ISTITUTO ONCOLOGICO VENETO

REGIONE DEL VENETO

Trattamenti in Oncologia: stato dell'arte

Ragusa, 29 aprile, 2016

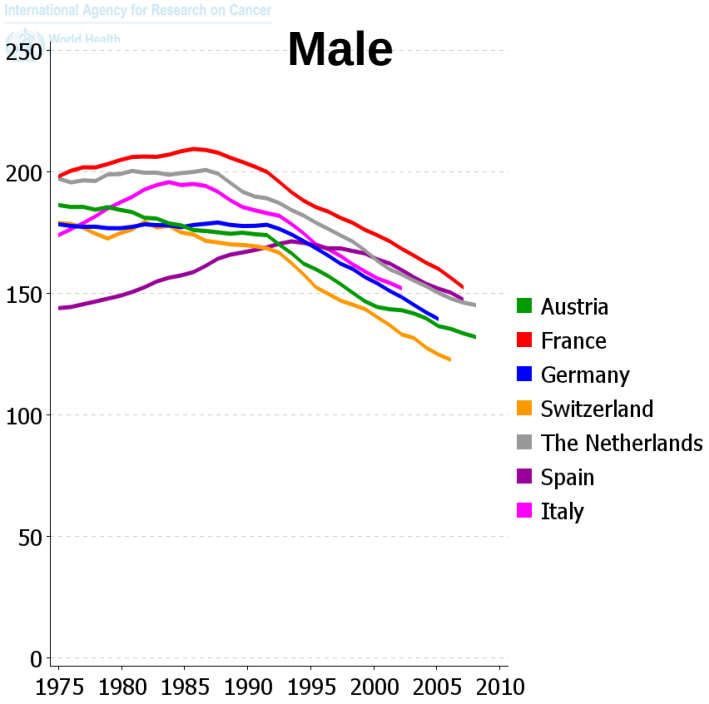
PierFranco Conte
Dipartimento di Chirurgia, Oncologia e Gastroenterologia
Università di Padova
Istituto Oncologico Veneto, Padova

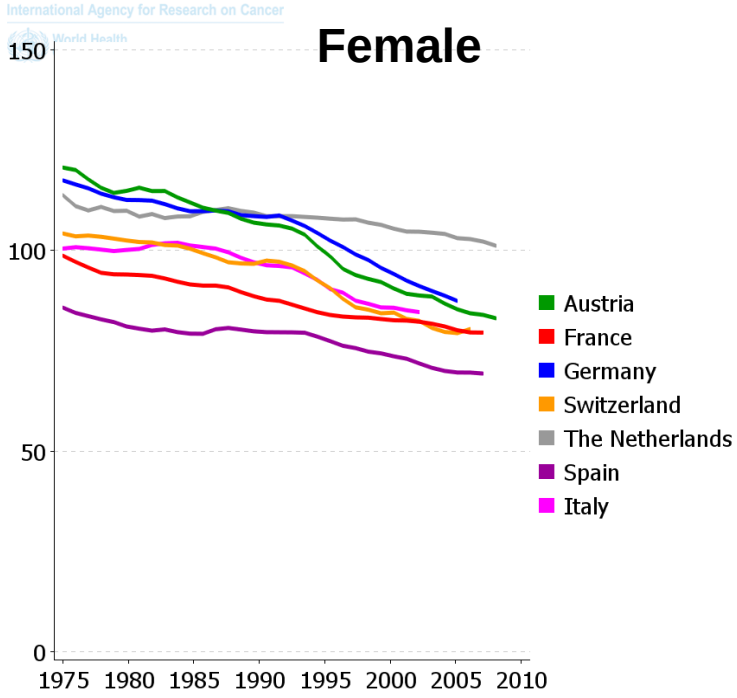
PierFranco Conte

Disclosure of potential conflicts of interests

- Consultant:
  Novartis, EliLilly, Astra Zeneca
- Honoraria:
  BMS, GSK, Roche, EliLilly, Novartis, AstraZeneca
- Research Funding from profit organizations:
  GSK, Novartis, Roche, EliLilly, BMS, Merck-Serono, Genomic Health
- Funding from non profit organizations:
  National Research Council, Ministry of Education and Research, , Italian Association for Cancer Research, Italian Drug Agency (AIFA), EmiliaRomagna Secretary of Health, Veneto Secretary of Health

Trends in mortality from cancer in Europe: age-standardised rate (W) per 100,000





www.who.int/gho

History of anti-cancer drug development

- **Serendipity (1943 – 1948)**
  (nitrogen mustard, alkylators, platinum salts)
- **Cytotoxicity (1948 – present)**
  (antimetabolites, antibiotics, alcaloids, marine products)
- **Cytostasis (1970 – present)**
  (hormones)
- **Immune-modulation (1970 – present)**
  (interferons, IL2, MoAb, vaccines, immune-checkpoint modulators)
- **Target-directed drugs (1990 - present)**
  (MoAb, TKI, STI)
- **Cell therapy**
- **Gene therapy**

