13 DICEMBRE 2021 ORE 09:00
CASA DELL'AVIATORE Viale dell'Università 20 ROMA

SOSTENIBILITÀ IN ONCOLOGIA
COME CONCILIARE
RICERCA, VALORE SCIENTIFICO, PREZZO E ACCESSIBILITÀ
OPINIONI A CONFRONTO

Medicina personalizzata e medicina di precisione: Innovazione, appropriatezza e sostenibilità

Dr. Giordano Beretta

Presidente Fondazione AIOM
Past President AIOM

Responsabile Oncologia Medica
Humanitas Gavazzeni Bergamo

Potenziali Conflitti d'interessi

Ai sensi dell'art. 3.3 del Regolamento applicativo dell'Accordo Stato-Regioni 05.11.2009, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- **Partecipazione ad Advisory Board:**
  - Roche
  - Lilly
  - Eisai
  - Incyte
- **Spese per invito a convegni:**
  - Roche
  - Servier
  - Celgene
  - Ipsen
  - Sanofi
- **Finanziamento istituzione per ricerca:**
  - Roche
  - MSD
  - Tahio

- **Relatore eventi (ECM e non ECM):**
  - Servier
  - Clovis Oncology
  - Ipsen
  - Lilly
  - Merck Serono
  - Amgen
  - Novartis
  - BMS

Come presidente AIOM ho avuto rapporti con tutte le Industrie Farmaceutiche che operano in Oncologia

Terapia oncologica

- Per decenni il trattamento era

"one size fits all"

- C'era scarsa disponibilità di farmaci attivi
- l'unica scelta era:

"Trattare o non trattare?"

- **Eppure già allora la terapia era personalizzata**
  - **Caratteristiche del paziente**
    - ✓ Comorbidità
    - ✓ PS
    - ✓ Età
  - **Estensione della malattia**
    - ✓ Stadio
    - ✓ Tipologia di metastasi
  - **Aggressività della malattia**
    - ✓ Rapidità di crescita

Nuove strategie

Più linee terapeutiche

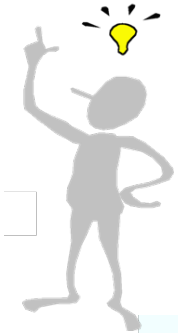
- Colon
- Mammella
- Polmone

Anche in pazienti oltre i 65 e 70 anni

- Minore tossicità
- Minore incidenza di effetti collaterali importanti
- Somministrazione più facile
  - Terapia orale

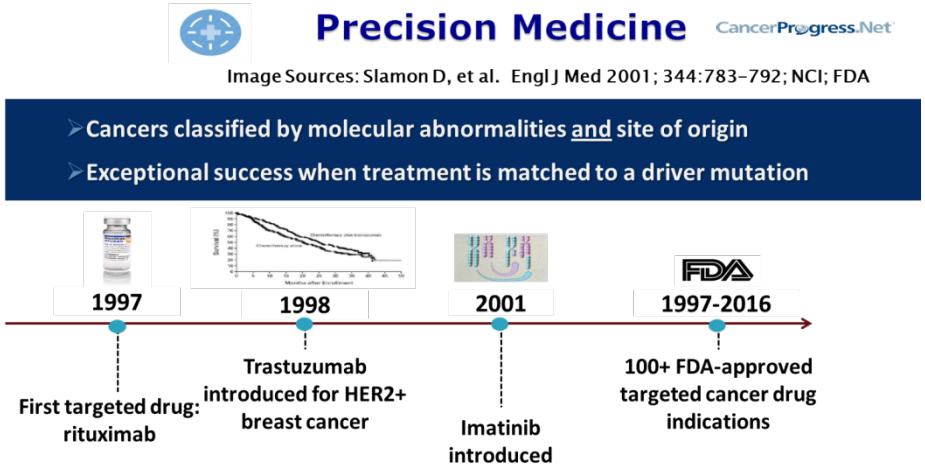
Miglioramento delle terapie

- Integrazione multidisciplinare di diversi specialisti
- PDTA (Percorsi Diagnostico Terapeutici Assistenziali) multiprofessionali
- Disponibilità di nuove terapie
- Nuove conoscenze biologiche e immunologiche



L'avvento della terapia molecolare: la *Target Therapy*

- **Dai farmaci tradizionali che colpiscono il DNA e le strutture cellulari ai farmaci che colpiscono selettivamente molecole di segnale coinvolte in tappe fondamentali di crescita e disseminazione cellulare:**



Maggiore efficacia

Minore tossicità

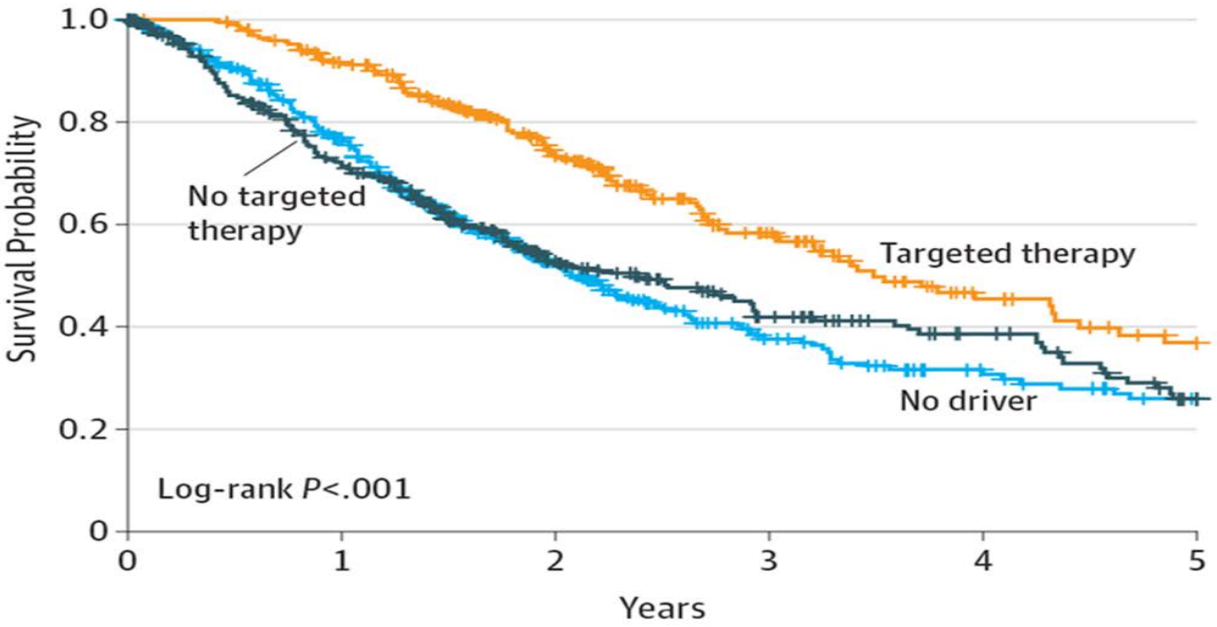
PRECISION MEDICINE
Target-based agents + predictive biomarkers:

La cosa giusta per i pazienti:

Abbinare il farmaco con i pazienti che ne avranno beneficio e non trattare quelli che non lo avranno

Chemioterapia vs target therapies

Survival of patients with oncogenic drivers – targeted therapy vs. *no* targeted therapy



Kris et al. JAMA 2014

Terapia target

Mammella

The NEW ENGLAND JOURNAL of MEDICINE

Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer

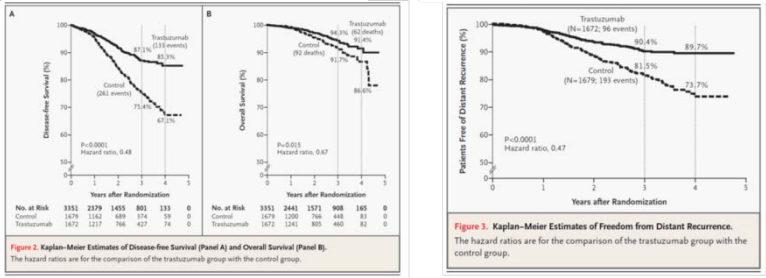


Figure 2. Kaplan–Meier Estimates of Disease-free Survival (Panel A) and Overall Survival (Panel B).
The hazard ratios are for the comparison of the trastuzumab group with the control group.

Figure 3. Kaplan–Meier Estimates of Freedom from Distant Recurrence.
The hazard ratios are for the comparison of the trastuzumab group with the control group.

Melanoma

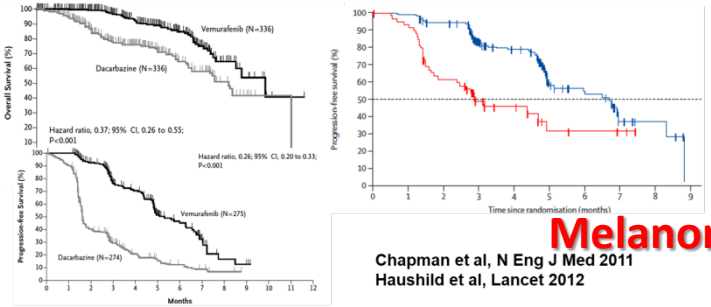
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

BRAF melanoma

Dabrafenib in *BRAF*-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial

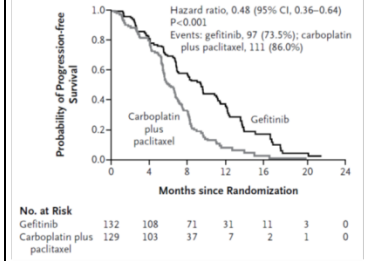


Chapman et al, N Eng J Med 2011
Haushild et al, Lancet 2012

Polmone

The NEW ENGLAND JOURNAL of MEDICINE

Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

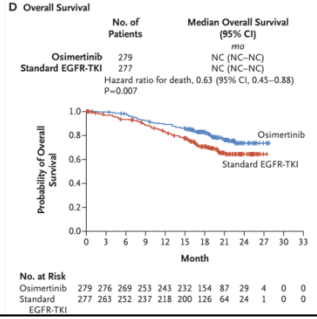


The NEW ENGLAND JOURNAL of MEDICINE

November 18, 2017

ORIGINAL ARTICLE

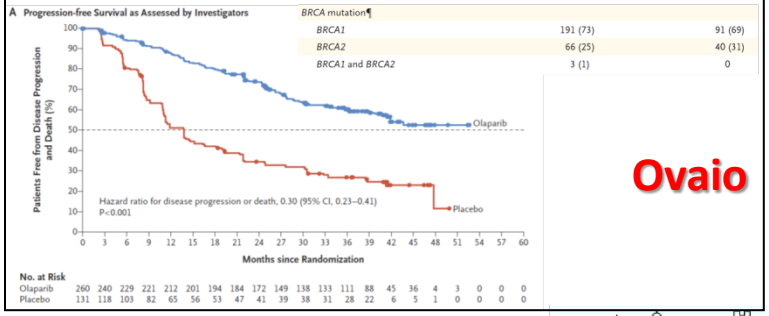
Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer



