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Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori
Istituto di Ricovero e Cura a Carattere Scientifico

ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

Biomarcatori predittivi nella pratica clinica: realtà e prospettive nei tumori solidi

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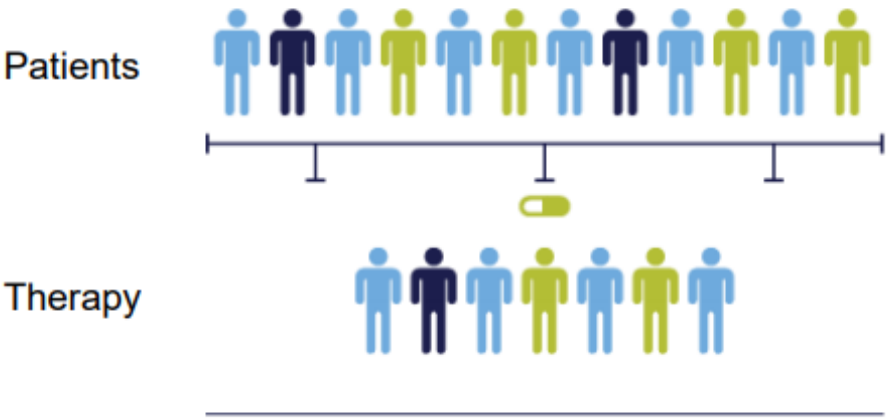
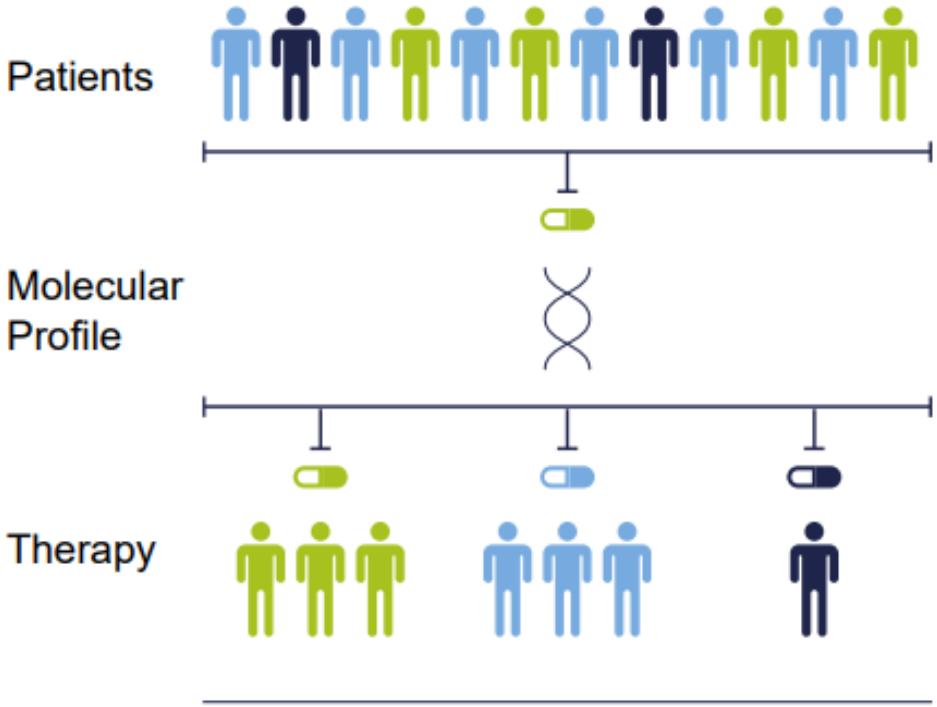
20 Febbraio 2020

Traditional Therapies



Some patients benefit, some patients do not benefit, and some patients experience adverse effects.

Precision Medicine



Each patient benefits from an individualized treatment.

