“Le nuove sfide della ricerca oncologica: verso una partnership tra Enti Pubblici e Industria nella regione Lazio”

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I biomarcatori nei tumori solidi

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Biomarcatore

Indicatore misurabile che è usato per distinguere con precisione, riproducibilità e obiettività sia uno stato biologico nomale da uno patologico sia la risposta ad uno specifico intervento terapeutico

Modificato da: Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework.
Clin. Pharmacol. Ther. 69, 89–95 (2001)

Quali altre caratteristiche dovrebbe avere un buon biomarcatore ?

- Facilità di accesso al campione
- Possibilità di ripetere l'esame nel tempo

Distinguiamo diversi tipi di biomarcatori?

- Prognostici
- Farmacodinamici
- Predittivi
- Surrogati
- Per il monitoraggio di efficacia

Perché i biomarcatori sono necessari

- Aumentare la probabilità che uno studio clinico evidenzi l'efficacia di un nuovo farmaco
- Identificare i pazienti che hanno una ragionevole probabilità di avere un beneficio dalla terapia / evitare di esporre a potenziale tossicità pazienti che non la abbiano
- Indirizzare le risorse disponibili per terapie generalmente molto costose in maniera costo efficace

Fallimento di studi clinici di fase II e III

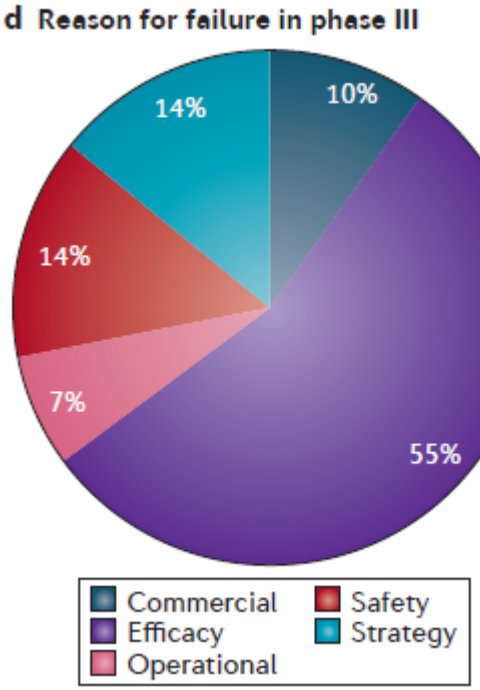
Studi clinici falliti nel periodo 2013-2015: **218**.

Dei 174 per i quali è stata comunicata la ragione sono falliti per:

- Mancato raggiungimento degli obiettivi di efficacia: **52 %**
- Mancato rispetto dei requisiti di sicurezza:

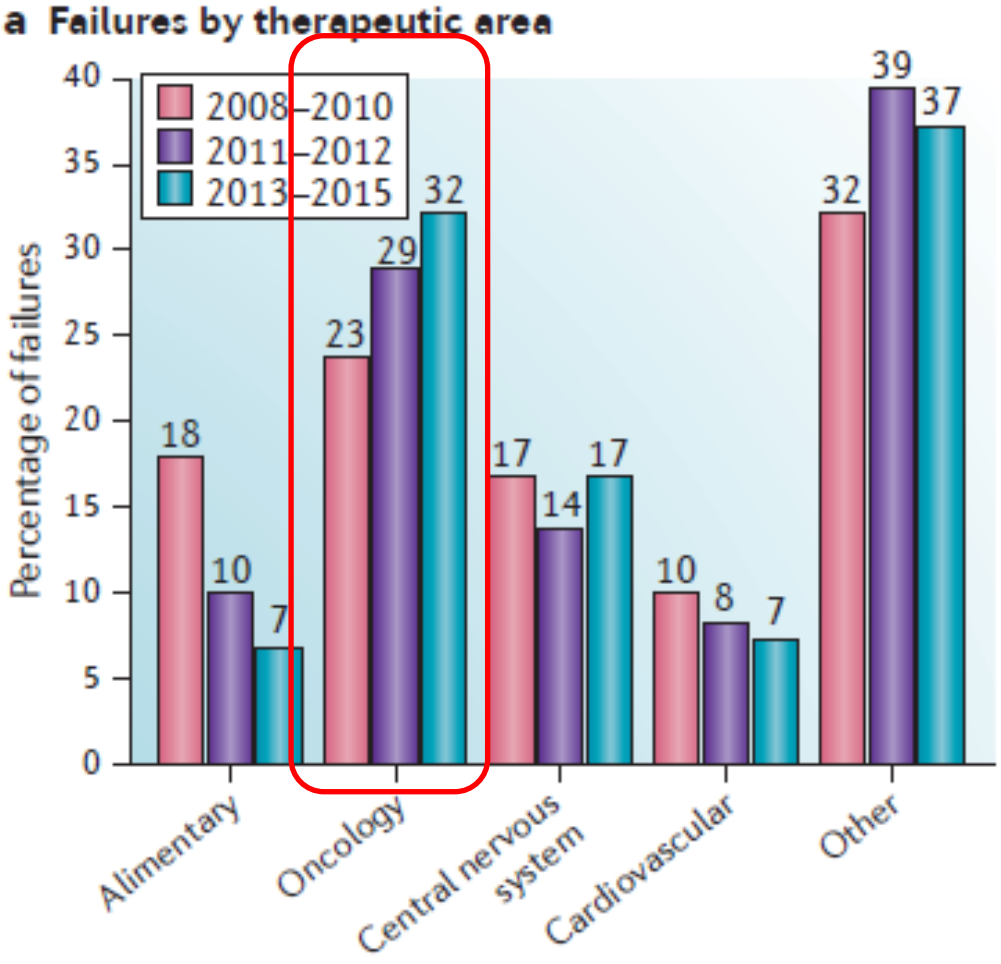
In quasi un terzo dei casi erano studi di

