



XLIX
CONGRESSO
NAZIONALE
AIEOP



Tossicità da target therapy

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Il sottoscritto Federico Mercolini

*ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-
Regione del 5 novembre 2009,*

dichiara

☒ *che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti
portatori di interessi commerciali in campo sanitario*

☐ *che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti
portatori di interessi commerciali in campo sanitario:*



Review

Targeting developmental pathways in children with cancer: what price success?

Lia Gore, James DeGregori, Christopher C Porter

Tumori adulto: possibile pathways analoghe ai tumori pediatrici

NB: queste pathways possono essere normalmente molto espresse nelle cellule sane a seconda dell'età

Possibile diversa tossicità nel bambino rispetto all'adulto

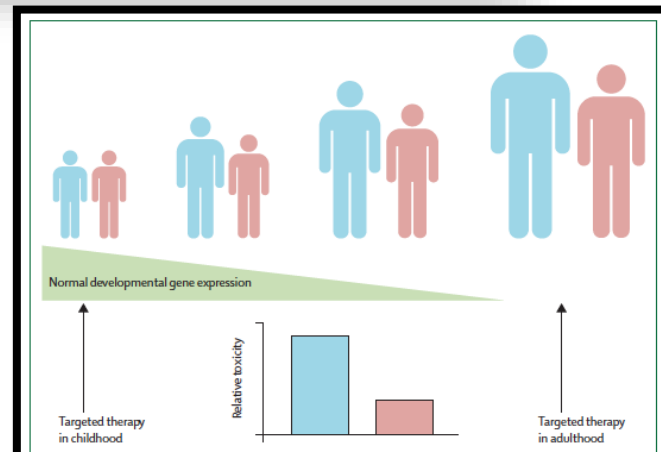


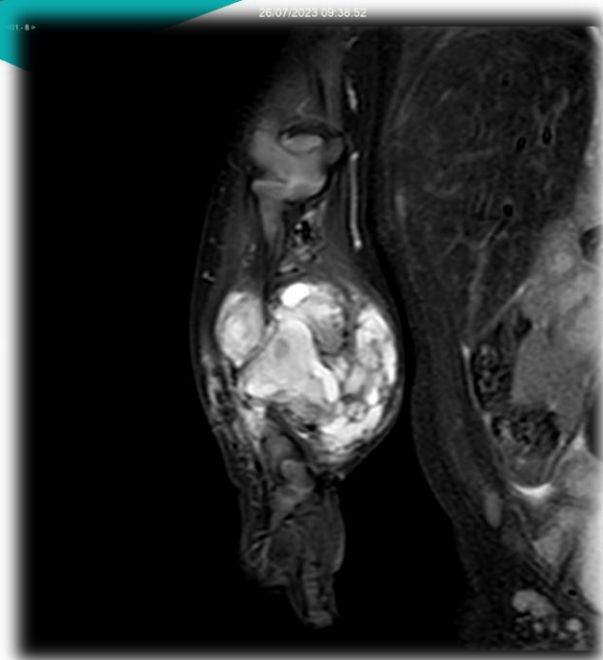
Figure 2: Targeting developmental pathways in children

Some genes that drive cancer are normally active only in specific stages of development (green triangle). Thus, targeting one of these developmental oncogenes in young children (left) might also impair a developmental pathway, in this example linear growth. However, if the oncogene is targeted later in life (right), this adverse effect will not occur.

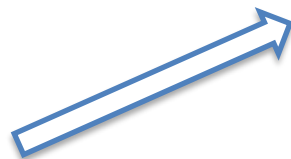


TARGET FUSIONS	AGENT	HISTOLOGY	RESPONSE RATE, %	NO.	REFERENCE
ALK	Crizotinib	Inflammatory myofibroblastic tumor	86	14	Mosse 2017 ⁷⁸
		Anaplastic large cell lymphoma	88	6	Mosse 2017 ⁷⁸
	Ceritinib	Inflammatory myofibroblastic tumor	70	10	Schulte 2020 ⁷⁹
		Anaplastic large cell lymphoma	75	8	Schulte 2020 ⁷⁹
	Entrectinib	Inflammatory myofibroblastic tumor	100	2	Robinson 2019 ¹⁵⁴
NTRK	Larotrectinib	Multiple, primarily sarcomas	94	34	van Tilburg 2020 ¹⁵²
ROS1	Crizotinib	Inflammatory myofibroblastic tumor, meningioma	100	2	Vassal 2016 ¹⁶⁵
	Entrectinib	Gliomas, inflammatory myofibroblastic tumor	100	3	Robinson 2019 ¹⁶⁶

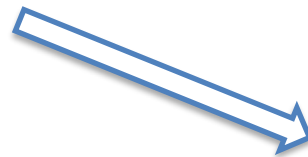




Fibrosarcoma Infantile
ETV6::NTRK3



Chemioterapia



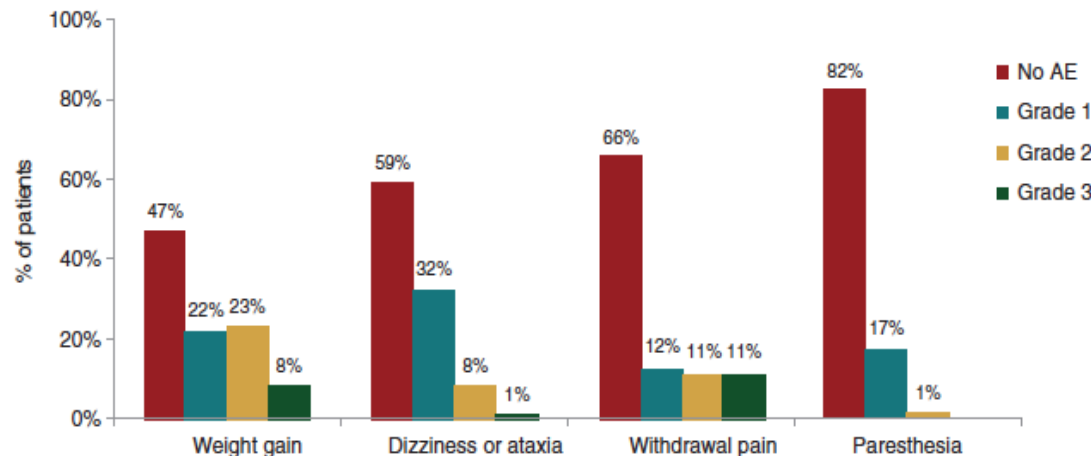
Target therapy



Larotrectinib (inibitore NTRK)

Recettore Tirocinico Chinasico Neurotrofico

SCOUT / NAVIGATE trials

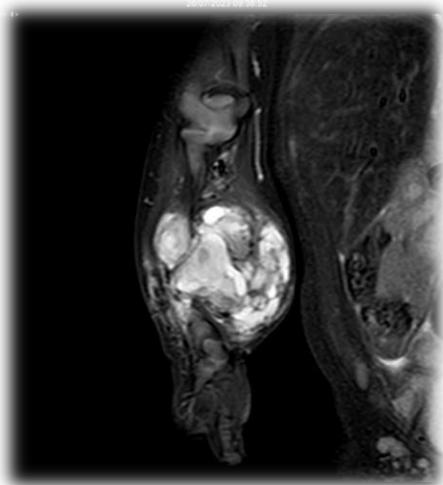


Tossicità < Grado 3:
anemia/leucopenia
aumento AST/ALT
aumento fosfatasi alcalina
nausea, vomito, stipsi