Ovaio

The NEW ENGLAND JOURNAL of MEDICINE

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

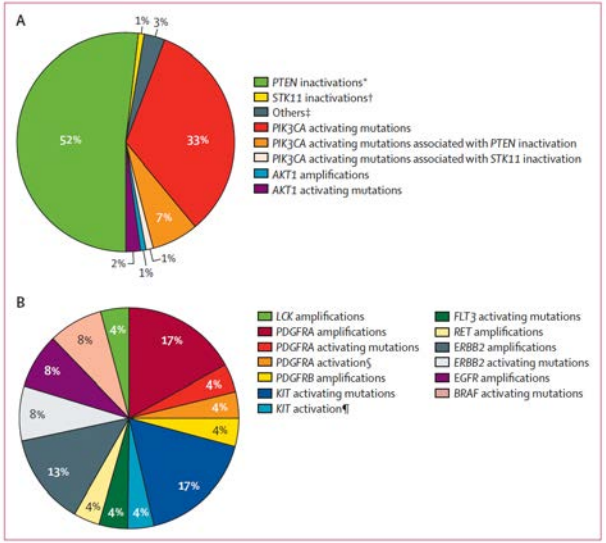


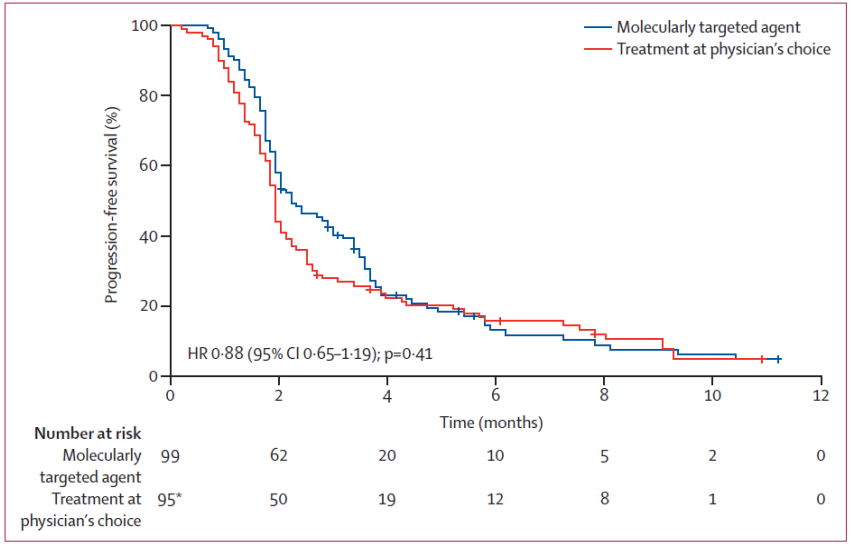
Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sebastien Armanet, Nicolas Servant, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezequel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Sablin, Maud Kamal, Xavier Paoletti, for the SHIVA investigators

Lancet Oncol 2015; 16: 1324–34

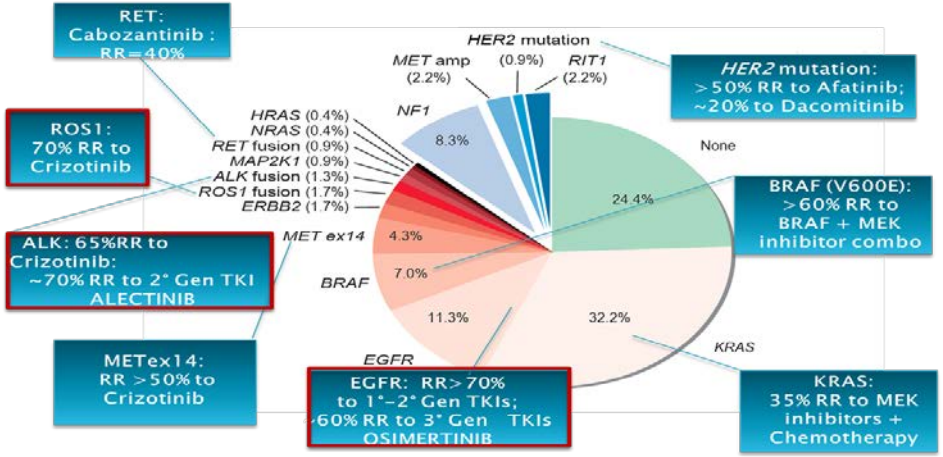
8 SEPTEMBER 2016 | VOL 537 | NATURE | S63



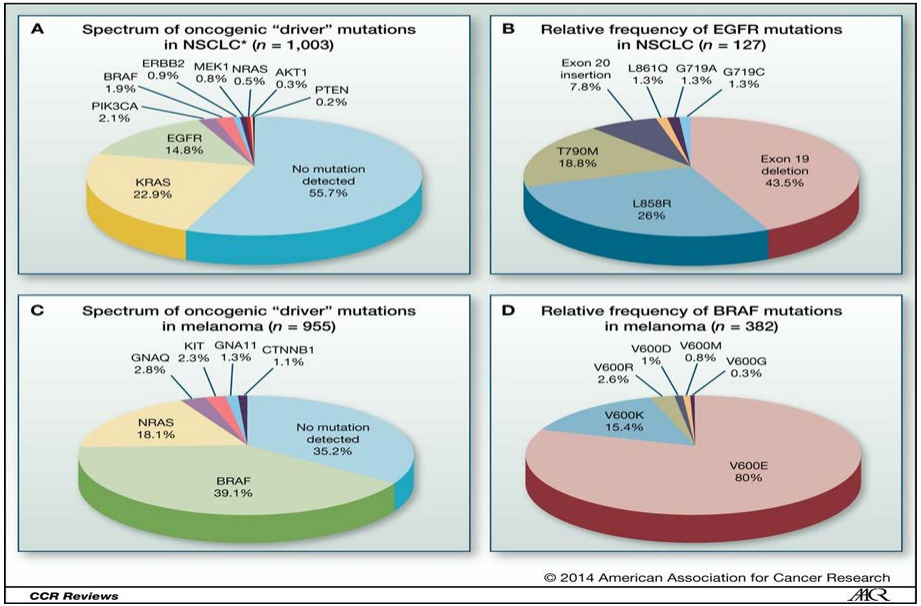


Dall'oncologia istologica all'oncologia mutazionale

Translating Genomic Profiling Data into Therapeutic Strategies (Lung Adenocarcinoma)



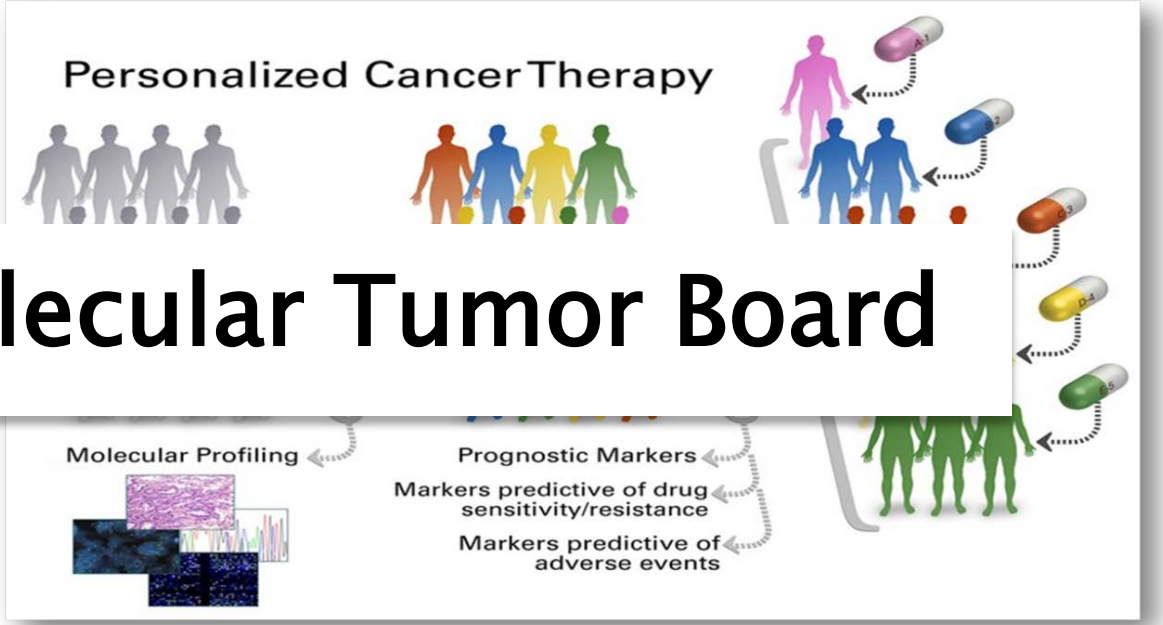
Neoplasie molto comuni sono in realtà un insieme di neoplasie rare



Caratterizzazione biologica

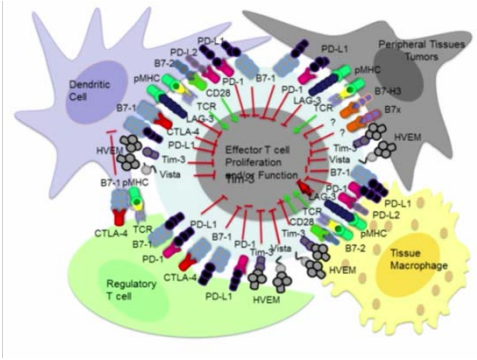
- Recettori ormonali
- Her-2
- KRAS
- BRAF
- EGFR
- ALK
- ROS-
- N-TRK
- BRCA

- NGS e registro mutazioni actionable



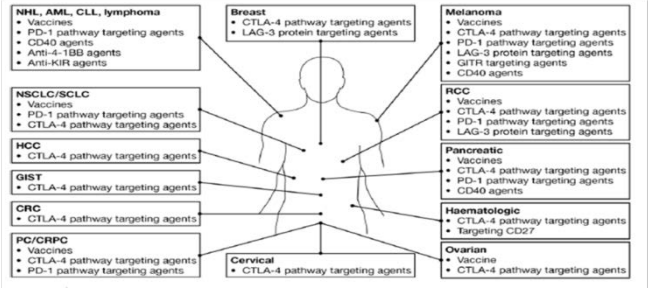
MTB Molecular Tumor Board

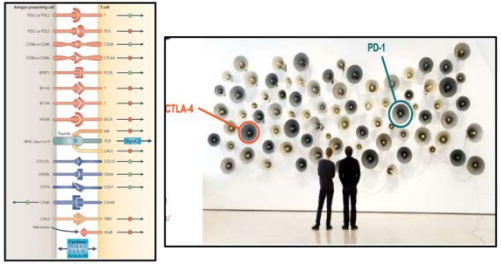
Immunoterapia



Non solo CTLA-4 & PD-1 !