oncologia



Dati da Harrison RK. Nature Rev Drug Discovery 15: 816-818; 2

Andamento temporale



Harrison RK. Nature Rev Drug Discovery 15: 816-818; 2016

Ragioni del fallimento

- Bersaglio sbagliato
- Molecola sbagliata

Biomarcatore farmacodinamico

- Sbagliato parametro clinico misurato

Biomarcatori prognostici o surrogati

- Sbagliata selezione dei pazienti

Biomarcatore predittivo

Sviluppo di biomarcatori

Per lo sviluppo di un biomarcatore si devono avere dati

FAIR

- Findable
- Accessible
- Interoperable
- Reusable

Fasi dello sviluppo di biomarcatori

- The **pre-validation** process that defines the intended purpose of the biomarker, considering pre-analytical variables and bioanalytical method feasibilit
- The **exploratory validation** process that assesses the basic assay performance
- The **advanced validation** process that characterizes the formal performance of the assay with regard to its intended use
- The **in-study validation** process that ensures that the assay method performs robustly across studies according to predefined specifications and facilitates the establishment of definitive acceptance criteria

Lee, J. W. *et al. Fit-for-purpose method development and validation for successful biomarker measurement. Pharm. Res. 23, 312–328 (2006).*

Sviluppo di un biomarcatore

Box 2 | Considerations for procedure standardization

Pre-analytical standardization

- Patient factors: anaesthetic agents; hydration; stress responses; drugs; concomitant diseases or co-morbidities; tissue ischaemia; sample-processing delays (phosphorylation); and other unknown factors
- Tissue factors: collection (device/process, tissue versus serum based specimen, sample volume, contamination); fixation (type, time, penetration); processing (methods, times for each step, temperature); storage; and stability and integrity

Analytical standardization

- Tissue factors: analyte differences (DNA, RNA, protein); antigen retrieval (for immunohistochemistry); antibody variability; detection reagents (chromagens); inconsistencies relating to kits and automation; control selection; and quality control
- Scoring systems for staining: intensity; extent; topography; nonlinearity of methodologies; and computerized image analysis ('precise measurement of the imprecise')

Post-analytical standardization

- Effects of volume of testing by laboratories: high-volume testing laboratories, such as central laboratories, usually have more expertise and proficiency than low-volume local laboratories
- Data interpretation: dichotomous variables; continuous variables (cut-points relevant to clinical decisions); and reproducibility
- Collaborative role of professional pathology organizations: at the international level, to define standards; at the local level, to facilitate implementation of these standards

de Gramont, A. *et al.*
Nat. Rev. Clin. Oncol. 12, 197–212 (2015)

FDA-approved targeted agents with demonstrated activity and an effective predictive biomarker of efficacy in solid cancers*

Year of approval	Drug	Clinical biomarker(s)	Target(s)	FDA-approved indication(s)	Patient population positive for biomarker	RR to treatment
1998	Trastuzumab	HER2 overexpression	HER2	HER2-positive mBC: single agent in second-line therapy, and in combination with paclitaxel in first-line treatment	18–20% (HER2-positive population)	15–50%1[45,146]
2003	Imatinib	KIT (CD117)	KIT, ABL and PDGFR	In unresectable and/or KIT-positive mGIST	CD117-positive: 95% *KIT*-mutation-positive: 80%	45–83%[147,148]
2004	Cetuximab	EGFR-protein expression‡	EGFR	With irinotecan or as single agent (2007) for EGFR-positive mCRC refractory to irinotecan	60–80%	11–55%[149,150]
2006	Trastuzumab	HER2 overexpression	HER2	With adjuvant treatment for node-positive, HER2-positive BC	18–20% (HER2-positive population)	38% DFS increase[145,151]
2006	Panitumumab	Wild-type§ *KRAS* (specifically at codons 12 or 13 in exon 2)	EGFR	EGFR-expressing mCRC with disease progression on chemotherapy regimens	40–60%	17–58%[92,152]
2007	Lapatinib	HER2 overexpression	HER2; EGFR	In combination with capecitabine in pretreated HER2-positive mBC	18–20% (HER2-positive population)	24–41%[153,154]
2008	Imatinib	*COL1A1–PDGFB* fusion	KIT, ABL and PDGFR	For *COL1A1–PDGFB* gene-fusion-negative metastatic DFSP (or DFSP with unknown mutation status), and as adjuvant therapy in KIT-positive GIST	>95%	36–100%[155,156]
2009	Gefitinib	*EGFR*-activating mutations	EGFR	NSCLC with *EGFR* mutations that respond to or had prior response to gefitinib (limited approval by FDA)	10–15% of white patients and 30–35% of East Asian patients	37–78%[157,158]

