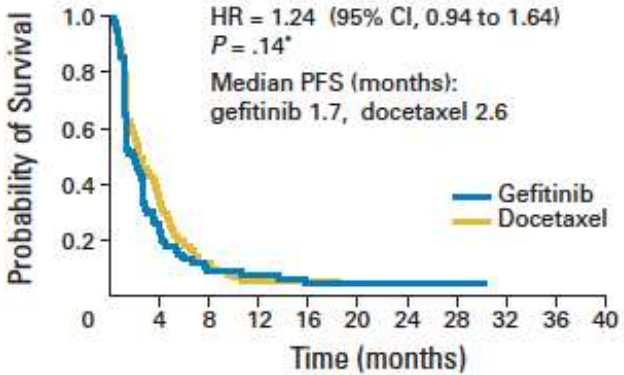
EGFR TKI benefit in EGFR mutated patients: data from a preplanned subgroup analysis



EGFR mut+

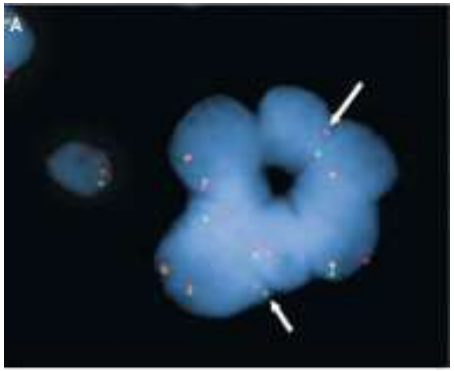


EGFR mut-



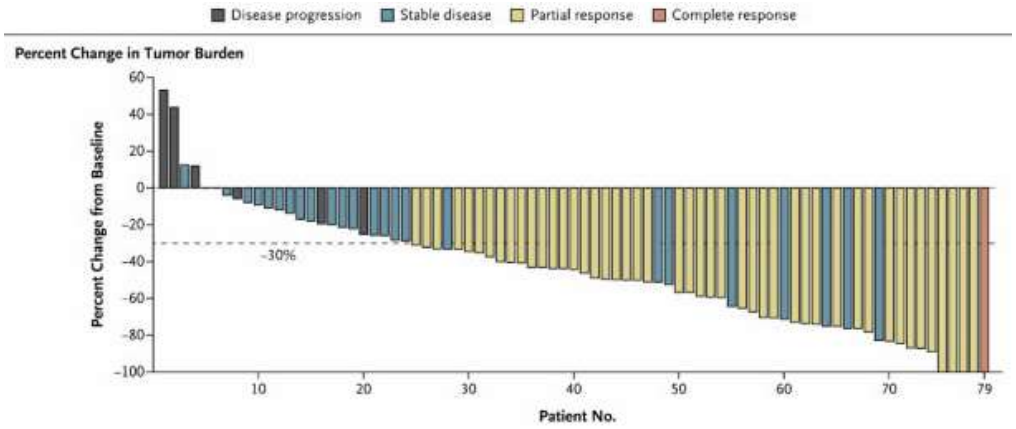
Douillard, JCO 2010

The lesson from EML4-ALK inhibitor Crizotinib



1. Screening for ALK rearrangement:
EML4-ALK positive NSCLC patients (5%)
Every treatment line

2. Treatment with EML4-ALK inhibitor
(Phase I-II study)



Kwak et al, NEJM 2010