Principali farmaci target utilizzati in pratica clinica in base alla presenza di un biomarcatore

NSCLC

Drug	Therapeutic target	Predictive marker	Predictive marker frequency
Gefitinib	EGFR	EGFR mutation	10-15%
Erlotinib	EGFR	EGFR mutation	10-15%
Afatinib	EGFR	EGFR mutation	10-15%
Osimertinib	EGFR	EGFR mutation	10-15%
Crizotinib	ALK/ROS1	ALK/ROS1 rearrangement	3-5%
Alectinib	ALK/ROS1	ALK/ROS1 rearrangement	3-5%
Ceritinib	ALK/ROS1	ALK/ROS1 rearrangement	3-5%
Trametinib+dabrafenib	MEK/BRAF	BRAF mutation	3%

Principali farmaci target utilizzati in pratica clinica in base alla presenza di un biomarcatore

Altri tumori solidi

	Drug	Therapeutic target	Predictive marker	Predictive marker frequency
Melanoma	Vemurafenib	BRAF	BRAF mutation	50%
	Dabrafenib	BRAF	BRAF mutation	50%
	Imatinib	CKIT	CKIT mutation	3-5%
GIST	Imatinib	CKIT	CKIT mutation	90%
	Imatinib	CKIT	PDGFRA mutation	5-10%
Gastric cancer	Trastuzumab	HER2	HER2 expr/amplif	10-30%
Breast cancer	Trastuzumab	HER2	HER2 expr/amplif	20%
	Alpelisib	PIK3CA	PIK3CA mutation	40%
	Olaparib	PARP	BRCA1 mutation	5-10%
Ovarian cancer	Olaparib	PARP	BRCA1 mutation	20-30%
Pancreatic cancer	Olaparib	PARP	BRCA1 mutation	5-7%
Colorectal cancer	Cetuximab	EGFR	RAS	50%
	Panitumumab	EGFR	RAS	50%
Multiple tumors	Entrectinib	NTRK1/2/3	NTRK rearrangements	0,2-100%
	Larotrectinib	NTRK1/2/3	NTRK rearrangements	0,2-100%

Prevalenza di mutazione di NTRK in diversi tumori solidi

Low frequency in common cancers

Tumor type	%
NSCLC	0.2 - 3.3
Colon	0.7 – 1.5
Breast	0.5
Melanoma	0.3
HNSCC	0.2
Sarcoma	1
Primary CNS tumors (high grade glioma/ astrocytoma)	1-2%

Higher frequency in uncommon cancers

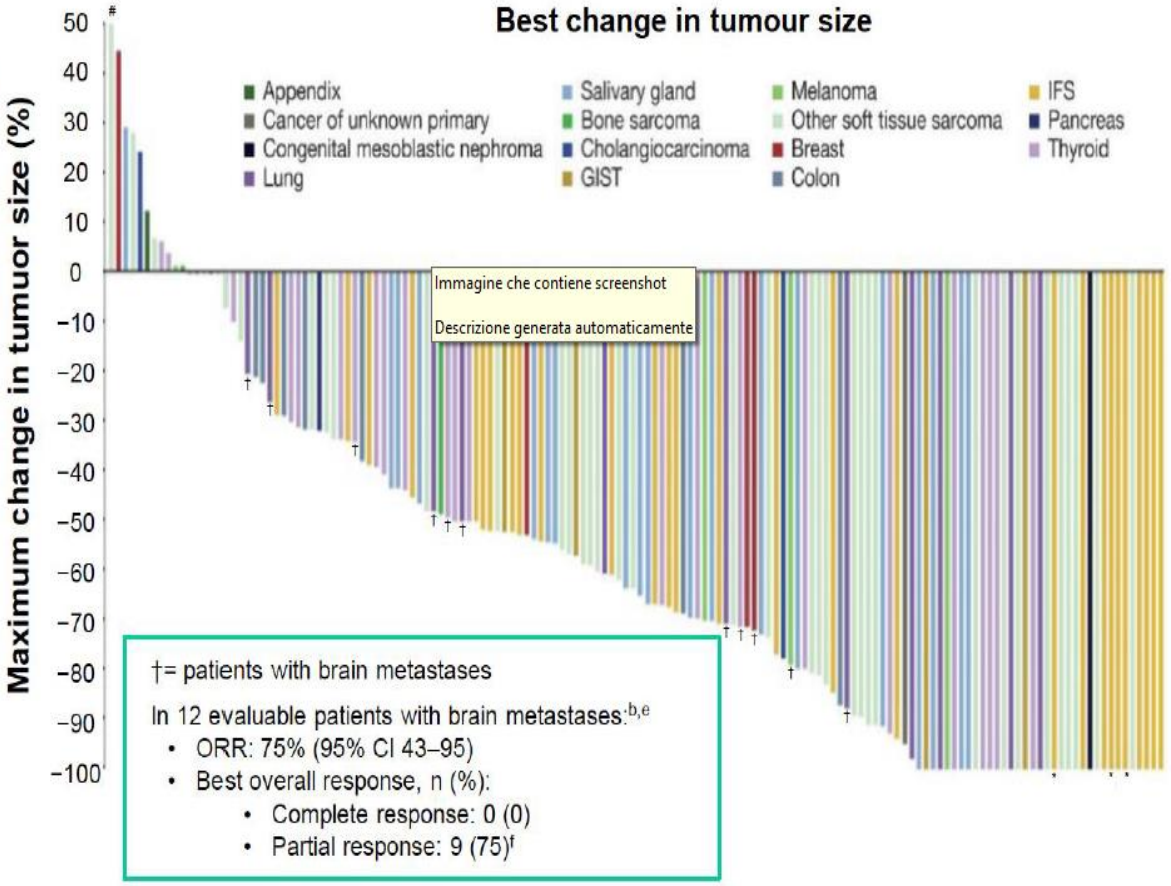
Tumor type	%
Mammary analogue secretory carcinoma	90 - 100
Infantile Fibrosarcomas	91 - 100
Secretory Breast Carcinomas	> 90
Congenital Mesoblastic Nephromas	83
Spitzoid Tumours	16
Thyroid	14.5

