Appropriatezza Prescrittiva in Oncologia

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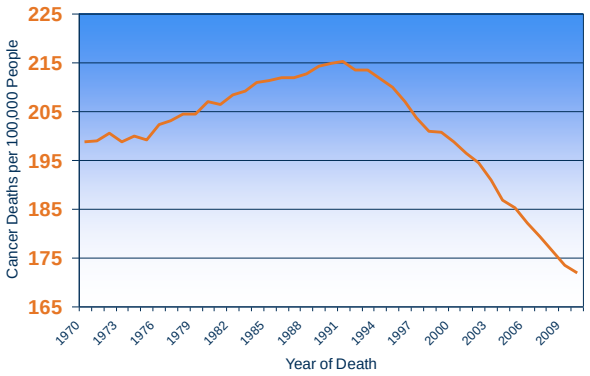
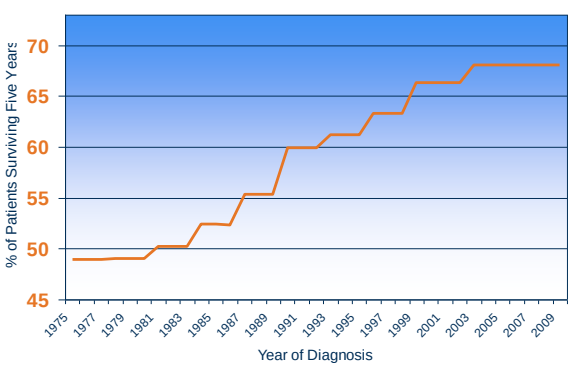
The Expanding Financial Burden of Cancer

Mortality*



Five-Year Survival*



		United States	United Kingdom	Canada	Italy	France	OECD average for 34 countries
Cancer statistics†	Cancer incidence rates per 100 000 (2008)	300.2	269.4	296.6	274.3	300.4	260.9
	Colorectal cancer, 5-year relative survival rate (2004–2009 or available years)	64.5	53.3	63.4		57.0	59.9‡
	Cancer mortality rates per 100 000 (2009 or nearest year)						
	Females	130	141	143	117	111	124
	Males	185	199	205	212	221	208
Health services utilization (2010 or nearest year)	Average length of hospital stay in days	4.9	7.7	7.7	6.7	5.7	7.1
	Average annual number of physician visits per capita	3.9	5.0	5.5	—	6.9	6.4
	Cervical cancer screening in women aged 20–69, %	85.9§	78.7§	75.3§	39.0‖	72.4§	61.1¶
	MRI exams per 1000 persons	97.7	40.8	46.7	—	60.2	46.3
	CT exams per 1000 persons	265	76.4	126.9		145.4	123.8
Overall health-care spending# (2010 or nearest year)	Health-care spending per capita	$8233	$3433	$4445	$2964	$3974	$3265
	Out-of-pocket health-care spending per capita	$970	$306	$631	$528	$290	$558
	% public expenditure on health	48.2%	83.2%	71.1%	79.6%	77.0%	72.2%

Yabroff KR, et al. J Natl Cancer Inst Monogr 2013 ****Source: National Cancer Institute***

Cancer is a **leading cause of morbidity and mortality** worldwide.

Cancer also accounts for a **substantial proportion of health-care expenditure**s as well as productivity losses due to morbidity and premature death

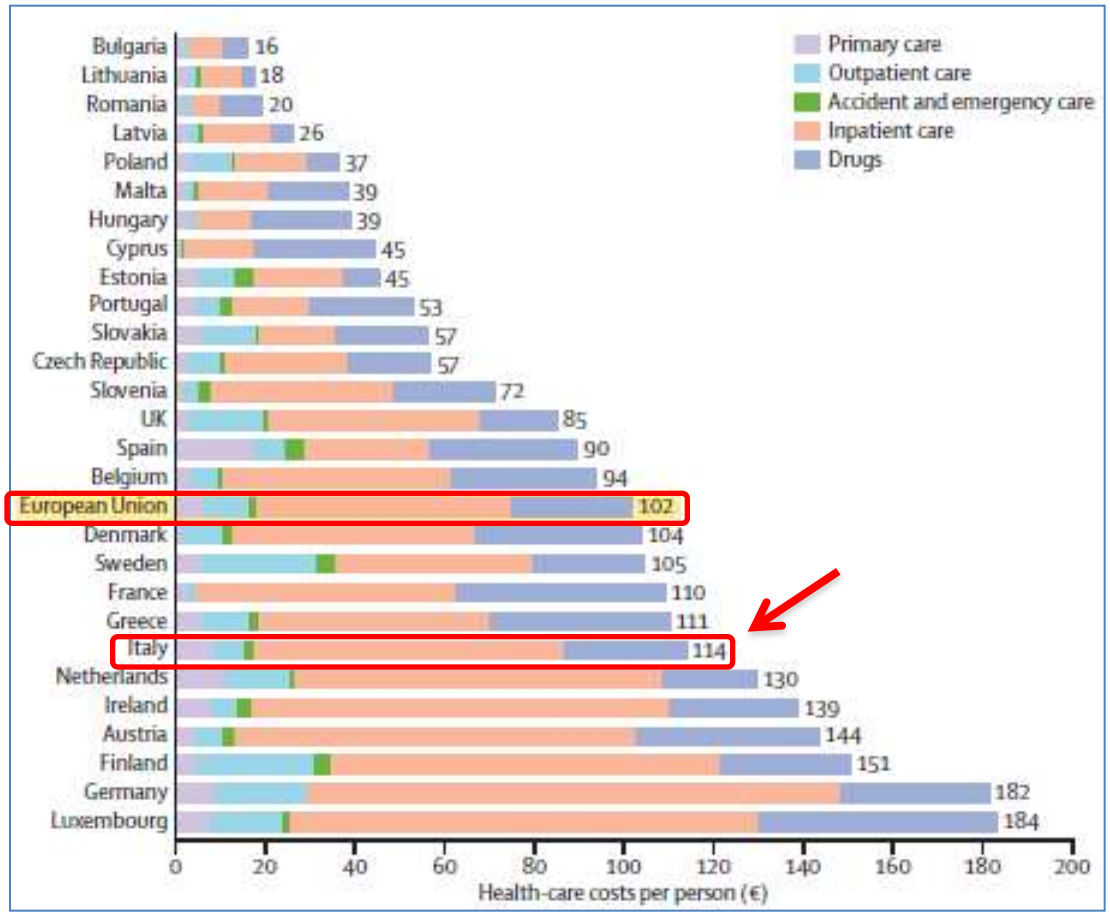
Because incidence increases with age for most cancer sites, and **populations are aging** in most developed countries, **prevalence is expected to increase** appreciably in the future.

Additionally, ongoing improvements in early detection and use of effective treatments are associated with **improved survival** following diagnosis, also increasing cancer prevalence.

As a result of these trends, **related medical expenditures and costs** associated with morbidity and premature mortality **are expected to be even larger in the future.**

Moreover, health-care delivery trends, in particular the **increasing use of expensive new chemotherapy drugs** are projected to be associated with increased costs of cancer care in the future.

Economic burden of cancer across the EU



Luengo-Fernandez R, et al. Lancet Oncol 2013

Cancer cost the EU €126 billion in 2009, with health care accounting for €51.0 billion (40%).

Across the EU, the health-care costs of cancer were equivalent to **€102 per citizen**, but varied substantially between countries.

Productivity losses because of early death cost €42.6 billion and lost working days €9.43 billion.

Lung cancer had the highest economic cost (€18.8 billion, 15% of overall cancer costs), **followed by breast cancer** (€15.0 billion, 12%), **colorectal cancer** (€13.1 billion, 10%), **and prostate cancer** (€8.43 billion, 7%).

Fighting Disparities in Cancer Health Care in Europe: The European Cancer Patient's Bill of Rights

- ✓ A group of European oncology leaders have formed a partnership with cancer patients and their representatives: the **European Cancer Concord (ECC), a unique patient-centered partnership** that will act as a catalyst to achieve improved access to an optimal standard of cancer care and research for European citizens

- ✓ **The ECC has created a European Cancer Patient's Bill of Rights**, a charter **to challenge the current inequalities that cancer patients in Europe experienc**e on a daily basis

- ✓ This bill of rights **defines fundamental pan-European quality standards for provision of information, access and delivery of cancer care and research to European citizens**

- ✓ **On 4th February, 2014 the ECC** launched the European Cancer Patient's Bill of Rights to coincide with World Cancer Day, in the European Parliament in Strasbourg:

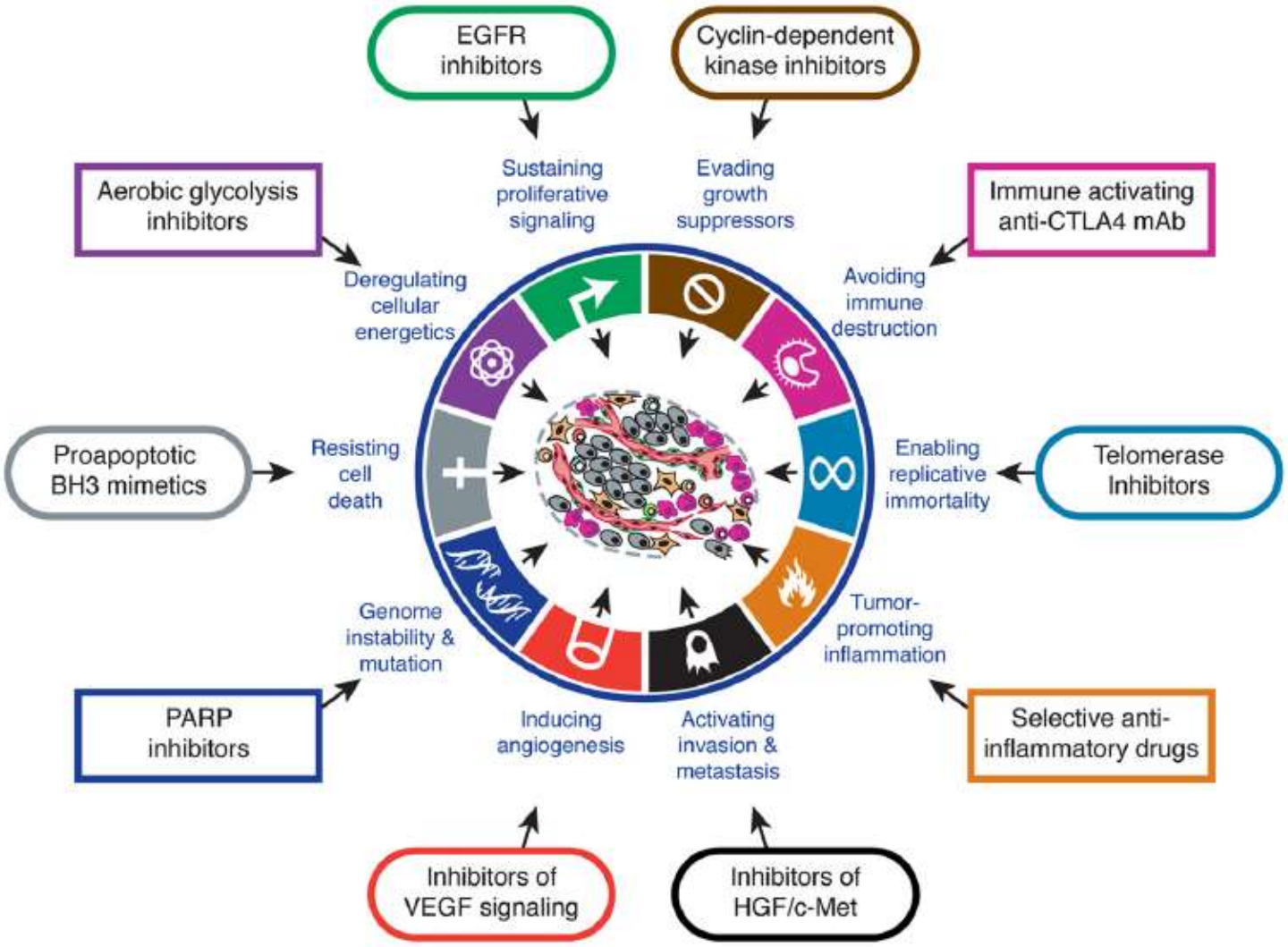
    - ✓ **Article 1**: *The right of every European citizen to receive the most accurate information and to be proactively involved in his/her care*

    - ✓ **Article 2**: *The right of every European citizen to optimal and timely access to appropriate specialised care, underpinned by research and innovation*

    - ✓ **Article 3:** *The right of every European citizen to receive care in health systems that ensure improved outcomes, patient rehabilitation, best quality of life and affordable healthcare*

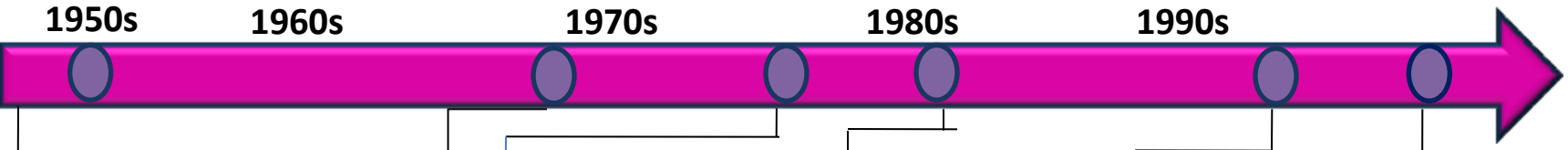
Lawler M, et al. Oncologist 2014

TARGETED THERAPIES & PERSONALIZED MEDICINE



Hanahan D & Weinberg RA. Cell 2011

PROGRESS IN BREAST CANCER RESEARCH



1950-1960s

Radical Mastectomy was the standard surgical approach to breast cancer: the concept of adjuvant therapy was newly formed and controversial

1970s

The first adjuvant trials of targeted therapy were initiated

Late 1970s

Combination chemotherapy as adjuvant treatment became the standard of care and opened the door to numerous treatments for node-negative disease and to more effective chemotherapy combinations

1980s

Randomized trials demonstrate breast-conserving surgery with whole-breast irradiation provides survival equivalent to mastectomy

1980s

The landmark NSABP B404 trial found little effect on survival when locoregional therapies were varied

1994-1995

Identification of BRCA1/2 mutations in families with high incidence of breast/ovarian cancers

1998

National Surgical Adjuvant Proiect (NSABP) P1 trial made breast cancer prevention a clinical reality

2001s

Trastuzumab plus chemotherapy was found to prolong overall survival in patients with HER"-overexpressing metastatic breast cancer

2001

Breast Cancer was identified to be a group of genetically distinct molecular subtypes vs a single disease

2005

Oxford Overview Analysis compiled individual patient-level data from multiple trials, enhancing researchers' ability to identify small but clinically significant improvements in the outcomes of both local and systemic therapy

Mid-2000s

Randomized trials demonstrate safety and good cosmetic outcome with hypofractionation of radiation therapy (RT), decreasing the burden of treatment for many patients with breast cancer

2010

Aromatase inhibitors were found to offer an incremental improvement in disease-free-survival and an improvement toxicity profile for postmenopausal women requiring endocrine therapy

2011

Axillary dissection no longer necessary for all women with nodal metastases

2012

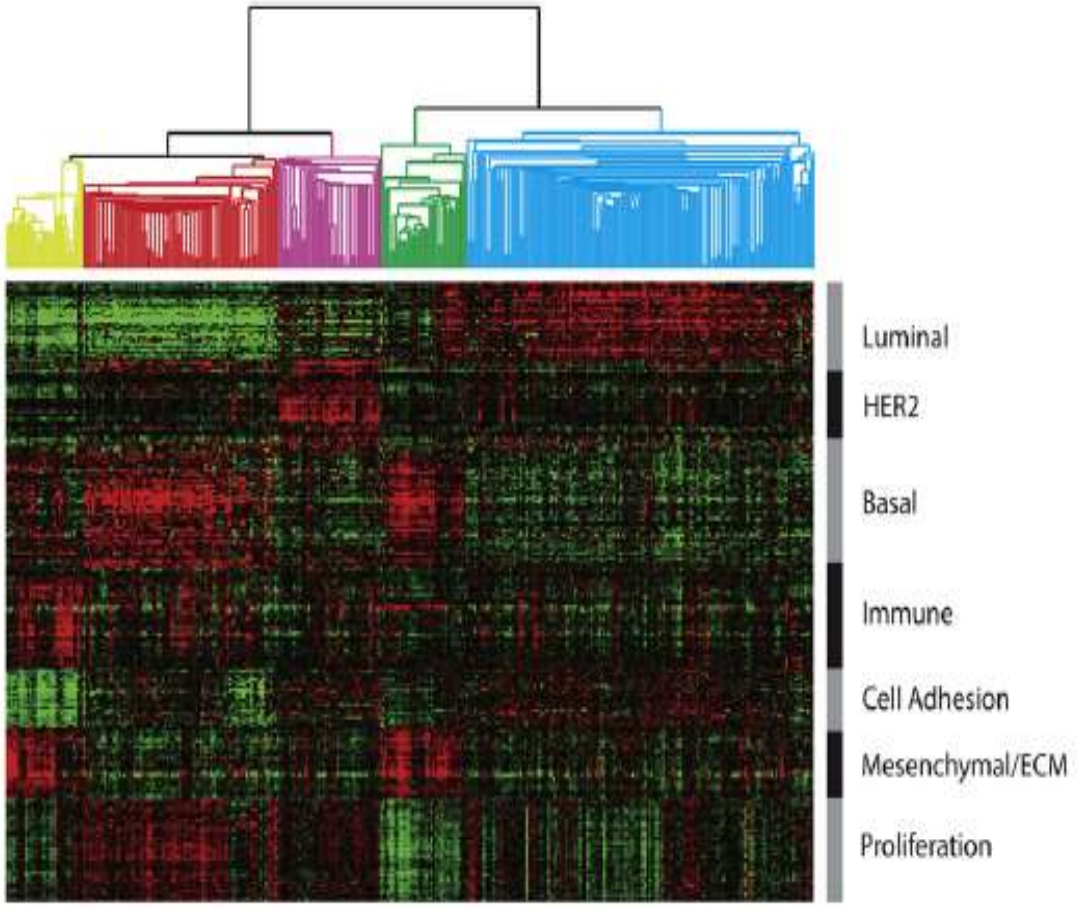
The addition of taxanes to adjuvant therapy was found to lead to a further decrease in recurrence and breast cancer mortality

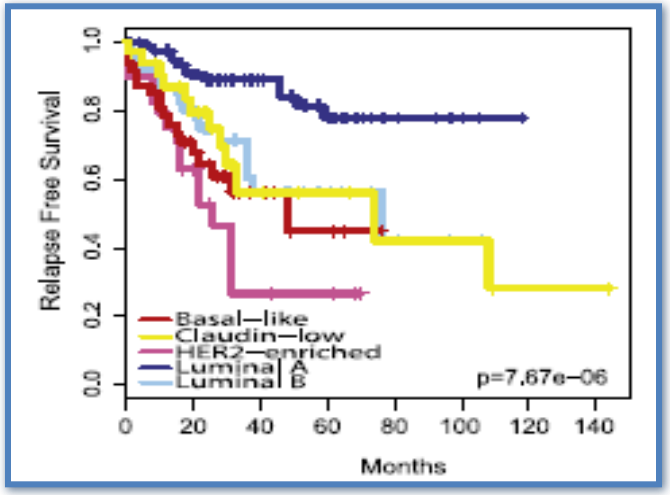
2013

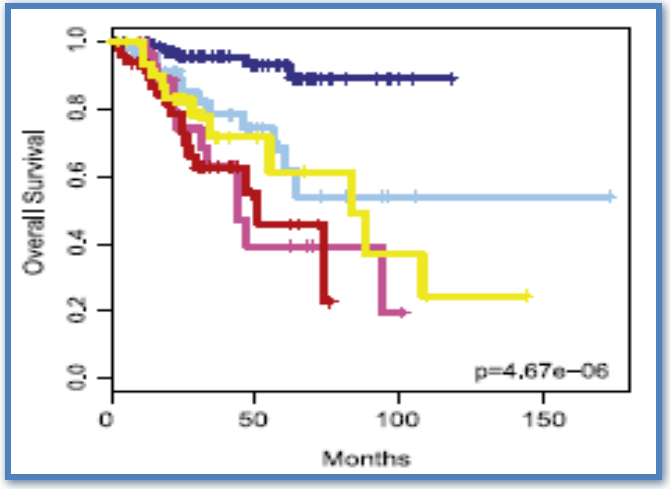
Pertuzumab is the first agent approved by U.S. Food an Drug Administration for use in the neoadjuvant setting based on the large improvement in pathologic complete response seen in the neoadjuvant trials