Cancer Immunotherapy

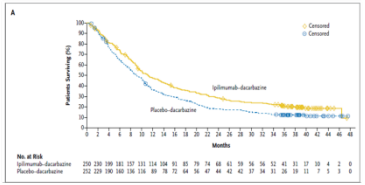


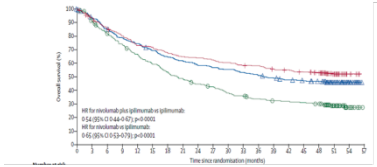


Pardoll et al., Nat Rev Cancer 2012

Checkpoint-Inhibitor

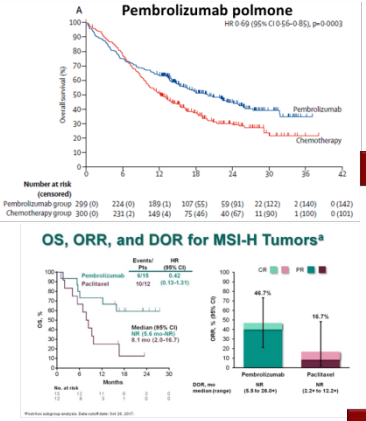
Melanoma Ipilimumab





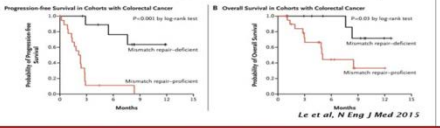
Melanoma Nivolumab +/-Ipilimumab vs Ipilimumab

Pembrolizumab polmone



Microsatellite instability & Pembrolizumab

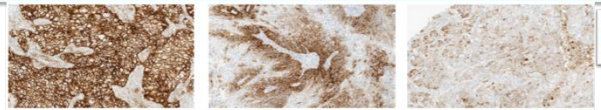
Type of response	MSI (n=10)	MSS (n=18)
Complete Response	0%	0%
Partial Response	40%	0%
Objective Response Rate	40%	0%
Disease Control Rate	90%	11%



Le et al, N Eng J Med 2015

Progetto AIOM-SIAPEC per la valutazione dell'espressione di PD-L1 nel NSCLC

- I Fase - Valutazione comparativa dei quattro test in commercio (Dako, Ventana) per definizione di positività
- II Fase - Correlazione con i dati clinici

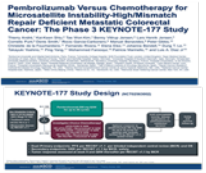


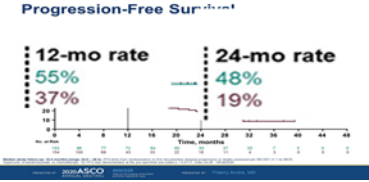
	Test Dako	Test Dako	Test Ventana	Test Ventana
Ab clone	28.8	22C3	SP142	SP263
Cellule valutate	Cellule tumorali	Cellule tumorali	Cellule tumorali Cellule immunitarie	Cellule tumorali

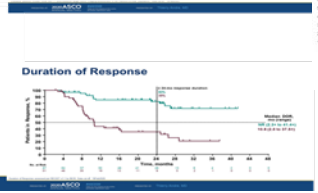
Pembrolizumab in MSI mCRC

Radiographic Response in Target Lesions

	Events	HR (95% CI)	P
Pembro	54%	0.60 (0.45-0.80)	0.0002
Chemo	73%		

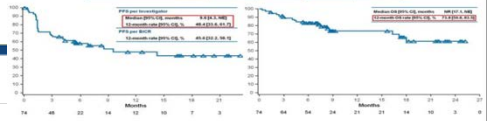






Microsatellite instability & Nivolumab

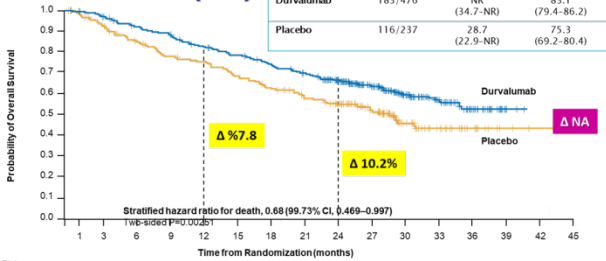
Patients, n (%)	dMMR/MSI-H per Local Laboratory (N = 74) Investigator	dMMR/MSI-H per Local Laboratory (N = 74) BICR	dMMR/MSI-H per Central Laboratory (N = 83) Investigator	dMMR/MSI-H per Central Laboratory (N = 83) BICR
ORR, n (%)	23 (31.1)	20 (27.0)	19 (22.9)	17 (20.5)
95% CI	20.8, 42.9	17.4, 38.6	23.1, 50.2	19.0, 46.3
Best overall response, n (%)				
CR	0	2 (2.7)	0	1 (1.9)
PR	23 (31.1)	18 (24.3)	19 (35.8)	16 (30.2)
SD	29 (39.2)	28 (37.8)	21 (39.6)	21 (39.6)
PD	18 (24.3)	20 (27.0)	10 (18.9)	12 (22.6)
Unable to determine	4 (5.4)	6 (11.1)	3 (5.7)	3 (5.7)
Disease control for ≥ 12 weeks, n (%)*	51 (68.9)	46 (62.2)	39 (73.6)	37 (69.8)



Overman et al, Lancet Oncol '17

Overall Survival* (ITT)

	No. of events / No. of patients	Median OS (95%CI) months	12-mo OS (95%CI) %	24-mo OS (95%CI) %
Durvalumab	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
Placebo	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)

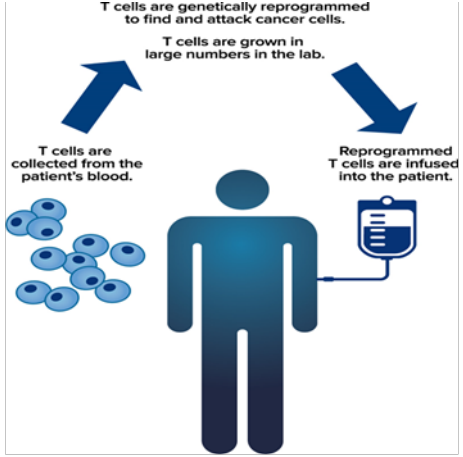


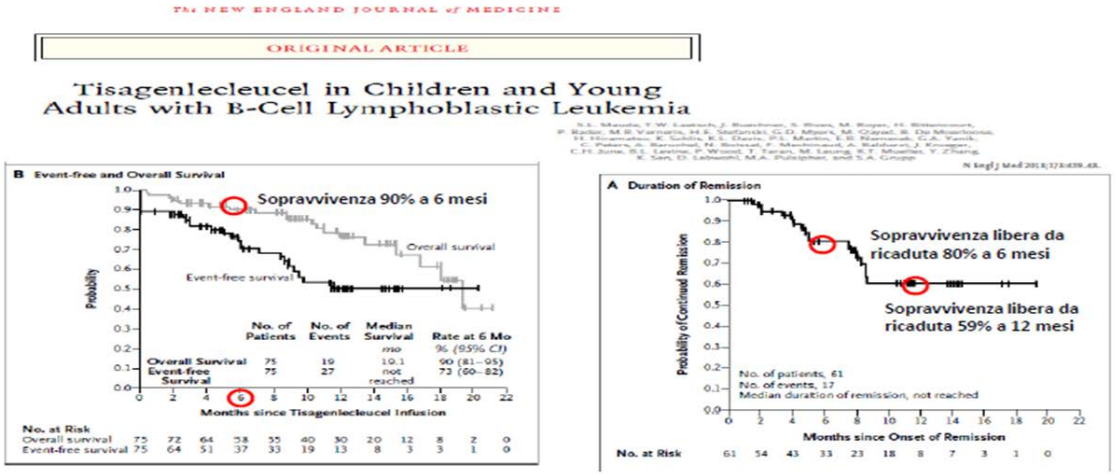
*Median duration of follow-up for OS was 25.2 months (range 0.2–43.1)

Sostenibilità in Oncologia: come conciliare valore scientifico, prezzo e accessibili

13 dicembre 2021 Casa dell'Aviatore, Roma

Rise of Immunotherapy





- ✓ 75 pazienti pediatrici affetti da LLA plurirecidivata o refrattaria ai trattamenti standard (compreso alloTCSE)
- ✓ 1 singola infusione di linfociti trasdotti con CAR CD19 (™Tisagenlecleucel)
- ✓ Remissione a 3 mesi→**81% dei pazienti**
- ✓ La remissione è stata duratura con un tasso di sopravvivenza libera da ricaduta a 6 mesi dell'**80%**
- ✓ Sopravvivenza a 6 mesi→ **90%**

On the Horizon:

- **CART-cell therapy**
- **Customized vaccines**

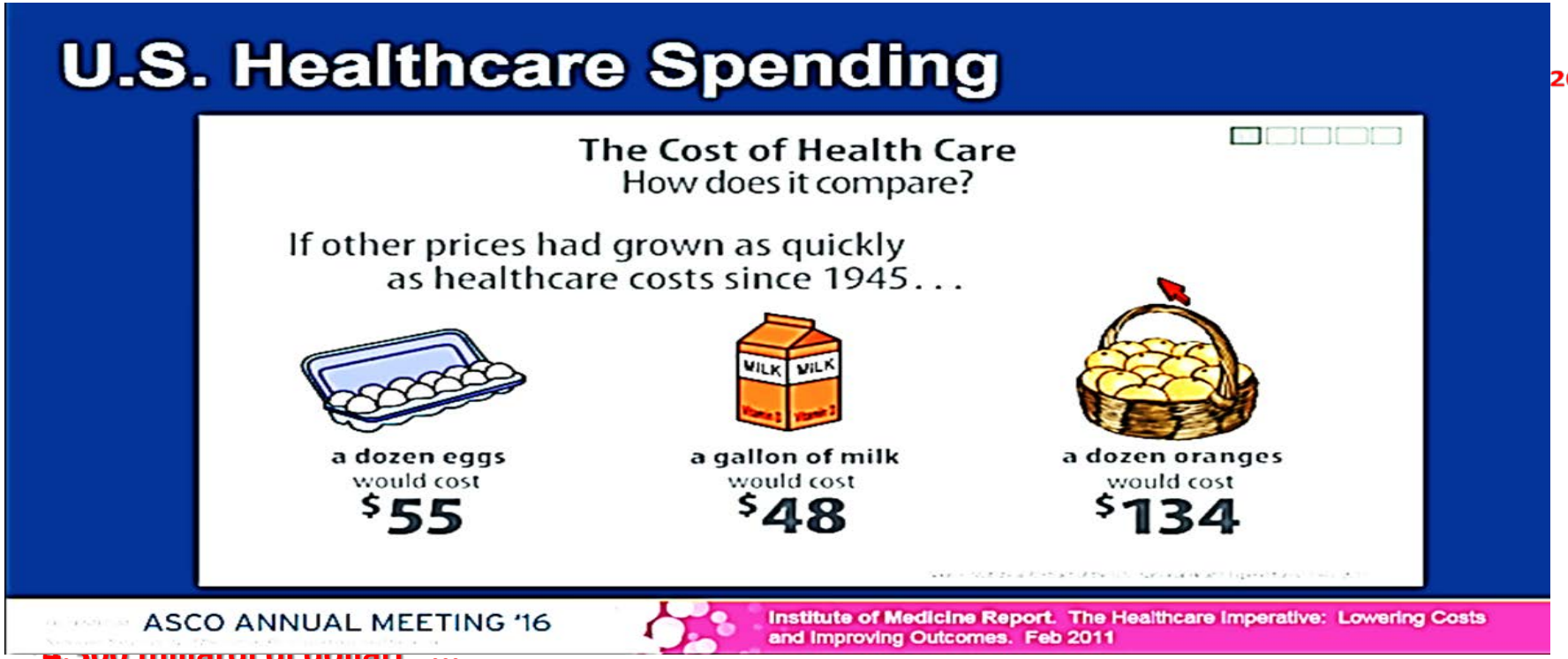
Nuovi farmaci, nuove speranze

Immuno-oncology evolution

IMS, Oncology Report 2015

Health care costs.

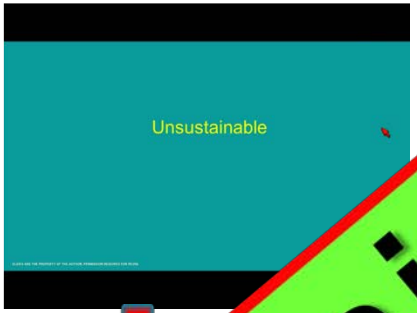
Shankaran V ASCO 2016



20

4.300 miliardi di dollari.....