**NO dati a lungo
termine sul
neonato/bambino**



Larotrectinib

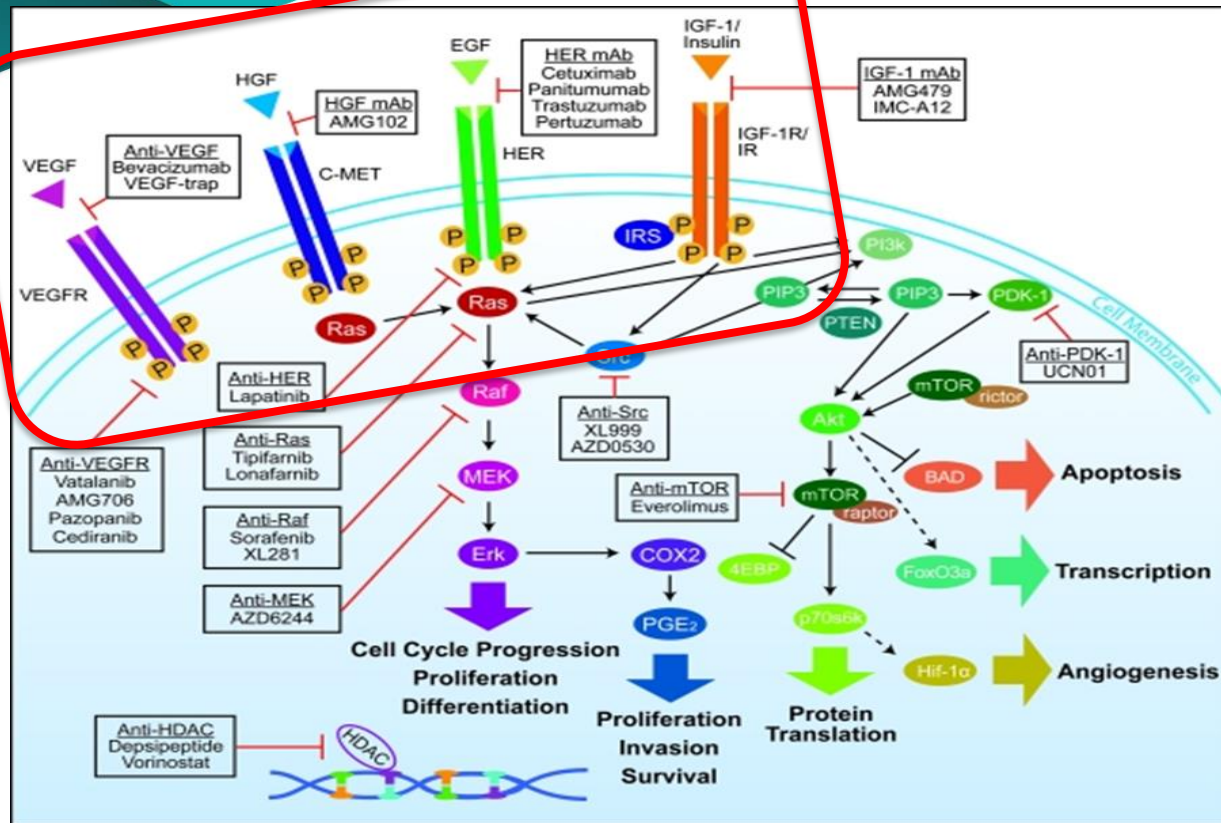


Fibrosarcoma Infantile
ETV6::NTRK3



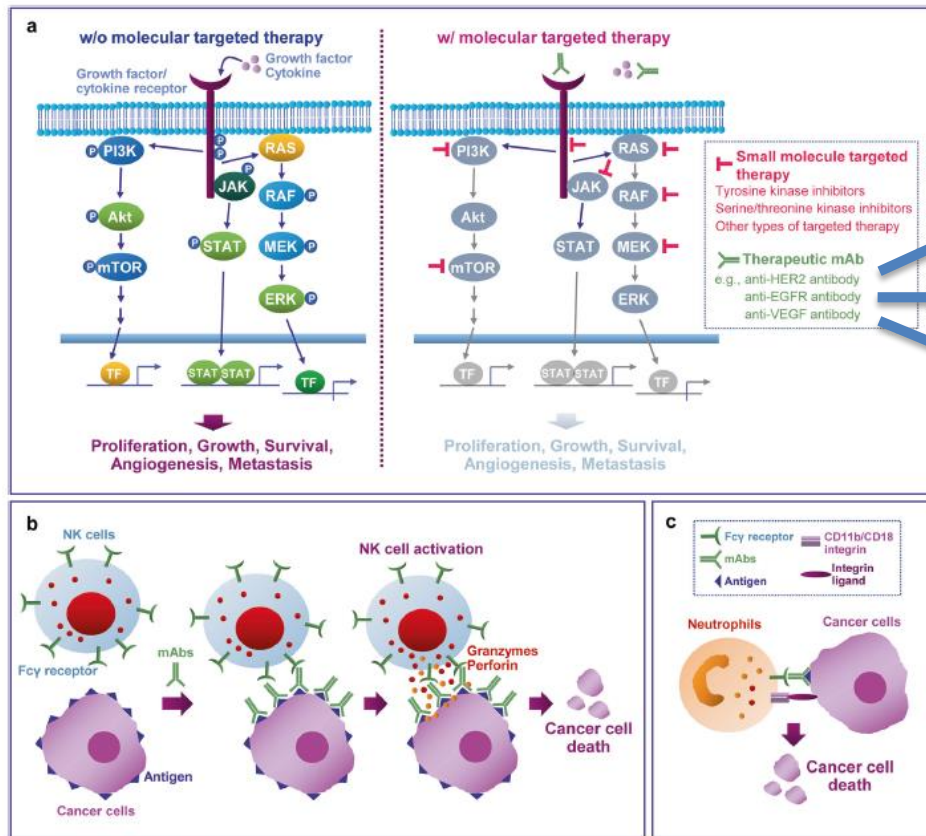
Chirurgia: non evidenza di
cellule tumorali vitali

2 tipi di Target Therapy:



- 1) **anticorpi monoclonali**, hanno generalmente come target specifiche proteine (spesso recettori) sulla superficie delle cellule o nell'ambiente circostante al tumore

MAB (bevacizumab, rituximab, trastuzumab, ...)