Penault-Llorca F et al J Clin Pathol 2019; Chen Y, et al J Hematol Oncol 2018

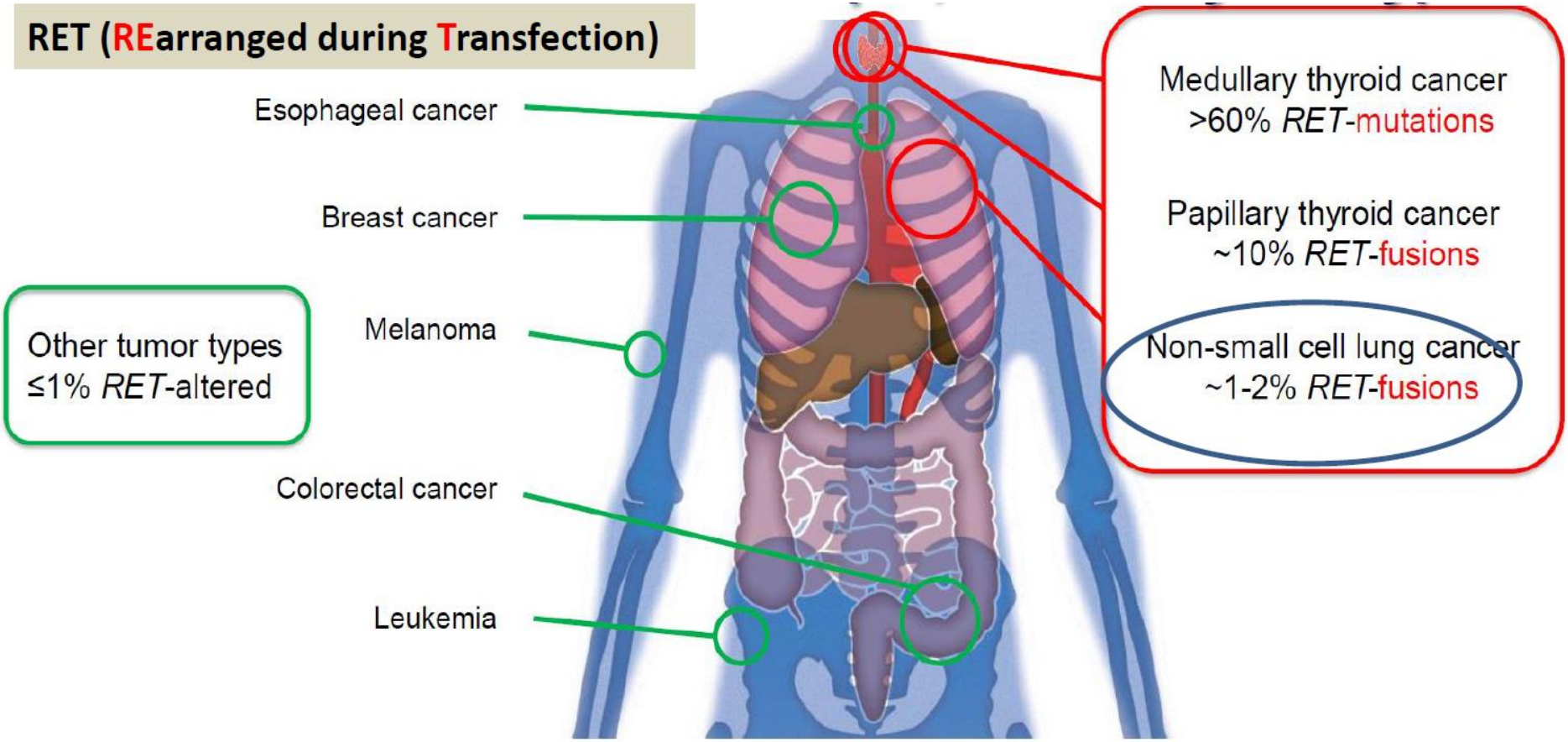
SINGAPORE 2019 ESMO ASIA

Larotrectinib demonstrates tumour-agnostic efficacy across a range of tumour types

	Integrated dataset (n=153)[a,b]
Overall response rate, % (95% CI)	79 (72–85)
Best overall response, n (%)	
Complete response	24 (16)[c]
Partial response	97 (63)[d]
Stable disease	19 (12)
Progressive disease	9 (6)