Precision medicine: lung adenoca, driver mutations and targeted therapies

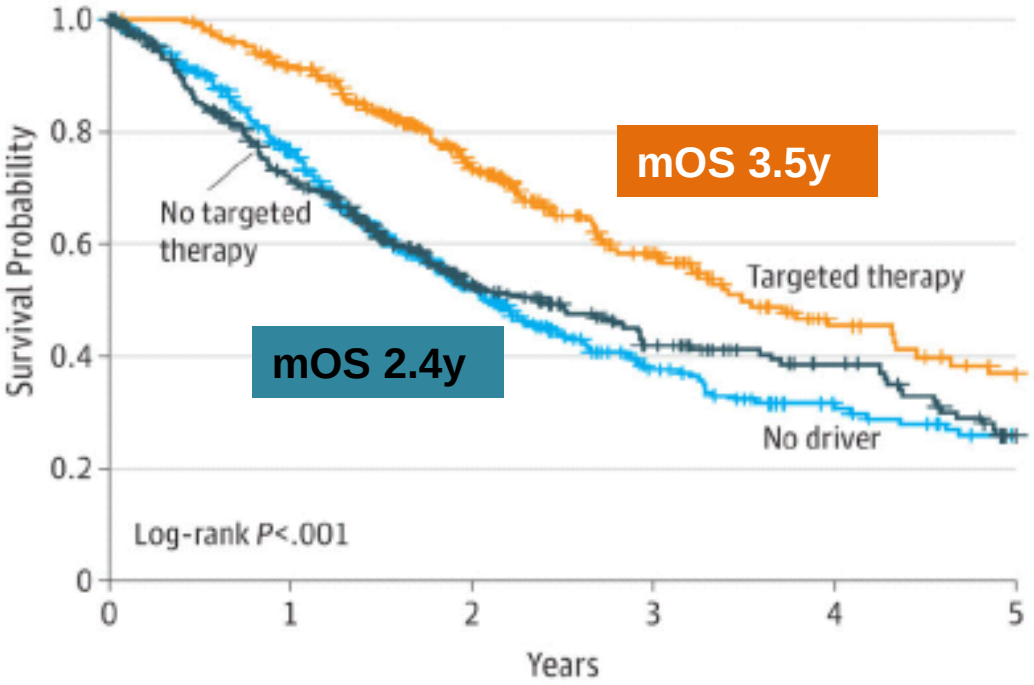
- 14 US sites from 2009-2012
- 10 oncogenic drivers
- 1007 patients with lung adenoca

OS in lung cancer patients:

oncogenic driver mutation and targeted therapy

oncogenic driver mutation without targeted therapy

without an oncogenic driver mutation



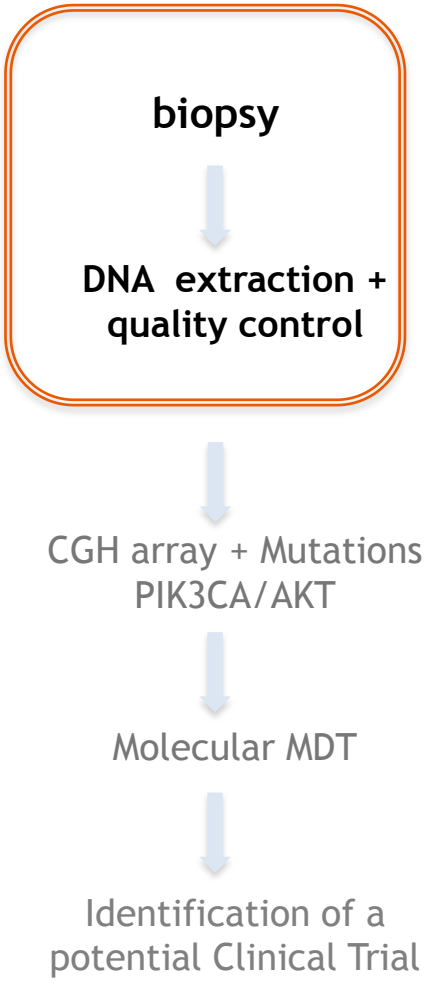
No. at risk						
Patients with oncogenic driver						
No targeted therapy	318	205	110	64	43	20
Targeted therapy	260	225	143	72	36	23
Patients with no driver	360	250	122	59	36	23

Kris MG, JAMA 2014

Reasons why targeted therapies MIGHT not be the «ULTIMATE WEAPON»

- Reproducibility & sensitivity of molecular tests
- Rare “drivers” mutations
- Secondary mutations (acquired? clonal selection?)
- Intra/inter-tumoral heterogeneity
- Redundancy (high mutational load)
- Segmentation of common cancers in rare diseases