1) anticorpi monoclonali

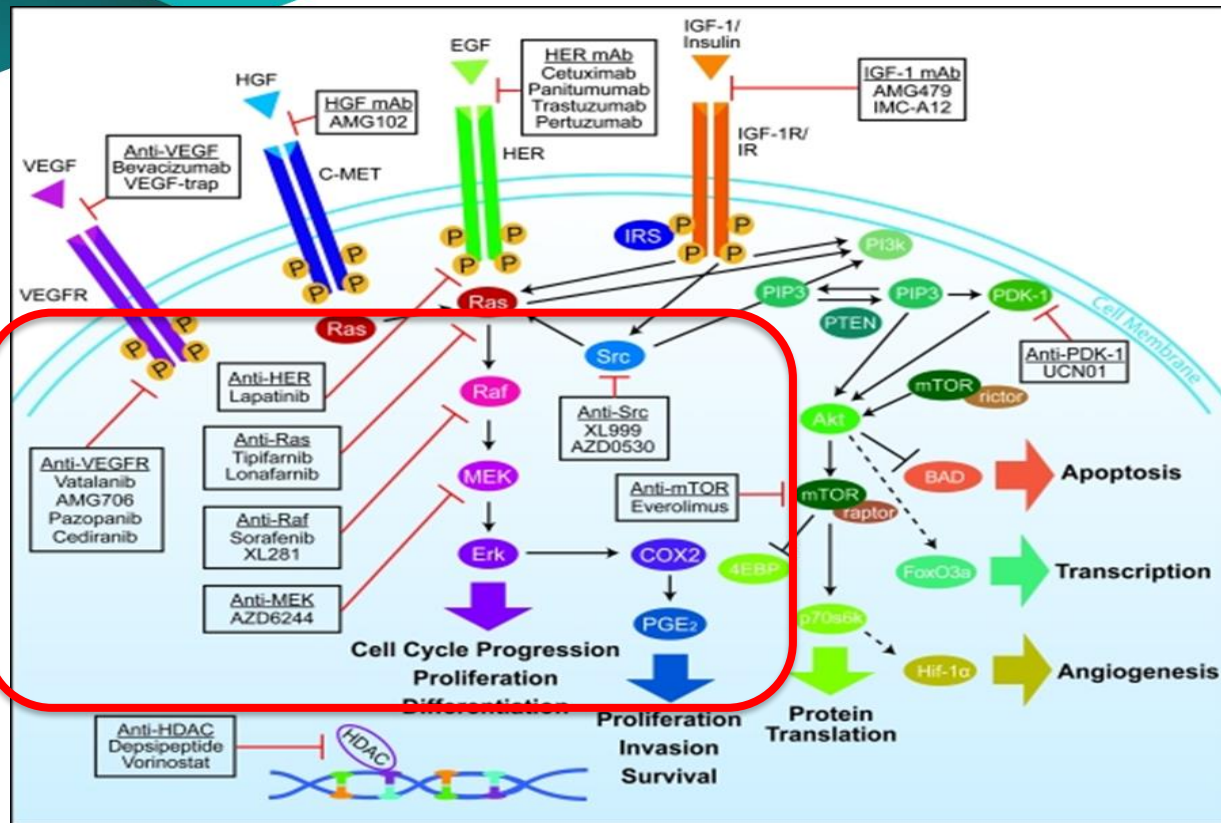
es: trastuzumab

es: cetuximab

es: bevacizumab

Fig. 2 Mechanism of the anticancer effect of molecular targeted therapy. a Schematic diagrams of the main protumor signal transduction pathways and their inhibition by molecular targeted therapeutic agents. b, c Schematic diagrams for antibody-dependent cellular cytotoxicity b and trogoptosis c. See the text and relevant references for details.

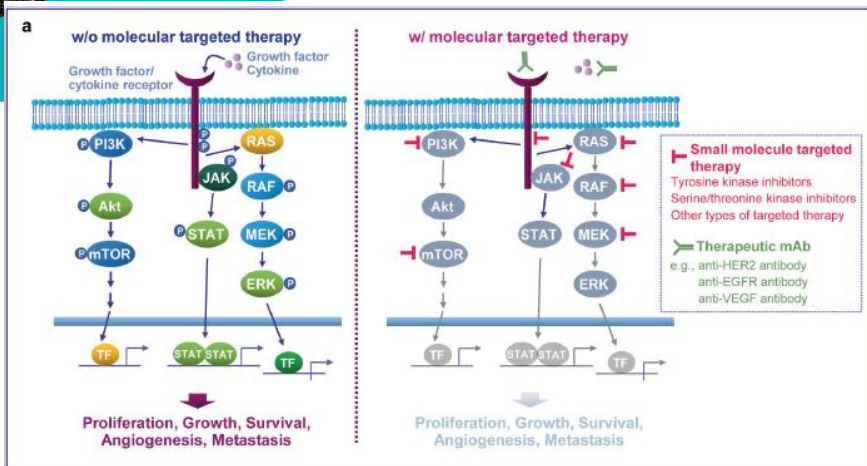
2 tipi di Target Therapy:



- **2) small-molecule drug** basso peso molecolare, passano attraverso la superficie della cellula fino a raggiungere *un target intracellulare* per rallentare la proliferazione o indurre la morte della cellula tumorale

- **MIB**, inibitori del proteosoma (bortezomib)

- **NIB**, inibitori chinasi (vemurafenib, regorafenib,)



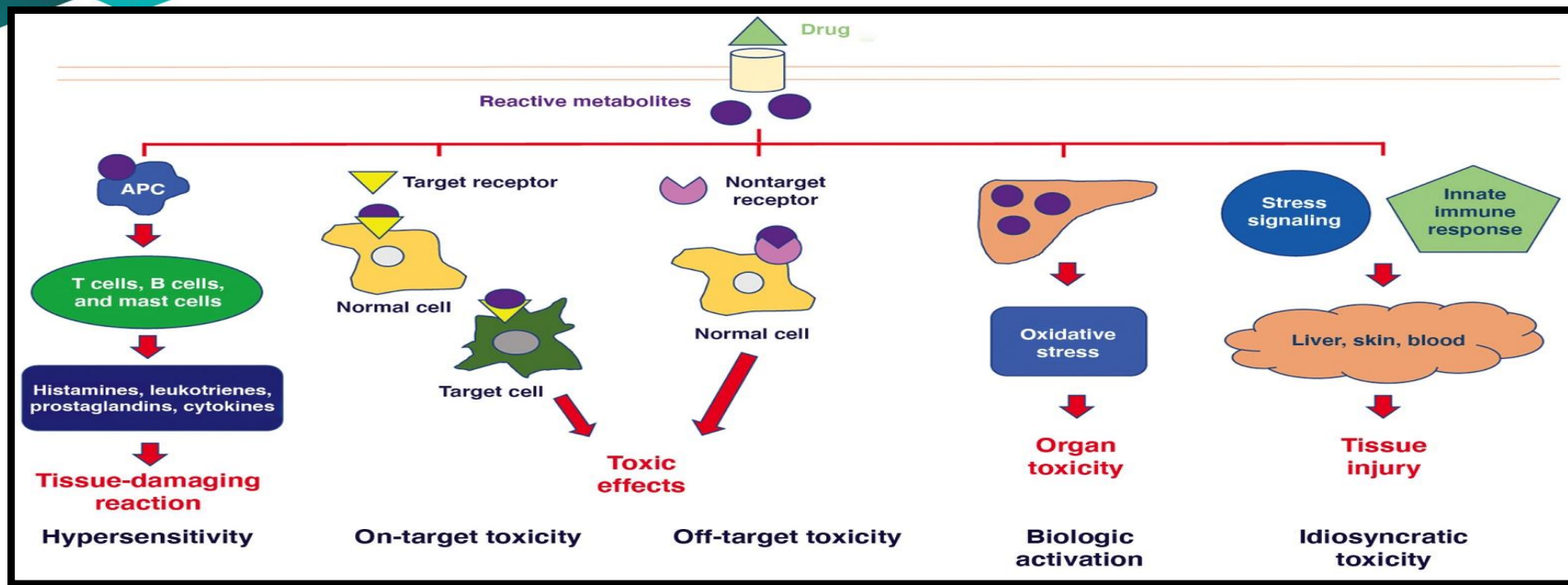
2) small-molecule drug

Table 1. Classes of selected kinase inhibitors^{26,28}.