Not determined	4 (3)
Overall survival, median (95% CI), months	44.4 (36.5–NE)



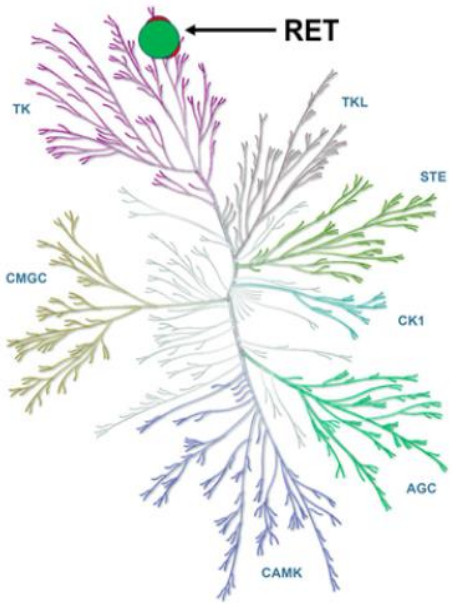
RET



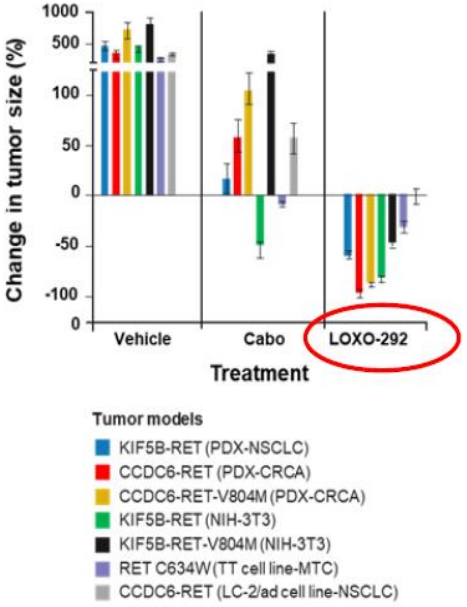
1. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15:151-67 2.Kato S, et al. *Clin Cancer Res* 2017;23:1988-1997.

Selpercatinib* (LOXO-292) is a potent and selective RET Inhibitor

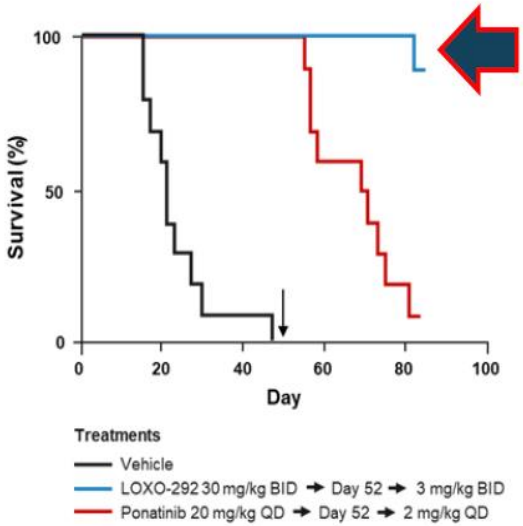
Kinome selectivity
Highly selective for RET



