L'IMMUNOTERAPIA, PRIMO APPUNTAMENTO PER IL FARMACISTA OSPEDALIERO, IL POLMONE: INNOVAZIONE, EFFICACIA E SOSTENIBILITÀ

Torino, 29 marzo 2017

Il punto di vista del farmacista

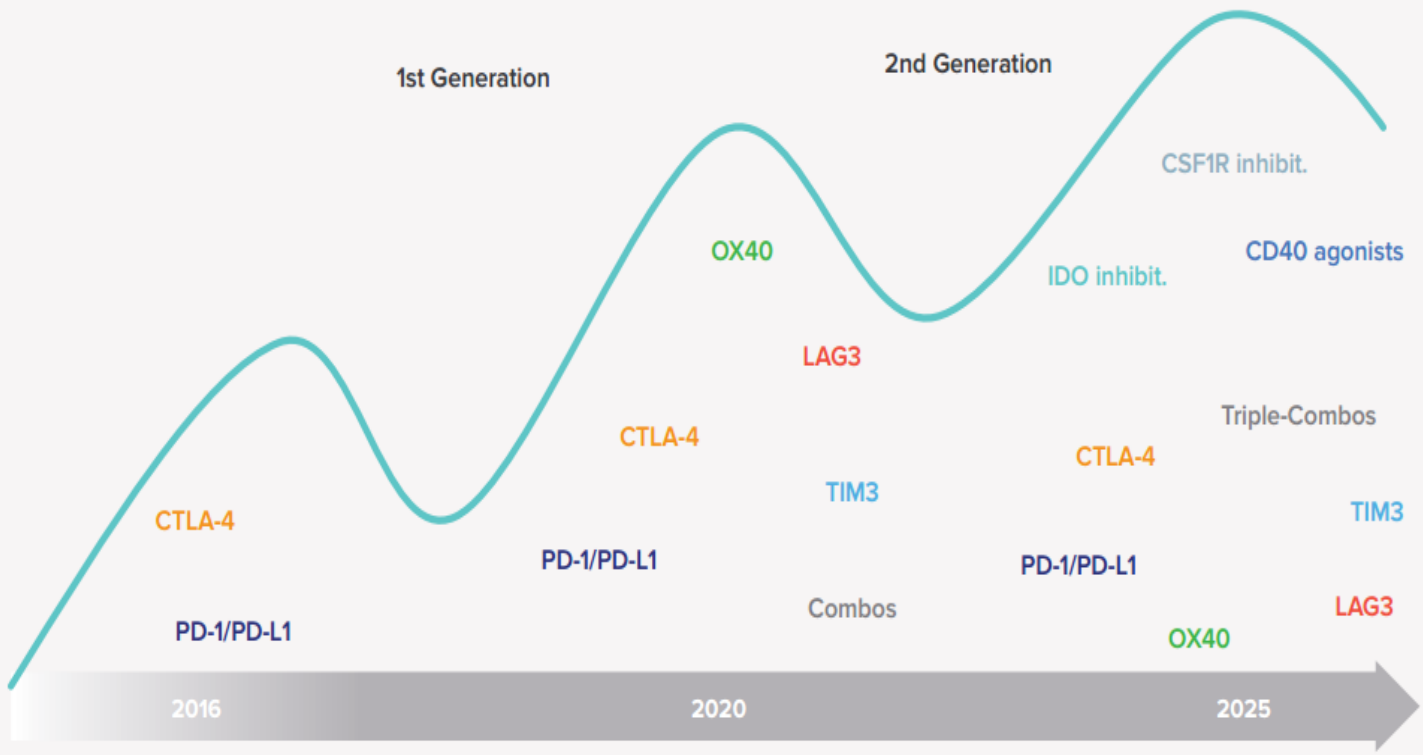
Emanuela Omodeo Salè

Direttore Farmacia Ospedaliera
Istituto Europeo di Oncologia Milano

IMMUNOTERAPIA

- Anticorpi monoclonali targettizzati sul tumore
- Terapia cellulare
- Vaccini (vaccini basati su specifici peptidi; ricombinanti; cellule dendritiche, vaccini per la prevenzione del cancro….)
- Citochine (interleuchine; Interferoni; TNF-alfa; GMCSF; Immunocitochine)
- Mediatori dell'attivazione delle T-Cells (<u>checkpoint inhibitors</u>; Co-stimulatory pathways)
- Virus modificati oncolitici (OGM) - (T-VEC)