Class	Mechanism of action	Examples
Type I	Binding in the ATP-binding pocket of the active conformation of the enzyme (DFG-in and α C-helix-in)	cabozantinib, ceritinib, gefitinib, palbociclib, pazopanib, ponatinib, ruxolitinib, tofacitinib
Type I ^{1/2} Type II	Binding in the ATP-binding pocket of the inactive conformation of the enzyme (type I ^{1/2} : DFG-Asp in; type II: DFG-Asp out)	dasatinib, imatinib, lapatinib, lenvatinib, nilotinib, regorafenib, sorafenib, sunitinib, vemurafenib
Type III Type IV	Allosteric inhibitors binding to a site in the kinase domain either next to the ATP-binding pocket or remote from the ATP-binding pocket	trametinib, everolimus, sirolimus, temsirolimus
Type V	Bivalent inhibitors that bind two different portions of the kinase lobe	lenvatinib ²⁸
Type VI	Covalent inhibitors	afatinib, ibrutinib

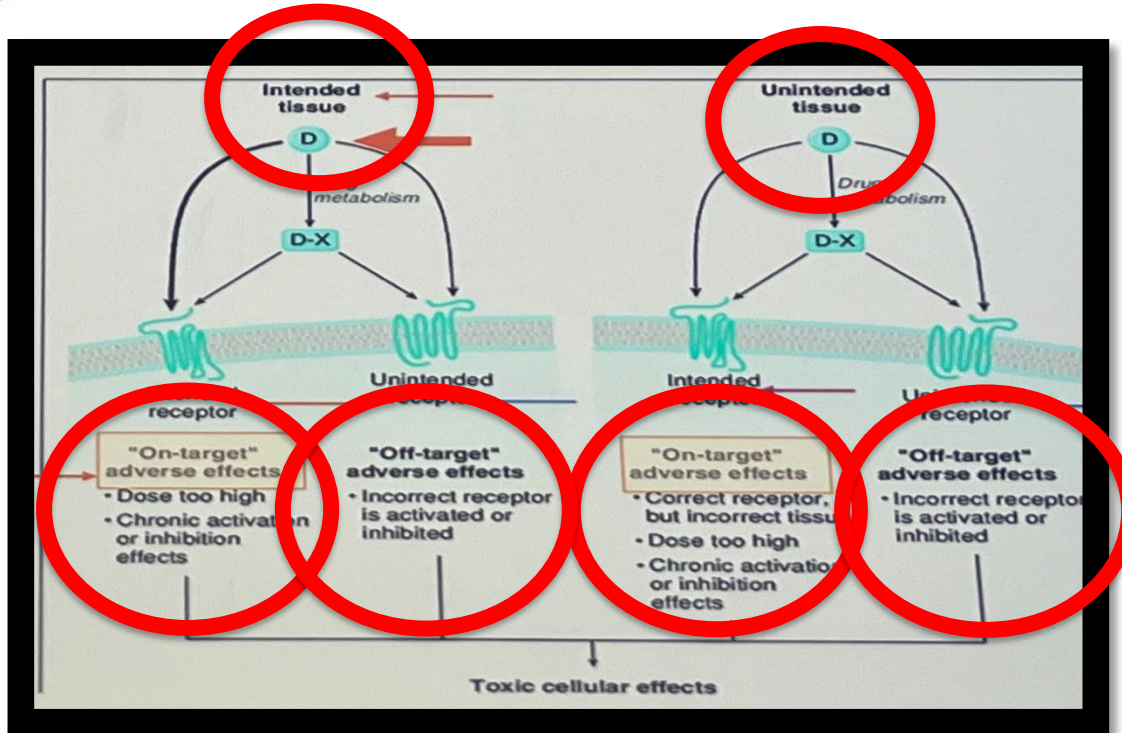
In Ref. ²⁶, lenvatinib is classified as a type I^{1/2} inhibitor.

Principali meccanismi di tossicità



Principali meccanismi di tossicità

Possibile correlazione
con efficacia



"ON target"

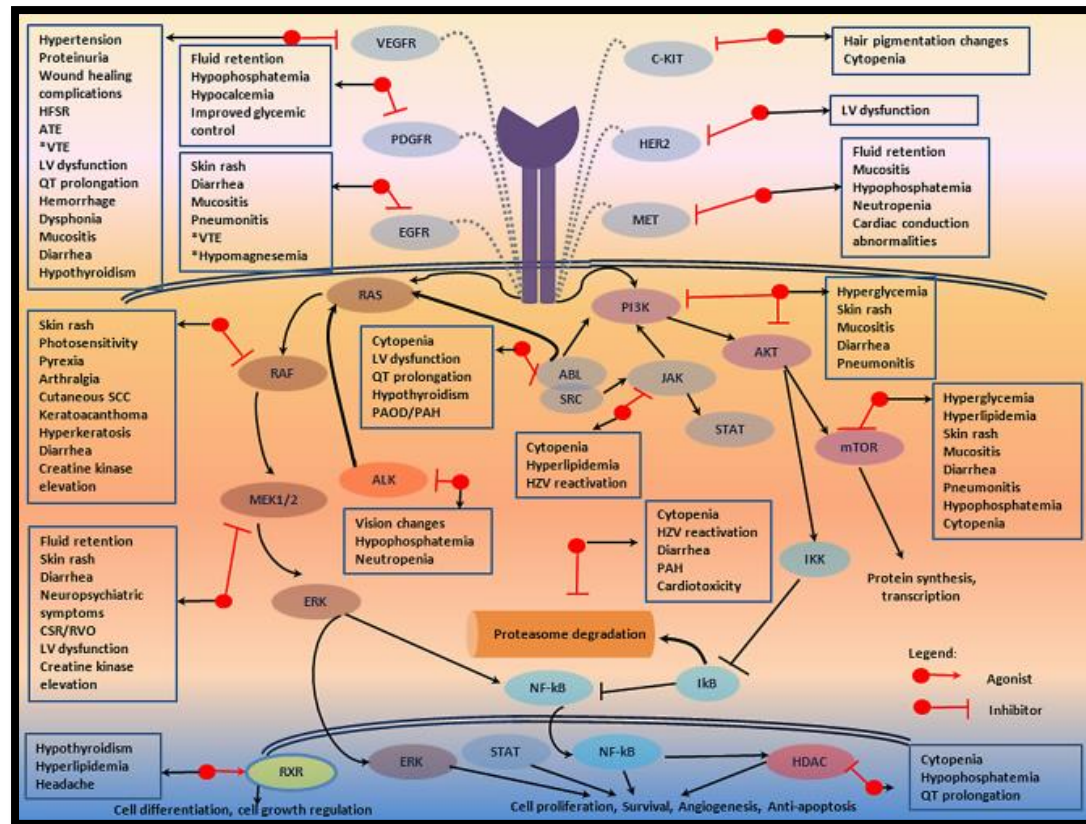
si riferisce all'azione del farmaco sul suo specifico recettore, che può avvenire sul tessuto che intendo colpire che lo esprime ma anche su un tessuto sano che analogamente esprime questo recettore o questa via attivata

"OFF target"

attivazione da parte del farmaco di recettori diversi da quelli per cui la molecola è specifica, sia sul tessuto che si intende andare a colpire che su altri tessuti sani



Tossicità da target therapy





CUTANEA

CARDIO-VASCOLARE

OCULARE

ENDOCRINOLOGICA

GASTROENTEROLOGICA

METABOLICA

TOSSICITÀ SEVERE



SKIN RASH

Table 1

Toxicities associated with targeted therapy: incidence, mechanism, genetic variations and correlation with outcome.