Xenograft models
Multiple fusions/mutations/histologies



Orthotopic brain model
CCDC6-RET orthotopic brain PDX



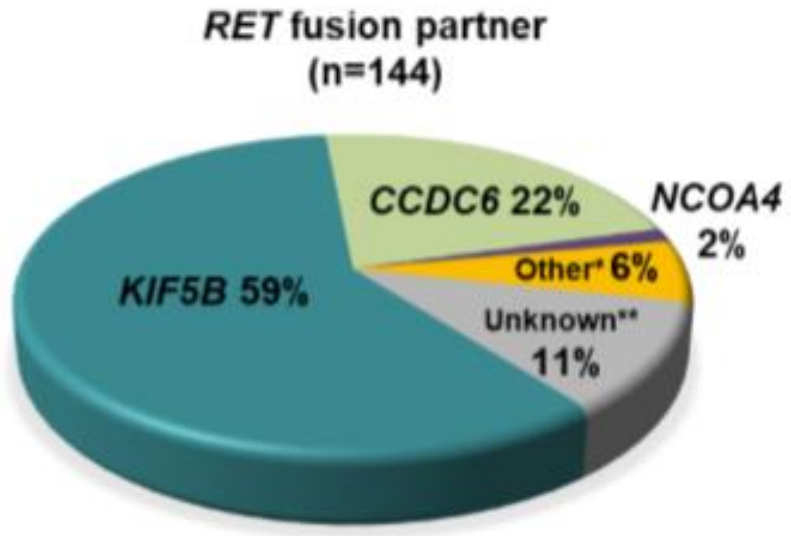
Subbiah et al. Ann Oncol 2018; Cabo = cabozantinib; PDX = patient-derived xenograft; NSCLC = non-small cell lung cancer; CRC = colorectal cancer; MTC = medullary thyroid cancer; BID = twice-daily; QD = once-daily

IASLC
2019 World Conference on Lung Cancer
September 7–10, 2019 | Barcelona, Spain
wclc2019.iaslc.com | #WCLC19
Conquering Thoracic Cancers Worldwide

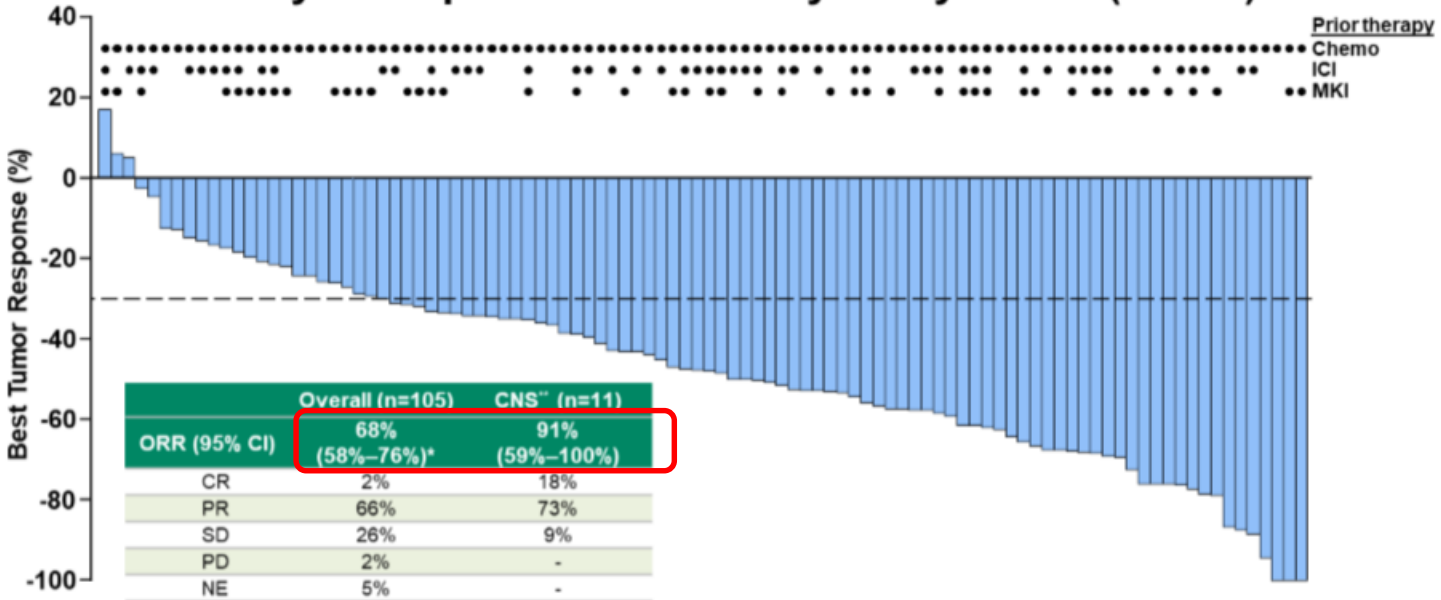
Registrational Results of LIBRETTO-001: A Phase 1/2 Trial of Selpercatinib (LOXO-292) in Patients with *RET* Fusion-Positive Lung Cancers