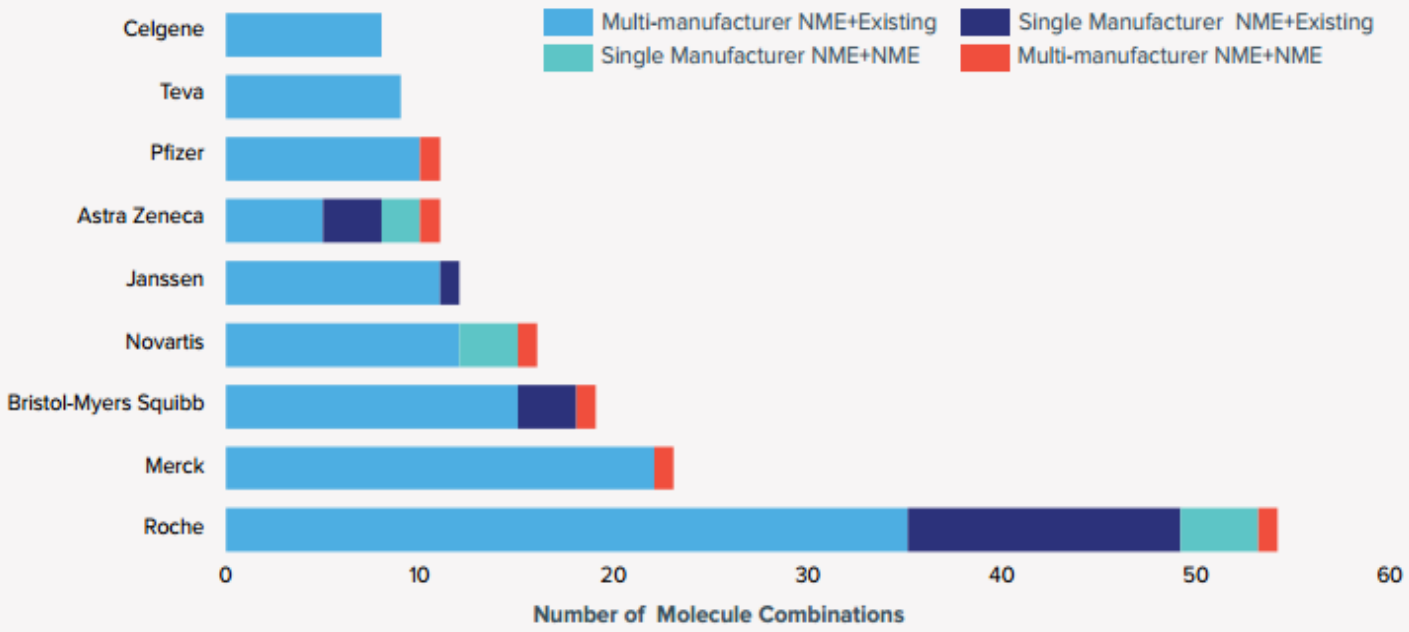
Immunology Oncology Evolution



Source : IMS Health European Thought Leadership

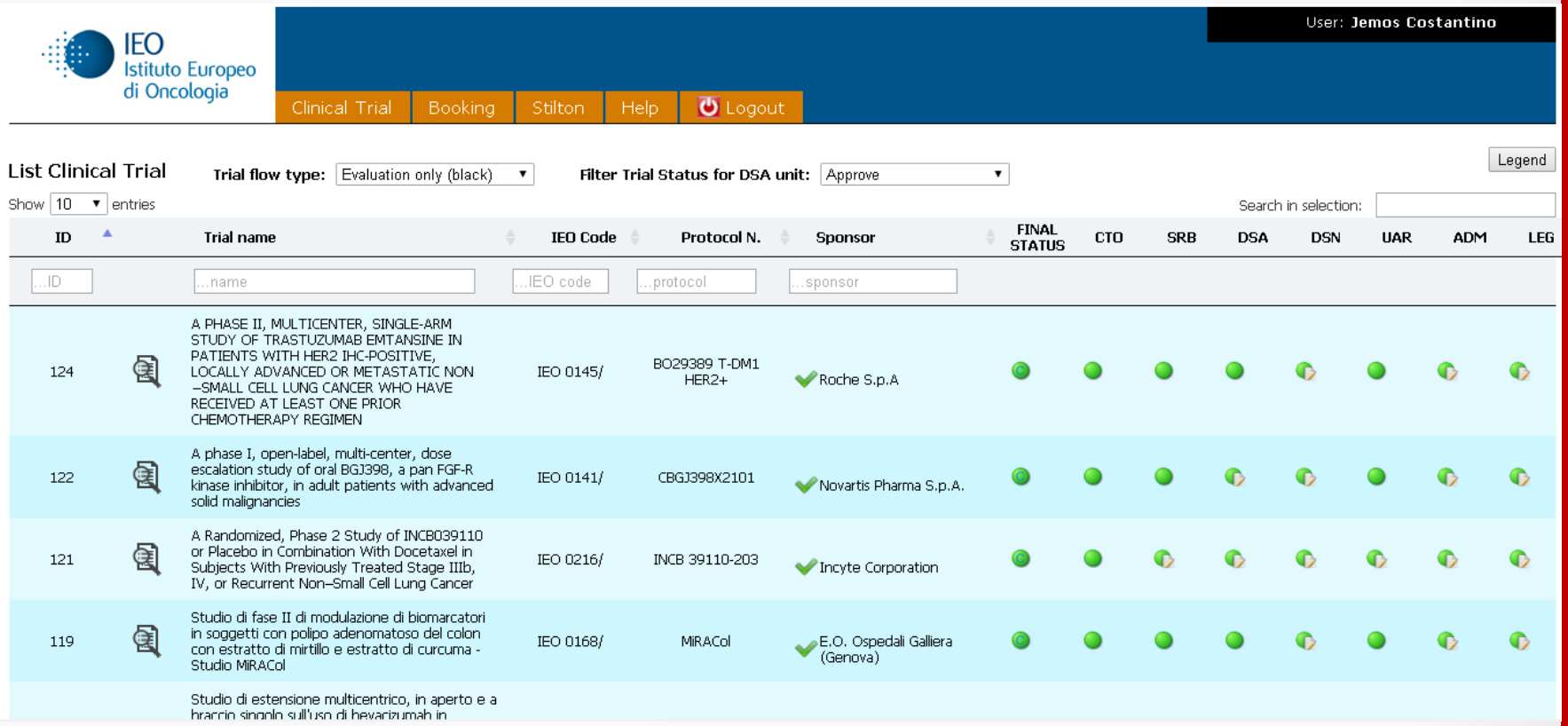
Combinations of targeted and immuno-oncology agents will improve outcomes, but complicate trial and commercialization strategies