Toxicity	Type of agent	Occurrence rate	Genetic polymorphism	Mechanism	Correlation with outcome	References
Skin Rash	EGFR TKIs	45-100%	Polymorphism in CYP450 3A4, 3A5, 1A2; EGFR Intron 1 (CA) repeats; EGFR -216G/T EGFR intron-1 CA repeats	EGFR inhibition	Increased skin rash correlated with survival or response rate	[6-12]
	EGFR antibodies	88%		EGF inhibition	Increased skin rash correlated with survival or response rate	[13-17]
	MEK inhibitors	80%		MEK inhibition	No reports	[18-22]
	PI3K/AKT/mTOR inhibitors	26-51%		PI3K/AKT/mTOR inhibition	No reports	[23-26]

	TUTTI I GRADI	GRADO 3/4
EGFR TKIs	45-100%	10%
mTOR i	26-51%	3-4%

EGFR: es Erlotinib

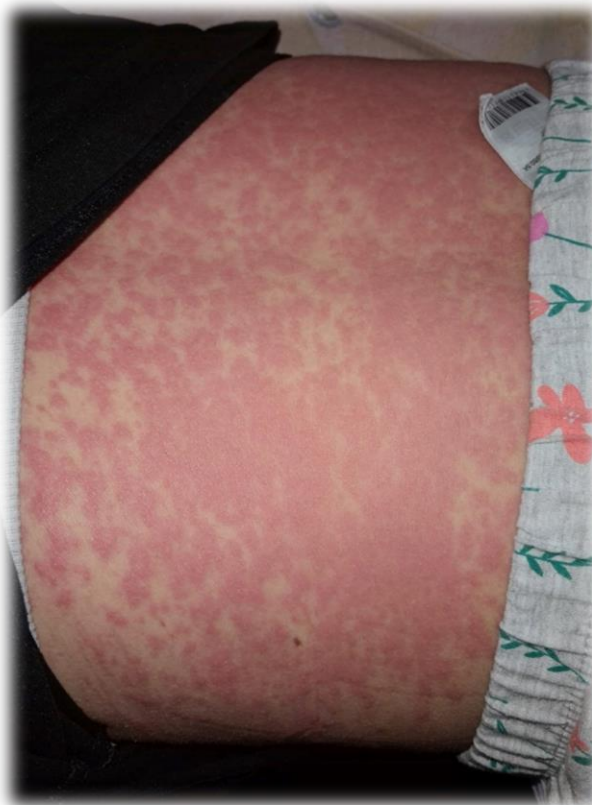
PDGFR: es Imatinib, Dasatinib, Pazopanib, Sorafenib, Sunitinib, Vandetanib

KIT: Imatinib, Dasatinib, Nilotinib

VEGFR: Pazopanib, Sorafenib, Sunitinib, Vandetanib

Multi-TKI: Regorafenib, Cabozantinib

- Li T. Skin toxicities associated with epidermal growth factor receptor inhibitors. Target Oncol 2009;4:107-19.
- Perez-Soler R. Can rash associated with HER1/EGFR inhibition be used as a marker of treatment outcome? Oncology (Williston Park) 2003;17:23-8.





HAND-FOOT SKIN REACTION



Più tipico dei **multi tirosin chinasi**:

Sorafenib 34%

Sunitinib 19%

Regorafenib 17%

Dose dipendente

Tipicamente nelle aree di pressione o frizione

Lesioni spesso ben demarcate e dolorose



REAZIONI IPERCHERATOSICHE

	TUTTI I GRADI	GRADO 3/4
Sorafenib	10-60%	15-30%
Sunitinib	10-30%	3-4%
BRAF-i	6-8%	1-2%

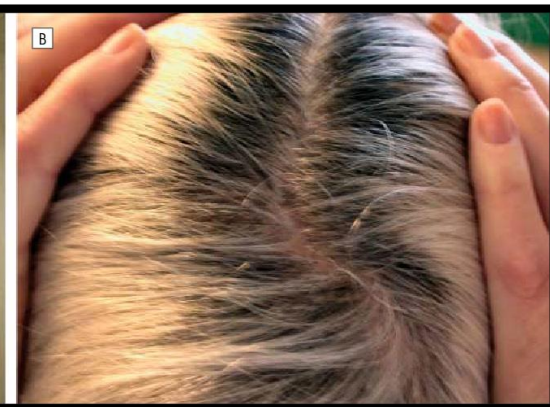




DEPIGMENTAZIONE CUTE-CAPELLI

	TUTTI I GRADI
Sunitinib	7-14%
Pazopanib	27-44%

Dose-dipendente
Reversibile alla sospensione
Dovuta a inibizione di c-kit (ruolo proliferazione melanociti)





ALTERAZIONI UNGUEALI

	TUTTI I GRADI
EGFR i	10-15%
MEK i	15-20%

Piega ungueale
Letto ungueale
Matrice ungueale





IPERTENSIONE

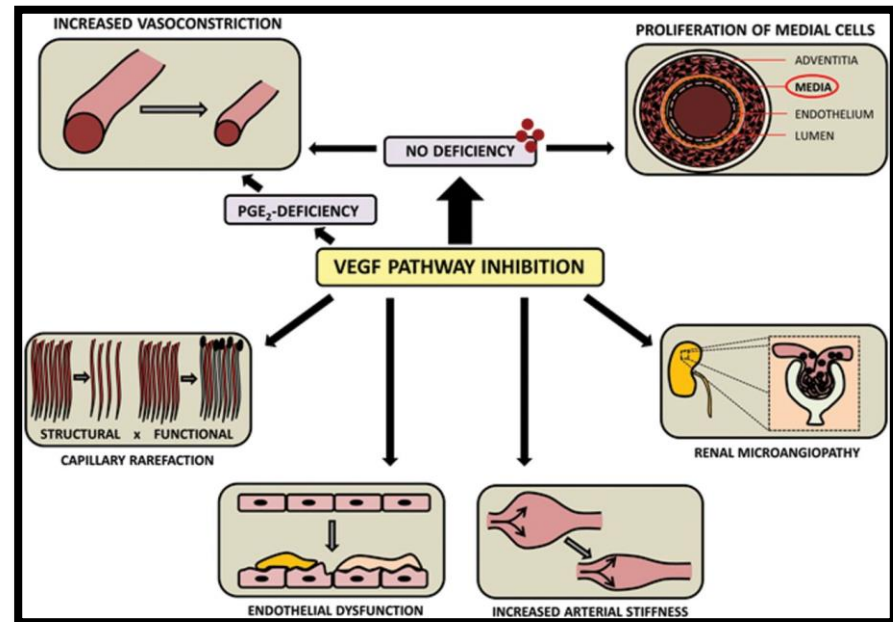
Hypertension	VEGFR TKIs	20-30%
	VEGF antibodies	20-30%

ACG Haplotype in VEGF (-2578A>C, -460C>T and 405C>G); C allele in eNOS; VEGF-634 GG
VEGF-1498 T/T, -634 C/C, -2578 C/C, 936 C/C, -1154A/A

VEGFR inhibition
VEGF inhibition

Hypertension correlated with better survival and or response rate [34-37]
Hypertension correlated with better survival and or response rate [38-44]

	TUTTI I GRADI	GRADO 3/4
BEVACIZUMAB	15-25%	11%
SUNITINIB	25%	8%
SORAFENIB	15-20%	4%





PROLUNGAMENTO QT

QT prolongation	Selected TKIs	14%
	Vandetanib	1-10%
	Nilotinib	4.8%
	Crizotinib	Rare
	EGFR or VEGFR antibodies	

Down-regulation of PI3K

No reports

[62-67]

+ anticorpi quali Trastuzumab, Alemtuzumab

No reports

[68]

TKI: grado 3-4 fino 6-8%

LONG QT SYNDROME ~



BAZETT'S FORMULA

$$QT_c = \frac{QT [ms]}{\sqrt{\frac{RR [s]}{1s}}} \rightarrow \frac{[ms]}{\sqrt{\frac{[s]}{[s]}}} = \frac{[ms]}{\sqrt{1}} = [ms] \checkmark$$

QT INTERVAL

Longer than normal

@ 60 bpm $\begin{cases} > 440 \text{ ms in MALES} \\ > 460 \text{ ms in FEMALES} \end{cases}$