Burstein HJ. ASCO 2014

BREAST CANCER MOLECULAR SUBTYPES: OUTCOME & THERAPEUTIC IMPLICATIONS

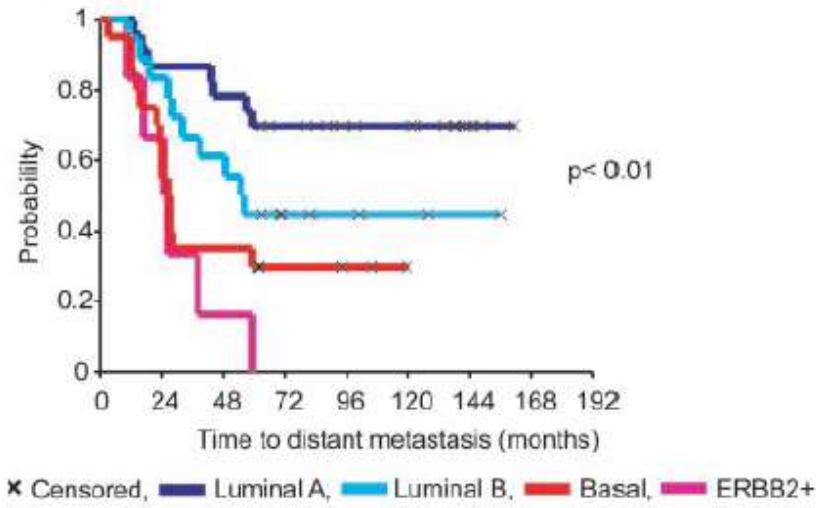


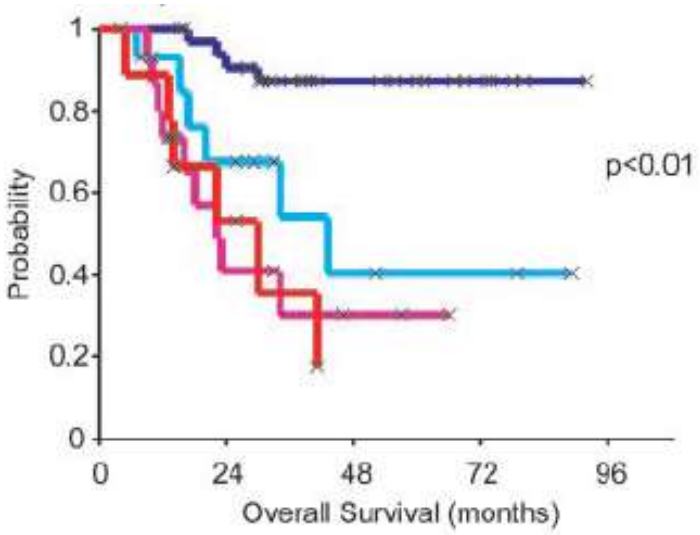


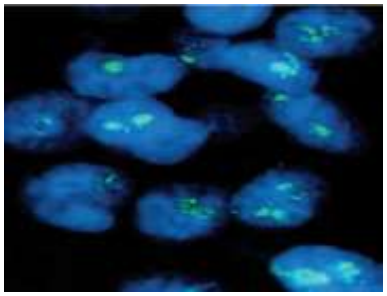


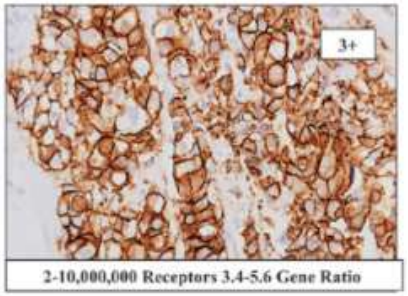
Prat A & Perou CM, Mol Oncol 2011

HER2 POSITIVE BREAST CANCER







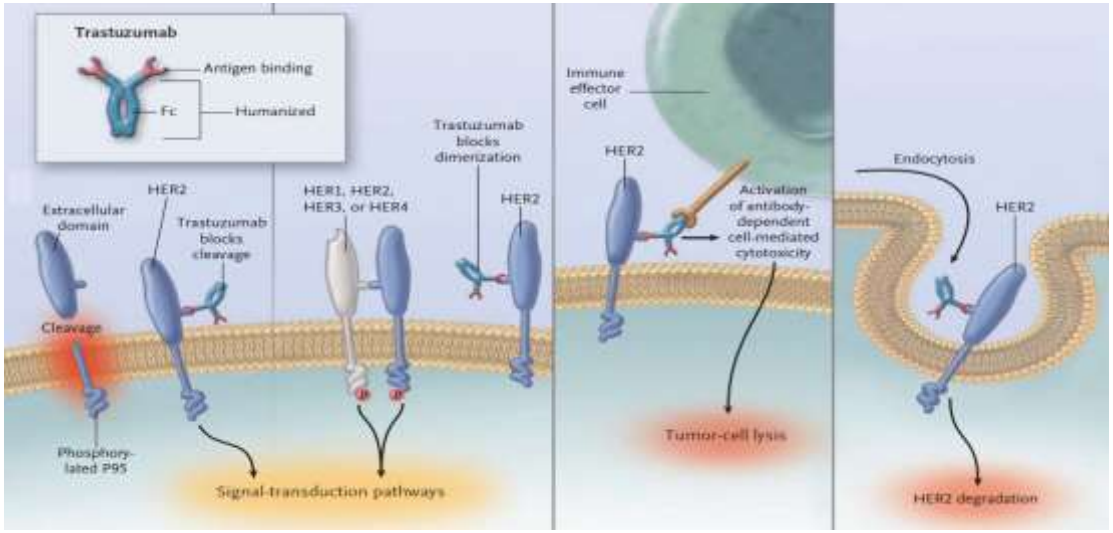


Amplification of the *HER2* gene and/ or overexpression at the messenger RNA or protein level **occurs in about 20% of patients** with early stage breast cancer

Before the advent of HER2-directed therapies, **this increased level of HER2 was associated with high recurrence rates and increased mortality** in patients with node-positive and node-negative disease

Sørlie T, et al. Proc Natl Acad Sci USA 2003

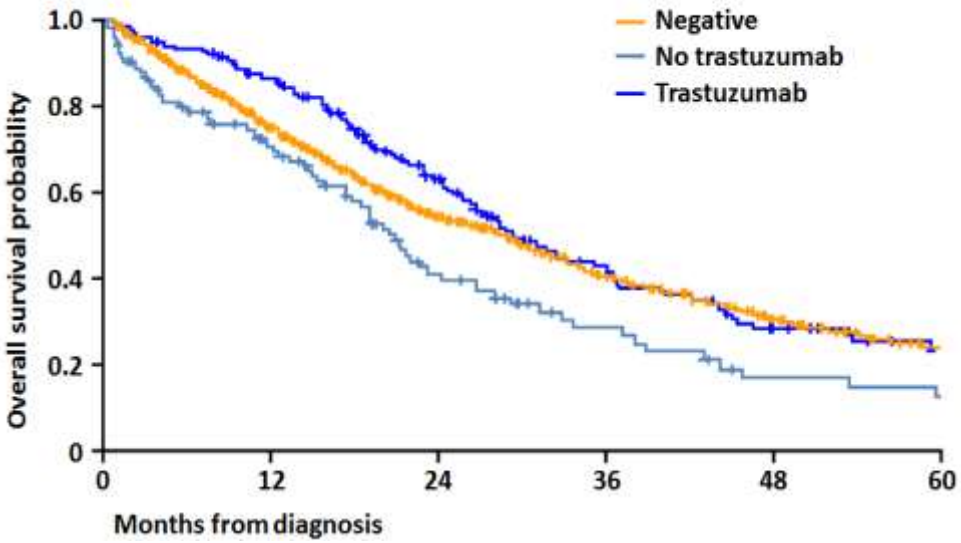
TRASTUZUMAB



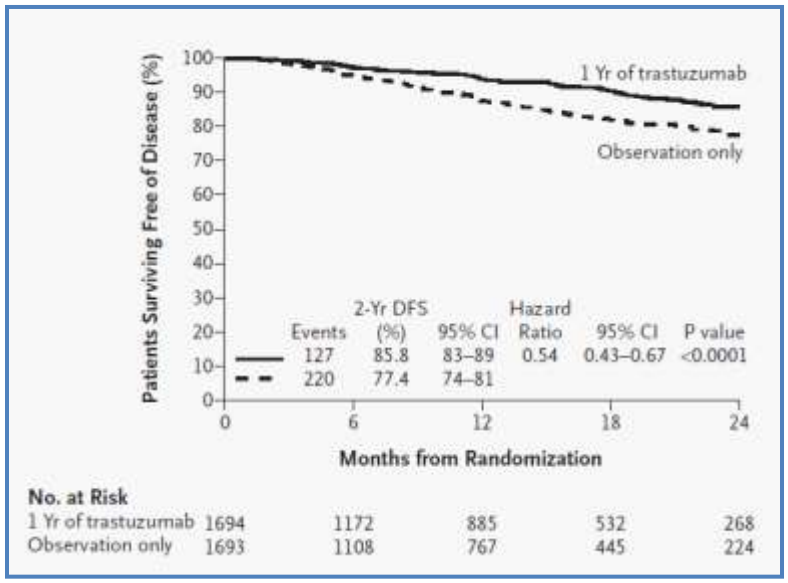
Hudis CA. N Engl J Med 2007

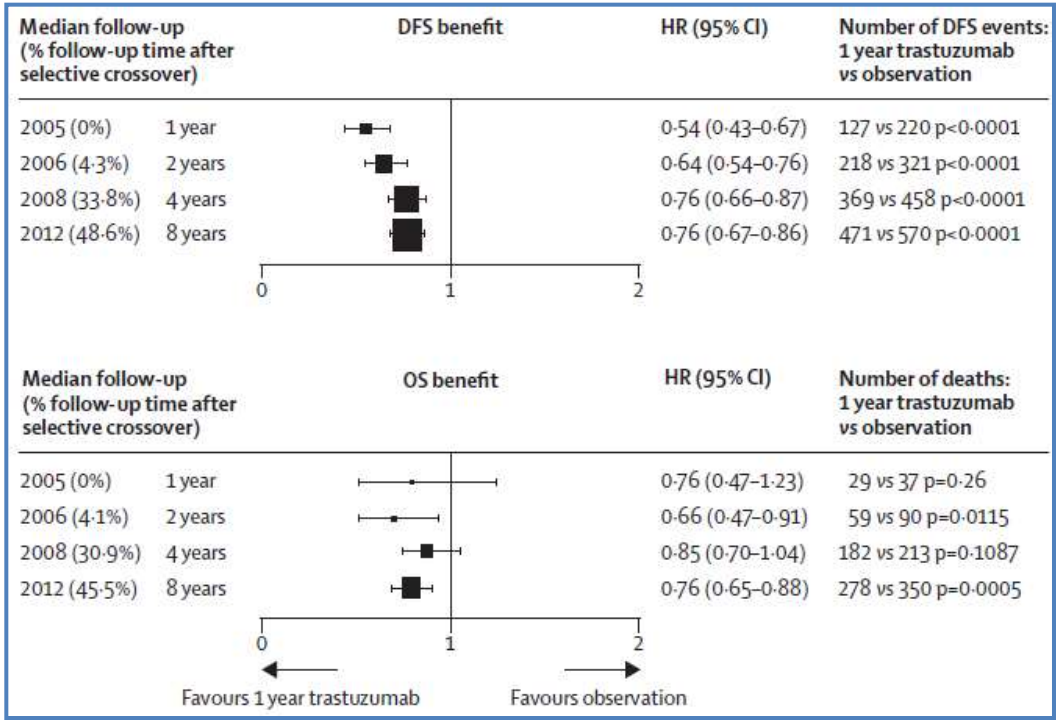
Trastuzumab overcomes the unfavourable prognostic value of HER2 overexpression

Dawood S, et al. J Clin Oncol 2008



Adjuvant Trastuzumab in HER2-Positive BC: the HERA trial





Patients with HER2-positive early breast cancer given adjuvant trastuzumab have shown **substantial improvements in DFS and OS outcomes compared with those given no trastuzumab; this benefit still continues even after 8 years**

On the basis of the results of HERA and several other trials, including NSABP B-31, NCCTG N9831 and BCIRG 006 **1 year of adjuvant trastuzumab in combination with, or sequential to, chemotherapy was established as the standard treatment for patients with HER2-positive early breast cancer**

The introduction of the HER2-targeting agent **trastuzumab in combination with chemotherapy has changed the natural history of patients with this subtype** in the adjuvant and metastatic setting

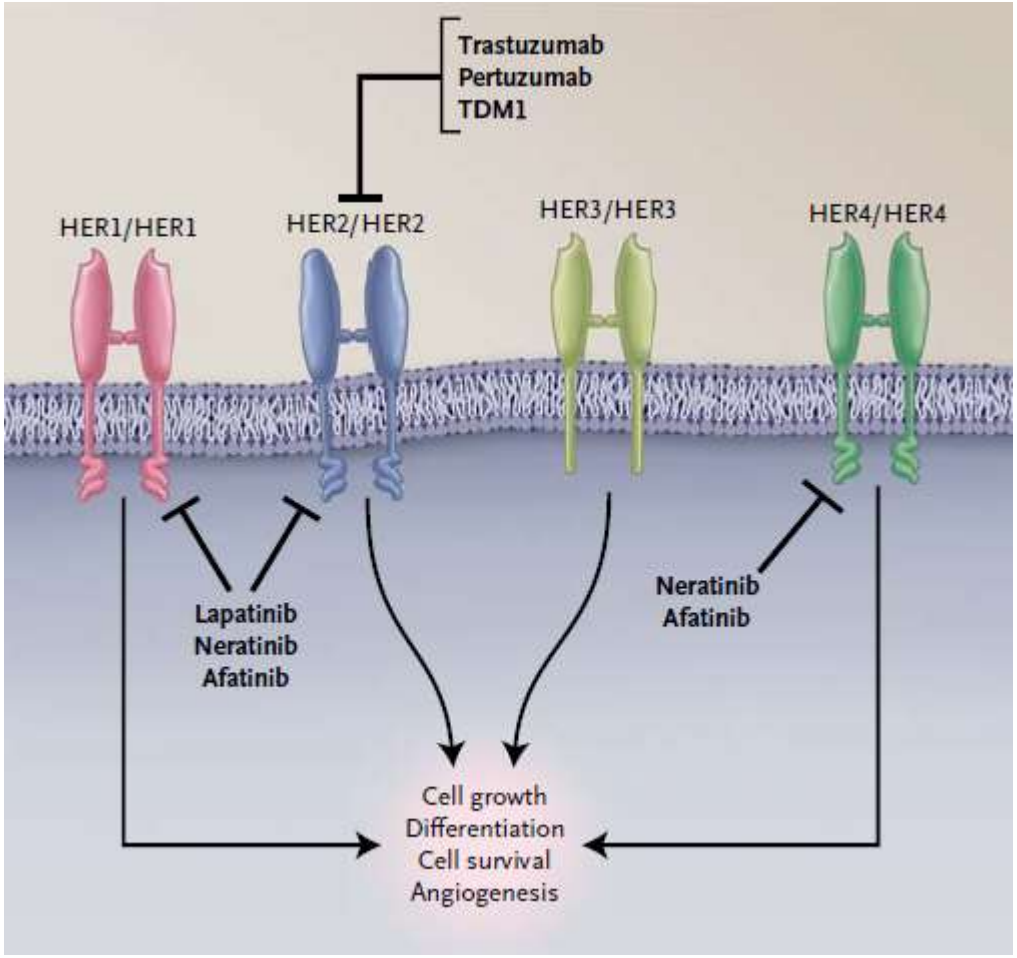
Piccart-Gebhart MJ, et al. N Engl J Med 2005; Goldhirsch A, et al. Lancet 2013

Adjuvant Trastuzumab in EBC provides benefit but…is it cost-effective?

- ✓ Adding trastuzumab to adjuvant chemotherapy provides significant clinical benefit in patients with HER2-positive breast cancer.
- ✓ A cost-effectiveness analysis was performed to assess clinical and economic implications of adding trastuzumab to adjuvant chemotherapy.
- ✓ In cost-effectiveness analysis the costs and effects of two or more interventions are compared.
- ✓ Effects are expressed in nonmonetary units, such as life years (LYs) gained or quality-adjusted life years (QALYs) gained.
- ✓ Over a lifetime, the projected cost of trastuzumab per quality-adjusted life year (**QALY**) gained was **$26,417** and, during a 20-year horizon, of $34,201 per QALY gained.
- ✓ The results of this analysis showed that **Trastuzumab for adjuvant treatment** of EBC was projected to be **cost effective** over a lifetime horizon, **achieving a cost-effectiveness ratio below that of many widely accepted oncology treatments.**

Garrison LP, et al. Cancer 2007

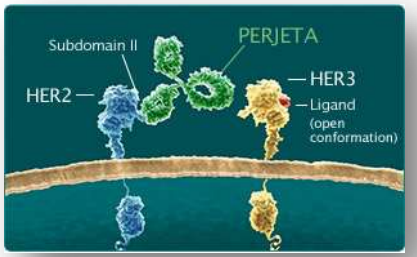
Dual Targeting: a novel therapeutic paradigm in HER-2 positive mBC

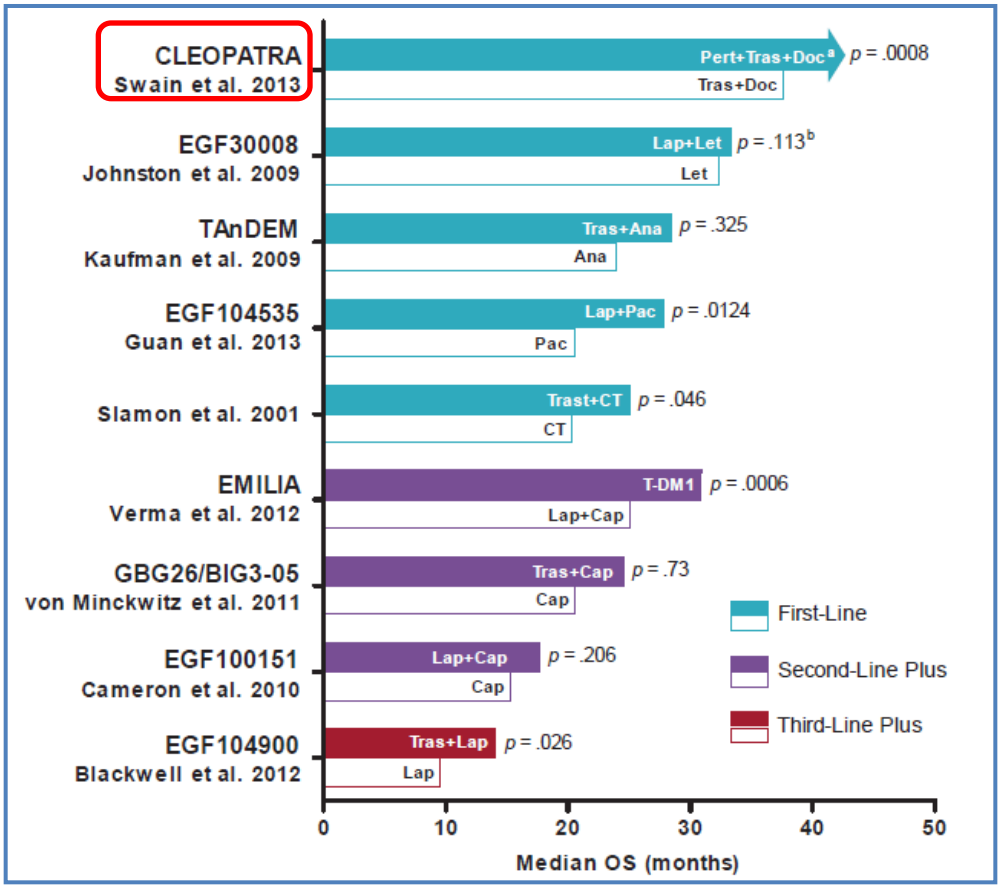


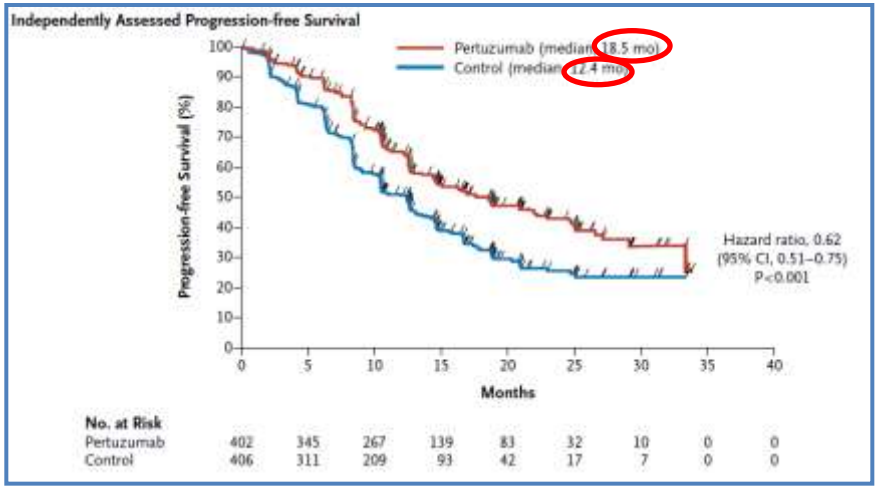
A more complete blockage of the HER2 and/or the HER signaling pathway by combining two or three inhibitors with non-overlapping mechanisms of action improves cell death and tumor shrinkage in HER2-positive models.

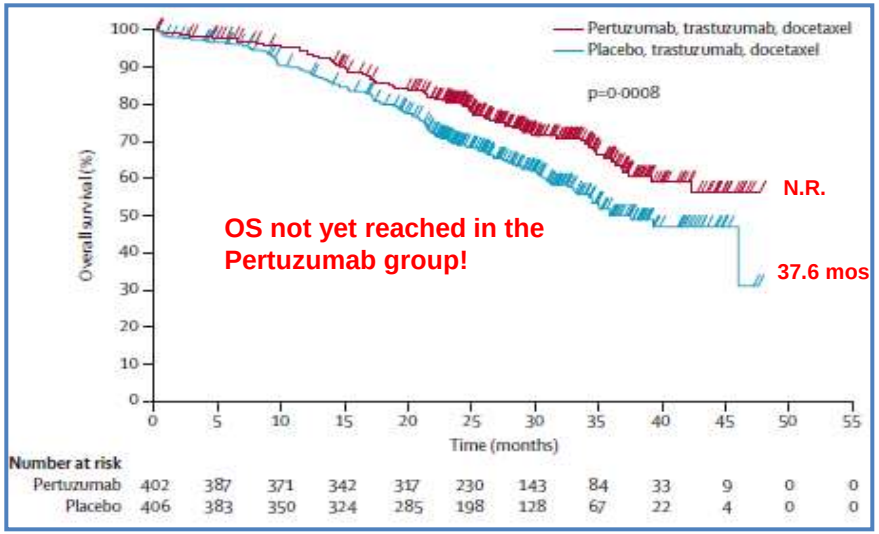
These preclinical findings have now been confirmed in the clinical setting with the combination of Trastuzumab + Lapatinib in heavily pretreated patients (EGF 104900 trial) and in the first line setting with the combination Trastuzumab-Pertuzumab-Docetaxel (CLEOPATRA trial).

Pertuzumab in HER2+ advanced BC









Baselga J, et al. NEJM 2012; Swain SM, et al. Lancet Oncol 2013; Verma S, et al. Oncologist 2013

REIMBURSEMENT ISSUES IN SICILY

Anno 155° - Numero 143

GAZZETTA UFFICIALE

DELLA REPUBBLICA ITALIANA

Roma - Lunedì, 23 giugno 2014

Art. 1.