Leonard Salts – ASCO 2015, plenary session



Pembrolizumab AWP (Redbook online): $51.792 / mg

$51.792 x 10 mg/kg x 75 kg x 26 doses/year

=

$1,009,944 per patient / per year

Selection of 2015 ASCO abstracts using Pe
mg/kg q 2 wks:

abstract # 4010 (esophageal ca)
abstract # 5510 (ovarian ca)
abstract # 7502 (Small cell Lu
abstract # 8035 (non-small cell
abstract # 9040 (melanoma)

veeks
onth

mbrolizumab
2 mg/kg q 2 weeks
$16,700/month

EDITORIAL

Perspectives o Cancer Care

Leonard B. Saltz, MD

JAMA Oncology Published online October 22, 2015

Unsustainable

The high price of anticancer drugs: origins, implications, barriers, solutions

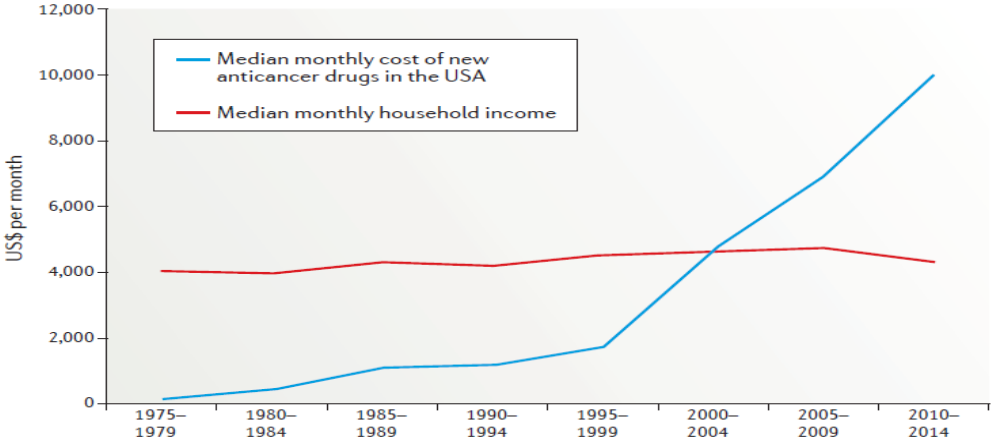


Figure 2 | **Median monthly launch price of a new anticancer drug, compared with median monthly household income from 1975–2014 in the USA.** Data on household incomes were

- **…….Thalidomide and imatinib, for example, increased from $1,869 to $7,564 and $3,346 to $8,479, respectively16 over 13–14 years.**
- **In both examples, prices have climbed despite the availability of similar, but more-advanced, next-in-class drugs……..**

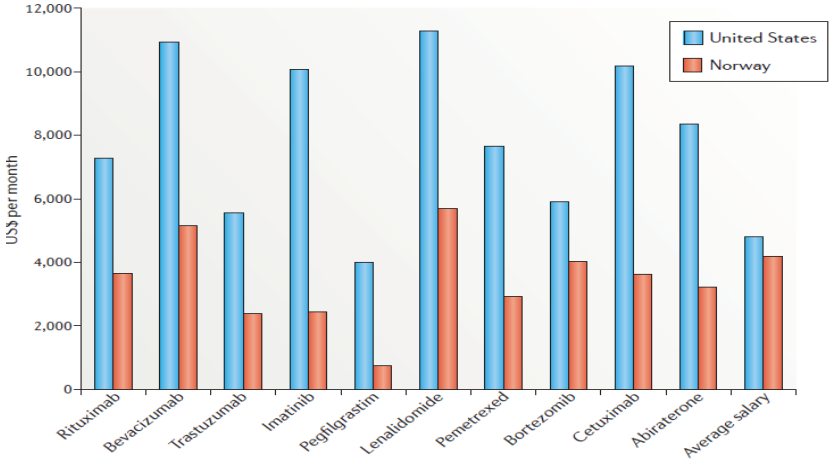


Figure 1 | **Cost of one month of treatment with the top 10 bestselling anticancer drugs in the USA[10] and Norway[130].** Drug prices are calculated for an adult weighing 70 kg, with a body surface area

Prasad V, Nature Reviews Clinical Oncology ,2017

On average, price is not justified by…

➢ **Innovation**

RESEARCH LETTER

Five Years of Cancer Drug Approvals: Innovation, Efficacy, and Costs

Results | From January 1, 2009, to December 31, 2013, the US FDA approved 51 drugs in oncology for 63 indications. During this

Type of drug	N (%)	Median price/yr
First-in-class	21 (41%)	$ 116.100
Next-in-class	30 (59%)	$ 119.765
		P=0.42

Sham Mailankody, MB BS
Vinay Prasad, MD, MPH

JAMA Oncology July 2015 Volume 1, Number 4

On average, price is not justified by…

- Innovation
- Research & development

Findings In this analysis of US Securities and Exchange Commission filings for 10 cancer drugs, the median cost of developing a single cancer drug was $648.0 million. The median revenue after approval for such a drug was $1658.4 million.

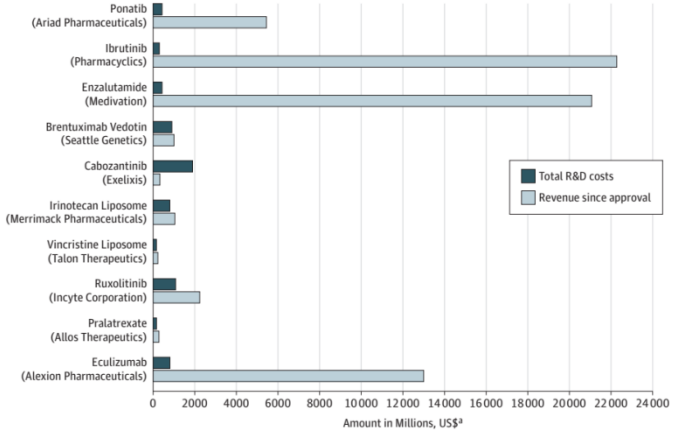
JAMA Intern Med. 2017;177(11):1569-1575. doi:10.1001/jamainternmed.2017.3601
Published online September 11, 2017. Last corrected on August 13, 2018.

JAMA Internal Medicine | Original Investigation

Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval

Vinay Prasad, MD, MPH; Sham Mailankody, MBBS

Figure. Comparison of Drug Development Costs With Revenue Earned After Approval



R&D indicates research and development.
[a] Adjusted to 2017 US dollars.

Recommended principles for development of payment models

IMPROVING ACCESS TO INNOVATIVE MEDICINES
Opinion by the Expert Panel on Effective Ways of Investing in Health (EXPH)

- The Expert Panel highlights that a single payment model will not be optimal for all situations. It proposes a broad list of principals that should be observed when developing innovative payment models.

1. **Greater price/cost transparency. This should include the acknowledgement that high cost to payers may or may not have a high underlying cost of R&D. A full chain of value of the product should be understood.**
2. Several mechanisms should be used to promote innovation. Patents and market exclusivity are not the only way to promote innovation and more incentives should be added. Good methodologies are needed to measure social value of medicinal products as well, this is important in the context of Health Technology Assessment (HTA).
3. An assessment of exercise of market power should be applied in each price negotiation that exists.
4. Set better rewards for higher therapeutic value-added, thus directing innovation towards more valued products and achieving better prices for better value.
5. **Payment systems should evolve in the direction of paying for the acquisition of a service instead of payments for pills. Different type of relationship is needed with the provision of service than just purchase of a product.**
6. **Exploring non-linear payments and bundling – price/volume arrangements, assessing differentiation across geographies and indications.** Differences in healthcare across the countries need to be acknowledged as under some conditions such arrangements can be helpful, but in some instances, can also be harmful.
7. Create dialogue platforms, involving all the relevant stakeholders in the process.

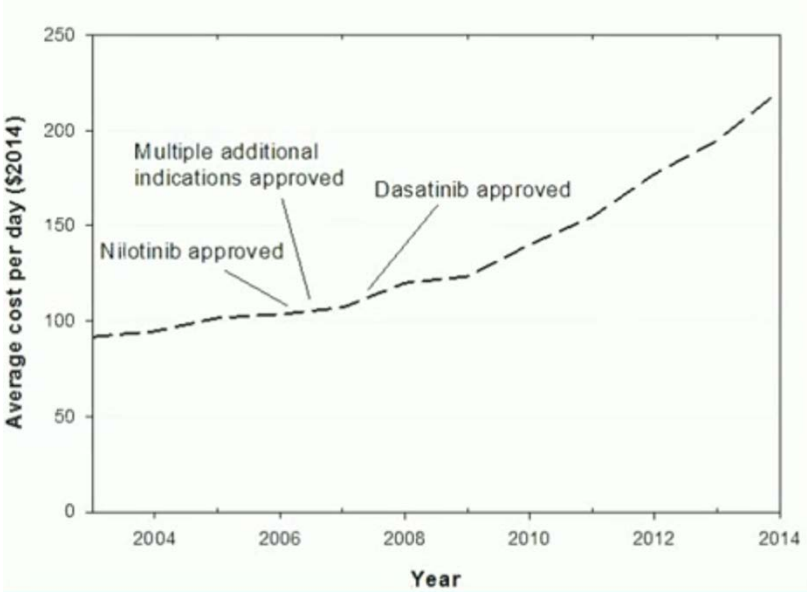
On average, price is not justified by…

- Innovation
- Research & development
- Lack of competition

Sham Mailankody, MB BS
Vinay Prasad, MD, MPH

JAMA Oncology July 2015 Volume 1, Number 4

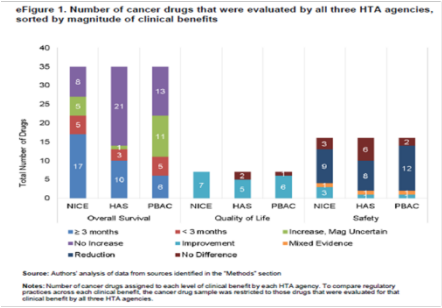
The trajectory of imatinib price



On average, price is not justified by…

- Innovation
- Research & development
- Lack of competition
- Greater efficacy

Assessment of Overall Survival, Quality of Life, and safety Benefits Associated with New Cancer Medicines

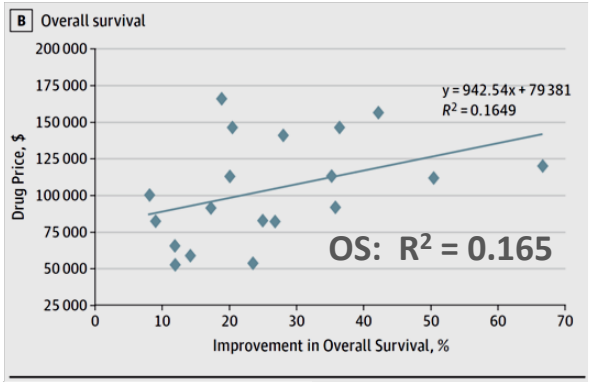


- 53 molecole approvate FDA ed EMA e rianalizzate da agenzia inglese, francese ed australiana
- 79% qualche beneficio in OS, QoL o tossicità
- 43% beneficio in OS > 3 mesi rispetto a quanto disponibile nel 2003
- 30% nessun beneficio in OS rispetto al 2003
- 42% beneficio in QoL
- 45% ridotta tollerabilità

Salas-Vega S, JAMA Oncology 2017

RESEARCH LETTER

Five Years of Cancer Drug Approvals: Innovation, Efficacy, and Costs



Sham Mailankody, MB BS
Vinay Prasad, MD, MPH

JAMA Oncology July 2015 Volume 1, Number 4

VIEWPOINT

Addressing Skyrocketing Cancer Drug Prices Comes With Tradeoffs

Pick Your Poison

Scott D. Ramsey, MD, PhD
Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Seattle, Washington; and Pharmaceutical Outcomes Research and Policy Program, University of Washington, Seattle, Washington.