@ 90 bpm $\rightarrow 400 \text{ ms}$
Find CORRECTED QT (QT_c)

**Rischio aritmia
(torsione di punta)
se QT_c > 500 ms**



TOSSICITÀ METABOLICA

Dyslipidemia/
hyperglycemia

PI3K/AKT/mTOR inhibitors

10-76%

Inhibition of PI3K/AKT/mTOR, insulin
resistance, impaired lipid clearance

Some studies suggested that the
best responders will experience
some metabolic toxicities [81]

[78-81]

Drug	Hypertriglyceridemia (%)		Hypercholesterolemia (%)		Hyperglycemia (%)	
	All Grades	Grades 3 to 4*	All Grades	Grades 3 to 4†	All Grades	Grades 3 to 4‡
Approved						
<u>Everolimus</u>	71	< 1	76	3	50	12
Placebo (n = 416) ⁹	30	0	32	0	23	1
<u>Temsirolimus</u>	27	3	24	1	26	11
IFN-α (n = 408) ¹⁰	14	1	4	0	11	2

TOSSICITÀ GASTROENTEROLOGICA

Diarrhea	EGFR TKIs	19-36%
	VEGFR TKIs	40-60%
	MEK inhibitors	42%
	PI3K inhibitor	21-48%
	EGFR or VEGFR antibodies	Rare

ABCG2 421C/A; ABCG2-15622T/T; EGFR -267G/T and -191C/A

No reports [27,28,11]

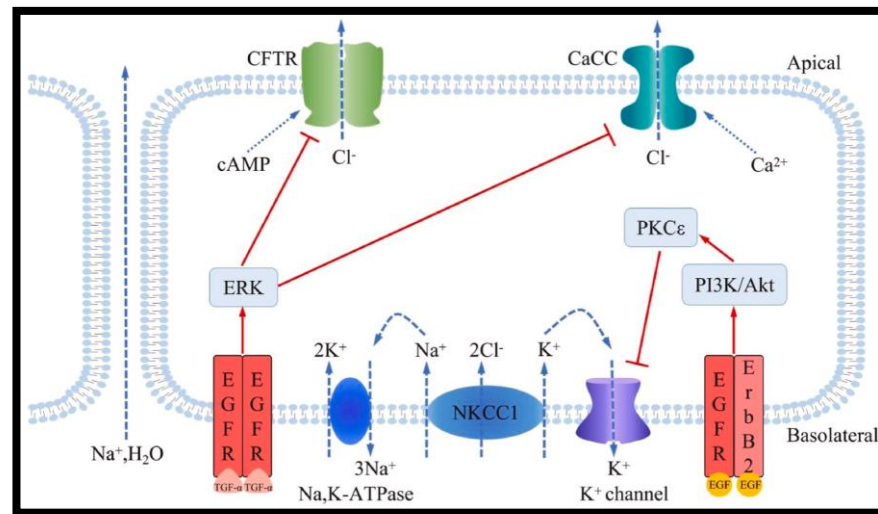
No reports [29]

No reports [22]

No reports [30,31]

No reports [32,33]

	TUTTI I GRADI	GRADO 3/4
EGFR TKI	30-40%	1-2%
EGFR Ab	50-60%	5%
HER2 i	55%	9%
Bortezomib	30-40%	4-8%
Temsirolimus	27%	<1%
Bevacizumab	12%	0%



TOSSICITÀ OCULARE

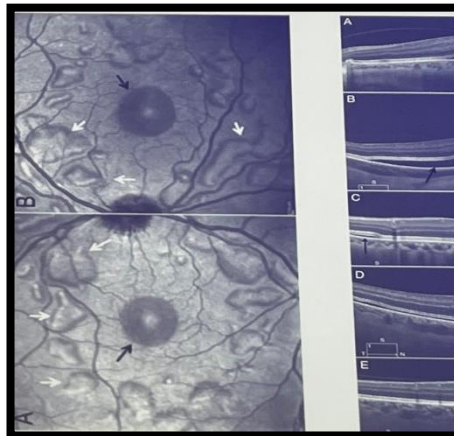
Ocular toxicity Various TKIs: 1-38%

EGFR inhibitor
Imatinib
VEGFR inhibitor
MEK inhibitor
BRAF inhibitor

Inhibition of
PDGFR, MAPK

Visione offuscata
Riduzione del campo visivo
Edema retinico

Reversibili dopo la
sospensione del trattamento



TKI	PMT	Cancer Indication	Adverse Ocular event
Afatinib (Gilotri®) Erlotinib (Tarceva®) Gefitinib (Iressa®)	<ul style="list-style-type: none"> EGFR 	<ul style="list-style-type: none"> Squamous cell carcinoma Non-small cell lung cancer Pancreatic cancer Colorectal cancer 	<ul style="list-style-type: none"> Conjunctivitis Blepharitis Dry eye syndrome Trichomegaly Keratitis Uveitis Corneal thinning and erosion
Crizotinib (Xalkori®)	<ul style="list-style-type: none"> ALK 	<ul style="list-style-type: none"> Non-small cell lung cancer 	<ul style="list-style-type: none"> Photopsia Photophobia Blurred vision Vitreous floaters Diplopia
Dabrafenib (Tafinlar®) Vemurafenib (Zelboraf®)	<ul style="list-style-type: none"> BRAF inhibitor 	<ul style="list-style-type: none"> Metastatic melanoma Thyroid cancer 	<ul style="list-style-type: none"> Photophobia Uveitis Central macular edema
Dasatinib (Sprycel®) Imatinib (Gleevec®) Nilotinib (Tasigna®)	<ul style="list-style-type: none"> BCR-ABL inhibitor c-Kit PDGFR 	<ul style="list-style-type: none"> Chronic myeloid leukemia Acute lympho-blastic leukemia Gastrointestinal stromal tumor 	<ul style="list-style-type: none"> Periorbital and eyelid edema Epiphora macular edema Conjunctival hemorrhage Optic disc edema Optic neuritis
Trametinib (Mekinist®)	<ul style="list-style-type: none"> Mek 	<ul style="list-style-type: none"> Metastatic melanoma Colorectal cancer Non-small cell lung cancer 	<ul style="list-style-type: none"> Blurred vision Halo vision Diplopia Central serous retinopathy Retinal vein occlusion Eyelid edema Subconjunctival hemorrhage Dry eye syndrome
Sunitinib (Sutent®)	<ul style="list-style-type: none"> PDGFR VEGF c-Kit 	<ul style="list-style-type: none"> Renal cell cancer 	<ul style="list-style-type: none"> Periorbital and eyelid edema Epiphora
Vandetanib (Caprelsa®)	<ul style="list-style-type: none"> VEGF EGFR 	<ul style="list-style-type: none"> Thyroid cancer 	<ul style="list-style-type: none"> Blurred vision Corneal opacities (cataract)



TOSSICITÀ ENDOCRINOLOGICHE

Hypothyroidism VEGFR TKIs 4-32%
VEGFR antibodies Rare

VEGF inhibition

Hypothyroidism correlated with better survival [45,46]
No reports [33]