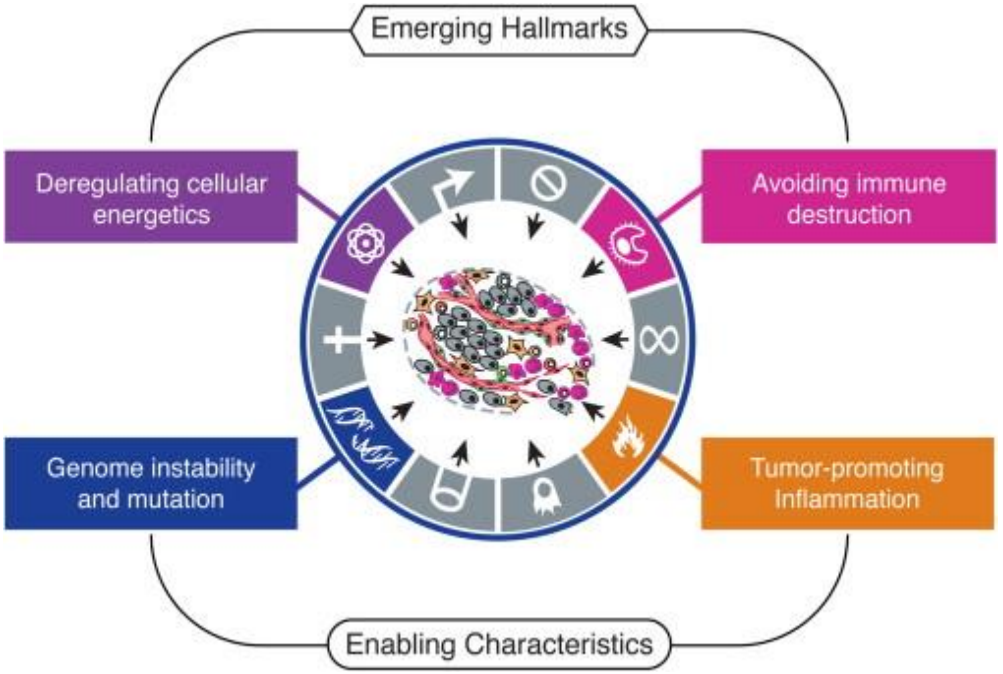
SAFIR project - Results



18 Investigational centers

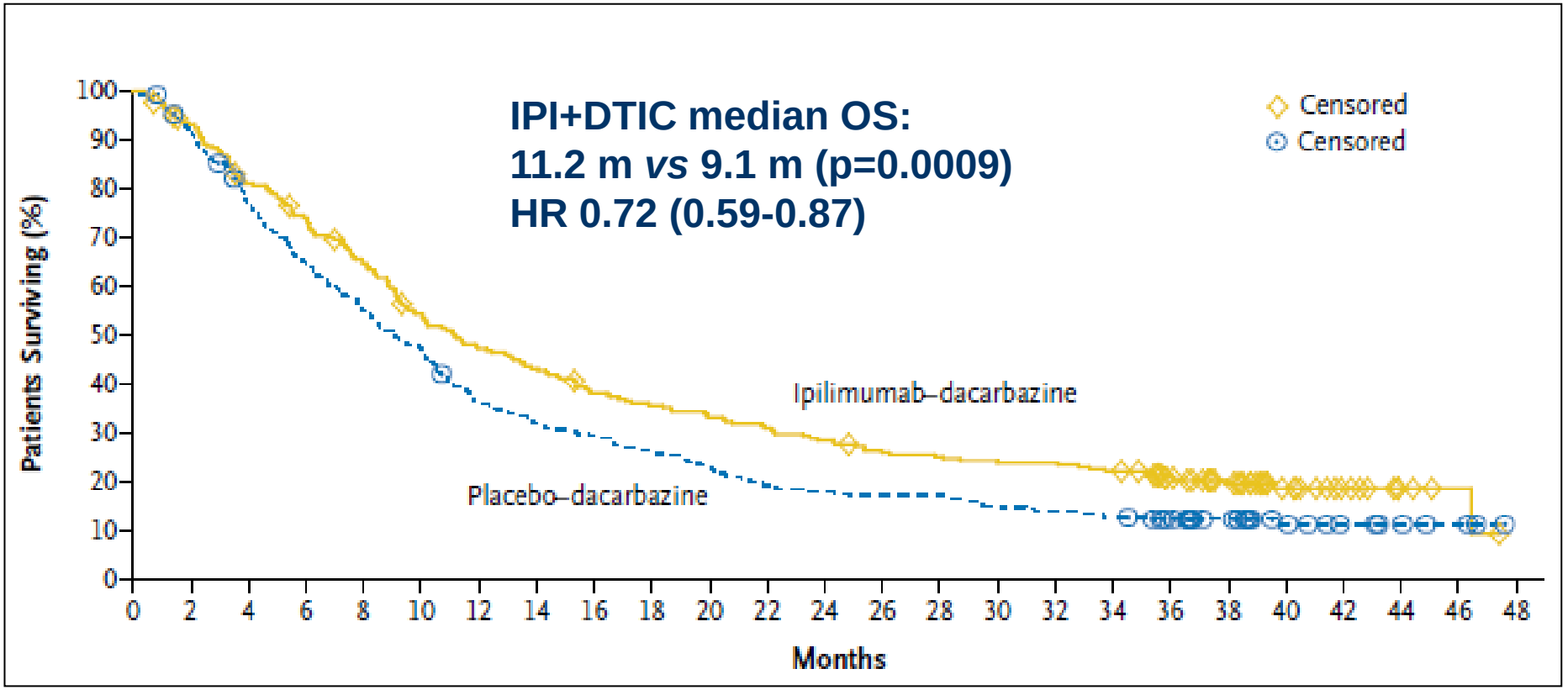
Results	n (%)
Patients screened	423
Patients biopsied	404 (95%)
CGH arrays	287 (68%)
Pts with targetable genomic alterations	194 (46%)
Patients treated	48 (11%)
Objective response	4 (1%)
SD>16 weeks	8 (2%)
OR + SD>16 weeks	12 (3%)