Potential Combination Therapies Launching by 2021



Sources: CenterWatch, FDA, clinicaltrials.gov, IMS R&D LifeCycle, IMSCG Analysis

Studi con checkpoint inhibitors in IEO (4D)



IEO Istituto Europeo di Oncologia

User: Jemos Costantino

Clinical Trial | Booking | Stilton | Help | Logout

List Clinical Trial — Trial flow type: Evaluation only (black) — Filter Trial Status for DSA unit: Approve — Legend

Show 10 entries — Search in selection:

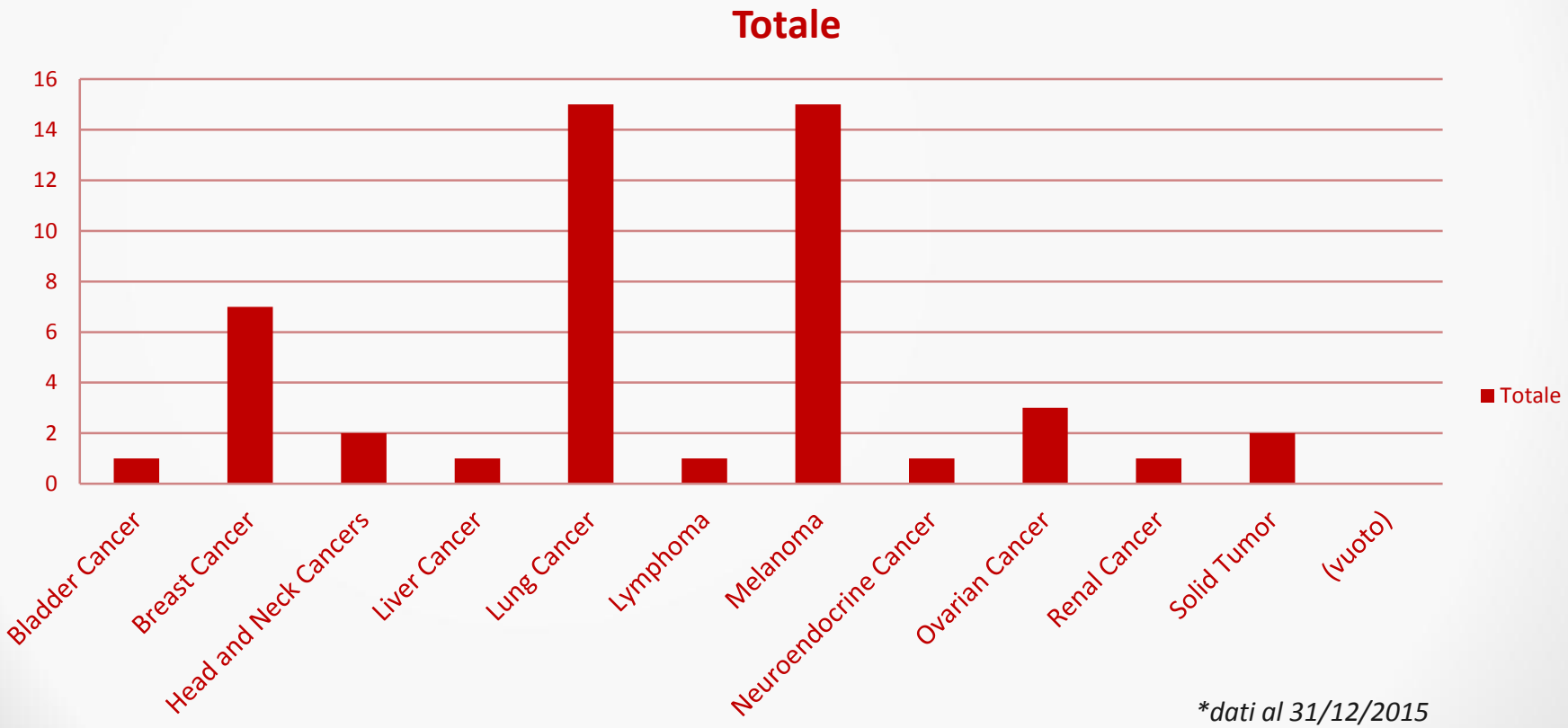
ID	Trial name	IEO Code	Protocol N.	Sponsor	FINAL STATUS	CTO	SRB	DSA	DSN	UAR	ADM	LEG
...ID	...name	...IEO code	...protocol	...sponsor								
124	A PHASE II, MULTICENTER, SINGLE-ARM STUDY OF TRASTUZUMAB EMTANSINE IN PATIENTS WITH HER2 IHC-POSITIVE, LOCALLY ADVANCED OR METASTATIC NON –SMALL CELL LUNG CANCER WHO HAVE RECEIVED AT LEAST ONE PRIOR CHEMOTHERAPY REGIMEN	IEO 0145/	BO29389 T-DM1 HER2+	Roche S.p.A								
122	A phase I, open-label, multi-center, dose escalation study of oral BGJ398, a pan FGF-R kinase inhibitor, in adult patients with advanced solid malignancies	IEO 0141/	CBGJ398X2101	Novartis Pharma S.p.A.								
121	A Randomized, Phase 2 Study of INCB039110 or Placebo in Combination With Docetaxel in Subjects With Previously Treated Stage IIIb, IV, or Recurrent Non–Small Cell Lung Cancer	IEO 0216/	INCB 39110-203	Incyte Corporation								
119	Studio di fase II di modulazione di biomarcatori in soggetti con polipo adenomatoso del colon con estratto di mirtillo e estratto di curcuma - Studio MiRACol	IEO 0168/	MiRACol	E.O. Ospedali Galliera (Genova)								
	Studio di estensione multicentrico, in aperto e a braccio singolo sull'uso di bevacizumab in											