A. Drilon[1], G. Oxnard[2], L. Wirth[3], B. Besse[4], O. Gautschi[5], S.W.D. Tan[6], H. Loong[7], T. Bauer[8], Y.J. Kim[9], A. Horiike[10], K. Park[11], M. Shah[12], C. McCoach[13], L. Bazhenova[14], T. Seto[15], M. Brose[16], N. Pennell[17], J. Weiss[18], I. Matos[19], N. Peled[20], B.C. Cho[21], Y. Ohe[22], K. Reckamp[23], V. Boni[24], M. Satouchi[25], G. Falchook[26], W. Akerley[27], H. Daga[28], T. Sakamoto[29], J. Patel[30], N. Lakhani[31], F. Barlesi[32], M. Burkard[33], V. Zhu[34], V. Moreno Garcia[35], J. Medioni[36], M. Matrana[37], C. Rolfo[38], D.H. Lee[39], H. Nechushtan[40], M. Johnson[41], V. Velcheti[42], M. Nishio[43], R. Toyozawa[44], K. Ohashi[45], L. Song[46], J. Han[47], A. Spira[48], M.Duca[49], K. Staal Rohrberg[50], S. Takeuchi[51], J. Sakakibara[52], S. Waqar[53], H. Kenmotsu[54], F. Wilson[55], B.Nair[56], E. Olek[56], J. Kherani[56], K. Ebata[56], E. Zhu[56], M. Nguyen[56], L. Yang[56], X. Huang[56], S. Cruickshank[56], S. Rothenberg[56], B. Solomon[57], K. Goto[58], V. Subbiah[59]

Patient Characteristics	PAS (n=105)	Treatment-naïve (n=39)
Female / Male, n (%)	62 (59) / 43 (41)	22 (56) / 17 (44)
Median age (range), years	61 (23–81)	61 (23–86)
ECOG performance status, n (%)		
0	31 (30)	19 (49)
1	72 (69)	20 (51)
2	2 (2)	0
Median prior systemic regimens (range)	3 (1–15)	0
Prior platinum-based chemotherapy, n (%)	105 (100)	-
Prior PD-1/PD-L1 inhibitor, n (%)	58 (55)	-
Concurrent with platinum-based chemotherapy	9 (9)	-
Sequential to platinum-based chemotherapy	49 (47)	-
Prior multikinase inhibitor (MKI), n (%)	50 (48)	-
1	37 (35)	-
≥2	13 (12)	-
Brain metastases, n (%)‡	37 (35)	7 (18)
Measurable disease	104 (99)	39 (100)