Antitumor immunity becomes a target



Hanahan D, Cell 2011, 144:646

IPILIMUMAB in metastatic melanoma



C Robert et Al, N Engl J Med, 2011

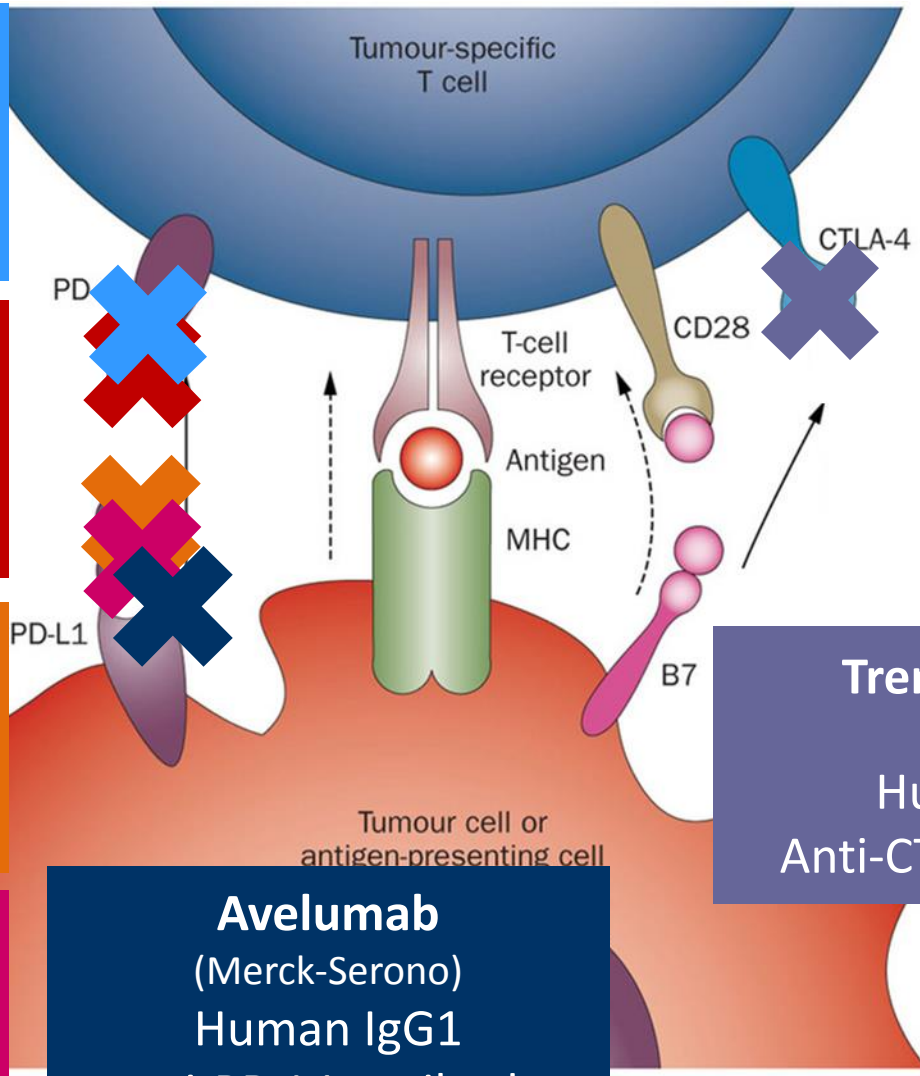
Immune checkpoint inhibitors under clinical development