*51/939 *(valutati) trials in IEO con checkpoint inhibitors*

27 sono ongoing

**dati al 31/12/2015*

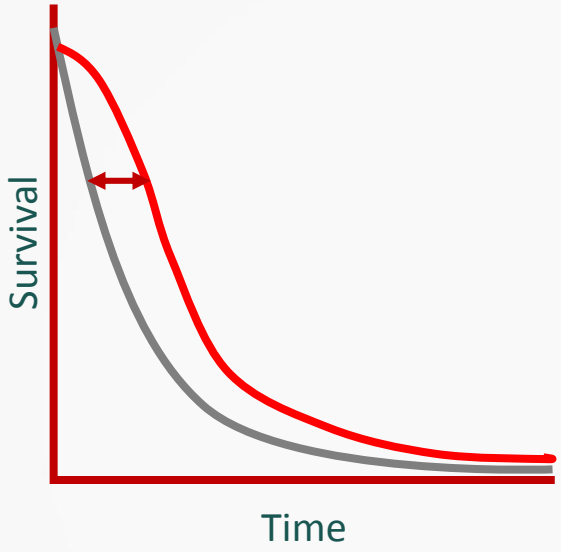
Organi bersaglio di terapie con checkpoint inhibitors* (Sperimentazioni valutate in IEO)



**dati al 31/12/2015*

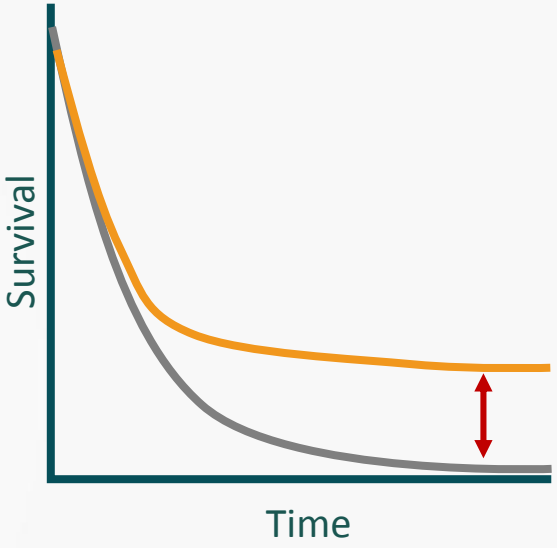
Come cambia la curva della sopravvivenza

Conventional therapy



Effetti antitumorali promettenti ma che non durano a lungo

Immuno-therapy



Effetti antitumorali durevoli che portano a miglioramento della sopravvivenza a lungo termine

- **Control**
- **Targeted therapies**
- **Immune checkpoint blockade**

1. Adapted from Ribas A, presented at WCM, 2013; 2. Ribas A, et al. *Clin Cancer Res.* 2012;18:336–341; 3. Drake CG. *Ann Oncol*. 2012;23(suppl 8):viii41–viii46.