Classificazione ai fini della rimborsabilità

Il medicinale PERJETA (pertuzumab) nella confezione sotto indicata è classificato come segue:

Confezione: 420 mg – concentrato per soluzione per infusione – uso endovenoso – flaconcino (vetro) – 30 mg/ml – 1 flaconcino - AIC n. 042682017/E (in base 10) 18QKP1 (in base 32)

Classe di rimborsabilità: H.

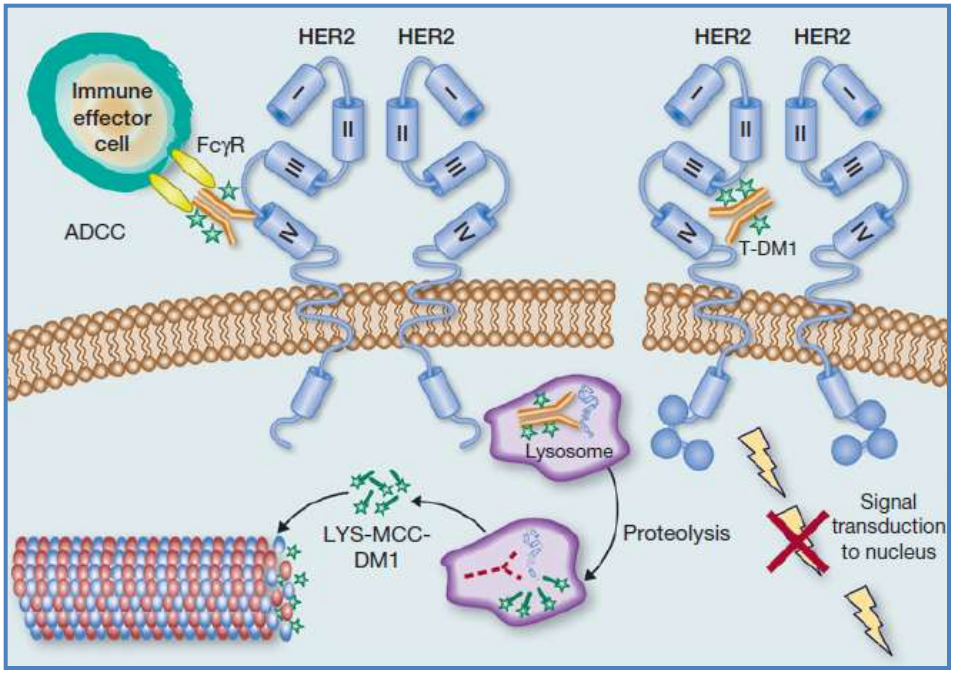
Prezzo ex factory (IVA esclusa): € 3.037,82.

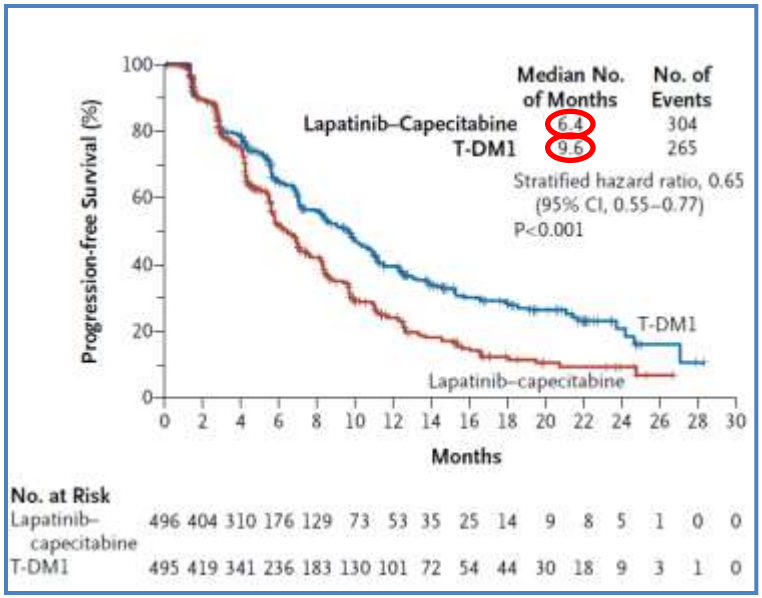
Prezzo al pubblico (IVA inclusa): € 5.013,62.

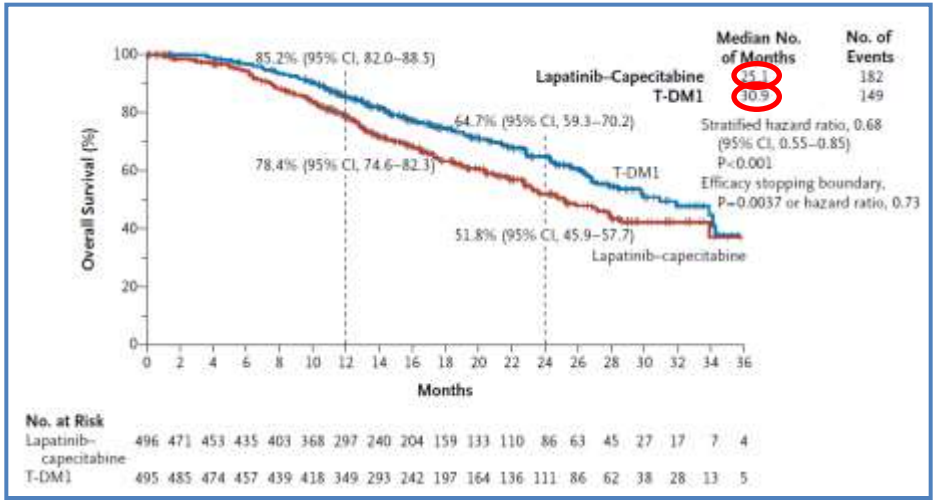
Validità del contratto: 24 mesi.

Innovazione terapeutica.

Trastuzumab Emtansine (T-DM1): A Novel Antibody–Drug Conjugate for HER2-Positive Breast Cancer







"In this phase 3 study, the antibody–drug conjugate T-DM1, as compared with lapatinib plus capecitabine, ***significantly improved progression-free and overall survival among patients with HER2-positive metastatic breast cancer who had previously received trastuzumab and a taxane****. The benefit was observed regardless of the line of therapy in patients with metastatic disease and was seen in patients with a disease-free interval of less than 6 months after completion of trastuzumab-based therapy in the adjuvant or neoadjuvant setting".*

Verma S, et al. N Engl J Med 2012; Krop I, et al. Clin Cancer Res 2013

Therapeutic Advances in Lung Cancer Management

1970s

- ✓ Cisplatin produces responses in SCLC + NSCLC
- ✓ Etoposide produces responses in SCLC
- ✓ EP produces high response rate in SCLC

1980s

- ✓ EP most effective, least toxic SCLC regimen
- ✓ CT/RT superior to either alone in LSCLC
- ✓ PCI improves survival in LSCLC
- ✓ Retreatment with EP effective with late recurrence of SCLC
- ✓ FDA approves etoposide for SCLC and carbo for NSCLC

1990s

- ✓ Adjuvant CT improves 5-yr and OS in stage II + III NSCLC
- ✓ CT/RT improves 5-yr and OS in inoperable stage III NSCLC
- ✓ Platinum doublets improve OS in stage IV, PS 0-1 NSCLC
- ✓ FDA approves paclitaxel, vinorelbine, gemcitabine for NSCLC

2000s

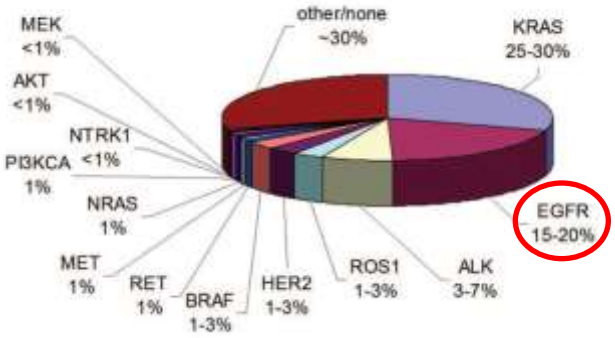
- ✓ Most platinum doublets equivalent
- ✓ Pem/Cis superior to Gem/Cis in non-Sq but inferior in Sq
- ✓ Bev added to carbo/taxol improves OS in non-SqCC
- ✓ Relationship between *EGFR* mutation and response to EGFR TKI reported ; EGFR TKIs superior to CT in first-line therapy of *EGFR*-mutant NSCLC
- ✓ *ALK* fusion identified as molecular driver in some ADCs and crizotinib effective in patients *ALK*+
- ✓ PCI improves survival in ESCLC
- ✓ Neoadjuvant CT improves survival in resectable NSCLC
- ✓ Docetaxel, Pem and erlotinib improve survival in second-line therapy; Docetaxel, Pem and erlotinb prolong survival as maintenance
- ✓ FDA approves docetaxel, Pem, gefitinib, erlotinib, bevacizumab for NSCLC; Pem approved for maintenance; zolendronic acid for prevention of bone problems; topotecan for SCLC

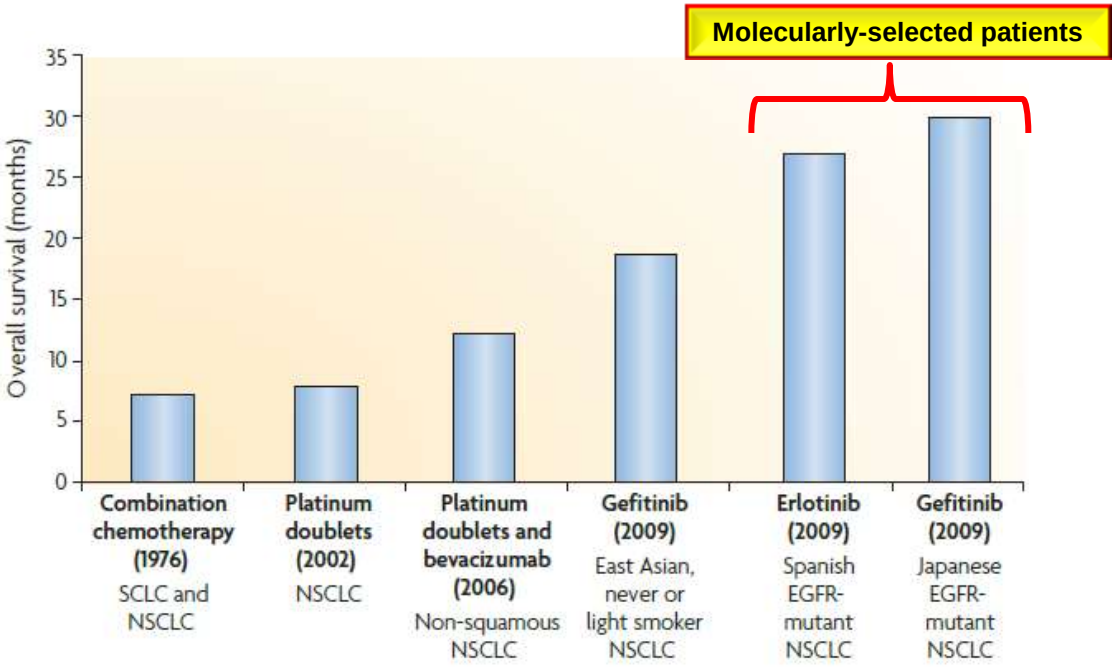
2010s

- ✓ Driver molecular abnormalities reported in up to 60% of lung ADCs and are associated with improved outcome after specific TKI therapy;
- ✓ Mechanisms of resistance to EGFR and ALK TKIs identified
- ✓ Responses to antibodies to immune regulatory proteins reported
- ✓ FDA approves paclitaxel/carbo; denosumab for bone metastases prevention, erlotinib and afatinib as first-line therapy for EGFR-mutant first-line therapy, erlotinib for maintenance therapy, crizotinib for ALK fusion

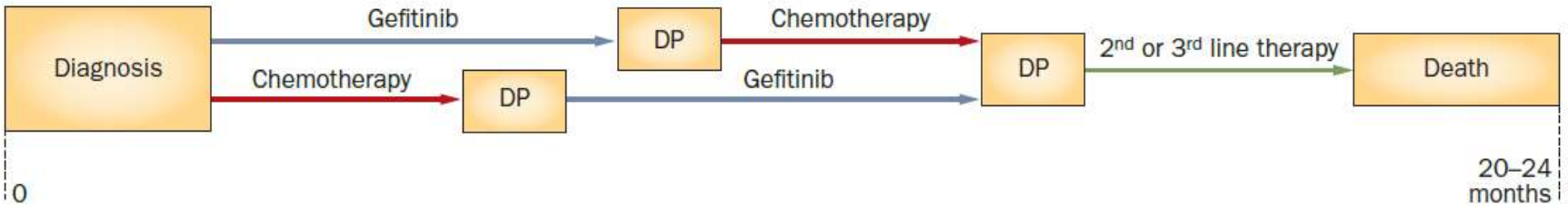
Johnson DH. J Clin Oncol 2014

Progresses in the treatment of advanced NSCLC: the EGFR story





- ✓ Driver oncogenes are important therapeutic targets in NSCLC and an increasing number of molecular subsets of NSCLC are being defined.
- ✓ EGFR and ALK are the most common driver oncogenes that have FDA-approved targeted therapeutic options with high rates of durable response.
- ✓ EGFR- and ALK-targeted therapies serve as models for ongoing development of targeted therapeutics against multiple newly defined molecular subsets of NSCLC.



Pao W & Chmielecki J. Nat Rev Cancer 2010; Mok TS. Nat Rev Clin Oncol 2011; Gerber DE, et al. ASCO 2014

Superiority of EGFR TKIs over chemotherapy in EGFR-mutated NSCLC

Clinically selected

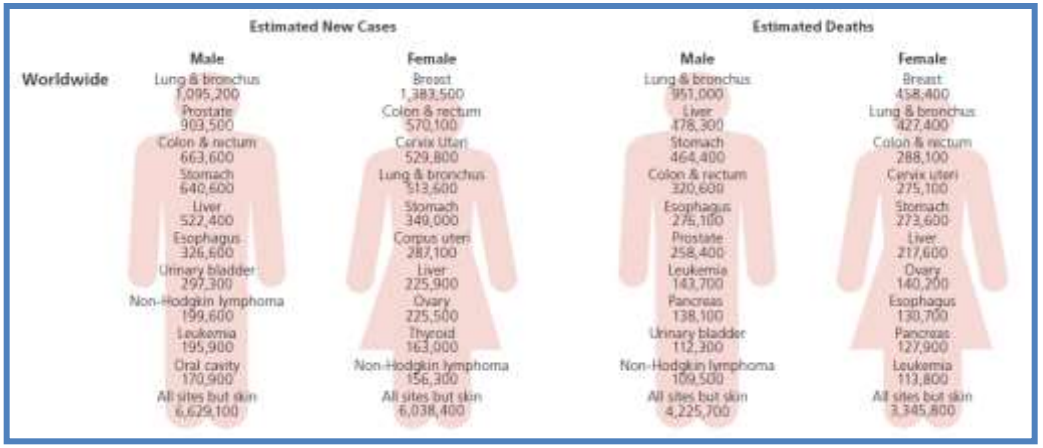
Trial	Selection criteria	Treatment	N	RR (%)	PFS (mo)	OS (mo)	Ref
IPASS	East-Asian, light/non-smoker, adenocarcinoma	Gefitinib vs. Carboplatin/Paclitaxel	132 129	71.2 Vs. 47.3	9.6 Vs. 6.3	21.6 Vs. 21.9	Mok TS, et al. NEJM 2009
First-SIGNAL	Korean, non-smoker, adenocarcinoma	Gefitinib Vs. Cisplatin/Gemcitabine	26 16	84.6 Vs. 37.5	8.0 Vs. 6.3	27.2 Vs. 25.6	Han JY, et al. JCO 2012
WJTOG 3405	Japanese, EGFR mutation	Gefitinib Vs. Cisplatin/Docetaxel	86 86	62.1 Vs. 32.1	9.2 Vs. 6.3	35.5 Vs. 38.8	Mitsudomi T, et al. Lancet Oncol 2010
NEJ 002	Japanese, EGFR mutation	Gefitinib vs. Carboplatin/Paclitaxel	114 114	73.7 Vs. 30.7	10.8 Vs. 5.4	27.7 Vs. 26.6	Maemondo M, et al. NEJM 2010
OPTIMAL	Chinese, EGFR mutation	Erlotinib vs. Carboplatin/Gemcitabine	82 72	83 Vs. 36	13.1 Vs. 4.6	Not yet mature	Zhou C, et al. Lancet Oncol 2011
EURTAC	European, EGFR mutation	Erlotinib Vs. Platinum agent + Gemcitabine or Docetaxel	86 87	58 Vs. 15	9.7 Vs. 5.2	19.3 Vs. 19.5	Rosell R, et al. Lancet Oncol 2012
LUX-Lung 3	Asian and European, EGFR mutation	Afatinib Vs. Cisplatin/Pemetrexed	230 115	56.1 Vs. 22.6	11.1 Vs. 6.9	27.3 Vs 24.3	Sequist LV, et al. JCO 2013
LUX-Lung 6	Asian, EGFR mutation	Afatinib Vs. Cisplatin/Gemcitabine	242 122	66.9 Vs. 23.0	11.0 Vs. 5.6		Wu YL, et al. Lancet Oncol 2014

The "*Lazarus Response*"

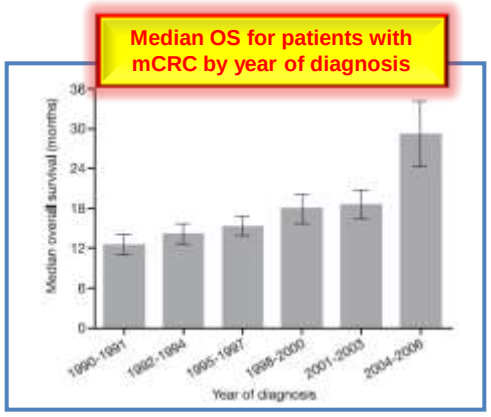
- Quality of life (QoL) studies reported a prevalence of poor performance status (PS; 2 to 4) among lung cancer patients between 34-48%.
- Unfortunately, there is no standard therapy in advanced NSCLC patients with very poor performance status (PS 3 to 4).
- Median survival (MS) without therapy, which is the norm, is typically fewer than 2-3 months in such individuals, whether the compromise in PS is due to disease burden or comorbidity.
- However, treatment with EGFR TKIs of patients with very poor PS (ECOG PS 3-4) with metastatic NSCLC, chemotherapy-naïve, harboring activating mutations of the EGFR have been associated with a median survival of ~18 months and a consistent improvement of performance status ("*Lazarus response*")
- Therefore, treatment with EGFR TKIs, may lead to treatment of patients with a very poor prognosis otherwise destined to exclusive palliative therapies

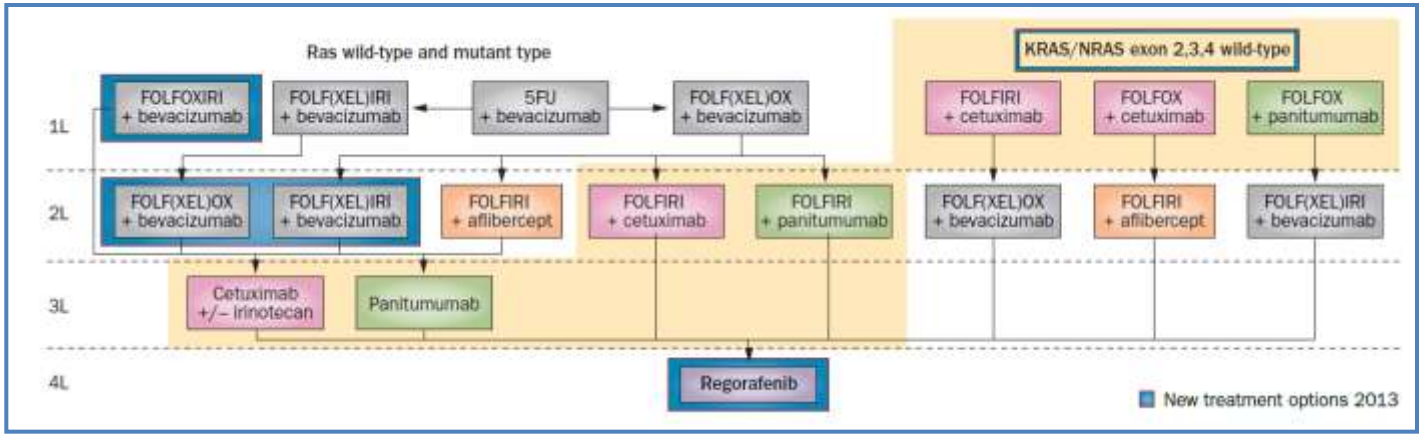
Langer CJ. J Clin Oncol 2009

Medical treatment of metastatic colorectal cancer (mCRC) in 2014



- ✓ Colorectal cancer is the **third most common cancer** and the **fourth most common cancer cause of death globally,** accounting for roughly 1.2 million new cases and 600 000 deaths per year.
- ✓ The **prognosis of patients with colorectal cancer has slowly but steadily improved during the past decades** in many countries. 5-year relative survival has reached almost 65% in high-income countries.
- ✓ The **medical treatment of mCRC has advanced significantly over the last 10 years** as the result of the introduction of several active cytotoxic and biologic agents into standard clinical practice

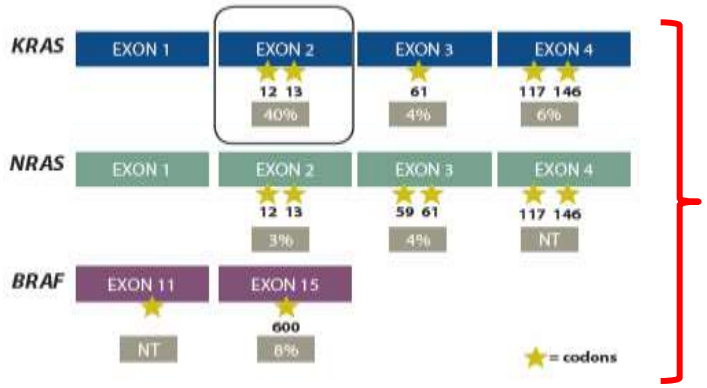




Brenner H, et al. Lancet 2014; Schmoll HJ & Stein A. Nat Rev Clin Oncol 2014; Heinemann V, et al. Cancer Treat Rev 2013