Nivolumab
(BMS)
Human IgG4
anti-PD-1 antibody

Pembrolizumab
(Merck)
Humanized IgG4
anti-PD-1 antibody

Atezolizumab
(Genentech)
engineered human IgG1
anti-PD-L1 antibody

Durvalumab
(AZ)
Human IgG1
anti-PD-L1 antibody



Tremelimumab
(AZ)
Human IgG2
Anti-CTLA-4 antibody

Avelumab
(Merck-Serono)
Human IgG1
anti-PD-L1 antibody

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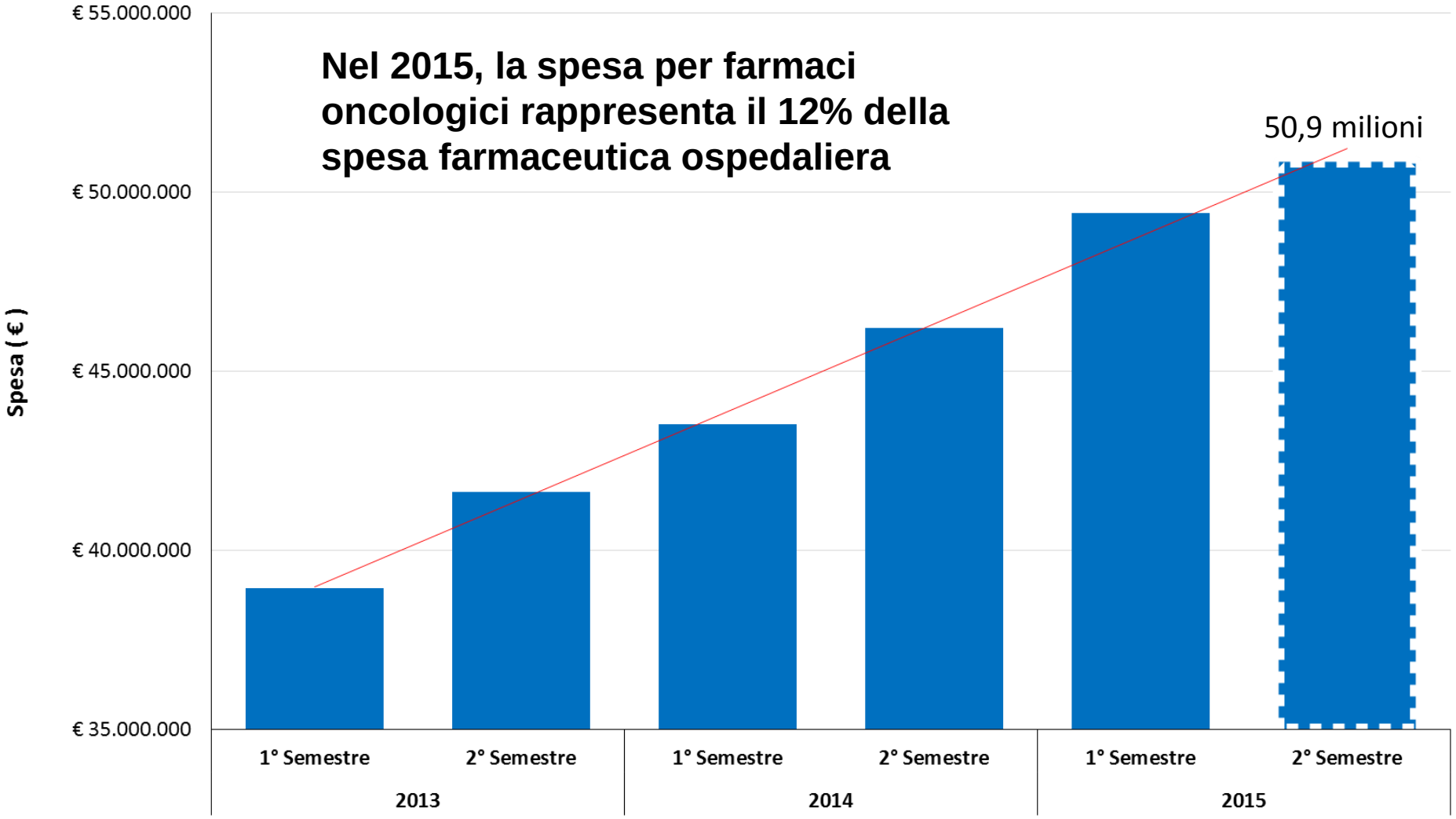
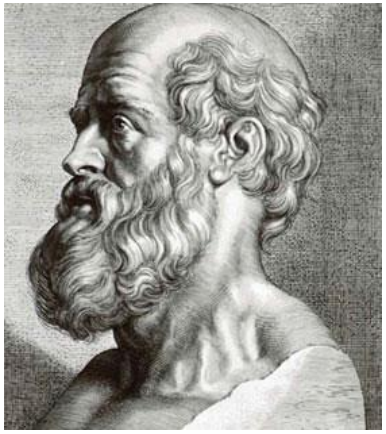
Some good reasons to change a winning strategy

- Health business & affordability
- Bias in biomedical research
- Uncertainty in medicine
- Health Systems

Andamento semestrale spesa oncologici 2013-2015



Fonte dati: **DWH Regione Veneto**



Hippocratic oath:

treat the sick to the best of one's ability, preserve patient privacy, teach the secrets of medicine to the next generation

Dear Prof. Pier Franco Conte,

From yr 2000, more than 1.5 million women have been treated with Trastuzumab (data from Roche-Genentech).
This represent 25-30% of the patients with HER2+ breast cancers (WHO).

great trial, which will bring good news for many families in financial difficulty, like mine. It is troubling my family that whether my mother choose the 3 months or

Approx 50% of HER2+ stage I to III EBC diagnosed in year 2010-2011 and covered by Medicare, DID NOT RECEIVE trastuzumab.
Comorbidity, poverty and black race were associated with lower trastuzumab administration (Reeder-Hayes, JCO 2016).

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Industry Sponsorship and Research Outcome

A Cochrane Review

- 48 studies for different diseases
- Industry-sponsored vs Non Industry-sponsored trials

«This Cochrane Review provides convincing and consistent evidence for the existence of an **Industry Bias** in drug studies»

- **In case of studies comparing 2 drugs sponsored by different companies, the drug with a more favourable risk/benefit was more often the drug manufactured by the sponsor of the study**

JAMA 2013

Bias in biomedical research

	Trial A	Trial B
Study design	Two Arms	Three Arms
Double Blinded	yes	yes
Primary End Point	PFS	PFS
Independent Review	yes	yes
Sample Size	808	1095
Patients receiving SoC before study entry	10.9 %	31.3 %

Publication Bias

Trial A has been published 2 times on NEJM (the first time on the same day of Oral presentation at SABCS 2011)

Trial B immediately rejected by NEJM; under major revision from JCO (10 months after Oral presentation at ASCO 2015)