Il valore dell'immuno-oncologia

L'aspetto del tutto nuovo dell'I-O è rappresentato da una quota rilevante di pazienti che sopravvivono a lungo termine

GRHTA
ISSN 2284-2403

Global & Regional Health Technology Assessment 2016; 3(1): 1-8
DOI: 10.5301/GRHTA.5000219
REVIEW

Open Access

L'immunoterapia nel trattamento del cancro: implicazioni per le valutazioni di efficacia ed economiche

Claudio Jommi[1,2], Francesco S. Mennini[3,4], Pier L. Canonico[1], Paolo Bruzzi[5] on behalf of the Scientific Board on Immuno-oncology and Cancer Treatment*

[1] Dipartimento di Scienze del Farmaco, Università del Piemonte Orientale, Novara - Italy
[2] Cergas (Centro di Ricerche sulla Gestione dell'Assistenza Sanitaria e Sociale), Università Bocconi, Milano - Italy
[3] CEIS - Economic Evaluation and HTA (EEHTA), Università "Tor Vergata", Roma - Italy
[4] Institute for Leadership and Management in Health, Kingston University London, London - UK
[5] IRCCS Azienda Ospedaliera Universitaria San Martino - IST - Istituto Nazionale per la Ricerca sul Cancro, Genova - Italy

* I nomi dei membri del Board sono riportati a fine articolo

Immuno-therapy in the treatment of cancer: implications for efficacy and economic evaluations

In the last few years, immuno-oncology has partially modified the paradigm of cancer treatment, due to the observation of long-term survivors among patients with advanced tumors and with a predicted limited life expectancy, if treated with immunotherapeutic agents. This paper illustrates the opinion of an expert panel (Scientific Board on Immuno-oncology and Cancer Treatment) regarding the clinical and economic assessments of immunologic anticancer treatments. The agreement on the document was reached through a Consensus Conference. Overall survival and/or survival rates at specific time-points are the ideal parameters to evaluate the efficacy and effectiveness of immunotherapies. Since benefits affect different patients at different times across cancer indications of immunotherapies, short-term (on most of targeted patients) and long-term effects on smaller groups should be considered. When market access decisions are taken, the benefit profile of immunotherapies has important implications for their economic assessment. Robust long-term extrapolation of expected survival rates should be carried out when cost-efficacy (effectiveness) of immunotherapies is estimated; mean instead of median incremental survival rate is a more appropriate measure; real-world data collection should be strengthened and used to eventually revise decisions taken on price and reimbursement.

Keywords: Cancer immunotherapy, Clinical endpoints, Cost-effectiveness, Market access

Il valore dell'immuno-oncologia (2)

L'overall survival medio cattura meglio il valore dell'I-O vs OS mediano

GRHTA
ISSN 2284-2403

Global & Regional Health Technology Assessment 2016; 3(1): 9-15
DOI: 10.5301/GRHTA.5000218
ORIGINAL ARTICLE

Open Access

Riflessioni sulla determinazione del valore dei farmaci oncologici: un'analisi sui farmaci di prima linea per i tumori metastatici

Federico Spandonaro[1], Diana Giannarelli[2], Barbara Polistena[1]

[1] Università di Roma Tor Vergata, CREA Sanità, Roma - Italy
[2] Istituto Nazionale Tumori Regina Elena IRCCS, Roma - Italy