Gary H. Lyman, MD, MPH
Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Seattle, Washington; and Pharmaceutical Outcomes Research and Policy Program, University of Washington, Seattle, Washington.

Rick Bangs, MBA, PMP
Patient Advocacy Committee, SWOG, Portland, Oregon.

…"Like most for-profit companies, drug manufacturers set the highest price they believe the market will support"

JAMA Oncology April 2016 Volume 2, Number 4

Ian Tannock
Princess Margaret Hospital, Toronto, Canada
ASCO meeting 2012

Tossicità finanziaria

VOLUME 32 · NUMBER 29 · OCTOBER 10 2014
JOURNAL OF CLINICAL ONCOLOGY — ART OF ONCOLOGY

Reporting and Grading Financial Toxicity

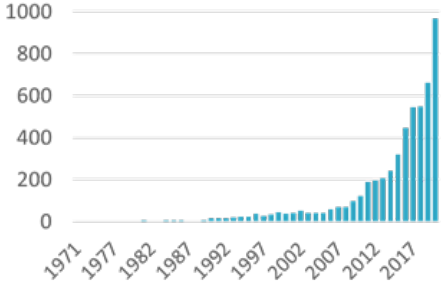
Nandita Khera

Her questions are difficult and thought provoking: "Will I have to sell my home? Should I declare bankruptcy? Do I need to stop spending money on food and utilities to be able to pay for medical care? Will I have to go to hospice when I am unable to pay any more? Does hospice charge very much?" These questions make me uncomfortable and aware of the fact that I am not really prepared to manage this adverse effect of cancer treatment.

October 13, 2020

[(Financial hardship) or (Financial toxicity)] and cancer

Create RSS Create alert Advanced



original article — Annals of Oncology Advance Access published October 26, 2016

The association of financial difficulties with clinical outcomes in cancer patients: secondary analysis of 16 academic prospective clinical trials conducted in Italy†

F. Perrone[1*], C. Jommi[2], M. Di Maio[1,2], A. Gimigliano[1], C. Gridelli[3], S. Pignata[4], F. Ciardiello[5], F. Nuzzo[6], A. de Matteis[6], L. Del Mastro[7], J. Bryce[1], G. Daniele[1], A. Morabito[8], M. C. Piccirillo[1], G. Rocco[9], L. Guizzaro[10,11] & C. Gallo[11]

EORTC C30 Q 28

During the last week, has your physical condition or medical treatment caused you financial difficulties?

Not at all	A little	Quite a bit	Very much
1	2	3	4

26% of 3670 patients with financial problems at baseline

OR of worse QOL response 1.35 (95%CI 1.08-1.70) P=0.009

22.5% of patients develop financial toxicity during treatment

HR of death 1.20 (95%CI 1.05-1.37) P=0.007

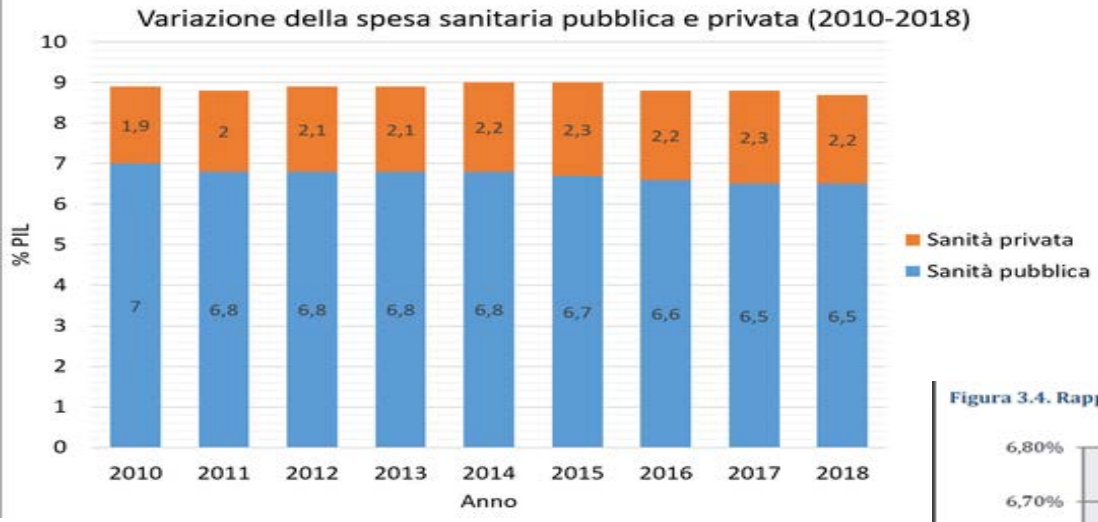
ESMO congress

Hazard ratio di morte

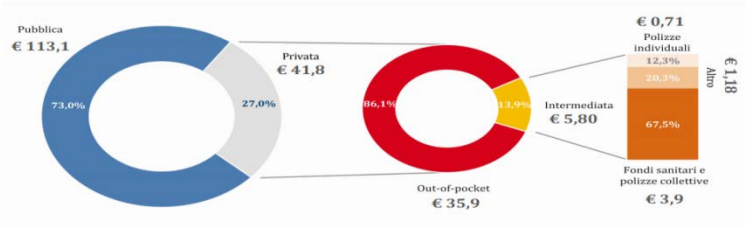
US (2015): **1.79**
IT (2016): **1.20**

Che il Δ sia una misura del valore del SSN?

Il finanziamento del SSN Italiano



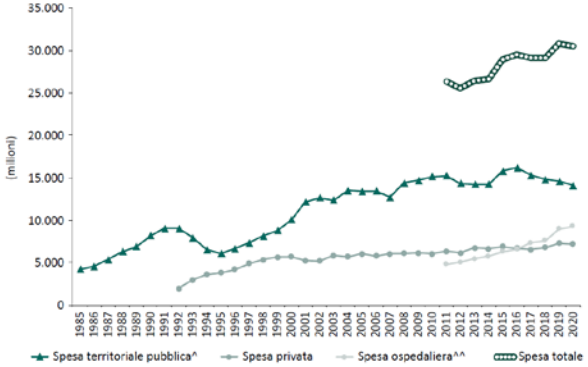
€ 154,9 miliardi di spesa sanitaria



Rapporto OSMED 2020

L'uso dei Farmaci in Italia
Rapporto Nazionale
Anno 2020

Figura 1.1.1. Spesa farmaceutica nel periodo 1985-2020 (Figura e Tabella)



Spesa Ospedaliera più che raddoppiata nell'ultimo decennio

Anno	Spesa convenzionata lorda*	Diretta di fascia A	Spesa territoriale pubblica^	Spesa privata	Strutture sanitarie	Spesa ospedaliera^^	Spesa totale
2011	12.387	2.832	15.219	6.346	7.606	4.774	26.339
2012	11.488	2.837	14.325	6.152	7.892	5.055	25.532
2013	11.226	3.003	14.229	6.732	8.425	5.421	26.383
2014	10.988	3.250	14.238	6.648	8.994	5.744	26.630
2015	10.863	4.921	15.784	6.859	11.203	6.282	28.926
2016	10.638	5.556	16.194	6.681	12.143	6.587	29.461
2017	10.499	4.792	15.291	6.526	12.124	7.332	29.149
2018	10.141	4.620	14.761	6.771	12.214	7.594	29.126
2019	10.089	4.481	14.570	7.261	13.461	8.980	30.811
2020	9.820	4.259	14.080	7.180	13.544	9.284	30.544

Rapporto OSMED 2020

I livello ATC	Spesa pro capite A-SSN Assistenza convenzionata (a)	Δ % 20-19	Spesa pro capite Strutture sanitarie pubbliche (b)	Δ % 20-19	Spesa SSN (a+b)	Δ % 20-19
L	4,30	2,3	102,88	6,4	107,19	6,2
A	31,20	-5,1	17,04	9,3	48,23	-0,5
J	9,94	-21,3	34,77	-21,2	44,71	-21,2
B	7,86	-1,3	30,78	8,1	38,64	6,1
N	23,65	1,1	7,81	6,0	31,47	2,3
R	17,13	1,6	4,76	21,8	21,89	5,4
M	5,02	-8,4	3,71	5,9	8,73	-2,8
H	3,93	-5,1	4,79	0,0	8,72	-2,4
G	5,42	-6,9	1,21	-21,7	6,63	-10,0
S	3,89	-1,1	2,14	-31,8	6,02	-14,7
V	0,14	-4,6	5,81	1,7	5,95	1,5
D	1,25	-4,0	1,28	51,9	2,53	17,9

1°

Tabella 3.3. Composizione della spesa farmaceutica 2020 per I livello ATC e classe di rimborsabilità (ordine decrescente per spesa totale)

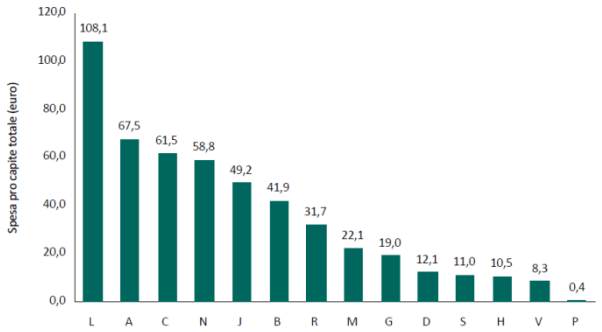
I livello ATC	Classe A-SSN^		Acquisto privato di classe A		Classe C con ricetta		Auto-medicazione SOP e OTC		Strutture pubbliche§		Totale
	€*	%*	€*	%*	€*	%*	€*	%*	€*	%*	€*
L	256.737.774	4,0	27.410.863	0,4	27.204.895	0,4		0,0	6.135.979.355	95,2	6.447.332.888
A	1.860.645.900	46,2	323.113.098	8,0	242.269.430	6,0	582.741.641	14,5	1.016.055.373	25,2	4.024.825.441
C	2.925.670.664	79,7	212.801.991	5,8	42.697.479	1,2	139.375.110	3,8	349.922.075	9,5	3.670.467.320
N	1.410.638.705	40,2	165.440.549	4,7	1.222.280.961	34,9	240.451.605	6,9	466.039.873	13,3	3.504.851.693
J	592.707.177	20,2	136.871.936	4,7	133.061.509	4,5		0,0	2.073.672.578	70,6	2.936.313.201
B	468.734.577	18,8	107.114.919	4,3	84.462.753	3,4	3.009.369	0,1	1.835.594.942	73,5	2.498.916.559
R	1.021.920.880	54,1	135.777.160	7,2	154.741.483	8,2	292.536.669	15,5	283.655.788	15,0	1.888.631.979
M	299.456.536	22,7	159.200.320	12,1	199.006.083	15,1	441.490.926	33,4	221.048.381	16,7	1.320.202.245
G	323.152.969	28,4	39.849.921	3,5	630.379.459	55,5	70.411.846	6,2	72.182.405	6,4	1.135.976.599
D	74.637.401	10,4	27.030.359	3,8	267.255.182	37,1	274.682.104	38,1	76.412.585	10,6	720.017.631
S	231.902.554	35,5	16.655.102	2,5	192.950.116	29,5	85.178.777	13,0	127.358.236	19,5	654.044.784
H	234.374.078	37,5	65.090.261	10,4	40.455.812	6,5		0,0	285.549.125	45,7	625.469.277
V	8.367.172	1,7	105.486.591	21,4	31.609.151	6,4	335.009	0,1	346.306.351	70,4	492.104.274
P	13.052.304	51,0	5.891.554	23,0	759.750	3,0	3.511.991	13,7	2.397.778	9,4	25.613.377
Totale	9.721.998.690	32,5	1.527.734.625	5,1	3.269.134.064	10,9	2.133.725.047	7,1	13.292.174.845	44,4	29.944.767.270

I farmaci antineoplastici e immunomodulatori rappresentano la prima categoria terapeutica a maggior spesa pubblica per il 2020, pari a 6.392 milioni di euro (107,19 euro pro capite) (+ 6,2%).