	CLEOPATRA		MARIANNE		
	TH # 406	THP # 402	TH # 365	T-DM1 # 367	T-DM1+P # 363
ORR %	69.3	80.2	67.9	59.7	64.2
Median PFS	12.4	18.5	13.7	14.1	15.2
Median OS	40.8	56.5	NR	NR	NR

Baselga J et al. NEJM 2012; Swain S et al NEJM 2015; Ellis ASCO 2015

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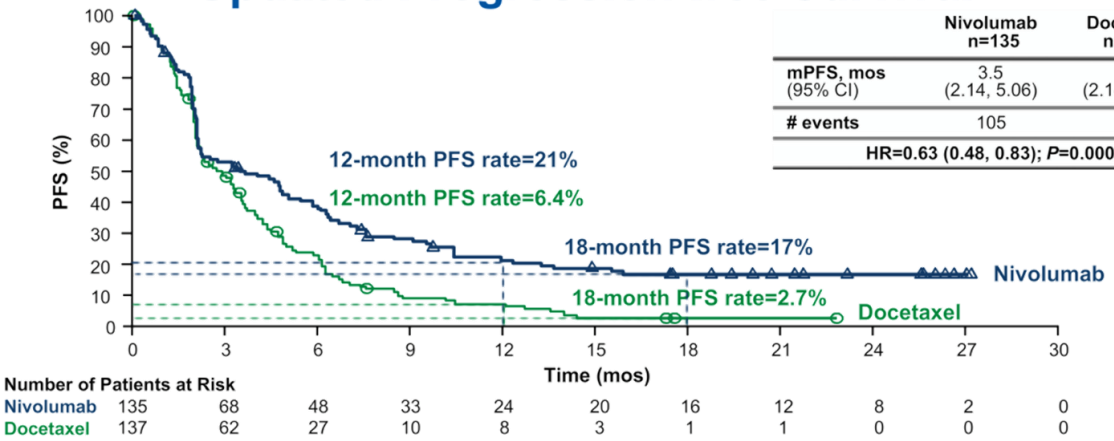
CheckMate 017 phase III trial – SQCC (all comers)

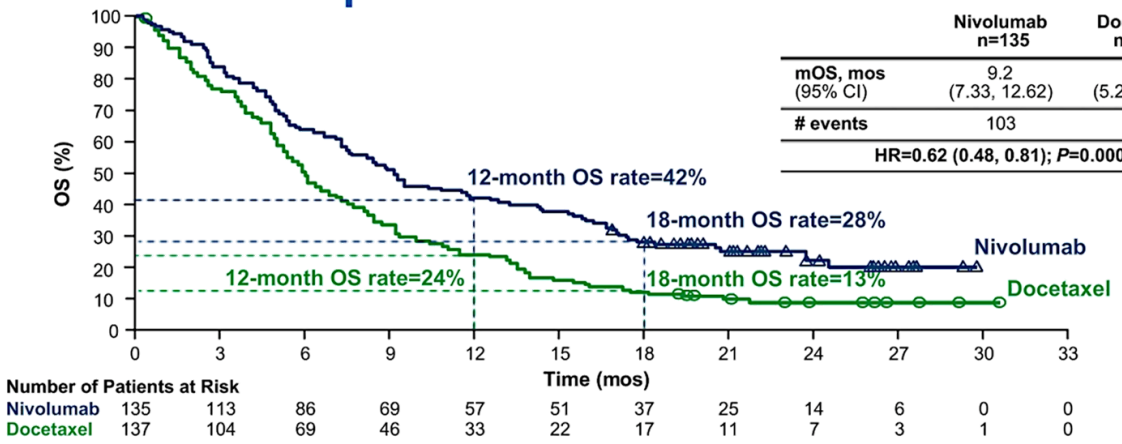
Updated Progression-free Survival



	Nivolumab n=135	Docetaxel n=137
mPFS, mos (95% CI)	3.5 (2.14, 5.06)	2.8 (2.14, 3.52)
# events	105	122
HR=0.63 (0.48, 0.83); *P*=0.0008		

Minimum follow-up for survival: 18 months

Updated Overall Survival



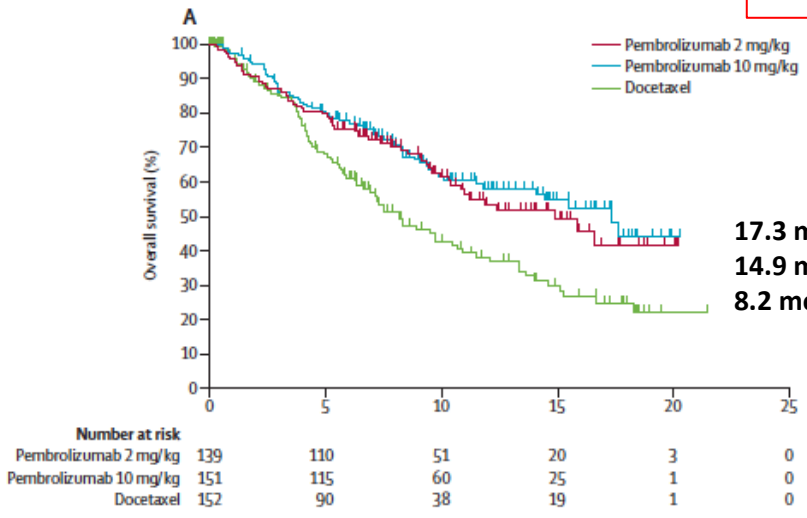
	Nivolumab n=135	Docetaxel n=137
mOS, mos (95% CI)	9.2 (7.33, 12.62)	6.0 (5.29, 7.39)
# events	103	122
HR=0.62 (0.48, 0.81); *P*=0.0004		