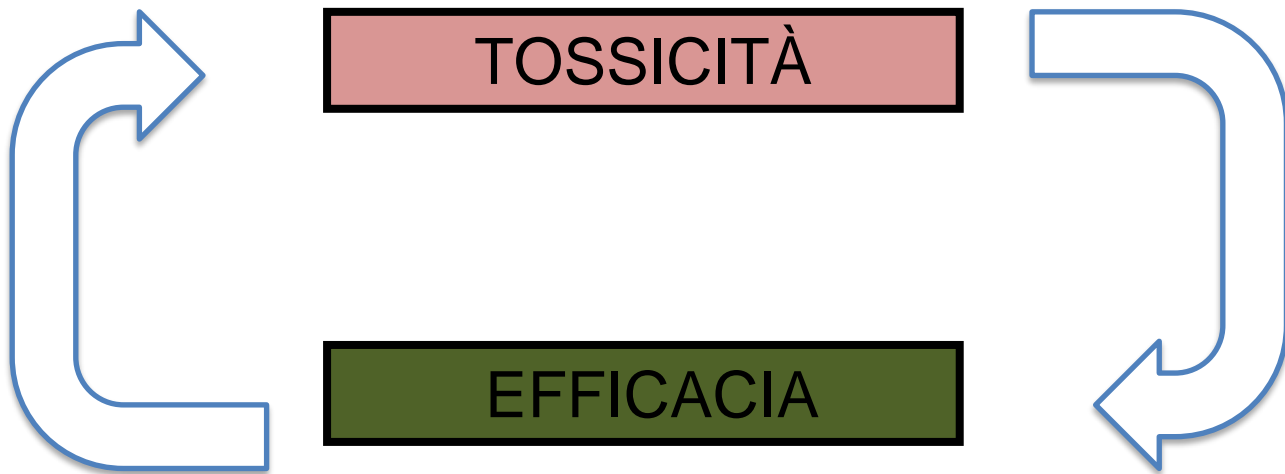
TABLE 3 Signal detections of thyroid dysfunction related to VEGFR-TKIs

Drug	N	ROR (95% CI)	PRR (χ^2)	IC (95% CI)	EBGM (95% one-sided CI)
Hyperthyroidism	290	2.57 (2.29, 2.89) ^a	2.57 (271.31) ^a	1.34 (1.12, 1.50) ^a	2.53 (2.25) ^a
Sunitinib	27	1.72 (1.19, 2.48) ^a	1.72 (8.68)	0.78 (0.54, 1.12) ^a	1.72 (1.19)
Sunitinib	91	2.78 (2.27, 3.42) ^a	2.78 (102.81) ^a	1.47 (1.19, 1.80) ^a	2.76 (2.25) ^a
Pazopanib	61	2.94 (2.29, 3.79) ^a	2.94 (77.70) ^a	1.55 (1.20, 1.99) ^a	2.93 (2.28) ^a
Vandetanib	0	-	-	-	-
Axitinib	15	1.79 (1.08, 2.98) ^a	1.79 (5.26)	0.84 (0.51, 1.40) ^a	1.79 (1.08)
Regorafenib	17	2.55 (1.58, 4.11) ^a	2.55 (15.97) ^a	1.35 (0.84, 2.17) ^a	2.54 (1.58)
Cabozantinib	39	2.80 (2.04, 3.83) ^a	2.79 (44.80) ^a	1.48 (1.08, 2.03) ^a	2.79 (2.03) ^a
Ponatinib	12	2.00 (1.14, 3.54) ^a	2.00 (6.04) ^a	1.00 (0.57, 1.77) ^a	2.00 (1.14)
Sunitinib	61	3.28 (2.23, 4.82) ^a	3.27 (40.92) ^a	1.71 (1.16, 2.51) ^a	3.26 (2.22) ^a
Hypothyroidism	1277	7.54 (7.12, 7.98) ^a	7.47 (6705.83) ^a	2.82 (2.66, 2.98) ^a	7.05 (6.66) ^a
Regorafenib	82	3.09 (2.48, 3.84) ^a	3.08 (114.85) ^a	1.62 (1.30, 2.01) ^a	3.07 (2.47) ^a
Sunitinib	575	11.53 (10.60, 12.54) ^a	11.35 (5279.45) ^a	3.47 (3.19, 3.77) ^a	11.05 (10.17) ^a
Pazopanib	169	5.20 (4.47, 6.06) ^a	5.17 (564.63) ^a	2.36 (2.03, 2.75) ^a	5.14 (4.41) ^a
Vandetanib	4	2.71 (1.01, 7.23) ^a	2.70 (4.29) ^a	1.43 (0.54, 3.83) ^a	2.70 (1.01)
Axitinib	97	7.44 (6.09, 9.09) ^a	7.37 (532.04) ^a	2.88 (2.35, 3.51) ^a	7.34 (6.00) ^a
Regorafenib	37	3.52 (2.55, 4.87) ^a	3.51 (66.40) ^a	1.81 (1.31, 2.50) ^a	3.50 (2.54) ^a
Cabozantinib	121	5.54 (4.63, 6.63) ^a	5.50 (443.62) ^a	2.45 (2.05, 2.93) ^a	5.47 (4.57) ^a
Ponatinib	27	2.86 (1.96, 4.18) ^a	2.86 (32.58) ^a	1.51 (1.04, 2.21) ^a	2.86 (1.95) ^a
Lenvatinib	165	13.47 (11.54, 15.72) ^a	13.21 (1850.45) ^a	3.71 (3.18, 4.33) ^a	13.11 (11.23) ^a

Abbreviations: CI, confidence interval; EBGM, the empirical Bayes geometric mean; IC, the information component; N, number of adverse event reports; PRR, the proportional reporting ratio; ROR, the reporting odds ratio; two-sided for ROR and IC, and one-sided for EBGM; χ^2 , chi-squared.

^aSignal detected, see "Methods" for the criteria of detection.

Liao X. Thyroid dysfunction related to vascular endothelial growth factor receptor tyrosine kinase inhibitors: A real-world study based on FAERS. J Clin Pharm Ther. 2021;46(5):1418-1425.



OPEN ACCESS Freely available online

PLOS ONE

Skin Rash could Predict the Response to EGFR Tyrosine Kinase Inhibitor and the Prognosis for Patients with Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis

Hong-bing Liu¹, Ying Wu², Tang-feng Lv¹, Yan-wen Yao¹, Yong-ying Xiao¹, Dong-mei Yuan¹, Yong Song^{1*}

¹Respiratory Department, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China, ²Department of Respiratory Medicine, Jiangsu Province Geriatric Hospital, Jiangsu Province Geriatric Institute, Nanjing, China

- Metanalisi su 33 trial
- 6798 pazienti
- ORR RR 3.28
- DCR RR 1.96

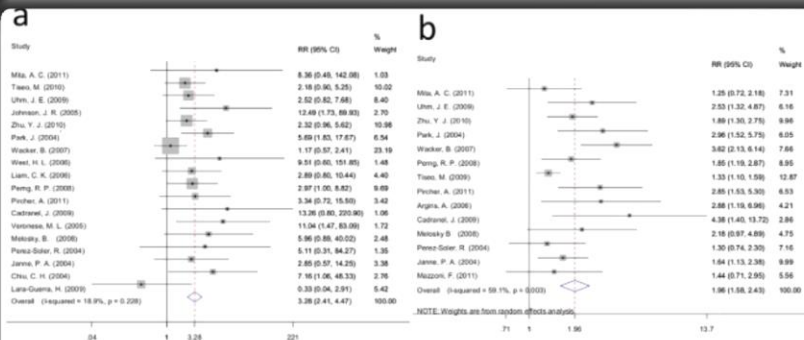


Figure 2. Forest plot of the RR for ORR and DCR for standard 1. **a:**ORR; **b:** DCR. The squares and horizontal lines correspond to the study-specific RR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary RR and 95% CI. doi:10.1371/journal.pone.0055128.g002

Conclusions: skin rash after EGFR-TKI treatment may be an efficient clinical marker for predicting the response of patients with NSCLC to EGFR-TKIs. Furthermore, skin rash is also the prognostic factor of patients with NSCLC. Patients with skin rash have a longer PFS and OS.