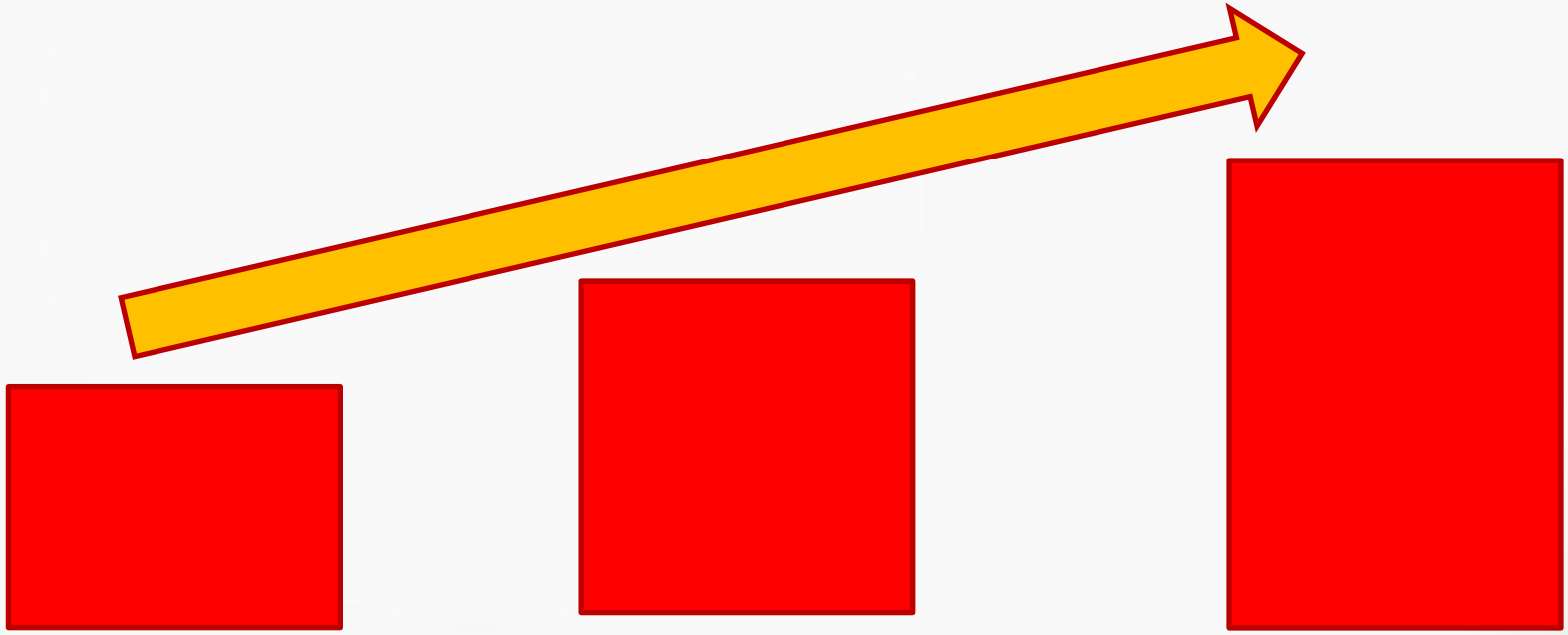
Some considerations about the value based pricing in oncology: an analysis on metastatic first line medicinal products

Introduction: In recent years public health systems have faced the challenge of ensuring sustainable costs for innovative medicinal products. The aim of this study is to analyse pricing behaviour applied in the Italian oncology sector.
Methods: The study examined all new oncologic compounds that are reimbursed in Italy, for utilization in the first-line metastatic setting. A regression model was developed to analyse the relation between drug price, clinical benefit, market potential and the year in which reimbursement was granted in Italy. The clinical benefit was measured by increment in Overall Survival respect to standard of care; two different metrics were considered, namely median and mean.
Results: The analysis revealed a strong correlation between price and clinical benefit and a weak negative correlation between prices and volumes; no time trends were observed in reimbursement price reduction. As regards pricing, the Italian Medicines Agency seems to have maintained basically consistent reference levels over the 10 years. Nevertheless, the analysis highlighted significant differences: some compounds showed lower prices than expected; conversely, vemurafenib, sunitinib and, to a much lesser degree, pazopanib prices were higher than expected. The only drug for which price evaluation is inverted depending on whether median or mean values are used is ipilimumab, the only immunotherapeutic compound considered.
Discussion: The study highlights the extent to which the value of oncological drugs depends on the endpoints considered in the analysis, as well as on the metric adopted, confirming that the decision must be multidimensional, as required by an Health Technology Assessment rationale.

Keywords: Italy, Mean, Median, Oncology, Pricing, Survival

I prezzi?

- Prezzo basato sul costo di produzione
- Prezzo basato sul costo di sviluppo
- Prezzo basato sulle politiche di mercato?

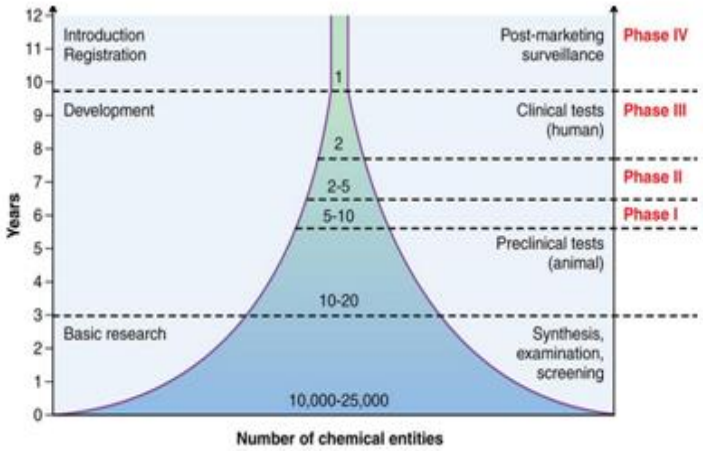


…value-based pricing?