Minimum follow-up for survival: 18 months

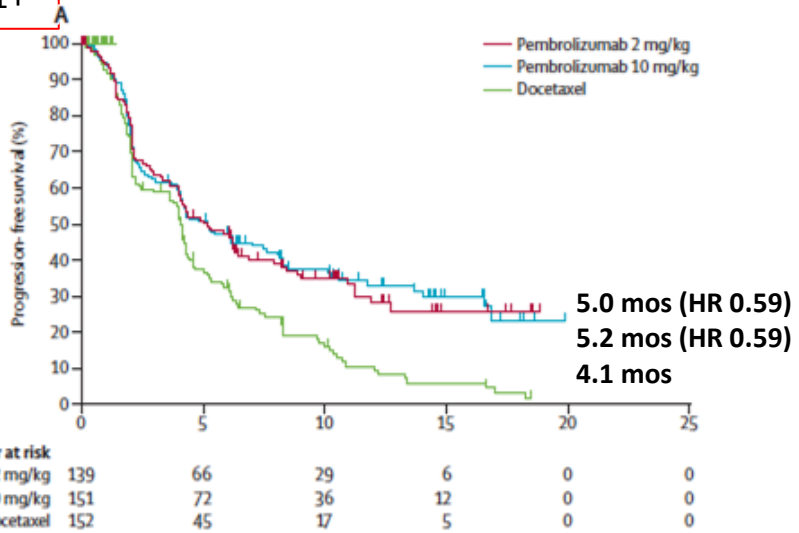
Reckamp K, 16th WCLC

KEYNOTE 010 phase II/III trial - NSCLC

PD-L1+≥50%
43% pf PD-L1+

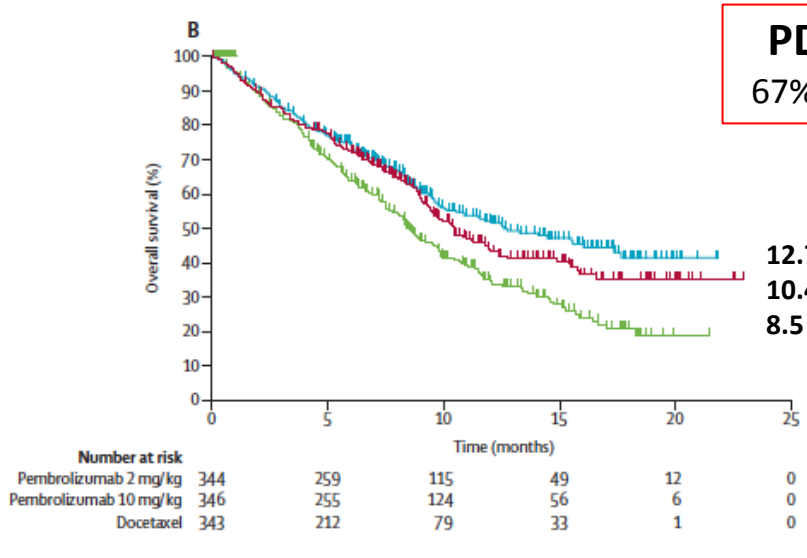


17.3 mos (HR 0.50)
14.9 mos (HR 0.54)
8.2 mos

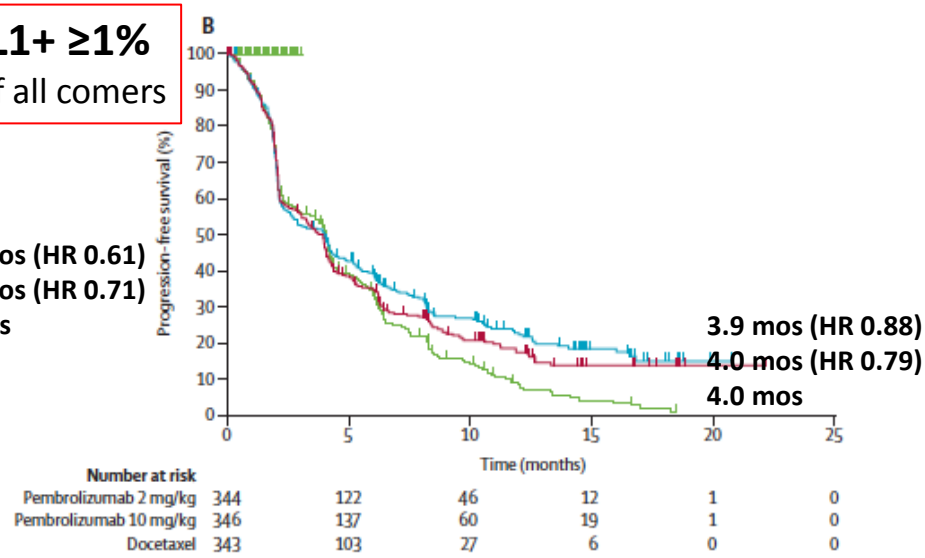


5.0 mos (HR 0.59)
5.2 mos (HR 0.59)
4.1 mos

PD-L1+ ≥1%
67% of all comers



12.7 mos (HR 0.61)
10.4 mos (HR 0.71)
8.5 mos



3.9 mos (HR 0.88)
4.0 mos (HR 0.79)
4.0 mos

Herbst RS, Lancet Oncol 2015

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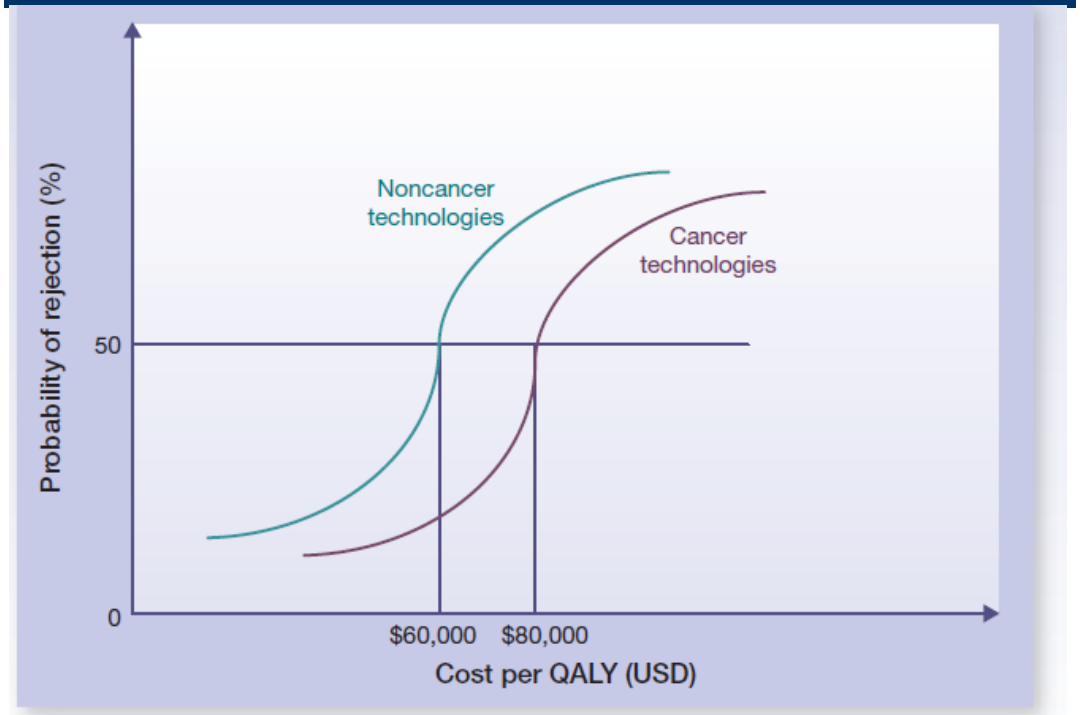
NICE Statement

"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



© 2012 American Association for Cancer Research

B Jonsson, CCR 2013

How can we boost patients' trust ?

- Independent (no profit) research
- Conflict of Interest Declaration

Ricerca “trasparente”

- Ricerca sponsorizzata:
  - sviluppo di nuovi farmaci o presidi diagnostici
  - grandi interessi economici
  - misure di salvaguardia dei pazienti e della società

  (anagrafi pubbliche delle ricerche, proprietà intellettuale dei dati, CE, conflitti di interesse)

- Ricerca indipendente:
  - risponde a domande di interesse dei SSN
  - appropriatezza più che innovazione

Swimming against the stream can be dangerous

Who actually pays for «independent» research?

How can we boost patients' trust ?

- Independent (no profit) research
- Conflict of Interest Declaration