I livello ATC	DDD/1000 ab die Assistenza convenzionata (a)	Δ % 20-19	DDD/1000 ab die Strutture pubbliche (b)	Δ % 20-19	DDD/1000 ab die SSN (a+b)	Δ % 20-19
C	484,7	1,3	17,4	-7,0	502,2	1,0
A	151,0	-2,2	30,4	4,1	181,4	-1,2
B	87,7	-1,5	49,0	2,5	136,7	-0,1
N	67,8	1,5	26,6	3,1	94,5	1,9
G	42,0	-0,5	2,2	-9,7	44,2	-1,0
R	41,8	-0,8	2,1	-17,2	44,0	-1,7
M	36,4	-3,5	5,2	4,4	41,6	-2,6
H	35,9	0,3	5,5	3,5	41,4	0,7
S	20,8	-0,4	2,2	-19,9	23,1	-2,7
L	6,4	1,8	10,6	3,8	16,9	3,0
V	0,1	-3,5	3,1	-2,8	3,2	-2,8
P	1,0	7,1	0,2	629,5	1,2	26,2
Totale	**993,1**	**-0,3**	**170,3**	**1,5**	**1.163,4**	**-0,1**

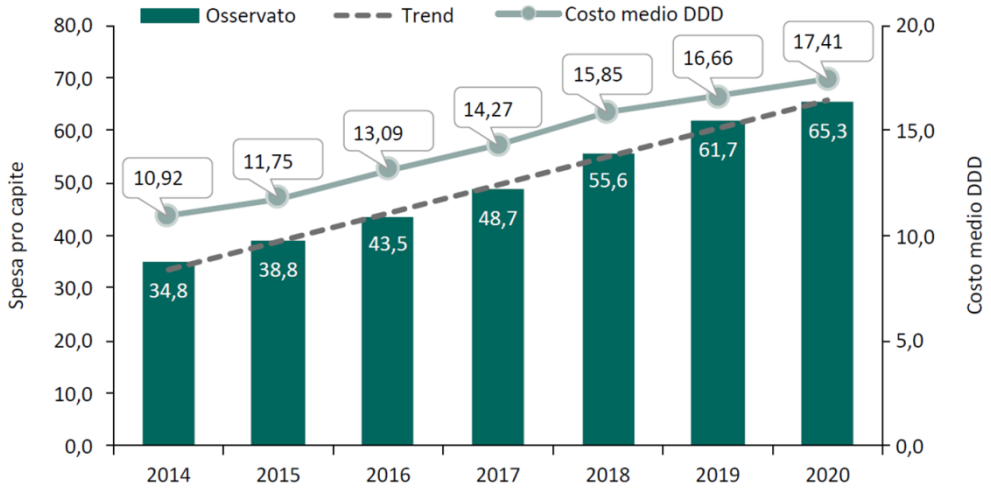
11°

Figura 3.1. Spesa farmaceutica totale pro capite 2020 per I livello ATC



Rapporto OSMED 2020

Figura 3.1.1a. Farmaci oncologici, andamento temporale 2014-2020 della spesa pro capite e del costo medio per giornata di terapia



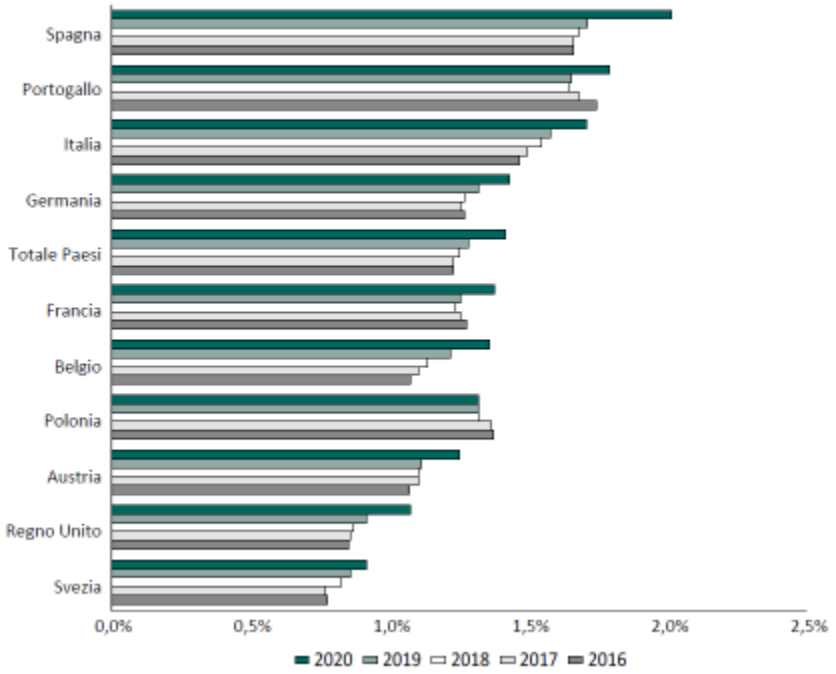
L'erogazione dei farmaci oncologici è notevolmente aumentata negli ultimi 6 anni, la spesa è infatti passata da 31,8 euro nel 2013 a 55,6 nel 2018 con ulteriore incremento nel 2019 a 61,1, nel 2020 a 65,3 che porta a oltre un raddoppio della spesa in 7 anni

I confronti con l'Europa

Tabella 1.9.3. Confronto internazionale della distribuzione percentuale della spesa farmaceutica ospedaliera 2020 per I livello ATC

ATC I livello	Italia	Austria	Belgio	Francia	Germania	Polonia	Portogallo	Spagna	Svezia	UK
L - Antineoplastici	40,5	54,0	58,4	47,8	36,4	49,6	44,1	48,2	40,6	45,2
J - Antimicrobici	17,6	15,9	8,8	11,4	22,0	11,4	20,1	19,1	13,0	16,4
B - Ematologici	13,0	9,2	9,5	10,8	11,6	5,0	5,7	5,7	13,1	6,1
N - SNC	9,9	7,4	6,5	13,5	15,3	19,7	11,7	9,1	10,6	7,2
A - Gastrointestinale	7,2	4,6	6,1	6,5	5,0	1,7	7,3	4,0	5,7	4,4
R - Respiratorio	2,6	1,0	1,9	1,0	1,2	2,3	2,8	4,3	1,4	7,3
C - Cardiovascolare	2,5	2,3	1,7	2,9	2,1	3,0	1,6	2,3	1,8	1,7
M - Muscolo-scheletrico	1,9	1,6	1,9	2,5	2,0	1,3	1,6	2,1	4,0	3,1
H - Ormoni sistemici	1,7	0,8	0,8	0,9	0,9	2,5	1,7	1,4	0,8	1,2
S - Organi di senso	1,0	1,4	3,2	0,5	1,7	2,5	1,5	2,1	7,9	5,4
D - Dermatologici	0,9	0,2	0,2	1,1	0,8	0,3	1,1	1,1	0,2	0,8
V - Vari	0,8	0,7	0,6	0,6	0,8	0,3	0,6	0,2	0,7	0,5
G - Genito-urinario e ormoni sessuali	0,5	0,7	0,5	0,5	0,3	0,3	0,2	0,3	0,3	0,5
P - Antiparassitari	0,0	0,0	0,0	0,0	0,0	0,0	0,1	0,0	0,0	0,0

Figura 1.9.1. Confronto internazionale: incidenza della spesa farmaceutica pubblica sul PIL nel periodo 2016-2020



Interventi a breve termine per la sostenibilità

- **Fondo per i farmaci innovativi in Oncologia**
  - 500 milioni di euro per il 2017
  - Riconosciuto alto livello di innovatività per bisogno terapeutico, efficacia, tollerabilità e qualità di vita
  - Definizione criteri innovatività (AIFA 31 marzo 2017)

- **Utilizzo del Fondo**
  - Inserimento nel Fondo per classe / farmaco sulla base della definizione di "alta innovatività" secondo i criteri AIFA
  - Fondo AIFA con accesso a fine anno per volume di spesa regionale per i farmaci considerati

Rapporto OSMED 2020

Regione	2017				2018				2019				2020					
	Non oncologici		Oncologici		Non oncologici		Oncologici		Non oncologici		Oncologici		Non oncologici			Oncologici		
	Spesa (€)	Spesa al netto payback	Spesa (€)	Spesa al netto payback	Spesa (€)	Spesa al netto payback	Spesa (€)	Spesa al netto payback	Spesa (€)	Spesa al netto payback	Spesa (€)	Spesa al netto payback	Spesa (€)	Spesa al netto payback	Δ% 20-19*	Spesa (€)	Spesa al netto payback	Δ% 20-19*
Piemonte	67,8	12,2	27,6	27,6	39,1	30,5	48,0	44,0	100,5	34,3	42,1	37,4	40,6	26,8	-73,2	78,5	67,6	-32,4
Valle d'Aosta	1,0	0,1	0,6	0,6	0,8	0,6	0,9	0,8	1,4	0,4	0,8	0,8	0,6	0,4	-99,6	1,3	1,2	-98,8
Lombardia	175,0	51,0	57,7	57,7	104,8	91,8	92,7	84,3	216,6	84,9	94,8	85,7	88,8	60,1	-39,9	196,3	173,5	73,5
PA Bolzano	3,3	0,9	4,1	4,1	2,1	1,9	6,7	6,2	5,7	3,1	6,2	5,6	2,3	1,9	-98,1	11,2	9,7	-90,3
PA Trento	3,6	0,5	2,7	2,7	2,8	2,1	4,0	3,7	8,0	2,8	3,1	2,7	3,2	2,0	-98,0	5,5	4,7	-95,3
Veneto	58,7	13,3	27,0	27,0	38,9	32,2	49,0	45,2	77,7	32,3	39,6	35,3	34,6	23,8	-76,2	84,9	73,8	-26,2
Friuli VG	12,7	5,0	11,1	11,1	10,2	9,2	15,9	14,3	25,8	9,4	13,8	12,2	11,1	6,9	-93,1	25,5	21,7	-78,3
Liguria	23,9	4,7	13,5	13,5	14,4	10,7	25,2	23,4	24,2	8,1	20,4	17,8	10,7	7,3	-92,7	36,0	30,7	-69,3
Emilia R.	64,5	6,3	37,2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	19,9	-80,1	98,8	84,8	-15,2
Toscana	47,7	-2,1	34,6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	20,8	-79,2	81,4	70,3	-29,7
Umbria	10,1	3,5	7,1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	4,7	-95,3	19,6	17,1	-82,9
Marche	14,8	2,5	12,7	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	8,4	-91,6	29,3	25,4	-74,6
Lazio	68,3	9,4	42,2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	28,3	-71,7	118,0	101,9	1,9
Abruzzo	12,9	3,6	9,1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	5,9	-94,1	21,0	18,2	-81,8
Molise	3,5	0,1	1,7	1,7	1,6	0,9	2,5	2,2	4,2	1,3	1,7	1,4	2,0	1,2	-98,8	4,2	3,8	-96,2
Campania	131,1	4,6	42,2	42,2	59,4	47,9	65,5	58,2	123,3	42,2	50,7	43,8	51,9	31,7	-68,3	106,7	92,6	-7,4
Puglia	66,5	5,3	29,1	29,1	33,2	26,5	49,0	44,9	70,5	24,6	39,1	35,1	27,4	19,6	-80,4	67,8	58,1	-41,9
Basilicata	8,3	2,1	3,7	3,7	4,5	3,8	5,5	4,9	7,8	2,6	5,4	5,0	2,9	1,8	-98,2	8,9	7,8	-92,2
Calabria	30,9	4,0	9,1	9,1	9,4	6,2	14,7	13,4	24,2	8,9	11,7	10,3	12,1	8,9	-91,1	23,5	20,4	-79,6
Sicilia	67,1	12,6	24,9	24,9	35,6	16,5	40,4	36,6	84,5	28,2	34,3	30,7	28,7	19,4	-80,6	66,0	56,8	-43,2
Sardegna	28,7	4,2	11,4	11,4	15,3	4,1	18,1	16,1	30,5	10,9	14,1	12,5	12,6	7,7	-92,3	28,5	24,1	-75,9
Italia	**900,4**	**143,7**	**409,2**	**409,2**	**524,8**	**405,4**	**676,3**	**613,8**	**1.108,7**	**413,3**	**581,4**	**516,4**	**454,5**	**307,6**	**207,[illegible]**	**1.113,0**	**964,2**	**864,2**