Se i costi della ricerca sono inferiori ai costi di marketing…

lo scenario…

Paprika
Paziente in Prima Classe



Utili reinvestiti in ricerca

1/10 mila molecole arriva al letto del malato

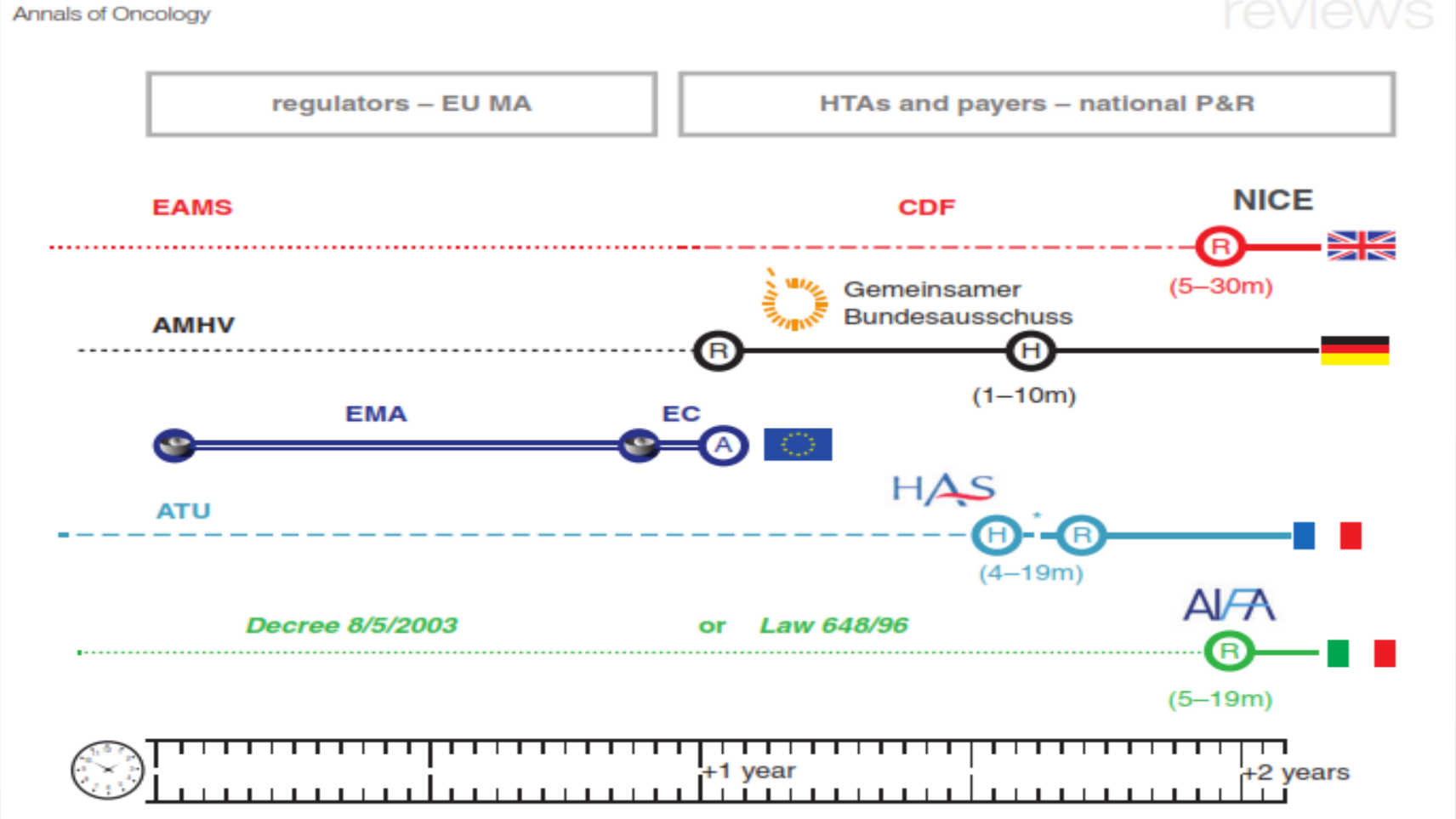
Ricerca incide in media per l'8-15% del prezzo

Il marketing per il 25%

CIPOMO
Collegio Italiano dei Primari Oncologi Medici Ospedalieri

XX Congresso Nazionale, Napoli 19-21 maggio 2016 - Relazione del Presidente

Presentato da dr. Claudio Verusio


Annals of Oncology
reviews
regulators – EU MA
HTAs and payers – national P&R
EAMS
CDF
NICE
R
(5–30m)
Gemeinsamer
Bundesausschuss
AMHV
R
H
(1–10m)
EMA
EC
A
HAS
ATU
H
R
(4–19m)
AIFA
Decree 8/5/2003
or
Law 648/96
R
(5–19m)
+1 year
+2 years

Quindi….