Molecular predictors to anti-EGFR mAbs Cetuximab and Panitumumab in mCRC

BIOMARKER	INCIDENCE	PROGNOSTIC VALUE	PREDICTIVE VALUE
B-RAF mutations	4-15%	Poor prognosis	Controversial data
K-RAS mutations	40%	Controversial data	Major predictor of resistance to anti-EGFR mAbs
Mut G13D	15-20%		Weaker resistance
N-RAS mutations	3-5%		Predictor of resistance
PI3KCA mutations	10-20%	Conflicting results	Controversial data
PTEN status	20-40%	Conflicting results	Controversial data



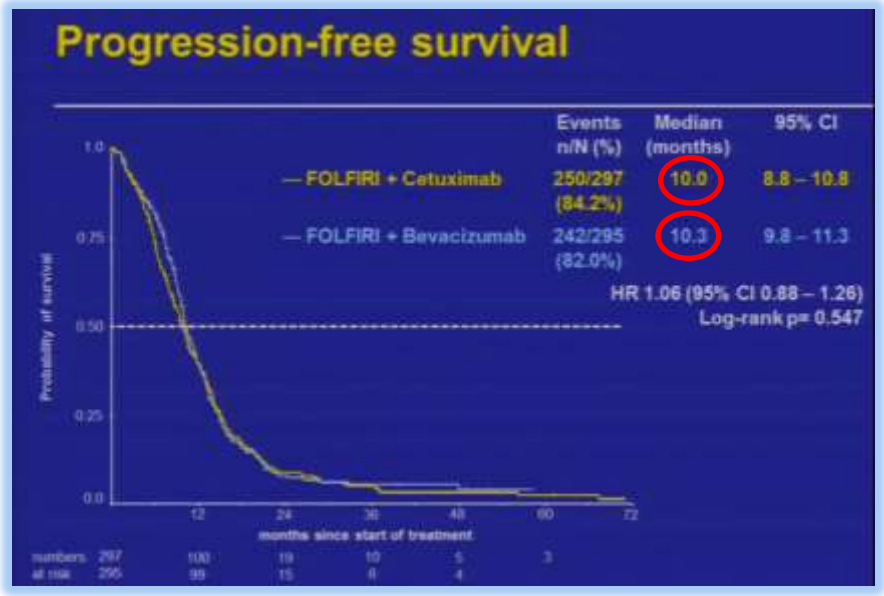
Frequency of KRAS and NRAS Mutations Beyond KRAS Exon 2 in the PRIME trial

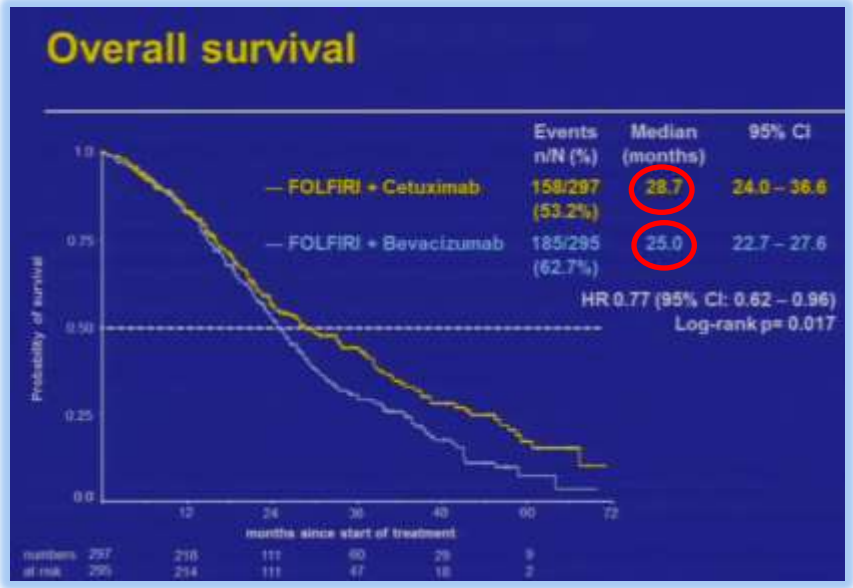
- ✓ Several recent phase III trials reported median overall survival data exceeding 30 months, an achievement inconceivable only 5 years ago.
- ✓ The first major step forward in the medical management of mCRC was provided by the addition of irinotecan and oxaliplatin to fluorouracil-based therapy; this increased survival from about 12 months to about 20 months.
- ✓ The introduction of biologic agents such as vascular endothelial growth factor inhibitors and epidermal growth factor inhibitors further increased survival—to more than 2 years in prospective trials.
- ✓ Seven specific mutations in exon 2 (codons 12 and 13) make up more than 90% of all *KRAS* mutations, and these are the mutations currently assessed in standard tests. However, while mutations in *KRAS* exon 2 comprise the most commonly seen mutations, there are still subsets of *KRAS* and other *NRAS* or *RAS* family “mutants” that are being missed with current testing.

Sridharan M, et al. Oncology 2014; De Stefano A, et al. World J Gastroenterol 2014

FOLFIRI/cetuximab vs. FOLFIRI/bevacizumab as first-line treatment of KRAS wild-type mCRC: the FIRE-3 trial

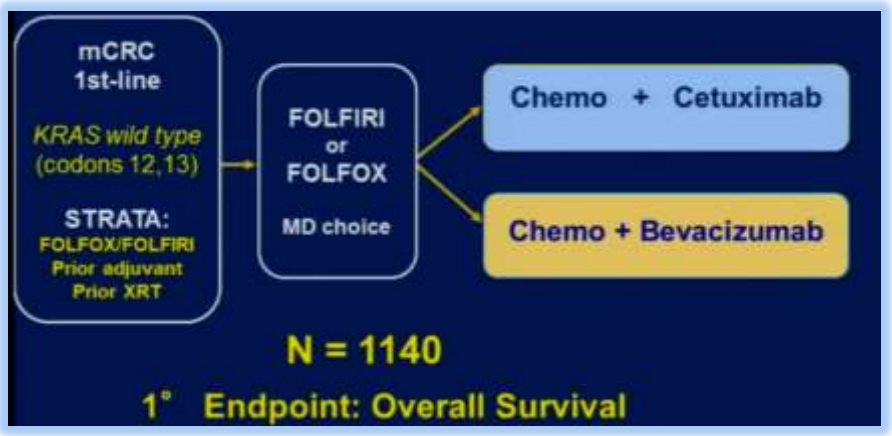
*"Median **PFS** of the ITT population **was nearly identical**, however, **significantly superior OS was observed in KRAS-WT patients receiving cetuximab plus FOLFIRI** as first-line treatment"*



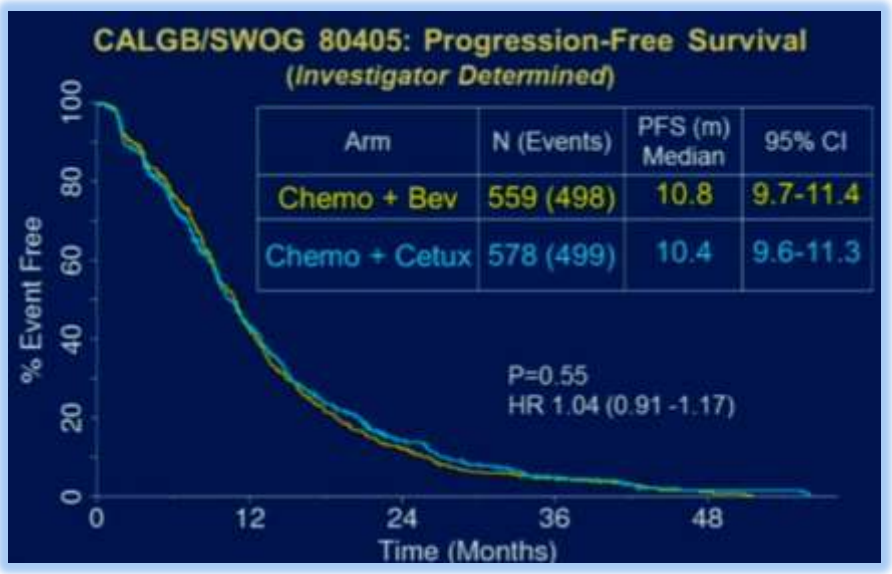


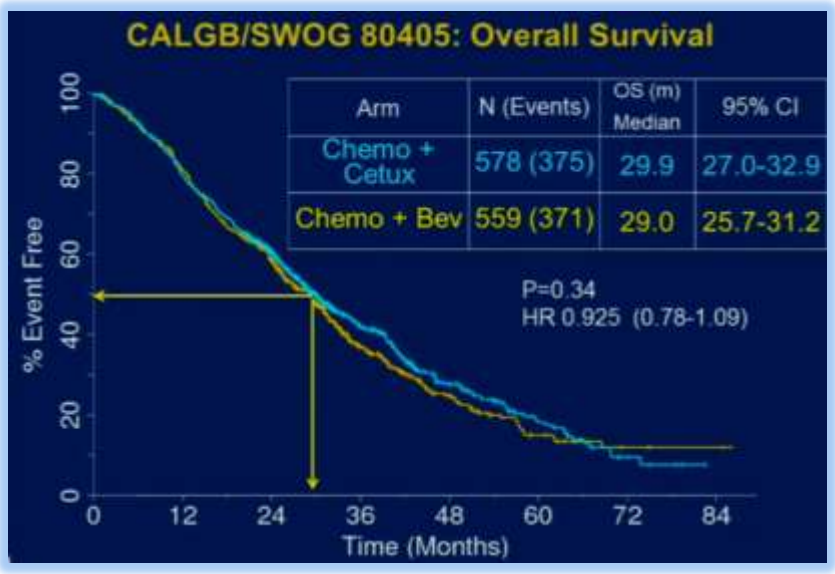
Heinemann V, et al. ASCO 2013

CHEMOTHERAPY + CETUXIMAB or BEVACIZUMAB: the CALGB/SWOG 80405 trial



"Chemotherapy/Cetuximab and chemotherapy/Bevacizumab are equivalent in terms of OS in pts KRAS wt *(codons 12 + 13) mCRC; either regimen is appropriate in first line.* ***Overall OS of 29 + mos and 8% long-term survivors confirms progress in mCRC****"*





Venook AP, et al. ASCO 2014

The NEW ENGLAND JOURNAL of MEDICINE

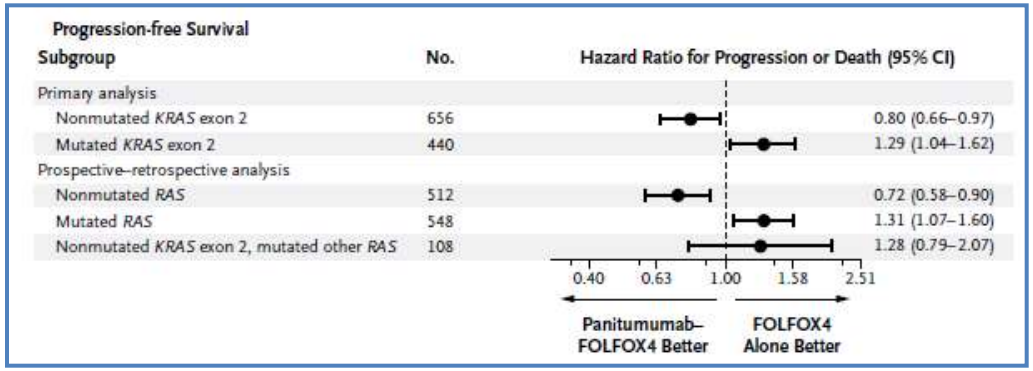
ORIGINAL ARTICLE

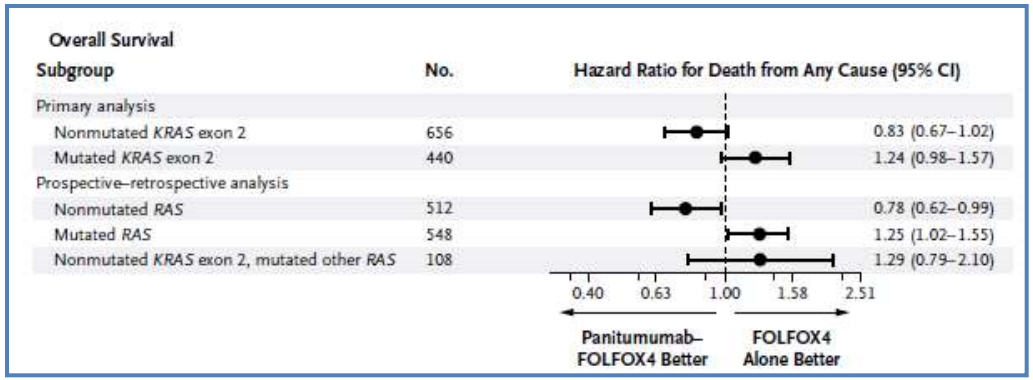
Panitumumab–FOLFOX4 Treatment and *RAS* Mutations in Colorectal Cancer

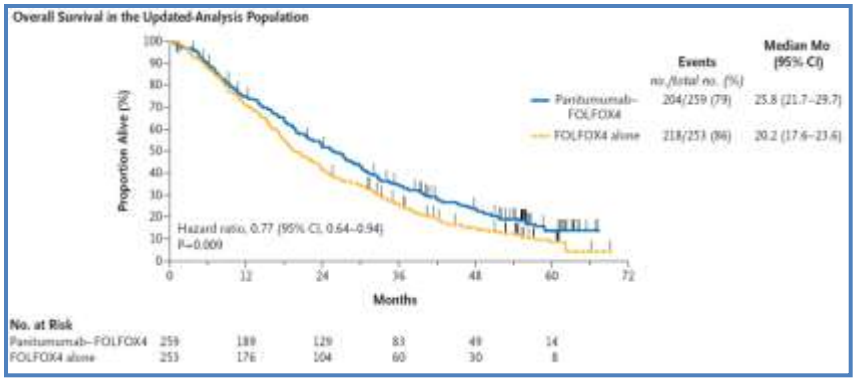
BIOMARKER ANALYSIS OF THE PRIME TRIAL

"In patients who had metastatic colorectal cancer without RAS mutations, improvements in overall survival were observed with panitumumab–FOLFOX4 therapy"

- ✓ Among 512 **patients without *RAS*** mutations, **progression-free survival was 10.1 months** with panitumumab–FOLFOX4 **versus 7.9 months** with FOLFOX4 alone.
- ✓ **Overall survival was 26.0 months** in the panitumumab–FOLFOX4 group **versus 20.2 months** in the FOLFOX4-alone group.
- ✓ **17% of patients with nonmutated *KRAS* exon 2 had other *RAS* mutations**. These mutations **were associated with inferior PFS and OS** with panitumumab– FOLFOX4 treatment.
- ✓ ***BRAF* mutations** were a **negative prognostic factor**

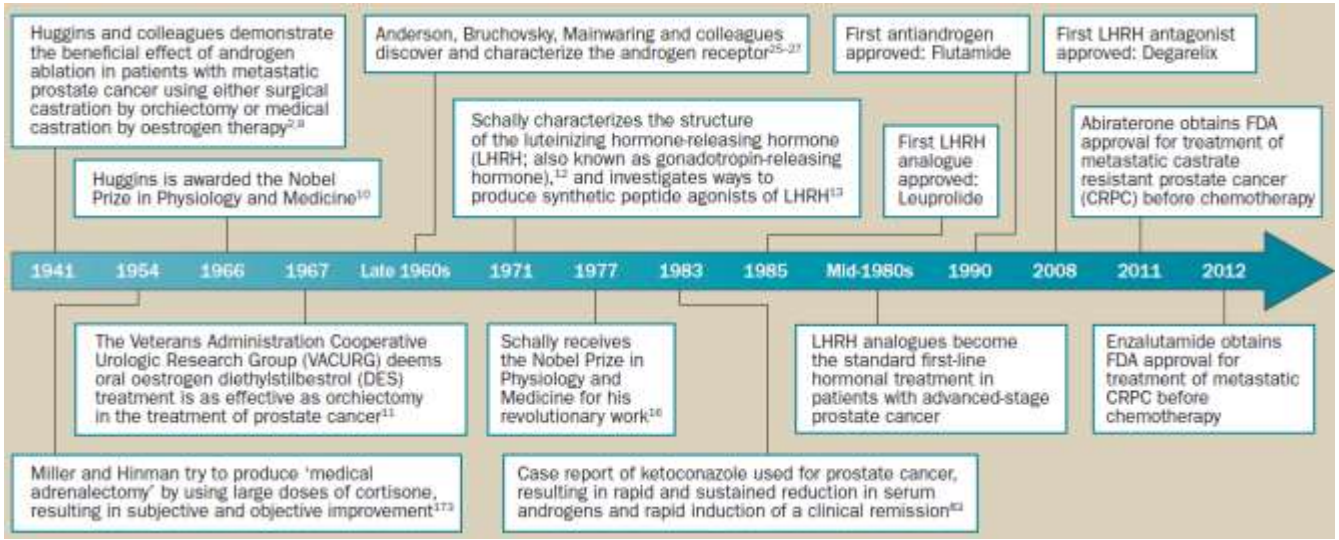




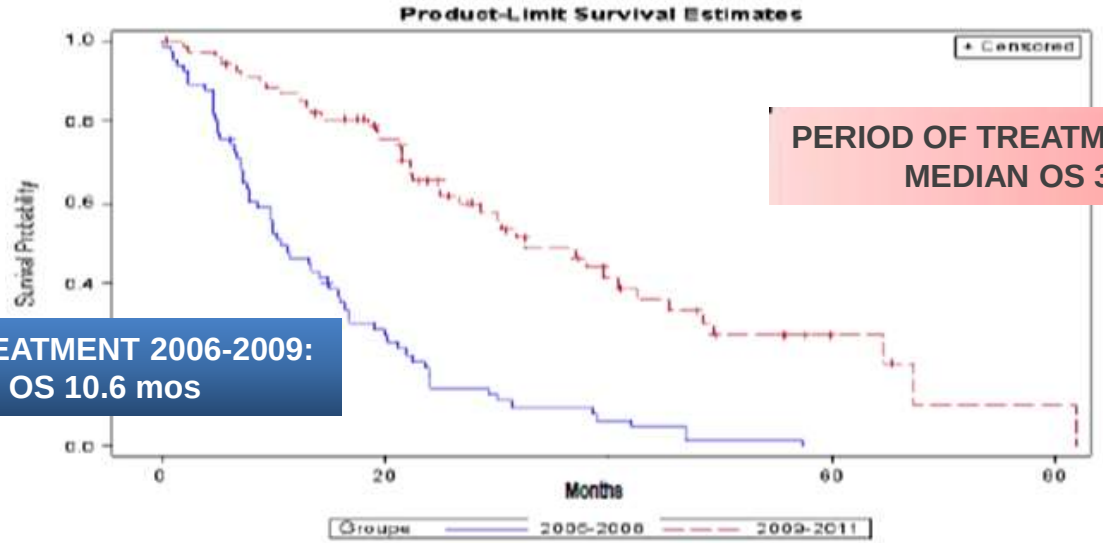


Douillard JY, et al. N Engl J Med 2013

Evolution of androgen receptor targeted therapy for advanced prostate cancer



Impact of news drugs in the median OS of patients with metastatic castration resistant prostate cancer

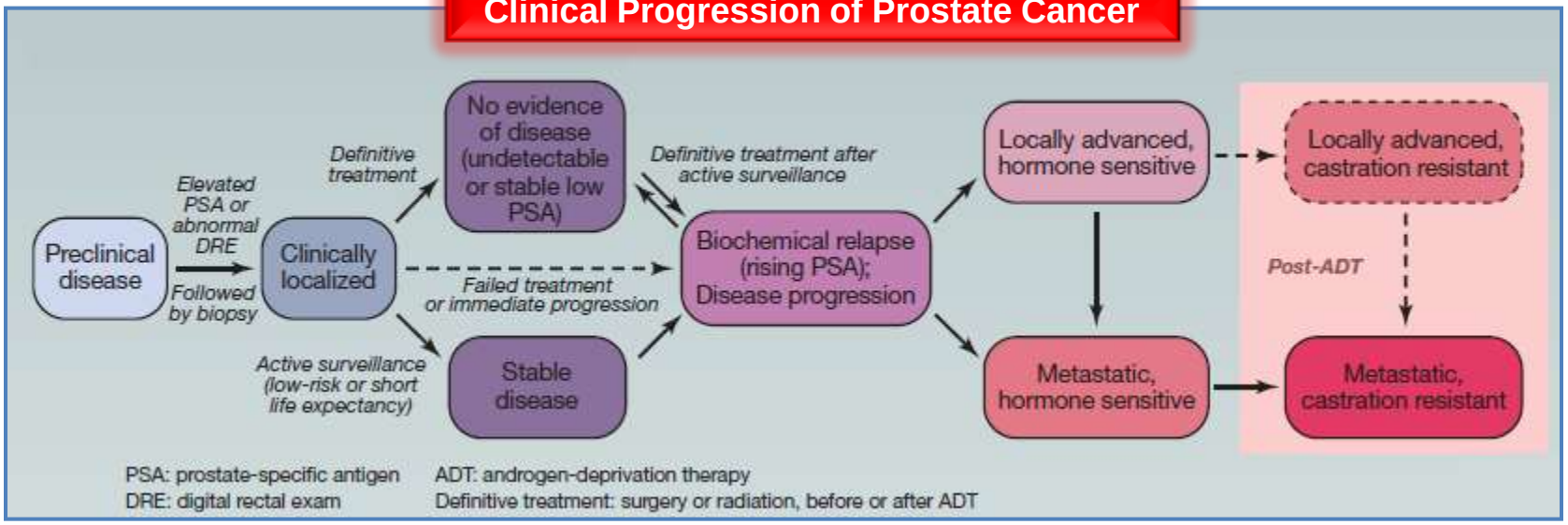


PERIOD OF TREATMENT 2009-2012: MEDIAN OS 32.5 mos

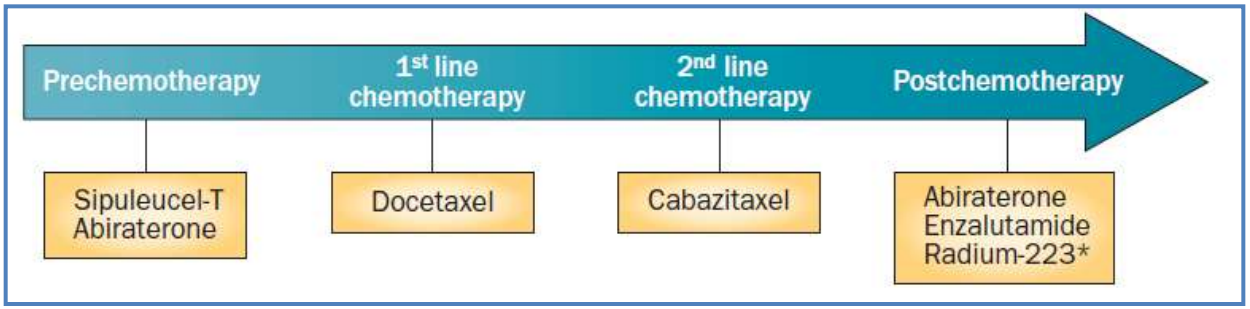
PERIOD OF TREATMENT 2006-2009: MEDIAN OS 10.6 mos