Guidelines International Network: Principles for Disclosure of Interests and Management of Conflicts in Guidelines

Holger J. Schünemann, MD, PhD, MSc; Lubna A. Al-Ansary, MBBS, MSc; Frode Forland, MD, DPH; Sonja Kersten, MSc; Jorma Komulainen, MD, PhD; Ina B. Kopp, MD; Fergus Macbeth, MA, DM; Susan M. Phillips, BSc (Hons), DPhil; Craig Robbins, MD, MPH; Philip van der Wees, PT, PhD; and Amir Qaseem, MD, PhD, MHA, for the Board of Trustees of the Guidelines International Network*

WHAT DOES THE G-I-N RECOMMEND?

G-I-N PRINCIPLES

Principle 1: Guideline developers should make all possible efforts to not include members with direct financial or relevant indirect COIs.

Although the G-I-N recognizes the need for exceptions when this is not practical, such issues should not diminish the importance of this principle. In situations in which panel members have COIs, conflicted members should represent a minority on a guideline panel and the guideline developer should be transparent about the reasons for including conflicted members and the management of COIs.

What Does the G-I-N Recommend?
G-I-N Principles

Principle 8: No member of the guideline development group deciding about the direction or strength of a recommendation should have a direct financial COI.

“ probabilmente lo sviluppo scientifico più importante del XX secolo è che l’ interesse economico ha rimpiazzato la curiosità come forza trainante della ricerca”

Karis Mullis

Nobel Laureate in Chemistry, 1993