Year of approval	Drug	Clinical biomarker(s)	Target(s)	FDA-approved indication(s)	Patient population positive for biomarker	RR to treatment
2010	Lapatinib	HER2 overexpression	HER2; EGFR	With letrozole in postmenopausal women with hormone-receptor-positive and HER2-positive mBC	18–20% (HER2-positive population)	8–48%[159,160]
2010	Trastuzumab	HER2 overexpression	HER2	With cisplatin and fluoropyrimidine in the first-line treatment of HER2-positive metastatic GC and GEC	7–34%	47%[161]
2011	Crizotinib	*EML4–ALK* translocation	ALK; MET	ALK-positive locally advanced or metastatic NSCLC	1–7%	50–65%[162,163]
2011	Vemurafenib	BRAF V600E mutation	BRAF	Metastatic melanoma with BRAF V600E mutation	80–90% of *BRAF*-mutated population	48–57%[164,165]
2012	Cetuximab	Wild-type§ *KRAS*	EGFR	In combination with FOLFIRI for the first-line treatment of *KRAS*-wild-type patients with EGFR-positive mCRC	40–60%	47–61%[166,167]
2012	Pertuzumab	*HER2* amplification	HER2	In combination with trastuzumab and docetaxel as first-line therapy for HER2-positive mBC	18–20% (HER2-positive population)	24–63%[168,169]
2013	Ado-trastuzumab emtansine	HER2 overexpression	HER2	HER2-positive mBC with prior exposure to trastuzumab and/or a taxane	18–20% (HER2-positive population)	26–64%[170,171]
2013	Afatinib	*EGFR* exon 19 deletions or exon 21 mutation (L858R)	EGFR, HER2 and HER4	First-line treatment of metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 mutations	45% with *EGFR* exon 19 deletion and 41% with *EGFR* exon 21 mutation	56–67%[172,173]
2013	Ceritinib	*ALK* rearrangement	ALK	ALK-positive NSCLC that progressed during or after treatment with crizotinib	2–5%	56%[174,175]

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2013	Erlotinib	*EGFR* exon 19 deletion or exon 21 mutation (L858R)	EGFR	First-line treatment of metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 mutations	45% with *EGFR* exon 19 deletion and 41% with *EGFR* exon 21 mutation	54–83%[176,177]
2013	Pertuzumab	*HER2* amplification	HER2	As neoadjuvant treatment with trastuzumab and docetaxel for HER2-positive advanced, inflammatory or early-stage BC	18–20% (HER2-positive population)	24–62%[178,179]
2013	Trametinib	BRAF V600E/K mutations	MEK	Unresectable/metastatic *BRAFV600E/K*-mutated melanoma	*BRAFV600E*-mutated: 80–90%; *BRAFV600K*-mutated: 20%	22–25%[180,181]
2014	Dabrafenib	BRAF V600E/K mutations	BRAF	With trametinib for metastatic melanoma with BRAF V600E/K mutations	*BRAFV600E*-mutated: 80–90%; *BRAFV600K*-mutated: 20%	31– 76%[180,182,183]

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Box 1 | **Specific requirements for a biomarker for immune checkpoint blockade**

What is so remarkable about immune checkpoint blockade?

- Immune checkpoint blockade works in a minority of patients for many types of cancers[2–6,8–11].
- When it works, it often works really well, with prolonged responses for many years[16,121]. By contrast, in most cancers, other treatments typically are effective for only a limited time.
- Responding tumours can first show increased size on imaging before they start to respond (pseudoprogression)[15].
- Immune checkpoint blockade can have severe, life-threatening side effects[13].
- These types of drugs are extremely expensive[14].
- Although the targets are defined, the exact mechanism of action of these compounds is incompletely understood.
- Combinations of immune checkpoint blockade may augment response[2], but the rationale for combination therapies is incompletely understood.

What are the necessary characteristics of a biomarker for immune checkpoint blockade?

- The biomarker needs a very high negative predictive value (that is, the biomarker should at least point out who will certainly not respond).
- Although a single pre-treatment biomarker would be ideal, a biomarker that could be used early in treatment would still be of great value.
- For example, response prediction during the first (or second) cycle would enable the identification of patients who may benefit from continuing or not; pseudoprogression would be readily identified; financial burden and potential toxicity would be limited as only one or two administrations of the antibody will be required, and the biomarker may identify new targets for intervention[39,117].
- An ideal biomarker would be non-invasive; that is, repeated biopsies would not be required.
- An ideal biomarker would be valid and reliable in different cancer populations.

Lesterhuis, WJ. *et al.*
Nat. Rev. Clin. Oncol. 16, 264-272 (2016)

Sviluppi futuri

- Presente
  - Biopsia del tumore

- Futuro
  - Acidi nucleici circolanti
  - Cellule tumorali circolanti