Chaumard-Billotey N, et al. ASCO 2013; Wong YN, et al. Nat Rev Clin Oncol 2014

Clinical Progression of Prostate Cancer



Emerging therapies for mCRPC

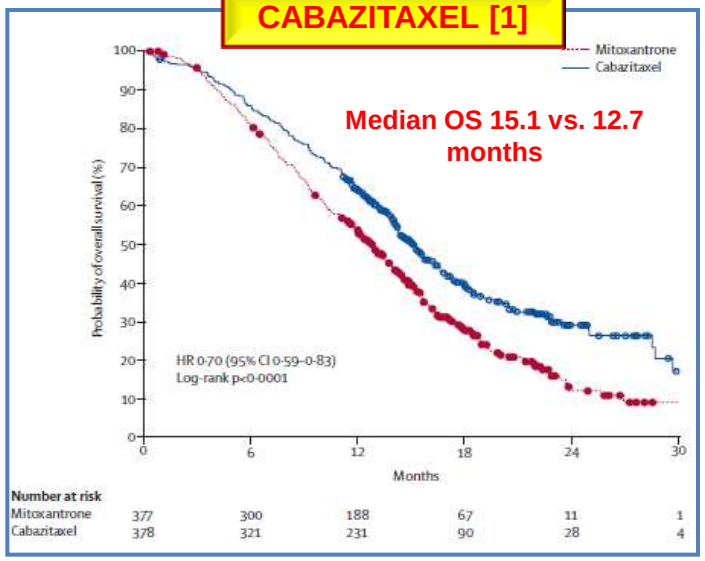


*"Overall, **the prostate cancer market is expected to grow from $4.1 billion in 2012 to $8.2 billion in 2019**. Most of this growth is expected to be in the symptomatic CRPC segment, driven by late-stage pipeline molecules and increasing uptake of recently approved therapies"*

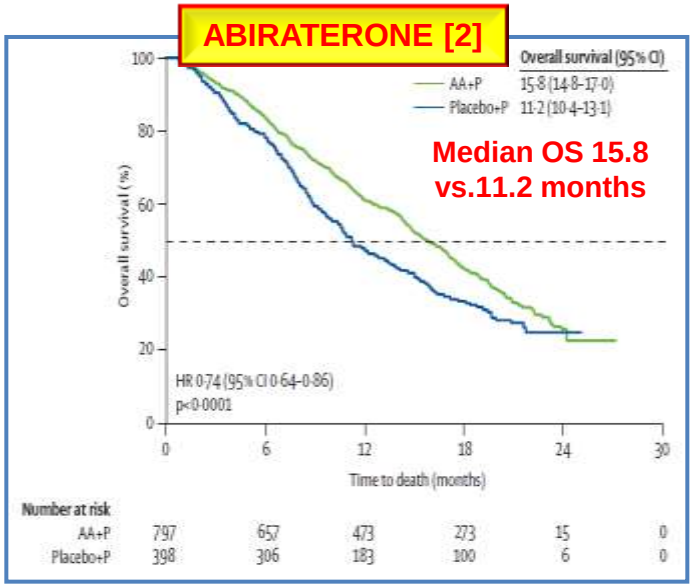
Barlow LJ & Shen MM, Cancer Cell 2013; Trewartha D, et al. Nat Rev Drug Discov 2013; Bishr M & Saad F. Nat Rev Urol 2013

New drugs demonstrating OS benefit in mCRPC patients progressing after docetaxel treatment

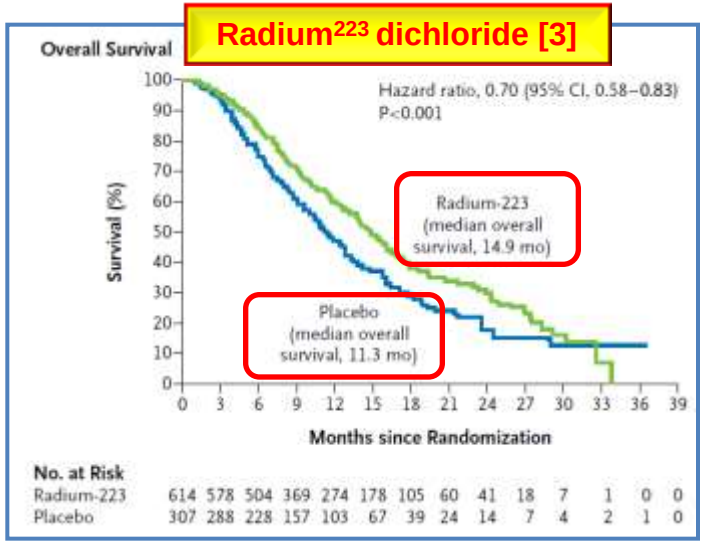
CABAZITAXEL [1]



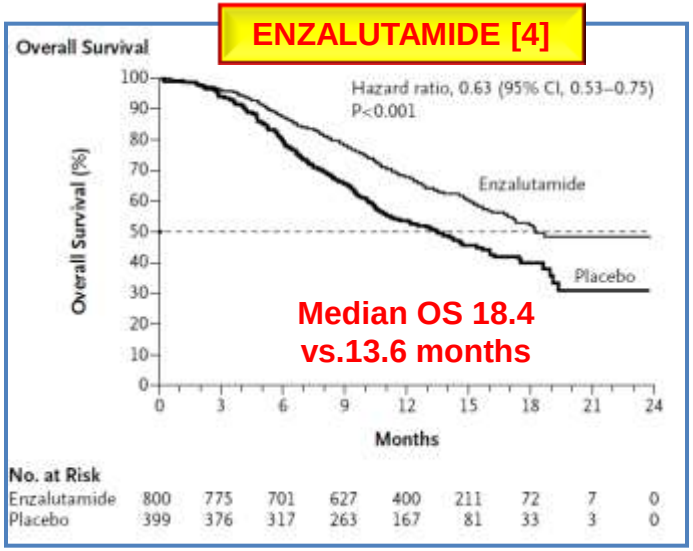
ABIRATERONE [2]



Radium^{223} dichloride [3]



ENZALUTAMIDE [4]



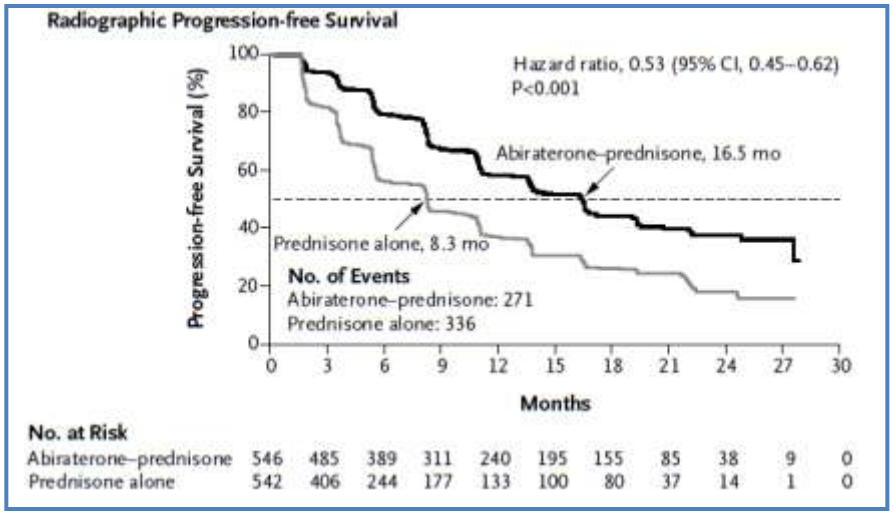
[1]de Bono JS, et al. Lancet 2010;

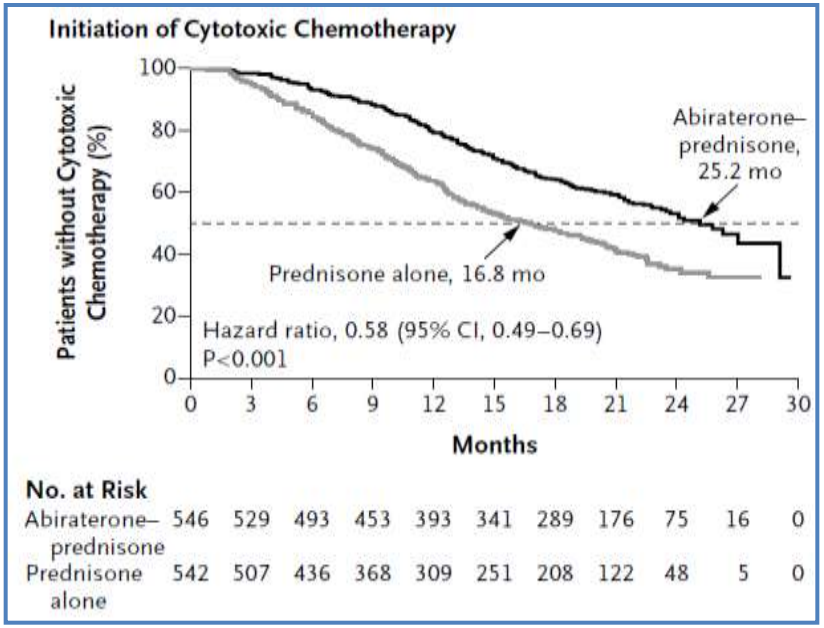
[2]Fizazi K, et al. Lancet Oncol2012;

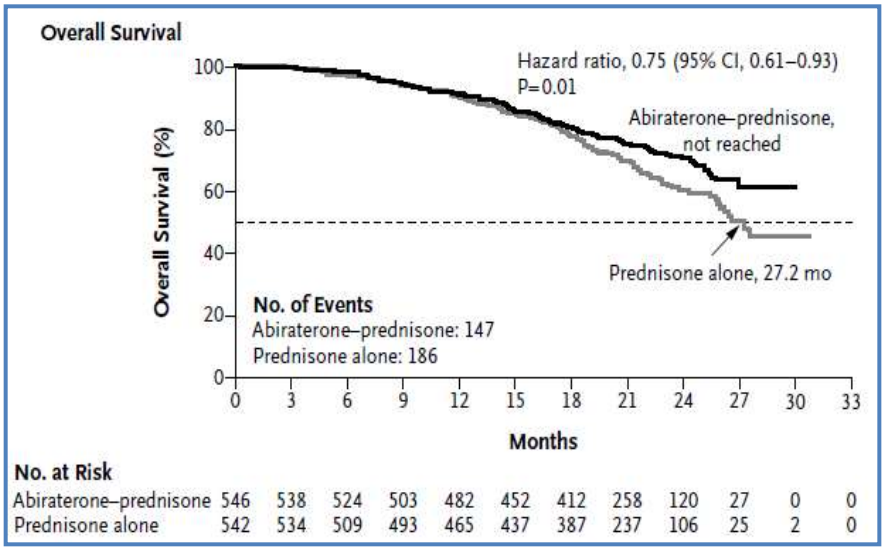
[3]Parker C, et al. N Eng J Med 2013;

[4]Scher HI, N Eng J Med 2012

Major advances in chemo-naive prostate cancer patients [1]



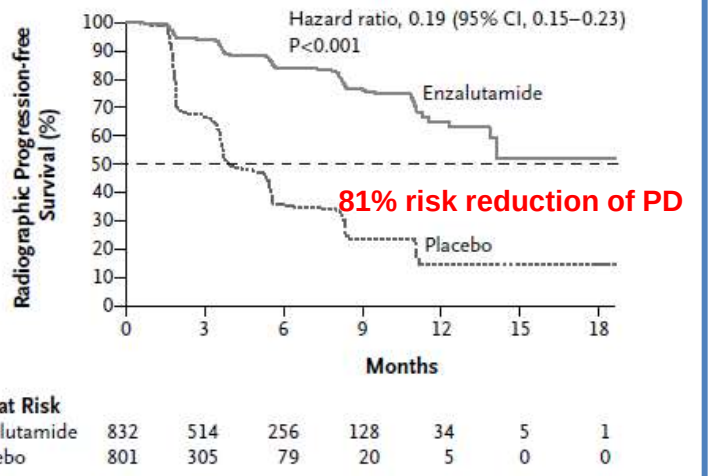


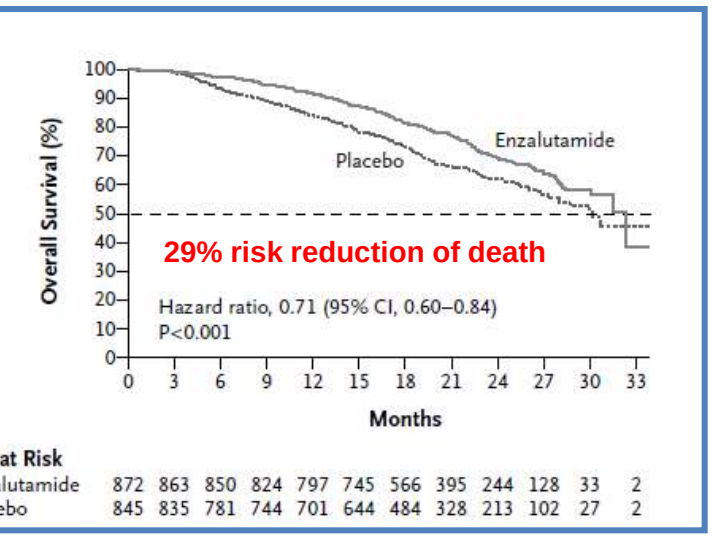


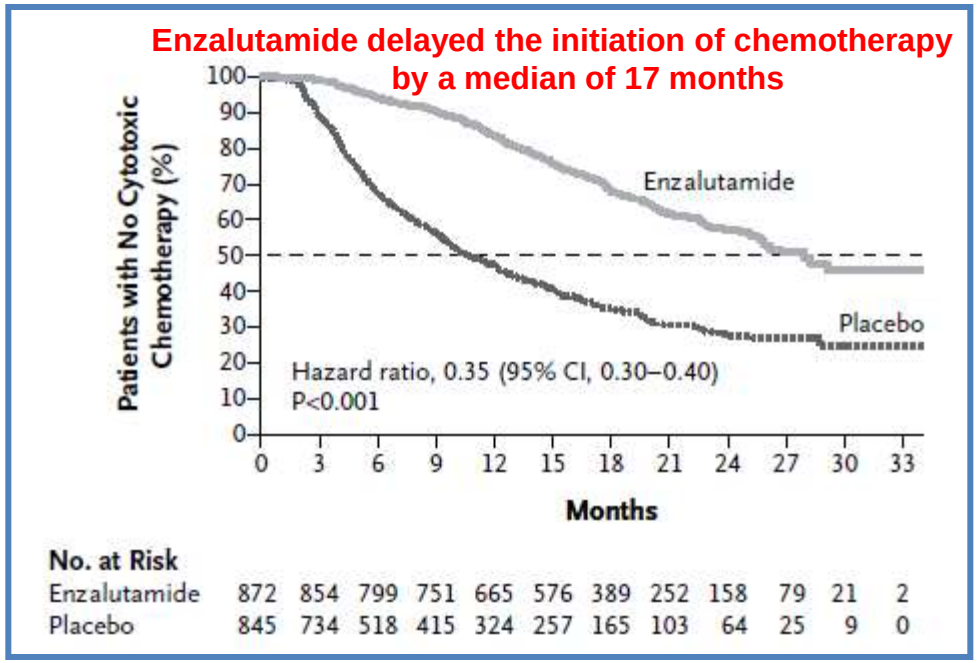
*"**Abiraterone** improved radiographic progression-free survival, showed a trend toward improved overall survival, and significantly delayed clinical decline and initiation of chemotherapy in patients with metastatic castration-resistant prostate cancer"*

Ryan CJ, et al. N Engl J Med 2013

Major advances in chemo-naive prostate cancer patients [2]







*"**Enzalutamide** significantly decreased the risk of radiographic progression and death and delayed the initiation of chemotherapy in men with metastatic prostate cancer"*

Beer TM, et al. N Engl J Med 2014

Metastatic Melanoma: where are we now

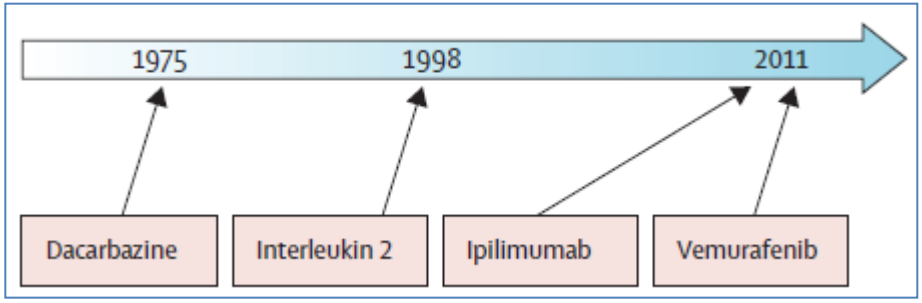
Leading New Cancer Cases and Deaths – 2014 Estimates

Estimated New Cases*		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 233,000 (27%)	Breast 232,670 (29%)	Lung & bronchus 86,930 (28%)	Lung & bronchus 72,330 (26%)
Lung & bronchus 116,000 (14%)	Lung & bronchus 108,210 (13%)	Prostate 29,480 (10%)	Breast 40,000 (15%)
Colon & rectum 71,830 (8%)	Colon & rectum 65,000 (8%)	Colon & rectum 26,270 (8%)	Colon & rectum 24,040 (9%)
Urinary bladder 56,390 (7%)	Uterine corpus 52,630 (6%)	Pancreas 20,170 (7%)	Pancreas 19,420 (7%)
Melanoma of the skin 43,890 (5%)	Thyroid 47,790 (6%)	Liver & intrahepatic bile duct 15,870 (5%)	Ovary 14,270 (5%)
Kidney & renal pelvis 39,140 (5%)	Non-Hodgkin lymphoma 32,530 (4%)	Leukemia 14,040 (5%)	Leukemia 10,050 (4%)
Non-Hodgkin lymphoma 38,270 (4%)	Melanoma of the skin 32,210 (4%)	Esophagus 12,450 (4%)	Uterine corpus 8,590 (3%)
Oral cavity & pharynx 30,220 (4%)	Kidney & renal pelvis 24,780 (3%)	Urinary bladder 11,170 (4%)	Non-Hodgkin lymphoma 8,520 (3%)
Leukemia 30,100 (4%)	Pancreas 22,890 (3%)	Non-Hodgkin lymphoma 10,470 (3%)	Liver & intrahepatic bile duct 7,130 (3%)
Liver & intrahepatic bile duct 24,600 (3%)	Leukemia 22,280 (3%)	Kidney & renal pelvis 8,900 (3%)	Brain & other nervous system 6,230 (2%)
All sites 855,220 (100%)	All sites 810,320 (100%)	All sites 310,010 (100%)	All sites 275,710 (100%)

*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder

- ✓ Melanoma accounts for **less than 2% of all skin cancer cases**, **but the vast majority of skin cancer deaths.**
- ✓ Melanoma **incidence rates have been increasing** for at least 30 years.
- ✓ From 2006 to 2010, incidence rates among whites increased by 2.7% per year.
- ✓ An estimated 9,710 deaths from melanoma and 3,270 deaths from other types of skin cancer will occur in 2014 in the United States.