*Calcolato su spesa al netto del *payback*

Spesa espressa in milioni

1.113,0 964,2 864,2

Attenzione

Sostenibilità e efficacia

- **Il posizionamento di un "nuovo" farmaco e la definizione di "innovativo" nell'ambito delle strategie terapeutiche deve considerare i vantaggi clinici insieme ai costi e la sostenibilità per il SSN**

- **Risulta necessario complementare il rapporto incrementale di costo-efficacia con altri criteri, quali**
  - **il volume, l'impatto epidemiologico e la rilevanza della patologia (compreso il suo peso sociale)**
  - **la disponibilità e l'efficacia di alternative terapeutiche**
  - **la dimensione assoluta del beneficio incrementale**
  - **la valutazione di impatto sulla spesa globale**

Accesso ai farmaci

- **Uguali diritti per tutti i pazienti alla "migliore cura"**
  - Impatto clinico (efficacia, tossicità, qualità di vita)
  - Innovatività
- **Rapporto valore/costo**
  - Compatibilità con le risorse
  - Costi e sistemi di rimborso
- **Tempi di accesso**

Criticità (studi marginali)

- Studi con molti pazienti
- Per garantire la significatività statistica
- In grado di catturare/ratificare **differenze marginali**
  - A causa della qualità dell'end-point
  - A causa della dimensione dell'effetto
- Qualche volta
  - Trattamenti di controllo discutibili
  - Criteri di selezione "ristretti" rispetto ai pazienti della pratica clinica

Courtesy of F. Perrone

Parametri per la valutazione di un farmaco innovativo

- Vantaggio relativo per l'end-point di efficacia considerato
- Vantaggio assoluto per l'end point di efficacia considerato
- Tossicità dimostrata
- Impiego generalizzabile in tutti i pazienti
- Incidenza della patologia considerata
- Terapie alternative possibili

Impatto economico dei cambiamenti in efficacia dei farmaci oncologici

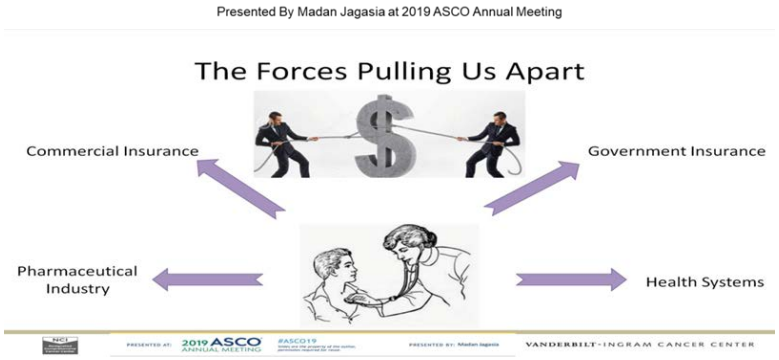
- Necessità di estrapolazione del dato di sopravvivenza nel medio-lungo periodo
- Significato più attendibile del valore medio rispetto alla mediana della sopravvivenza
- Periodo di esposizione alla terapia più lungo nel tempo (somma di responsivi + lungo-sopravviventi)

Innovazione, valore e costo

Costo	Valore	Variabili
I fascia	Prolungamento ≥1/3 dell'aspettativa di vita nel setting di pazienti considerato (attesa di vita 12 mesi incremento significativo ≥16 mesi; attesa di vita 6 mesi incremento significativo ≥8 mesi)	Frequenza della neoplasia Volume clinico Fase dello studio (fase III vs fase II) Tossicità Qualità di vita
II fascia	Farmaci ad efficacia intermedia	
III fascia	Prolungamento statisticamente significativo <15% dell'aspettativa di vita nel setting di pazienti considerato	

Potenziali interventi strutturali per l'implementazione delle risorse per i farmaci innovativi in oncologia

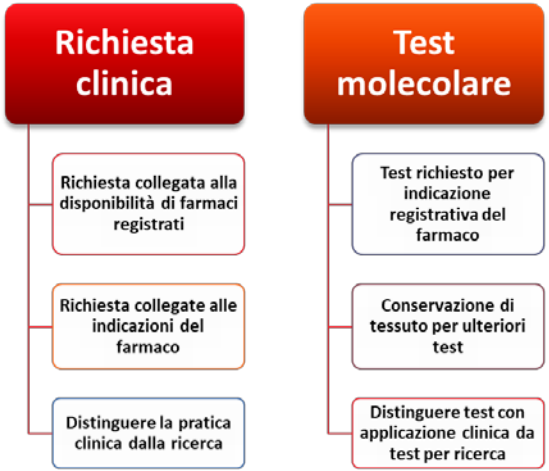
- Strategia e regia unitaria per il controllo dei tumori dalla prevenzione, alla diagnosi, alla cura e alla riabilitazione
- Implementazione delle Reti Oncologiche Regionali
- Implementazione e cooperazione pubblico/industria nella ricerca
- Linee guida nazionali e appropriatezza prescrittiva
- Selezione dei pazienti sula base di criteri biologici/clinici
- Ottimizzazione della preparazione dei farmaci ("drug day", UFA centralizzate per aree territoriali)
- Gare per acquisto centralizzate su base almeno regionale
- Introduzione dei biosimilari di anticorpi monoclonali
- Rivalutazione del "costo" dei farmaci già rimborsati sulla base dei dati dei registri AIFA
- Fondo nazionale per i farmaci oncologici innovativi



La parola magica "Appropriatezza"

- Valutare <u>se</u> il soggetto con l'indicazione riceve la terapia indicata
- Valutare <u>se</u> il soggetto senza indicazione non riceve la terapia non indicata
- Valutare <u>come</u> il soggetto con l'indicazione riceve la terapia

Appropriatezza dei test molecolari



Il "Valore" del farmaco

JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Incremental Advance or Seismic Shift? The Need to Raise the Bar of Efficacy for Drug Approval

Alberto Sobrero, *Ospedale San Martino, Genova, Italy*
Paolo Bruzzi, *Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy*

- **If a trial was designed to detect a target difference with a power > 50%, statistical significance will be achieved ALSO FOR OBSERVED DIFFERENCES SMALLER THAN TARGET ONE**
- **for example, a trial designed to detect a 20% risk reduction (H.R.<0.8) with a 90% power, it will provide a statistically significant result (with a p value < 0.05) if the observed risk reduction is as low as 10%**

KEY QUESTIONS

- What is a plausible Δ in terms of a measurable clinical effect?
- What is a worthwhile Δ in terms of substantive clinical benefit?

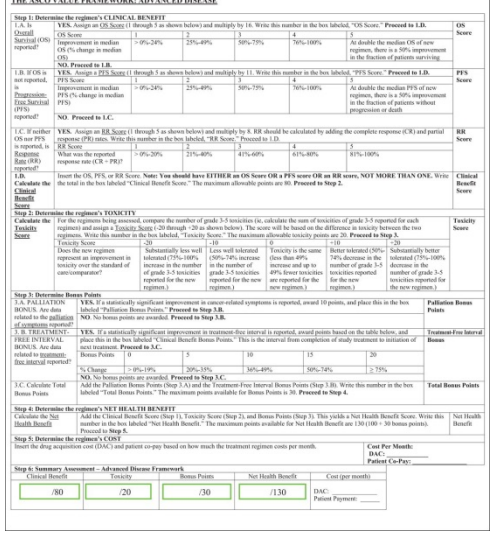
PALLIATIVE SETTING (Advanced disease)				
CRITICAL ELEMENT	KEY PARAMETER	CATEGORIZATION	WEIGHTED	MAXIMUM SCORING
CLINICAL BENEFIT	OVERAL SURVIVAL	1 to 5	16 (x 5)	80
	PROGRESSION-FREE-SURVIVAL	1 to 5	11 (x 5)*	55
	RESPONSE RATE	1 to 5	8 (x 5)**	40

*** PFS is less clinically meaningful than OS and is not always a proven surrogate for OS;**
**** RR improvement not always will translate in OS improvement.**

CURATIVE SETTING (Adjuvant and neo-adjuvant therapies)				
CRITICAL ELEMENT	KEY PARAMETER	CATEGORIZATION	WEIGHTED	MAXIMUM SCORING
CLINICAL BENEFIT	OVERAL SURVIVAL	1 to 5	16 (x 5)	80
	DISEASE-FREE-SURVIVAL	1 to 5	15 (x 5)*	75

TOXICITY		SCORING
GRADE 3 – 5 (CTC-NCI)	Less frequent than control arm	Awarded up to 20
	More frequent than control	Subtracted up to 20

+
BONUS POINTS if PALLIATION OF SYMPTOMS and/or PROLONGED TREATMENT-FREE-INTERVAL (only in the palliative setting)