[Home](#) > [Targeted Oncology](#) > [Article](#)

The predictive role of skin rash with cetuximab and panitumumab in colorectal cancer patients: a systematic review and meta-analysis of published trials

Review | Published: 16 January 2013

Volume 8, pages 173–181, (2013) [Cite this article](#)

- 14 trial
- 3833 pazienti
- skin rash: predittivo per sopravvivenza (HR 0.51; $p < 0.00001$)
 predittivo per progressione (HR 0.58; $p < 0.00001$)

Conclusione:

significant predictor of the efficacy of these drugs. The hypothesis that, in patients who lack substantial skin toxicity, this treatment is not beneficial and requires early discontinuation deserves further study.

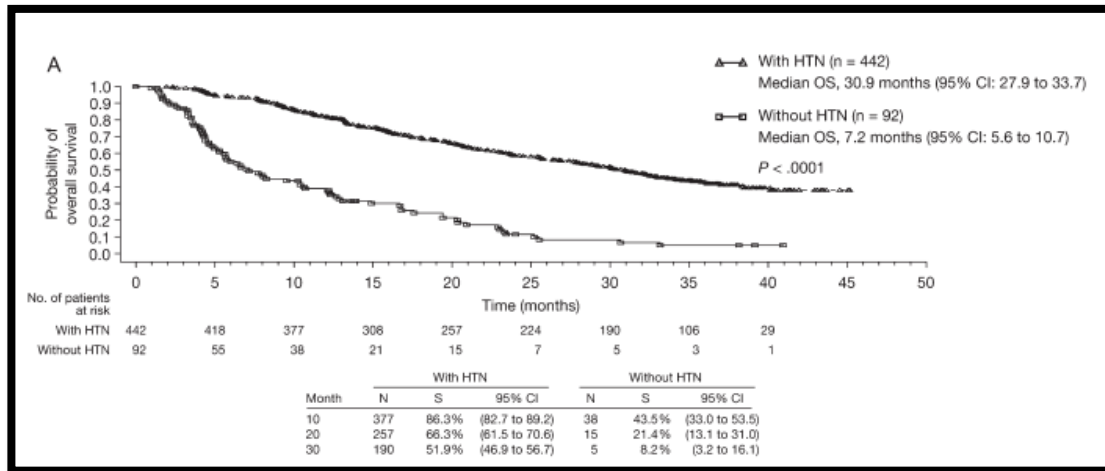


Hypertension as a Biomarker of Efficacy in Patients With Metastatic Renal Cell Carcinoma Treated With Sunitinib

Brian I. Rini, Darrel P. Cohen, Dongrui R. Lu, Isan Chen, Subramanian Hariharan, Martin E. Gore, Robert A. Figlin, Michael S. Baum, Robert J. Motzer

Manuscript received May 3, 2010; revised January 27, 2011; accepted March 7, 2011.

ORR 54.8% vs 8.7% ($p < 0.001$)
PFS 13.7 mesi vs 2.5 mesi ($p < 0.001$)



British Journal of Cancer (2011) 104, 599–604
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www.bjancer.com

Hypertension and overall survival in metastatic colorectal cancer patients treated with bevacizumab-containing chemotherapy

P Österlund¹, L-M Soveri¹, H Isoniemi², T Poussa³, T Alanko³ and P Bono^{1,4}

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ORR 30% vs 20% ($p = 0.025$)
PFS 10.5 mesi vs 5.3 mesi ($p = 0.008$)

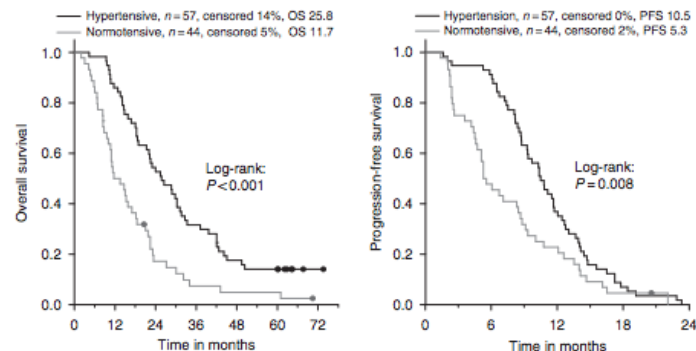


Figure 2 Overall survival and progression-free survival by hypertension during bevacizumab-containing treatment.



Terapia: Sunitinib e Sorafenib

Cancer

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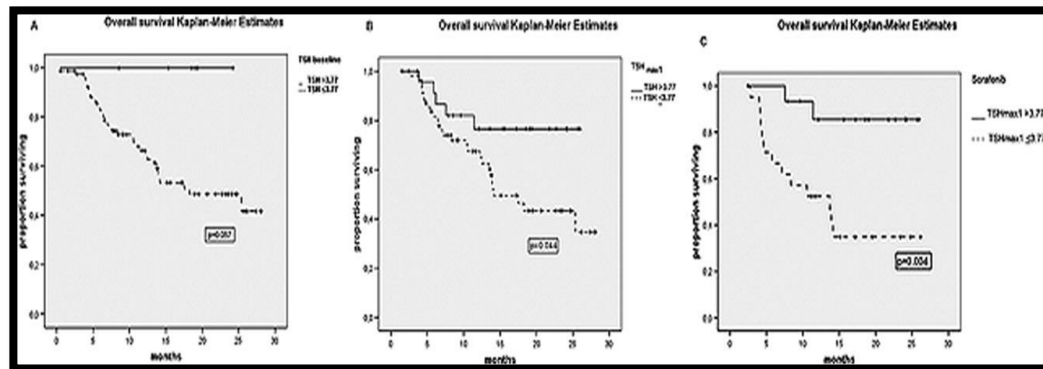
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Hypothyroidism in patients with renal cell carcinoma

Blessing or curse?

Manuela Schmidinger MD , Ursula M. Vogl MD, Marija Bojic, Wolfgang Lamm MD, Harald Heinzl PhD,
Andrea Haitel MD, Martin Clodi MD, Gero Kramer MD, Christoph C. Zielinski MD

First published: 15 September 2010 | <https://doi.org/10.1002/cncr.25422> | Citations: 163



Ipotiroidismo subclinico: ORR 28.3% vs 3.3% ($p < 0.001$)

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PMID: 22465830

Insulin Growth Factor-Receptor (IGF-1R) Antibody Cixutumumab Combined with the mTOR Inhibitor Temsirolimus in Patients with Refractory Ewing's Sarcoma Family Tumors

Aung Naing,¹ Patricia LoRusso,² Siqing Fu,¹ David S. Hong,¹ Pete Anderson,³ Robert S. Benjamin,⁴ Joseph Ludwig,⁴
Helen X. Chen,⁵ Laurence A. Doyle,⁵ and Razelle Kurzrock¹

4 di 7 pazienti con la migliore risposta:
iperglicemia con necessità di terapia con metformina
(tossicità grado 3)



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New Drug Development and Clinical Pharmacology

Toxicity as a Biomarker of Efficacy of Molecular Targeted Therapies:
Focus on EGFR and VEGF Inhibiting Anticancer Drugs

RODRIGO DIENSTMANN, IRENE BRAÑA, JORDI RODON, JOSEP TABERNERO

Medical Oncology Department, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona,
Barcelona, Spain



CONCLUSIONI

- Target therapy = specifiche tossicità
- Possibili tossicità gravi
- Tossicità – efficacia (“on target” toxicities)
- Sospensione/riduzione del farmaco VS gestione della tossicità
- Necessario raccogliere dati in trial clinici



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