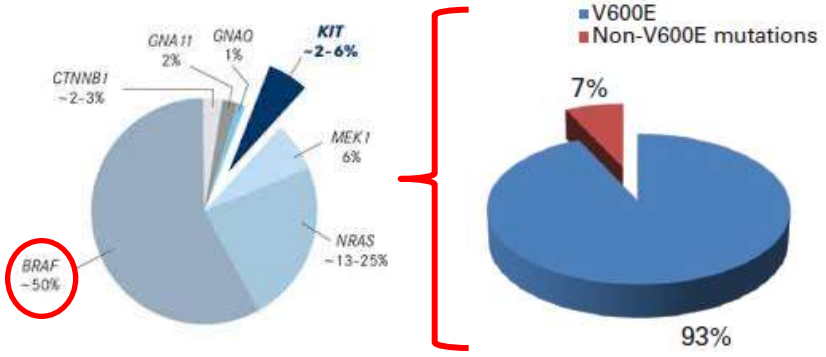
Timeline of FDA-approved treatments for advanced melanoma

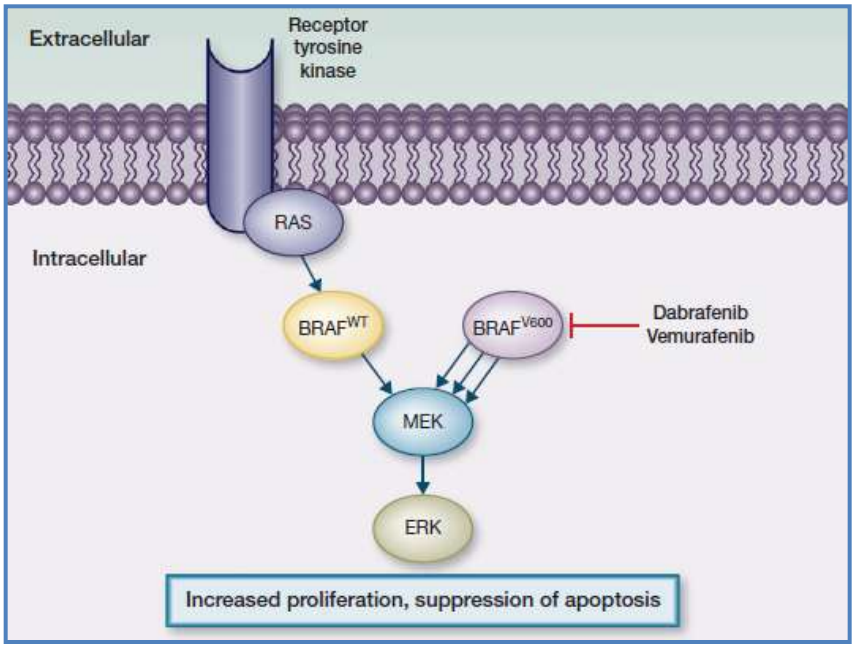


*"**Just 3 years ago, patients could only be offered chemotherapy and/or interleukin-2 . Ultimately, few patients benefited from that treatment**, although, for reasons still not completely understood, there were occasional stunning successes. Now, seemingly all of a sudden, RAF inhibitors, ipilimumab, and soon anti-PD1 antibodies have led to the expectation that tumors will shrink and that patient's lives can be extended with treatment".*

Jang S & Atkins MB. Lancet Oncol 2013; Chapman PB. ASCO Ed. 2014

$BRAF^{V600E}$-driven melanoma and BRAF inhibitors

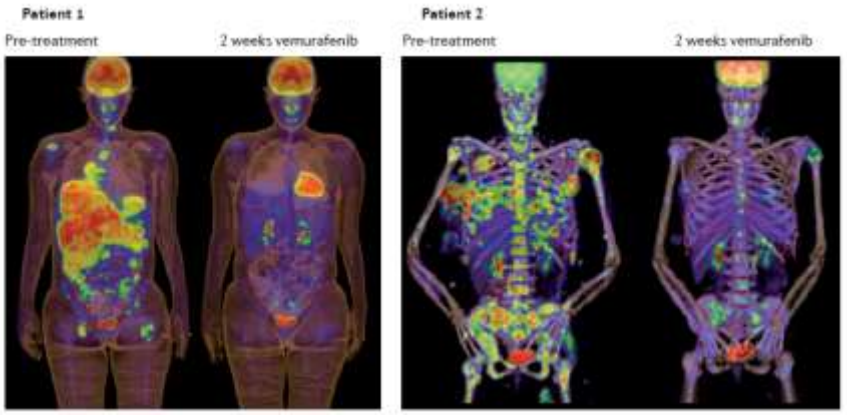




Mutations in BRAF have been found in 8% of human cancers, including **50-60% of cutaneous melanomas.**

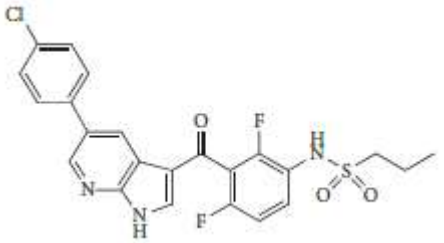
A valine-to-glutamate substitution in the glycine-rich loop is **the most frequent BRAF mutation (V600E**), **accounting for approximately 90% of cases**, although other activating mutations are known (e.g., BRAF V600K and BRAF V600R).

Vemurafenib is a potent inhibitor of mutated BRAF. It has marked antitumor effects against melanoma cell lines with the BRAF V600E mutation but not against cells with wild-type BRAF.



Salama AK, et al. Clin Cancer Res 2013; Bollag G, et al. Nat Rev Drug Discov 2012

VEMURAFENIB

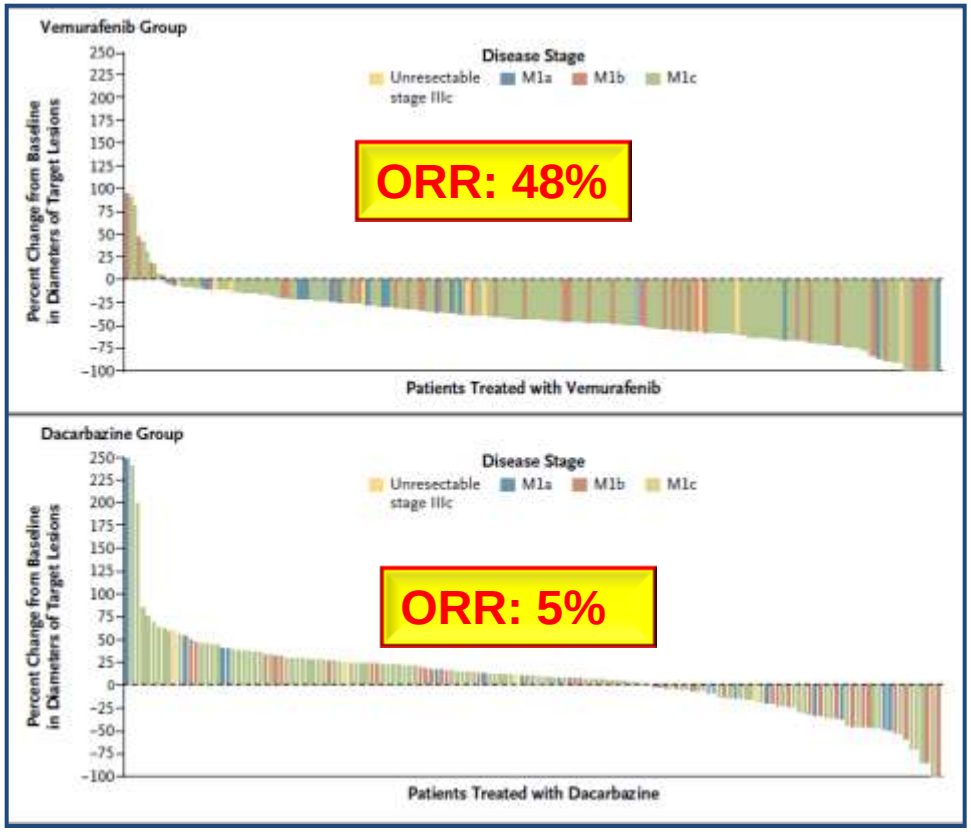


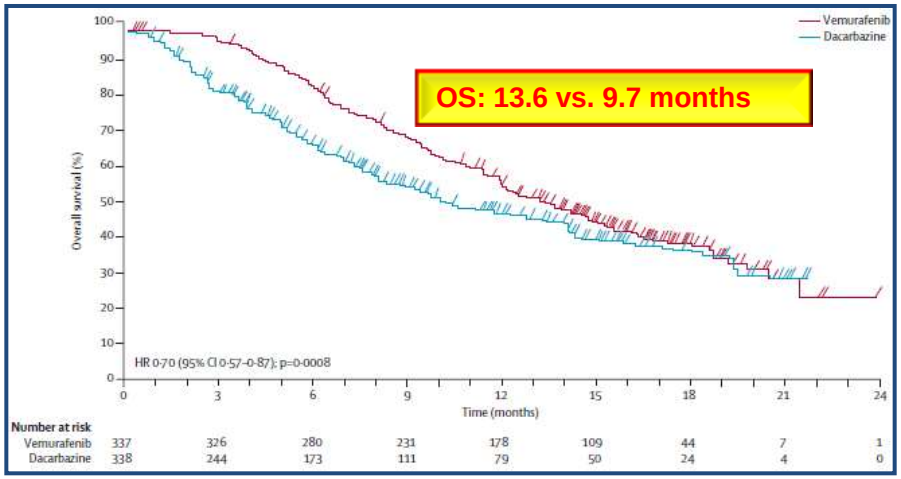
BRIM-3 (NO25026): Phase III Study in Previously Untreated Patients with Metastatic Melanoma

- Estimated enrollment: 680 patients
- Unresectable metastatic melanoma (stage IIIc/IV, AJCC)
- *BRAF*^{V600E} mutation positive, determined by cobas® 4800 *BRAF* V600 Mutation Test
- Chemo-naive for advanced disease

1:1
N=680

- Vemurafenib (960 mg BID orally)
- Dacarbazine (1000 mg/m² IV q3w)

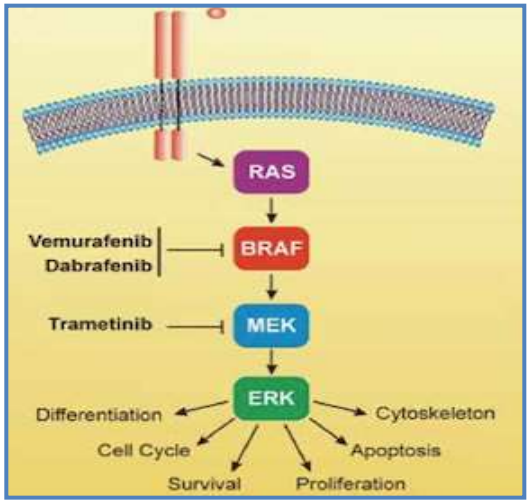


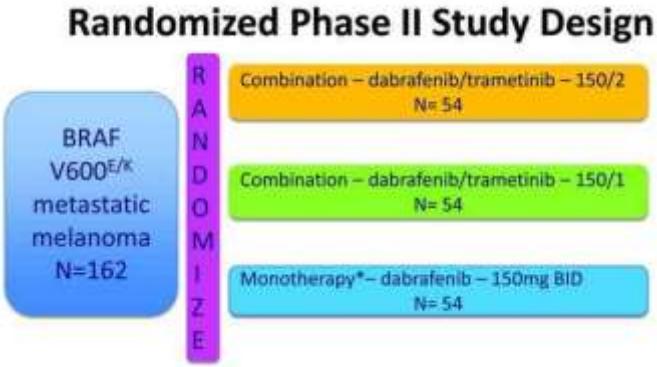


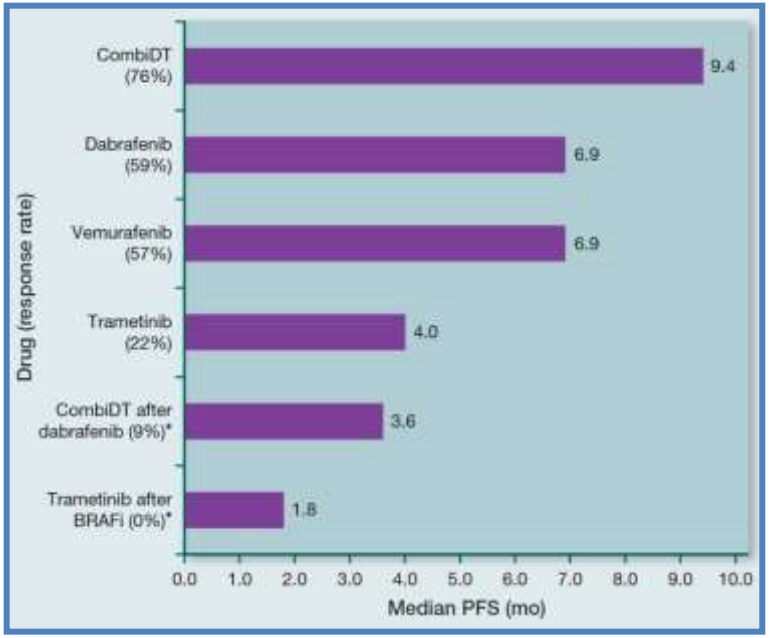
"*Vemurafenib was associated with a* ***relative reduction of 63% in the risk of death and of 74% in the risk of tumor progression*** *in patients with previously untreated, unresectable stage IIIC or stage IV melanoma with the BRAF V600E mutation, as compared with dacarbazine.* ***Benefit was seen in all subgroups*** *of patients who were included in the analysis,* ***including patients*** *with stage M1c disease or an elevated lactate dehydrogenase level, both of which are associated* ***with particularly poor prognoses****".*

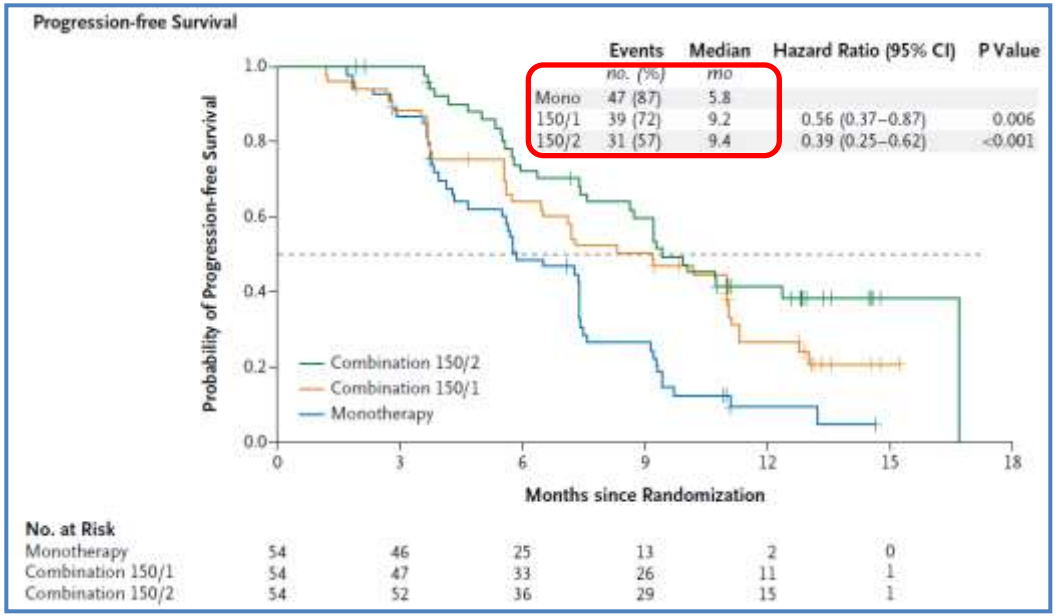
Chapman PB, et al. N Engl J Med 2011; Gnant A, et al. Lancet Oncol 2014

DUAL TARGETING IN BRAF^{V600E} MELANOMA: DABRAFENIB + TRAMETINIB



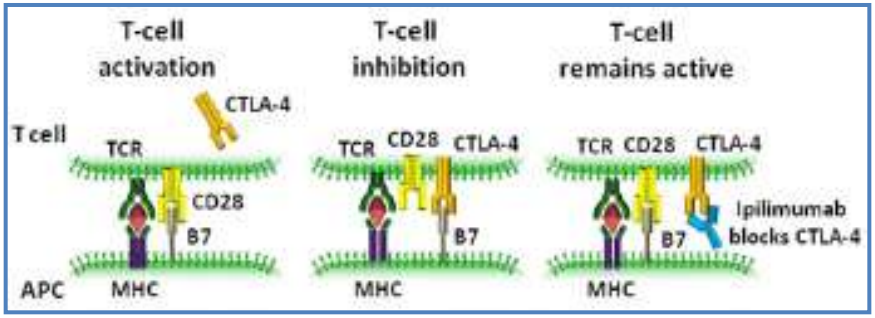


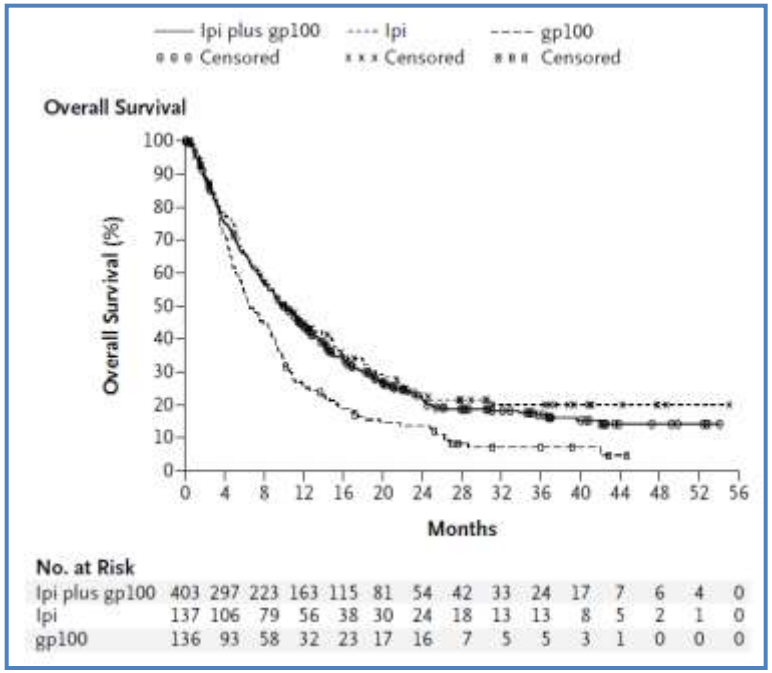




Flaherty KL, et al. N Engl J Med 2012; Menzieres AM, et al. Clin Cancer Res 2014

Ipilimumab

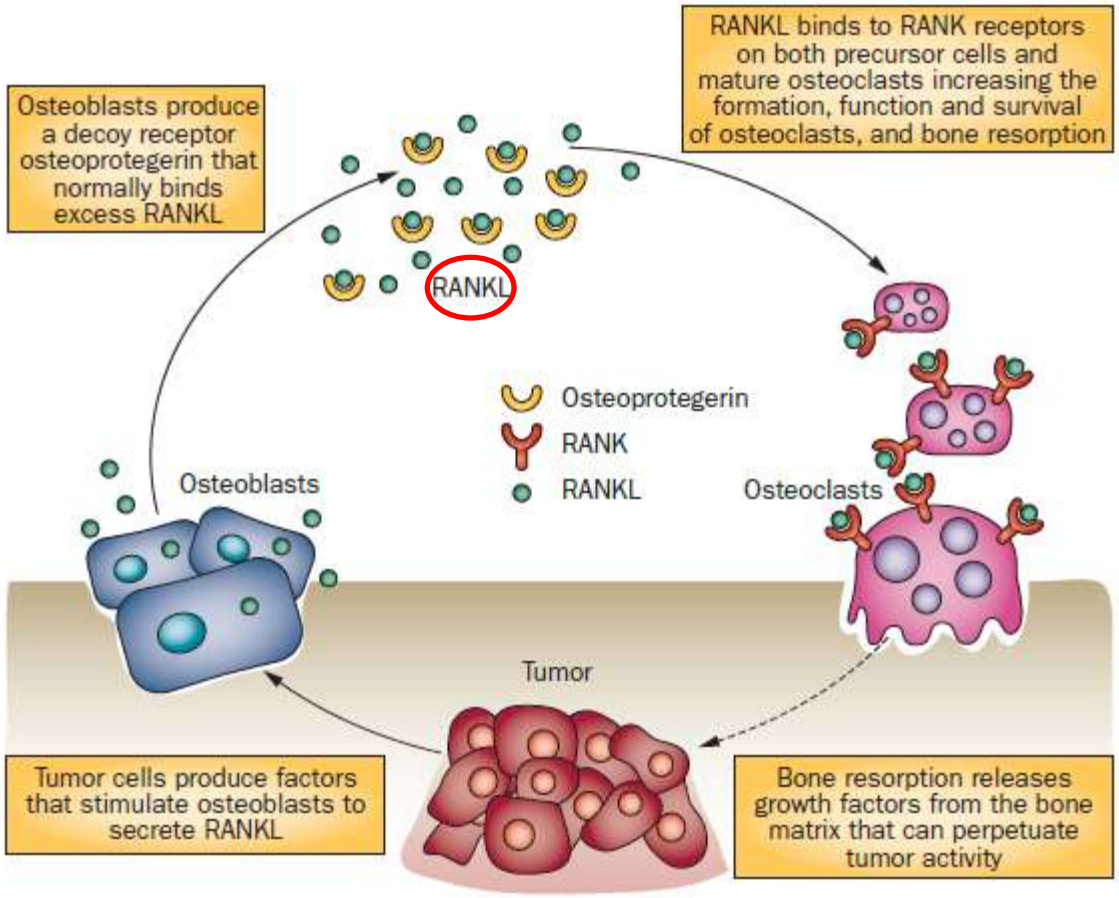




- ✓ Ipilimumab is an IgG1 mAb against CTLA4
- ✓ The study documented an **improvement in median OS of approximately 3.6 months**, including **a subset of patients who exhibited a long-term durable benefit of up to 4.5 years**
- ✓ **Ipilimumab's improvement of OS has changed the therapeutic landscape for melanoma**, but most patients still do not receive a significant clinical benefit.
- ✓ **Predictive biomarkers** of clinical benefit and toxicity **need to be developed** to better select patients for this therapy.
- ✓ Several factors have been preliminarily indicated as biomarkers for ipilimumab activity, although none have been prospectively validated. To date, neither immune-mediated toxicity nor HLA haplotype was significantly associated with clinical benefit in prospective or retrospective analyses

Hodi FS, et al. NEJM 2010; Walchok JD, et al. Ann N Y Acad Sci. 2013

Bone metastases in solid tumors



- ✓ Bone metastases are a **common complication of cancer** and occur in 65–80% of patients with metastatic breast and prostate cancers.
- ✓ The incidence of bone metastases is also increasing in other cancers, probably owing to improved tumour control at other disease sites.
- ✓ Tumour invasion into bone is associated with osteoclast and osteoblast recruitment, resulting in the liberation of growth factors from the bone matrix, which can feed back to enhance tumour growth resulting in the '*vicious cycle*' of bone metastases
- ✓ **RANKL is essential for the formation, function and survival of osteoclasts**. Stimulation of osteoblasts by tumor-secreted factors increases the expression of RANKL in bone metastasis, which binds osteoprotegerin and leads to increased bone resorption.