N° pazienti

Durata del trattamento

N° di farmaci

Prezzi

Tempi per la rimborsabilità

Sostenibilità ed accessibilità…

Hospital Pharmacy

Surgery/
medical devices

Investigational drug management

Drug and Therapeutics committee

Reimbursement procedures , AIFA register and payment by results

Drug orders and logistics

Pharmacovigilance activities

Prescription check

Drug Aseptic Manipulation Unit

Drug Dispensing Unit

Improving practice and cost saving

Criticità e sfide

- **Aggiornamento**

Risposta

Tossicità

- **Gestione prontuari**
- **Gestione economico/amministrativa**

- **Farmacovigilanza, Outcome Research e Registri AIFA**

Tossicità AI da anti-PD1

- Tossicità gastointestinale (diarrea,coliti, perforazione)
- Tossicità renale
- Tossicità polmonare
- Tossicità epatica
- Endocrinopatie (tiroiditi,ipofisiti)
- Tossicità cutanee (rash)
- Tossicità neurologica

Lo schema generale è:
G1 incrementare l'osservazione, terapia sintomatica
G2 ritardare il trattamento con IO, aggiungere metilprednisolone 1mg/Kg/die
G3-G4 aumentare il metiprednisolpone a 2 mg/Kg/die e sospendere IO
Se persiste considerare micofenolato, Infliximab, IV-IG o altri immunosoppressori
Profilassi antibiotica durante la terapia cortisonica.
Consultare specialisti del distretto interessato

Esempio: algoritmo di gestione della tossicità GI da anti-PD1 / anti LAG3

Grade of Diarrhea/Colitis (NCI CTCA v4)	**Management**	**Follow up**
Grade1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	Continue I-O therapy; Symptomatic treatment	Close monitoring and educate patient to report worsening
Grade2 Diarrhea: 4-6 stools/day over baseline;IV fluids indicated <24hrs; not interfering with ADL; Colitis: abdominal pain; blood in stool	Delay I-O therapy; Symptomatic treatment	<u>if improves to grade1</u>: resume I-O therapy; <u>If persists > 5-7 days or recur</u>: 0,5-1,0mg/Kg/die Methylprednisolone or oral equivalent; when symptoms improve to G1 taper steroids over (1 month) , consider prophylactic antibiotics and resume I-O therapy. If worsen or persist > 3-5 days with oral steroids: treat as G3-4
Grade3-4 Diarrhea(G3): ≥ 7 stools/day over baseline; incontinence; IV fluids indicated ≥24hrs; interfering with ADL; Colitis(G3): severe abdominal pain; medical intervention indicated;peritoneal signs; G4: life-threatening, perforation	Discontinue I-O therapy; 1,0 to 2,0 mg/kg/die Methylprednisolone IV or IV equivalent; prophylactic antiobiotics; consider lower endoscopy	<u>if improves:</u> continue steroids until G1, then taper over at least 1 month. <u>If persists>3-5 days or recurs after improvement</u> : add ***infliximab 5mg/kg (Infliximab should not be used in cases of perforation or sepsis)***

Gestione prontuari

Introduzione rapida di diversi principi attivi con meccanismo ed indicazioni sovrapponibili

- Mancanza di studi di comparazione diretta ("nessuna company ne farà mai uno")…. Quale ruolo per le società scientifiche?
- Necessità di definire criteri di scelta sulla singola indicazione, soprattutto su farmaci appartenenti alla medesima classe!
- Utilizzo Off label di anti PD1… esistono studi di fase II in corso su praticamente tutte le patologie

Farmaci Immuno-oncologici rimborsati in Italia:

Scheda di Monitoraggio Web

-Ipilimumab nel melanoma metastatico (Payment by result)

-Nivolumab nel melanoma metastatico (P/V agreement)
-Nivolumab nel trattamento del NSLSC con istologia Squamosa (P/V agreement)

-Pembrolizumab nel melanoma metastatico (P/V agreement)

Farmacovigilanza e dati di outcome research

- Il farmacista ha un ruolo fondamentale nella raccolta, analisi e diffusione di questi dati

- Condividere le informazioni

- Strutturare percorsi di rivalutazione dei farmaci post marketing

- Potenziare il finanziamento di progetti di farmacovigilanza attivi specifici dei farmaci innovativi

Conclusioni

- Grande opportunità terapeutica
- Gestione accurata dei prontuari e dei programmi di trattamento per patologia
- Supporto al clinico per il riconoscimento di reazioni avverse autoimmuni e per la loro gestione (formazione in pronto soccorso?)
- Importantissimo il nostro ruolo in farmacovigilanza.
- Promozione di team multidisciplinari

Grazie per l’attenzione