THE ASCO VALUE FRAMEWORK: ADVANCED DISEASE

Step 1: Determine the regimen's CLINICAL BENEFIT

1.A. Is Overall Survival (OS) reported?	**YES.** Assign an OS Score (1 through 5 as shown below) and multiply by 16. Write this number in the box labeled, "OS Score." **Proceed to 1.B.**						**OS Score**
	OS Score	1	2	3	4	5	
	Improvement in median OS (% change in median OS)	> 0%-24%	25%-49%	50%-75%	76%-100%	At double the median OS of new regimen, there is a 50% improvement in the fraction of patients surviving	
	NO. Proceed to 1.B.						
1.B. If OS is not reported, is Progression-Free Survival (PFS) reported?	**YES.** Assign a PFS Score (1 through 5 as shown below) and multiply by 11. Write this number in the box labeled, "PFS Score." **Proceed to 1.D.**						**PFS Score**
	PFS Score	1	2	3	4	5	
	Improvement in median PFS (% change in median PFS)	> 0%-24%	25%-49%	50%-75%	76%-100%	At double the median PFS of new regimen, there is a 50% improvement in the fraction of patients without progression or death	
	NO. Proceed to 1.C.						
1.C. If neither OS nor PFS is reported, is Response Rate (RR) reported?	**YES.** Assign an RR Score (1 through 5 as shown below) and multiply by 8. RR should be calculated by adding the complete response (CR) and partial response (PR) rates. Write this number in the box labeled, "RR Score." Proceed to 1.D.						**RR Score**
	RR Score	1	2	3	4	5	
	What was the reported response rate (CR + PR)?	> 0%-20%	21%-40%	41%-60%	61%-80%	81%-100%	
1.D. Calculate the Clinical Benefit Score	Insert the OS, PFS, or RR Score. **Note: You should have EITHER an OS Score OR a PFS score OR an RR score, NOT MORE THAN ONE.** Write the total in the box labeled "Clinical Benefit Score." The maximum allowable points are 80. **Proceed to Step 2.**						**Clinical Benefit Score**

Step 2: Determine the regimen's TOXICITY

Calculate the Toxicity Score	For the regimens being assessed, compare the number of grade 3-5 toxicities (ie, calculate the sum of toxicities of grade 3-5 reported for each regimen) and assign a Toxicity Score (-20 through +20 as shown below). The score will be based on the difference in toxicity between the two regimens. Write this number in the box labeled, "Toxicity Score." The maximum allowable toxicity points are 20. **Proceed to Step 3.**						**Toxicity Score**
	Toxicity Score	-20	-10	0	+10	+20	
	Does the new regimen represent an improvement in toxicity over the standard of care/comparator?	Substantially less well tolerated (75%-100% increase in the number of grade 3-5 toxicities reported for the new regimen.)	Less well tolerated (50%-74% increase in the number of grade 3-5 toxicities reported for the new regimen.)	Toxicity is the same (less than 49% increase and up to 49% fewer toxicities are reported for the new regimen.)	Better tolerated (50%-74% decrease in the number of grade 3-5 toxicities reported for the new regimen.)	Substantially better tolerated (75%-100% decrease in the number of grade 3-5 toxicities reported for the new regimen.)	

Step 3: Determine Bonus Points

3.A. PALLIATION BONUS. Are data related to the palliation of symptoms reported?	**YES.** If a statistically significant improvement in cancer-related symptoms is reported, award 10 points, and place this in the box labeled "Palliation Bonus Points." **Proceed to Step 3.B.** **NO.** No bonus points are awarded. **Proceed to Step 3.B.**							**Palliation Bonus Points**
3. B. TREATMENT-FREE INTERVAL BONUS. Are data related to treatment-free interval reported?	**YES.** If a statistically significant improvement in treatment-free interval is reported, award points based on the table below, and place this in the box labeled "Clinical Benefit Bonus Points." This is the interval from completion of study treatment to initiation of next treatment. **Proceed to 3.C.**							**Treatment-Free Interval Bonus**
	Bonus Points	0	5	10	15	20		
	% Change	> 0%-19%	20%-35%	36%-49%	50%-74%	≥ 75%		
	NO. No bonus points are awarded. **Proceed to Step 3.C.**							
3.C. Calculate Total Bonus Points	Add the Palliation Bonus Points (Step 3.A) and the Treatment-Free Interval Bonus Points (Step 3.B). Write this number in the box labeled "Total Bonus Points." The maximum points available for Bonus Points is 30. **Proceed to Step 4.**							**Total Bonus Points**

Step 4: Determine the regimen's NET HEALTH BENEFIT

Calculate the Net Health Benefit	Add the Clinical Benefit Score (Step 1), Toxicity Score (Step 2), and Bonus Points (Step 3). This yields a Net Health Benefit Score. Write this number in the box labeled "Net Health Benefit." The maximum points available for Net Health Benefit are 130 (100 + 30 bonus points). Proceed to **Step 5.**	Net Health Benefit

Step 5: Determine the regimen's COST

Insert the drug acquisition cost (DAC) and patient co-pay based on how much the treatment regimen costs per month.

Cost Per Month:
DAC: _____
Patient Co-Pay: _____

Step 6: Summary Assessment – Advanced Disease Framework

Clinical Benefit	Toxicity	Bonus Points	Net Health Benefit	Cost (per month)
/80	/20	/30	/130	DAC: _____ Patient Payment: _____

Fig 1. ASCO Value Framework: advanced disease. Future versions of the framework will allow for patients weighting their preferences such that the fractional contribution of each element (clinical benefit, toxicity) to the overall score can be modified, thereby individualizing the net health benefit. ASCO, American Society of Clinical Oncology; CR, complete response; DAC, drug acquisition cost; OS, overall survival; PFS, progression-free survival; PR, partial response; RR, response rate.

Mezzi per controllare i costi

- **Posto che i costi della sanità NON sono solo i costi farmacologici (4% della spesa sanitaria)**
  - **Quanti esami diagnostici di scarsa utilità vengono effettuati solo per «medicina difensiva»?**
  - **Quanto la crescita dell'offerta ha comportato una smisurata crescita della domanda, spesso non giustificata?**
  - **Quanto costano le protesi ortopediche? E le valvole cardiache? E gli interventi chirurgici non appropriati?**
  - **Quanto costa l'apparato burocratico posto in essere allo scopo di controllare l'appropriatezza?**

- **Posto che la spesa farmaceutica non è solo quella oncologica e che spesso ci sono spese che non consideriamo**
  - **quanto costano le statine per prevenire la dislipidemia in soggetti ultraottantenni?**
  - **quanti pazienti con malattia oncologica metastatica proseguono comunque le statine perché il colesterolo va tenuto sotto controllo?**

- **Possono i farmaci equivalenti ed i biosimilari aiutare il contenimento dei costi?**

Rapporto OSMED 2020

L'uso dei Farmaci in Italia
Rapporto Nazionale
Anno 2020

Figura 1.8.5. Andamento 2016-2020 del prezzo medio per trastuzumab

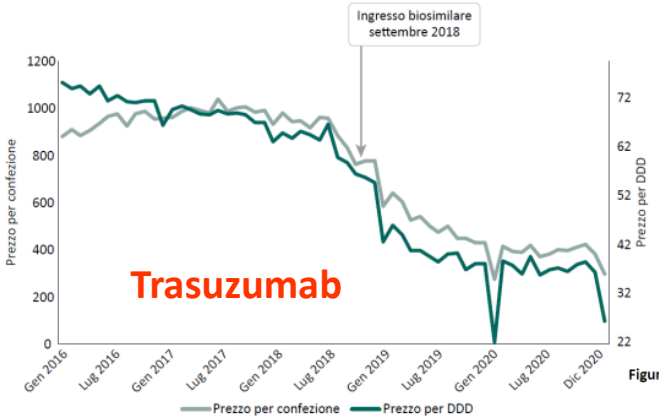


Figura 1.8.6. Andamento 2016-2020 del prezzo medio per bevacizumab

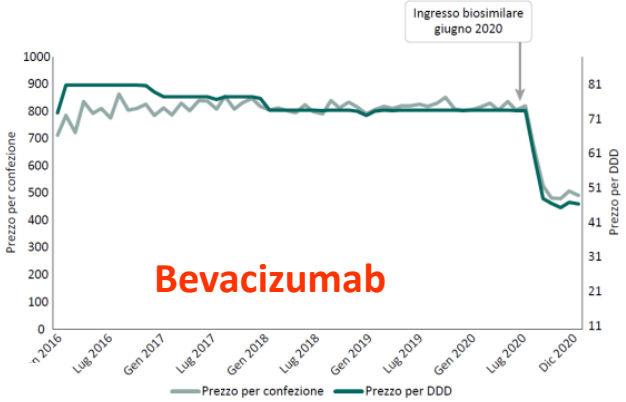
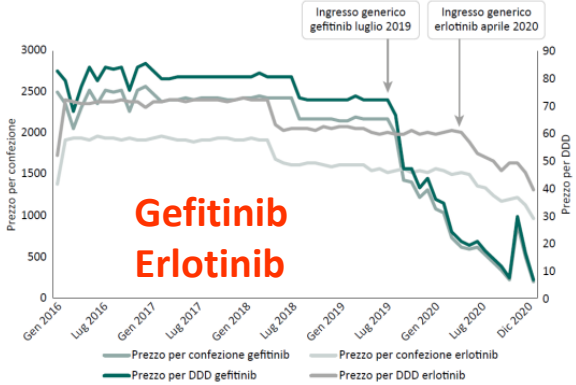


Figura 1.8.10. Andamento 2016-2020 del prezzo medio per gefitinib ed erlotinib



I confronti con l'Europa

Figura 1.9.7. Confronto internazionale della distribuzione percentuale dei consumi dei farmaci biosimilari 2020

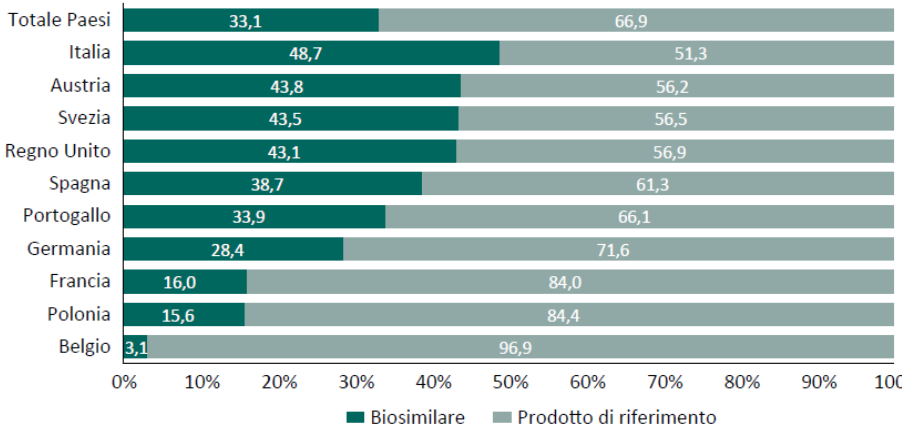
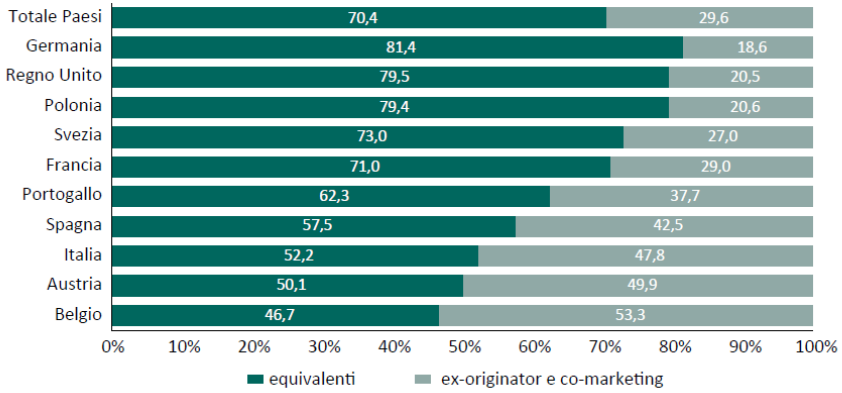


Figura 1.9.5. Confronto internazionale della distribuzione percentuale del consumo territoriale 2020 per i farmaci a brevetto scaduto



Grazie dell'attenzione

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