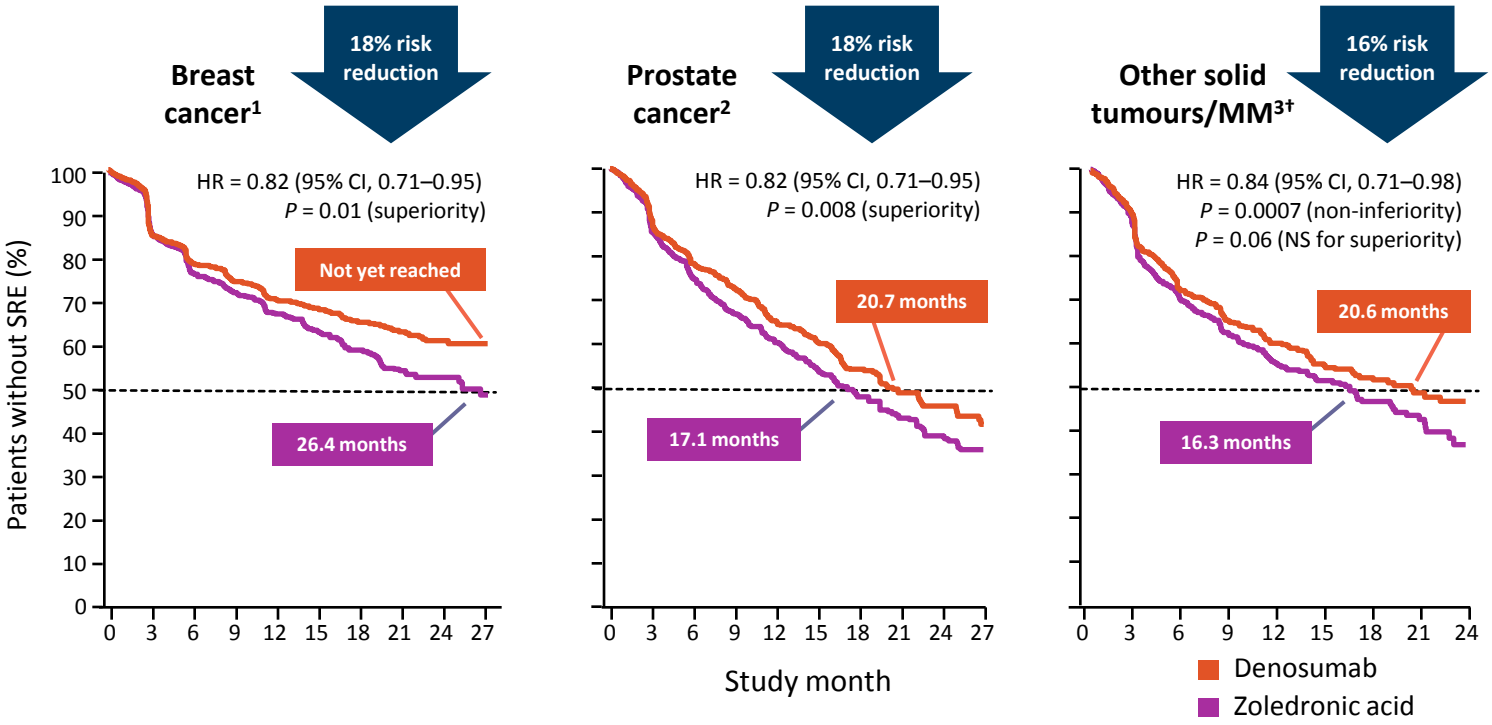
Brown JE, et al. Nat Rev Clin Oncol 2012

Denosumab

- Denosumab, a human monoclonal antibody, inhibits receptor activator of nuclear factor-κB ligand (RANKL), which mediates the increased bone resorption resulting from bone metastasis and cancer treatment
- Three phase III trials established denosumab as an effective new option to reduce skeletal morbidity in patients with solid tumors that have metastasized to bone.
- Denosumab is superior to zoledronic acid for patients with prostate or breast cancers and is noninferior for patients with other solid tumors.
- Denosumab is less likely than zoledronic acid to induce renal toxic effects and acute-phase reactions, but both drugs are associated with similar incidence of osteonecrosis of the jaw

Stopeck AT, et al. J Clin Oncol 2010; Fizazi K, et al. Lancet 2011; Henry DH, et al. J Clin Oncol 2011

Denosumab consistently reduced risk of first SRE across different tumor types



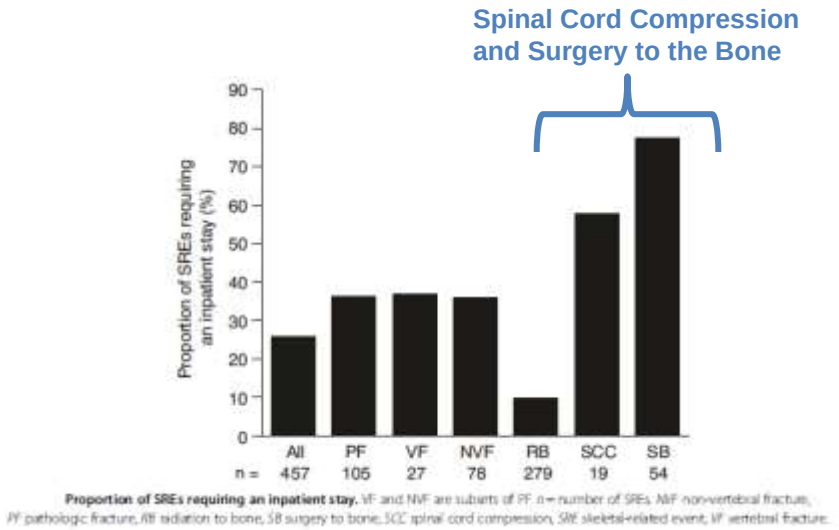
1. *Stopeck AT, et al. J Clin Oncol 2010*
2. *Fizazi K, et al. Lancet 2011*
3. *Henry DH, et al. J Clin Oncol 2011*

†Excluding breast and prostate.

Health resource utilization (HRU) associated with skeletal-related events (SREs)

- **Patients with bone metastases often experience skeletal complications** (skeletal-related events) pathologic fracture, radiation to bone, surgery to bone or spinal cord compression
- A recent prospective, observational study collected health resource utilization data independently attributed to SREs across Europe
- The mean duration of stay was 19.5 days per SRE
- Surgery to bone and spinal cord compression were the SREs most likely to require inpatient stays (77.8% and 57.9% of SREs, respectively), while radiation to bone was the most likely requiring an outpatient visit (85.7%) and also the greatest number of outpatient visits per event (6.8 visits).
- Collectively, all SREs were associated with substantial HRU; **therefore, preventing SREs in patients with bone metastases may reduce the burden imposed on healthcare systems**.

Proportion of SREs requiring an inpatient stay



Proportion of SREs requiring an inpatient stay. VF and NVF are subsets of PF. *n* = number of SREs. *NVF* non-vertebral fracture, *PF* pathologic fracture, *RB* radiation to bone, *SB* surgery to bone, *SCC* spinal cord compression, *SRE* skeletal-related event, *VF* vertebral fracture.

Lüftner D, et al. SpingerPlus 2014

Use of cancer drugs in the right patient: AIFA Approved Indications

NAME	CANCER TYPE	APPROVED INDICATIONS
Everolimus (Afinitor®)	➢ Renal Cancer ➢ Breast Cancer	➢ Advanced renal cancer after prior VEGF-inhibitors ➢ In association with exemestane in HR+/HER2- postmenopausal advanced BC after failure of a previous non steroideous AI
Sorafenib (Nexavar®)	➢ Renal Cancer ➢ Hepatocellular Carcinoma	➢ Advanced renal cancer after prior and/or not eligible for IFNα or IL-2 therapy ➢ Treatment of advanced HCC
Temsirolimus (Torisel®)	➢ Renal Cancer	➢ First-Line Advanced RCC with at least 3/6 risk factors
Sunitinib (Sutent®)	➢ Renal Cancer	➢ Advanced Renal Cancer
Erlotinib (Tarceva®)	➢ NSCLC	➢ Advanced NSCLC after at least one chemotherapeutic line ➢ First-line NSCLC with activating EGFR mutations
Cetuximab (Erbitux®)	➢ Colorectal Cancer ➢ Head & Neck Cancer	➢ In combination with Irinotecan after failure of previous Irinotecan-based CT KRAS *wt* mCRC ➢ In pts with mCRC KRAS wt in association with CT ➢ Monotherapy in mCRC KRAS *wt* after failure of CT oxaliplatin and irinotecan-based ➢ Advanced HNSCC in association with platinum-based CT
Panitumumab (Vectibix®)	➢ Colorectal Cancer	➢ KRAS *wt* mCRC in association with FOLFOX (1 st line) or FOLFIRI (2 nd line) or monotherapy after failure of regimens containing oxaliplatin, irinotecan and fluoropirimidines
Trabectidin (Yondelis®)	➢ Soft Tissue Sarcomas ➢ Ovarian Cancer	➢ STSs after failure of antracyclines and iphosphamide regimens ➢ Ovarian cancer platinum-sensitive in association with PLD
Eribulin (Halaven®)	➢ Breast Cancer	➢ mBC after failure of at least 2 CT lines, containing antracyclines and taxanes
Vinflunine (Javlor®)	➢ Urothelial Carcinoma	➢ Urothelial Carcinoma after failure of platinum-based regimen
Cabazitaxel (Jevtana®)	➢ Prostate Cancer	➢ In association with prednisone in mCRPC after failure of docetaxel
Trastuzumab (Herecptin®)	➢ Gastric Cancer	➢ First line therapy in association with cisplatin and 5FU or capecitabine
Ipilimumab (Yervoy®)	➢ Melanoma	➢ Second-line therapy in advanced melanoma

NAME	CANCER TYPE	APPROVED INDICATIONS
Denosumab (Xgeva®)	➢ Bone Metastases from Solid Tumors	➢ Prevention of SREs in solid tumors pts with bone metastases
Abiraterone (Zytiga®)	➢ Prostate Cancer	➢ mCRPC after failure of docetaxel therapy
Crizotinib (Xalkori®)	➢ NSCLC	➢ ALK positive NSCLC after at least one chemotherapy line
Pemetrexed (Alimta®)	➢ Non-squamous NSCLC	➢ First-line chemotherapy in association with Cisplatin ➢ Second-line monotherapy ➢ Maintenance therapy in non-progressive pts after first line CT
Gefitinib (Iressa®)	➢ NSCLC	➢ EGFR-mutated advanced NSCLC
Pazopanib (Votrient®)	➢ Renal Cancer ➢ Sof Tissue Sarcomas	➢ First line therapy of advanced RCC after cytokines-based therapy ➢ STSs after failure of a previous CT regimens
Lapatinib (Tyverb®)	➢ Breast Cancer	➢ In association with capecitabine in mBC HER2+ after failure of previous regimens containing antracyclines, taxanes and trastuzumab ➢ In association with an AI in HER2+/HR+ mBC with postmenopausal status
Vemurafenib (Zelboraf®)	➢ Melanoma	➢ BRAF V600-mutated advanced melanoma
Bevacizumab (Avastin®)	➢ Colorectal Cancer ➢ Breast Cancer ➢ NSCLC ➢ Renal Canncer	➢ In mCRC in association with fluoropirimine-based CT ➢ In association with Paclitaxel in first line mBC ➢ Fist line CT in non-squamous advanced NSCLC ➢ First-line treatment of mRCC in association with IFα2
Vandetanib (Caprelsa®)	➢ Medullary Thyroid Carcinoma	➢ Adavnced MTC
Axitinib (Inlyta®)	➢ Renal Cancer	➢ Advanced RCC after failure of sunitinib or cytokine treatment

How to reduce rising costs of cancer care ?

•Advancements in the prevention, diagnosis, and treatment of cancer have contributed to improved survival, better quality of life, and declining death rates.

•With these successes have come increases in cost to a level that is now causing serious financial burdens to patients, families, and society at large.

•The basis for the rising cost of care is complex and is due, in part, to **unnecessary use of health care resources**: for instance, the Congressional Budget Office estimates that up to 30% of care delivered in the US goes toward unnecessary tests, procedures, physician visits, hospital stays, and other services that do not improve a patient's health!

Schnipper LE, et al. J Clin Oncol 2012

The ASCO top 5 list to improve care and reduce costs

1. **Do not use cancer-directed therapy for patients with solid tumors who have low performance status (3 or 4), no benefit from prior evidence-based interventions, not eligible for a clinical trial, and with no strong evidence supporting the clinical value of further anticancer treatment.**
    - *Exceptions include patients with functional limitations due to other conditions resulting in a low performance status or those with disease characteristics (e.g. mutations) that suggest a high likelihood of response to therapy.*
    - *Implementation of this approach should be accompanied with appropriate palliative and supportive care.*

2. **Don't perform PET, CT and radionuclide bone scans in the staging of early prostate cancer at low risk for metastasis.**
    - *Evidence does not support the use of these scans for staging of newly diagnosed low grade carcinoma of the prostate (stage T1c/T2a, PSA < 10 ng/ml, Gleason score < 6) with low risk of distant metastasis.*
    - *Unnecessary imaging can lead to harm through unnecessary invasive procedures, over-treatment, unnecessary radiation exposure, and misdiagnosis*

3. **Don't perform PET, CT and radionuclide bone scans in the staging of early breast cancer at low risk for metastasis**
    - *In breast cancer there is a lack of evidence demonstrating a benefit for the use of PET, CT or radionuclide bone scans in asymptomatic individuals with newly identified DCIS, or clinical stage I or II disease.*

4. **Don't perform surveillance testing (biomarkers) or imaging (PET, CT and radionuclide bone scans) for asymptomatic individuals who have been treated for breast cancer with curative intent**

5. **Don't use white cell stimulating factors for primary prevention of febrile neutropenia for patients with less than 20% risk for this complication**
    - *Exceptions should be made when using regimens that have a lower chance of causing febrile neutropenia if it is determined that the patient is at high risk for this complication (as a result of age, medical history, or disease characteristics).*

Schnipper LE, et al. J Clin Oncol 2012

Controlling the cost of innovative cancer therapeutics

- The cost of targeted therapies for cancer is soaring out of control
- Healthcare payers and patients are increasingly struggling to meet the high costs, which can be up to US$100,000 a year
- Companies defend high drug prices by citing the escalating cost of research and development: **it costs on average $1.2 billion to bring a new biologic to the market**
- **How we can manage with these rising costs?**
  - ✓ **Government price controls on cancer drugs**
  - ✓ **Biosimilars Drugs**
    - *Biosimilars are expected to be discounted by 20–40%.*
    - *Biosimilars should nonetheless help control the cost of anticancer monoclonal antibodies. Their most important benefit to society, however, will come from their ability to drive innovation forward, by preventing pharmaceutical companies from resting on their past product successes*
  - ✓ **Novel drug pricing strategies**
    - *Pay-for-performance reimbursement*
    - *Products could be launched at a discount, and prices increased if robust data for effectiveness emerge*
    - *Another pricing policy could be to discount a product once a patient has used it for a certain period of time*

Malik NN. Nat Rev Clin Oncol 2009

Moving towards a rapid and efficient regional drug reimbursement: the Emilia-Romagna experience

- Nel 2009 è partita l'attività di un sottogruppo della Commissione regionale del farmaco (in collaborazione con la Commissione oncologica regionale) per la definizione di raccomandazioni evidence-based sui nuovi farmaci oncologici: il Gruppo regionale farmaci oncologici (GReFO).

- Il GReFO è un panel/gruppo multidisciplinare composto da oncologi clinici, palliativisti, radioterapisti, internisti, farmacisti e direzione sanitaria.

- Per l'elaborazione delle raccomandazioni è utilizzato il metodo GRADE, che consente un processo trasparente e strutturato attraverso votazione degli outcome di interesse; sintesi delle evidenze scientifiche e definizione della qualità complessiva delle evidenze; votazione del rapporto benefici/rischi; discussione dei fattori da considerare nel procedere dalle evidenze alla forza della raccomandazione; forza della raccomandazione e indicatori d'uso atteso.

- I documenti elaborati offrono gli elementi scientifici per definire il ruolo in terapia di alcuni farmaci inclusi nel Prontuario Terapeutico Regionale.

The French national network of 28 hospital molecular genetics platforms

- The Institute National du Cancer has been supporting a **national network of 28 hospital molecular genetics platforms** throughout France since 2006. They include several laboratories, which may belong to various institutions, offering patients all essential molecular genetics techniques for all relevant diseases.

- **The platforms perform innovative molecular testing** that:
  - ✓ determines **access to targeted therapy**;
  - ✓ guides the **diagnostic process**;
  - ✓ contributes to **establishing a diagnosis** in addition to clinical, morphological and biological parameters;
  - ✓ **guides patient treatment strategy;**
  - ✓ **allows monitoring of residual diseases**.

- **Molecular tests conducted by the platforms are relevant to a large number of diseases**, some of which are common such as lung cancer, colorectal cancer or breast cancer.

- **They perform testing of all patients in the region, regardless of the institution where they are treated**, i.e. university hospitals, cancer centers, hospital centers or private institutions

Multiple Biomarkers Platform: the example of NSLC

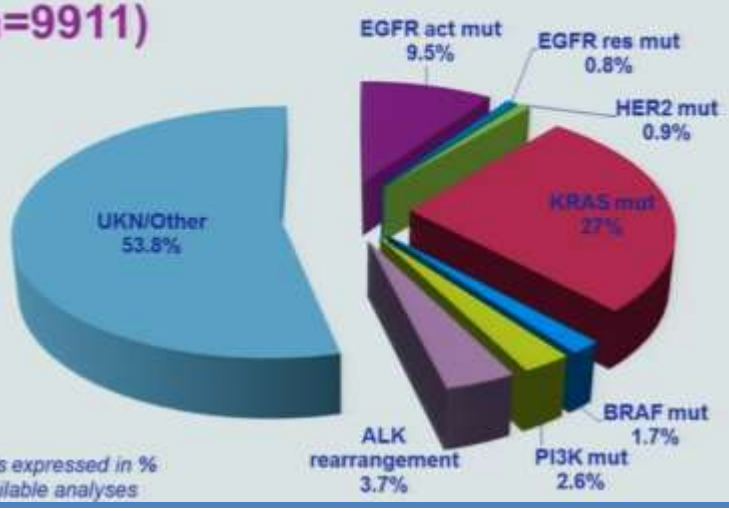
The French platforms* network

- 28 platforms (2006)
- 7 biomarkers for Non-sq NSCLC (starting 2010)

Cancer	Molecular Target
Lung	EGFR mutations (activating and resistant)
Non-sq NSCLC	EML4-ALK transloc.
	KRAS mutations
	HER2 ex20 mutations
	BRAF mutations
	PI3K mutations

*i.e. Regional molecular genetics centers

Results: biomarkers assessment (n=9911)



Results expressed in % on available analyses

- ✓ **Biomarkers France** is the **largest ever** conducted **biomolecular study on advanced NSCLC** patients and provides solid data on the value of a nationwide BM screening policy for NSCLC patients
- ✓ **NSCLC tumor profiling is feasible**
- ✓ Tumor profiling **identified a known target in 46% of samples** and **helped to manage patients in 57% of the cases**

PRESENTED AT: ASCO Annual '13 Meeting

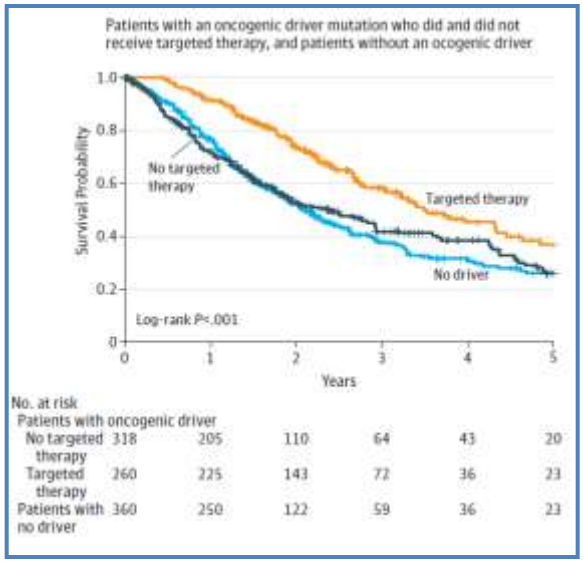
Barlesi F, et al. ASCO 2013

Multiple Biomarkers Platforms and Targeted Therapies

SAFIR 01 trial

- **Designed early 2010**
- **Primary goal: to detect genomic alteration on metastatic tissue and enrich phase I/II trials in patients with a genomic alteration located in the pathway targeted by the drug**
  Goal: 30% of the patients treated according to a genomic alteration (n=120)
- **Secondary goals:**
  To show feasibility of whole genome approach in a large population
  To suggest that the use of a whole genome technology improves outcome
- **Target accrual: 400 patients**

Lung Cancer Mutation Consortium (LCMC)



- This multi-institutional consortium identified patients with rare genomic changes and used the information to select treatments and facilitate trials.
- Although the frequency of any individual oncogenic driver may be small, **an actionable driver was detected in 64% of tumors from patients with lung adenocarcinomas**
- Multiplexed testing aided physicians in selecting therapies.
- **Individuals with drivers receiving a matched targeted agent lived longer**

André F, et al. ASCO 2013; Kris MG, et al. JAMA 2014

Final remarks

- ✓ Introduction of targeted therapies have substantial changed the therapeutic landscape of most cancer types, moving from the old statement "*one size fits all*" to tailored medicine

- ✓ However, this paradigm shift was associated with a dramatic increase in cancer care cost

- ✓ Many challenges and pitfalls remain in selecting optimal targets, interpreting data on genetic aberrations, designing effective targeted drugs and antibodies, dealing with resistance to treatments, identifying appropriate combinations of therapies, and performing the complex clinical trials that are required

- ✓ To maximize the effectiveness of these new strategies, close collaboration between academic, industry, and regulatory agencies will be required

- ✓ Novel strategies in drug cancer development may help a more rapid and less expensive regulatory approval, as well new strategies for drug reimbursement may reduce healthcare burden of innovative cancer drugs

- ✓ Importance of evidence-based decision making in order to reduce unnecessary use of health care resources

6th International Conference on Integrated Therapies in Oncology

Women's Projectnin Ocol ogy: Looking towards the Future

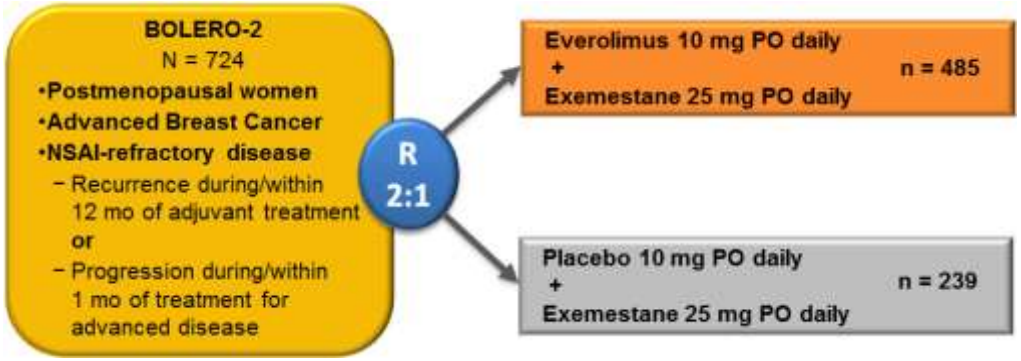
President: Vincenzo Adamo

November 13th 2014 **Aula Magna University of Messina**

November 14th-15th 2014 **Hotel Hilton Giardini Naxos**

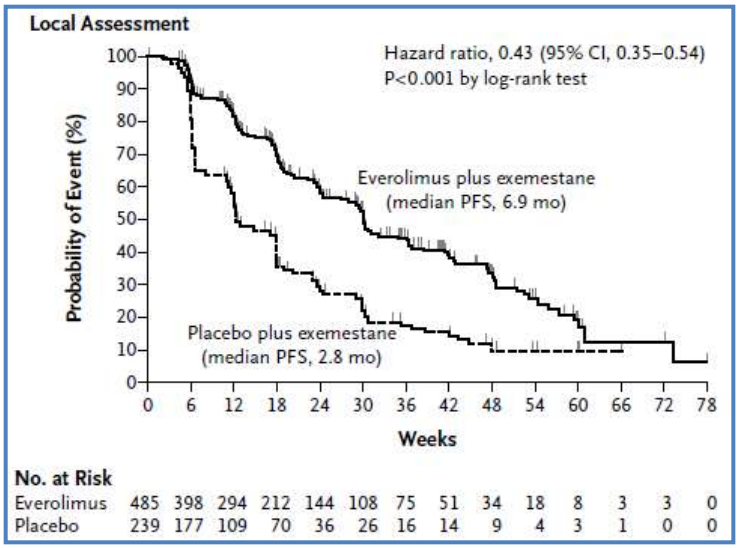
www.womensprojectinoncologyconference.it

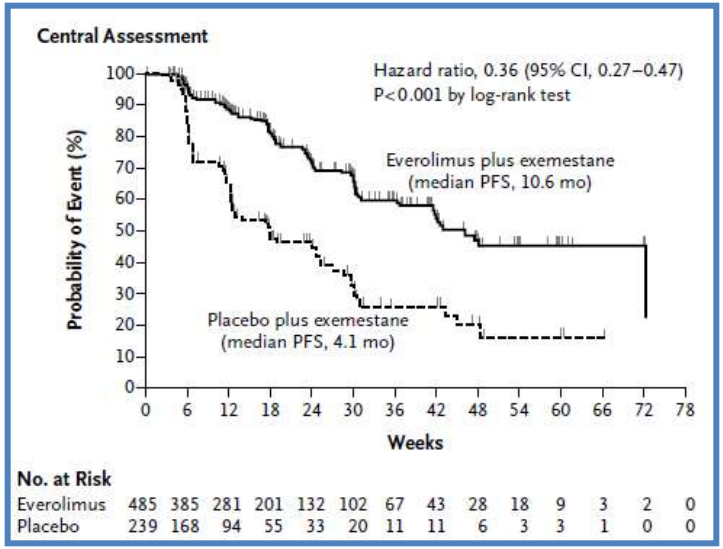
Everolimus-Exemestane in Postmenopausal HR+ HER2 negative Advanced Breast Cancer: BOLERO-2 Trial



Key Baseline Characteristics

Median age, years	62
Race, %	
Caucasian	75
Asian	20
Visceral involvement, %	56
Bone metastases, %	77

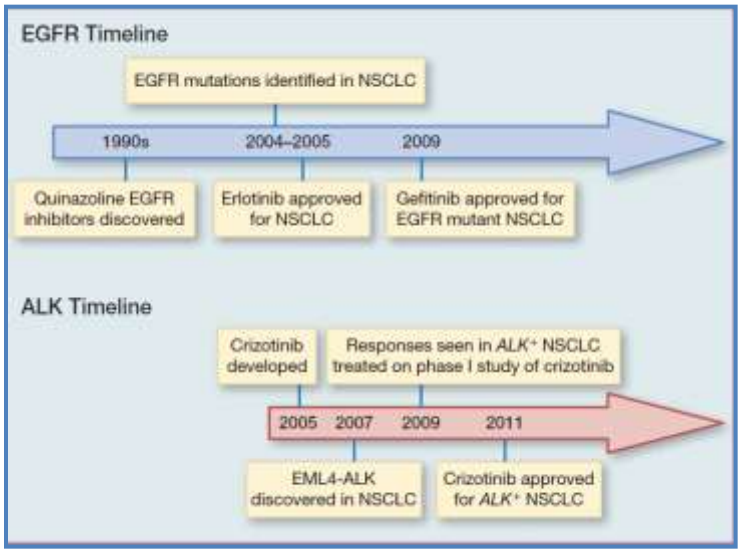




*"The BOLERO-2 study showed that the **addition of everolimus to exemestane significantly improves PFS**, with observed medians of 6.9 and 2.8 months, corresponding to a 57% reduction in the hazard ratio"*

Baselga J, et al. NEJM 2012

Novel approches for drug development: the incredible story of ALK inhibitors



The approval of Crizotinib was based on dramatic response rates in ALK-positive NSCLC patients of 54% to 61% in phase I and II trials. These results led to the **accelerated FDA approval of crizotinib for ALK-positive patients with NSCLC in record time**—the timeframe from discovery of the target in late 2007 to FDA approval of a targeted therapy in August 2011 was <4 years. **The approval was granted while both the phase I and phase II trials were ongoing.**

"The old saw that phase I is all about safety and phase II is all about efficacy no longer applies. ***Phase I is all about Proof of Principle and efficacy,*** *once a safe dose is reached".*


The Oncologist

Editorial

Approval After Phase I: Ceritinib Runs the Three-Minute Mile

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Disclosures of potential conflicts of interest may be found at the end of this article.

On April 29, 2014, the U. S. Food and Drug Administration granted accelerated approval to ceritinib (ZYKADIA, LDK 378) for the treatment of patients with ALK-positive, metastatic NSCLC with disease progression on or who are intolerant to crizotinib.

The approval of ceritinib was based on the results of a multicenter, single-arm, open-label clinical trial enrolling a total of 163 patients with metastatic, ALK-positive, NSCLC who had progressed on or were intolerant to crizotinib. All patients received ceritinib at a dose of 750 mg once daily.

*"**A well-designed phase I trial**, even if it requires the participation of multiple institutions,* ***can readily attract sufficient patients with uncommon tumors to prove efficacy and safety sufficient for accelerated approval"***

Ghandi L, et al. Clin Cancer Res 2012; Chabner BA. Oncologist 2014

Global Burden of Cancer

Estimated New Cancer Cases and Deaths Worldwide for Leading Cancer Sites

	Estimated New Cases				Estimated Deaths			
	Male		Female		Male		Female	
Worldwide	Lung & bronchus	1,095,200	Breast	1,383,500	Lung & bronchus	951,000	Breast	458,400
	Prostate	903,500	Colon & rectum	570,100	Liver	478,300	Lung & bronchus	427,400
	Colon & rectum	663,600	Cervix Uteri	529,800	Stomach	464,400	Colon & rectum	288,100
	Stomach	640,600	Lung & bronchus	513,600	Colon & rectum	320,600	Cervix uteri	275,100
	Liver	522,400	Stomach	349,000	Esophagus	276,100	Stomach	273,600
	Esophagus	326,600	Corpus uteri	287,100	Prostate	258,400	Liver	217,600
	Urinary bladder	297,300	Liver	225,900	Leukemia	143,700	Ovary	140,200
	Non-Hodgkin lymphoma	199,600	Ovary	225,500	Pancreas	138,100	Esophagus	130,700
	Leukemia	195,900	Thyroid	163,000	Urinary bladder	112,300	Pancreas	127,900
	Oral cavity	170,900	Non-Hodgkin lymphoma	156,300	Non-Hodgkin lymphoma	109,500	Leukemia	113,800
	All sites but skin	6,629,100	All sites but skin	6,038,400	All sites but skin	4,225,700	All sites but skin	3,345,800

Global Cancer Facts & Figures, 2nd edition

At a global level**, the burden of cancer is rising,** with incidence projected to increase from 12.7 million in 2008 to 21.4 million in 2030.

In addition to the human toll of cancer, the financial cost of cancer is substantial.

The **direct costs** include payments and resources used for treatment, as well as the costs of care and rehabilitation related to the illness.

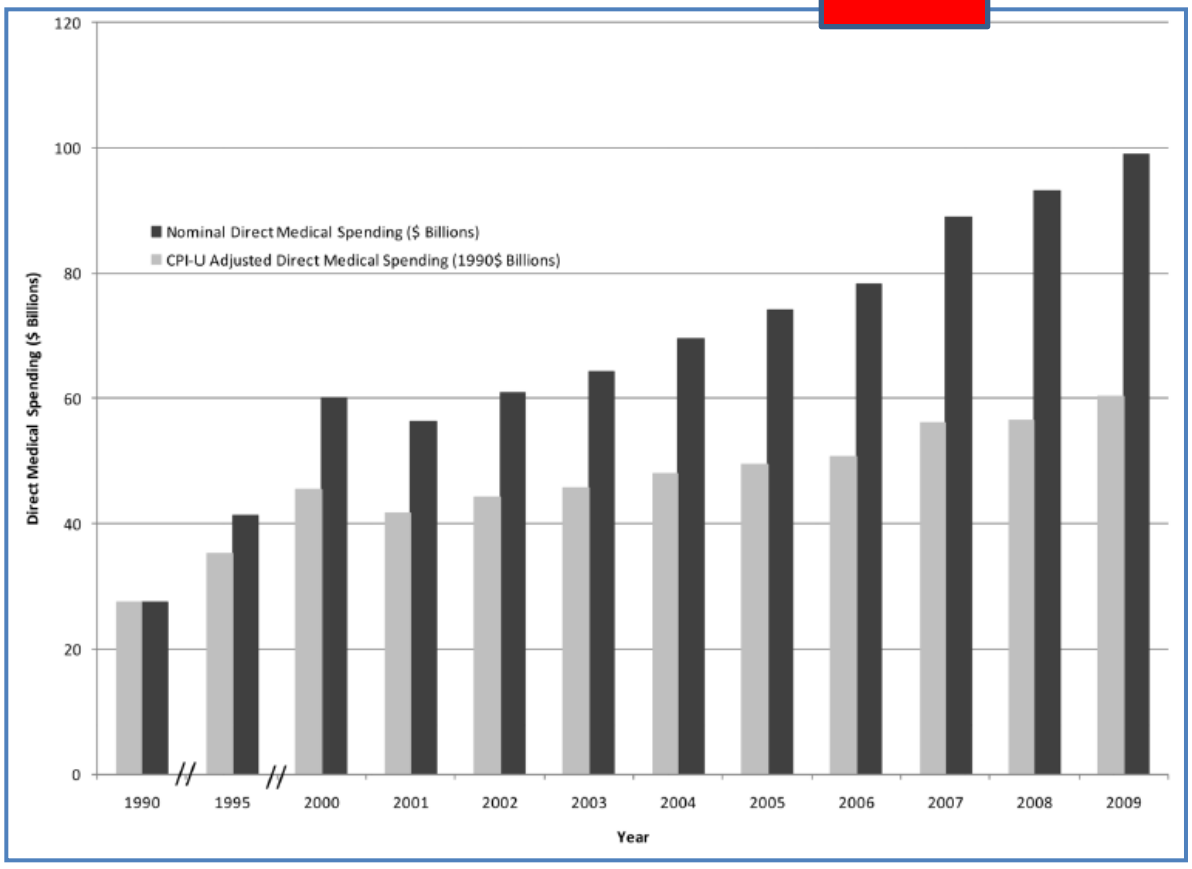
Indirect costs include the loss of economic output due to days missed from work (morbidity costs) and premature death (mortality costs).

There are also **hidden costs** of cancer, such as health insurance premiums and nonmedical expenses (transportation, child or elder care, housekeeping assistance, wigs, etc.).

Recent research has shown that **cancer has the most devastating economic impact** of any cause of death in the world.

Portions of the total costs of cancer have been estimated to be as high as **$895 billion (US) worldwide (1.5% of the world's gross domestic product)**

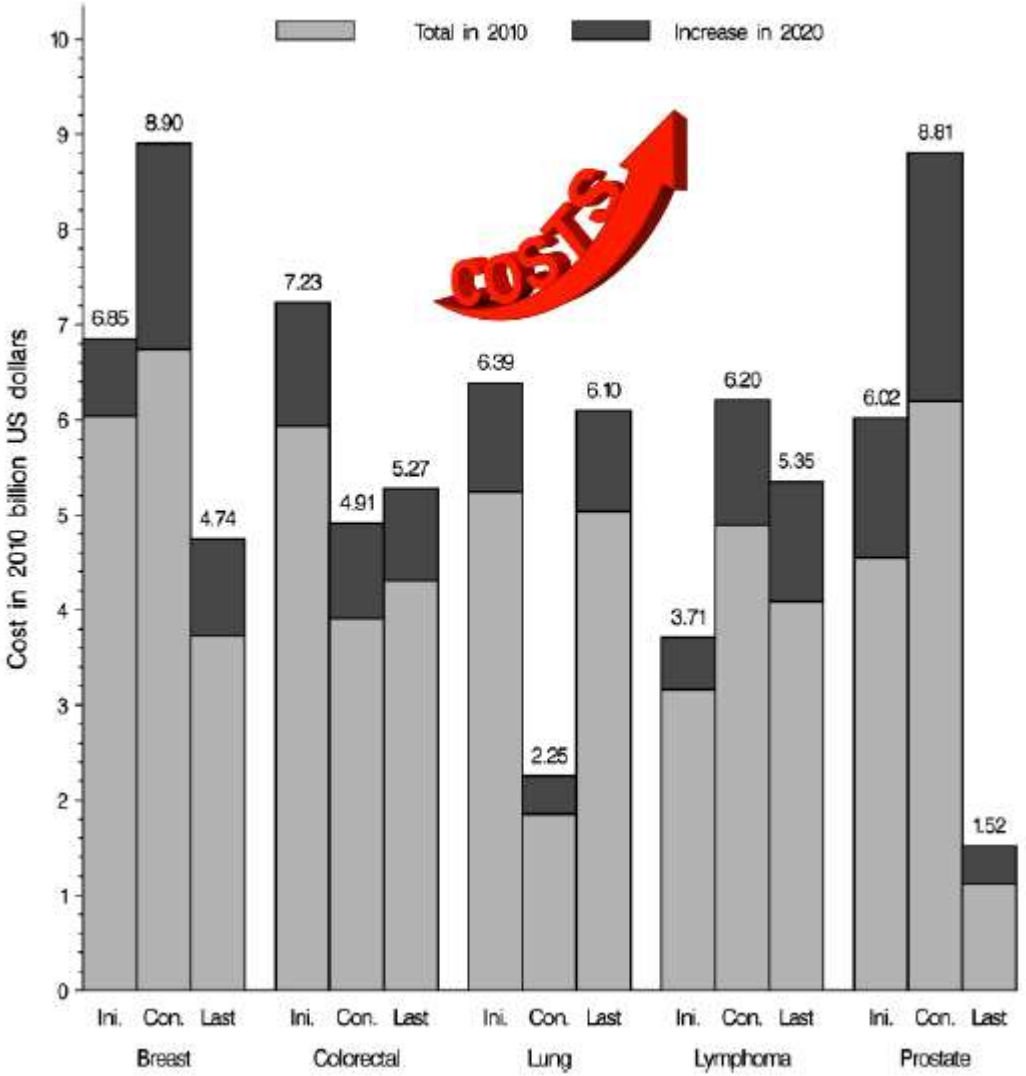
Nominal and inflation-adjusted direct medical spending attributed to cancer, 1990–2009.



- ✓ The direct medical costs of cancer have grown dramatically in the past two decades.
- ✓ By one set of estimates, expenditures rose from about $27 billion in 1990 to more than $90 billion in 2008, **a more than two-fold increase** even after adjusting for inflation.
- ✓ The overall growth in spending is due to **increases in both the price** (i.e. costs of the drugs) **and the quantity of care** (i.e. patients receiving active therapies).
- ✓ **Newer cancer therapies** are not only more expensive than the prior standard of care, but they also **expand the pool of treatment candidates**.

Elkin EB & Bach PB. JAMA 2010

Projections of the Cost of Cancer Care in the United States: 2010–2020



- ✓ Assuming constant incidence, survival, and cost, the authors projected 13.8 and 18.1 million cancer survivors in 2010 and 2020, respectively, with associated costs of cancer care of 124.57 and **157.77 billion 2010 US dollars**.
- ✓ This **27% increase in medical costs** reflects US population changes only.
- ✓ However, if costs of care increase annually by 2% in the initial and last year of life phases of care, **the total cost in 2020 is projected to be $173 billion, which represents a 39% increase from 2010**

Mariotto AB, et al. J Natl Cancer Inst 2011


Herceptin® 150 mg
powder for concentrate for solution for infusion
Trastuzumab
150 mg
For intravenous use after reconstitution and dilution
Roche


PERJETA
pertuzumab

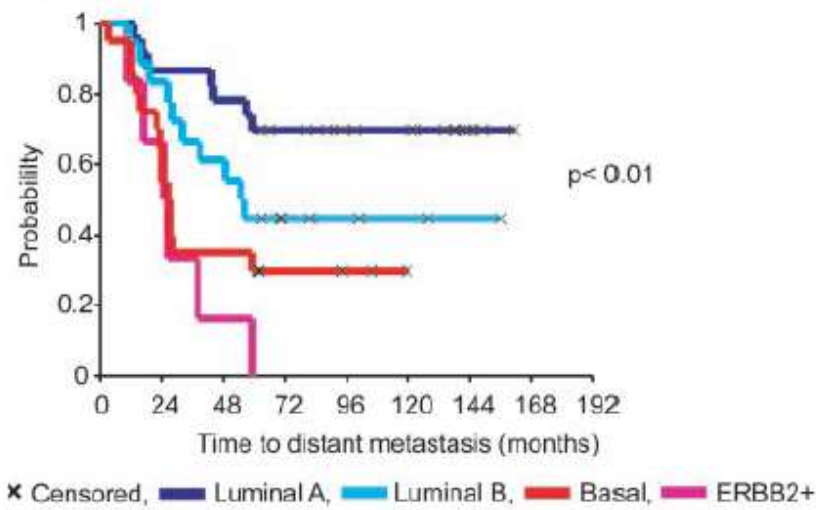

Zelboraf
(vemurafenib
tablets)
240 mg

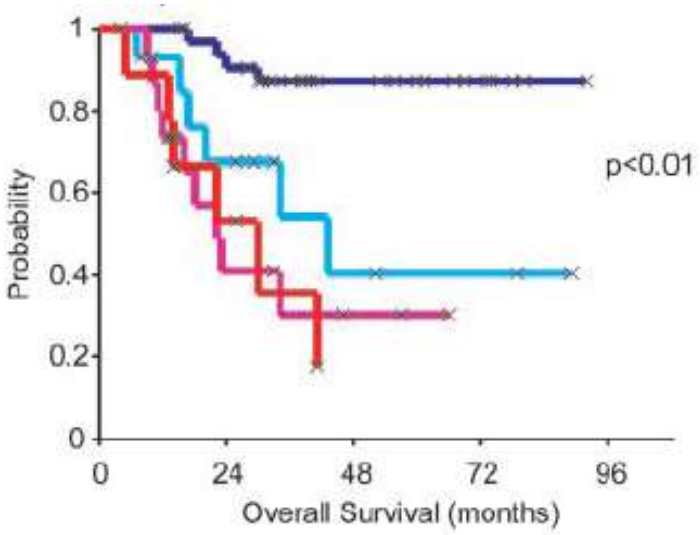

YERVOY
(ipilimumab)
injection
50 mg/10 mL

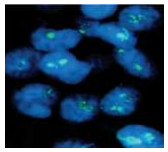

XGEVA

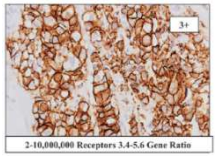
(XGEVA®)

HER2 POSITIVE BREAST CANCER





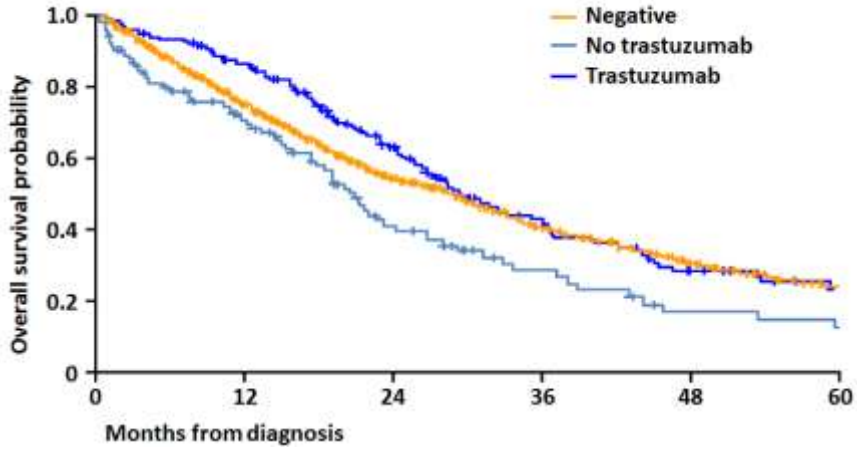




Amplification of the *HER2* gene and/ or overexpression at the messenger RNA or protein level **occurs in about 20% of patients** with early stage breast cancer

Before the advent of HER2-directed therapies, **this increased level of HER2 was associated with high recurrence rates and increased mortality** in patients with node-positive and node-negative disease

Trastuzumab overcomes the unfavourable prognostic value of HER2 overexpression



Sørlie T, et al. Proc Natl Acad Sci USA 2003; Dawood S, et al. J Clin Oncol 2008