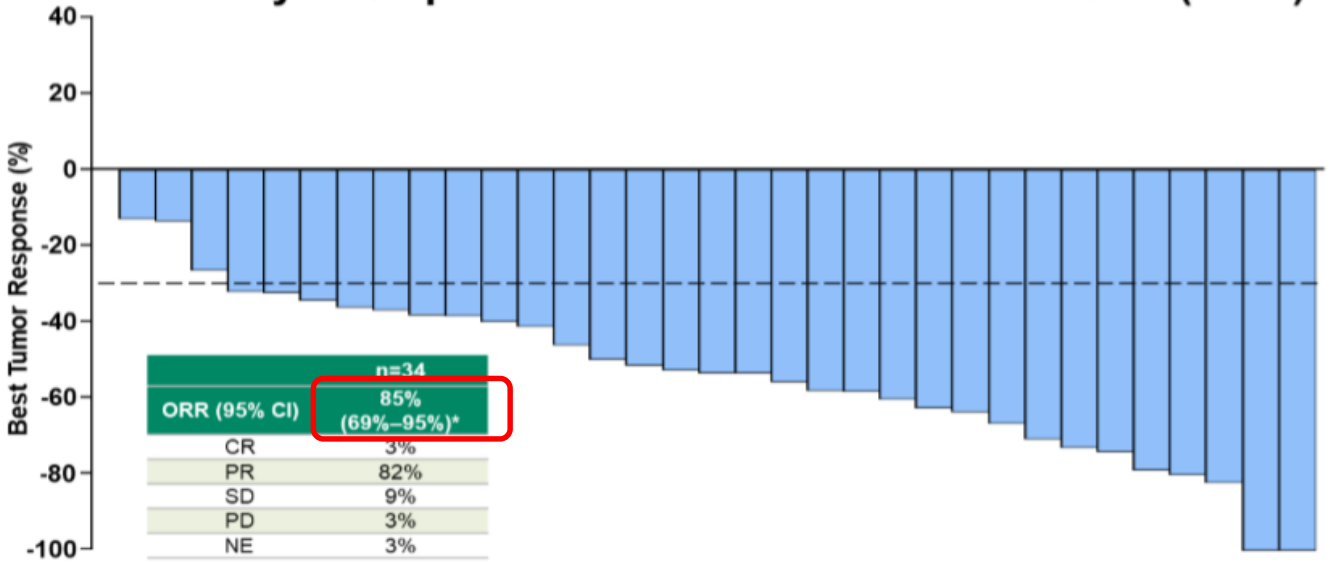


Efficacy of Selpercatinib: Primary Analysis Set (n=105)



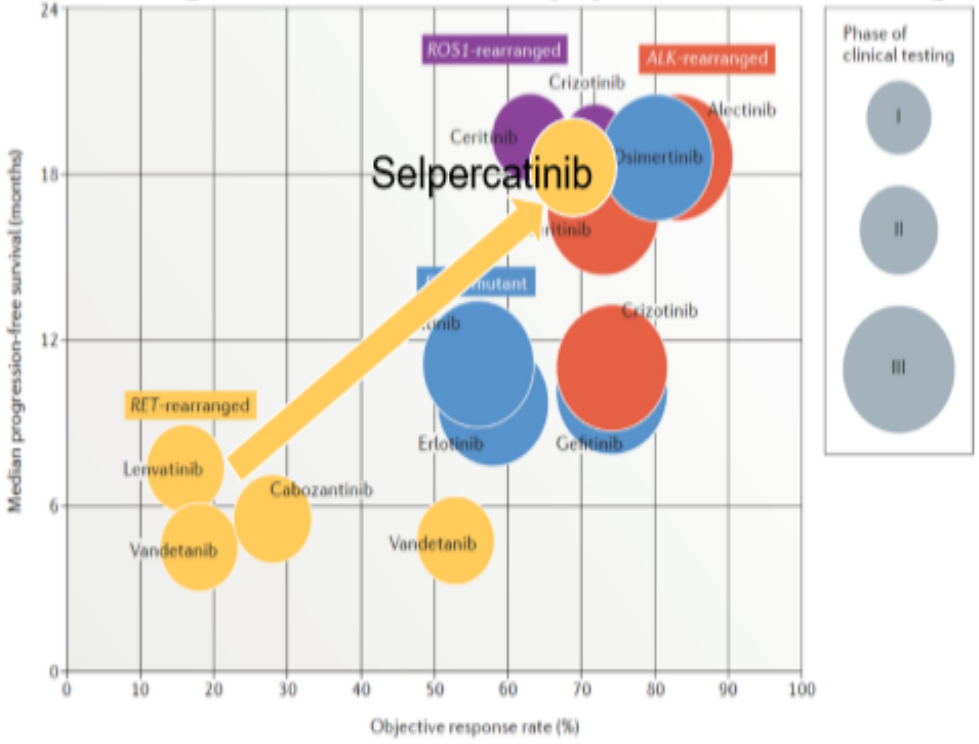
	Overall (n=105)	CNS** (n=11)
ORR (95% CI)	68% (58%–76%)*	91% (59%–100%)
CR	2%	18%
PR	66%	73%
SD	26%	9%
PD	2%	-
NE	5%	-

Efficacy of Selpercatinib: Treatment-naïve Patients (n=34)



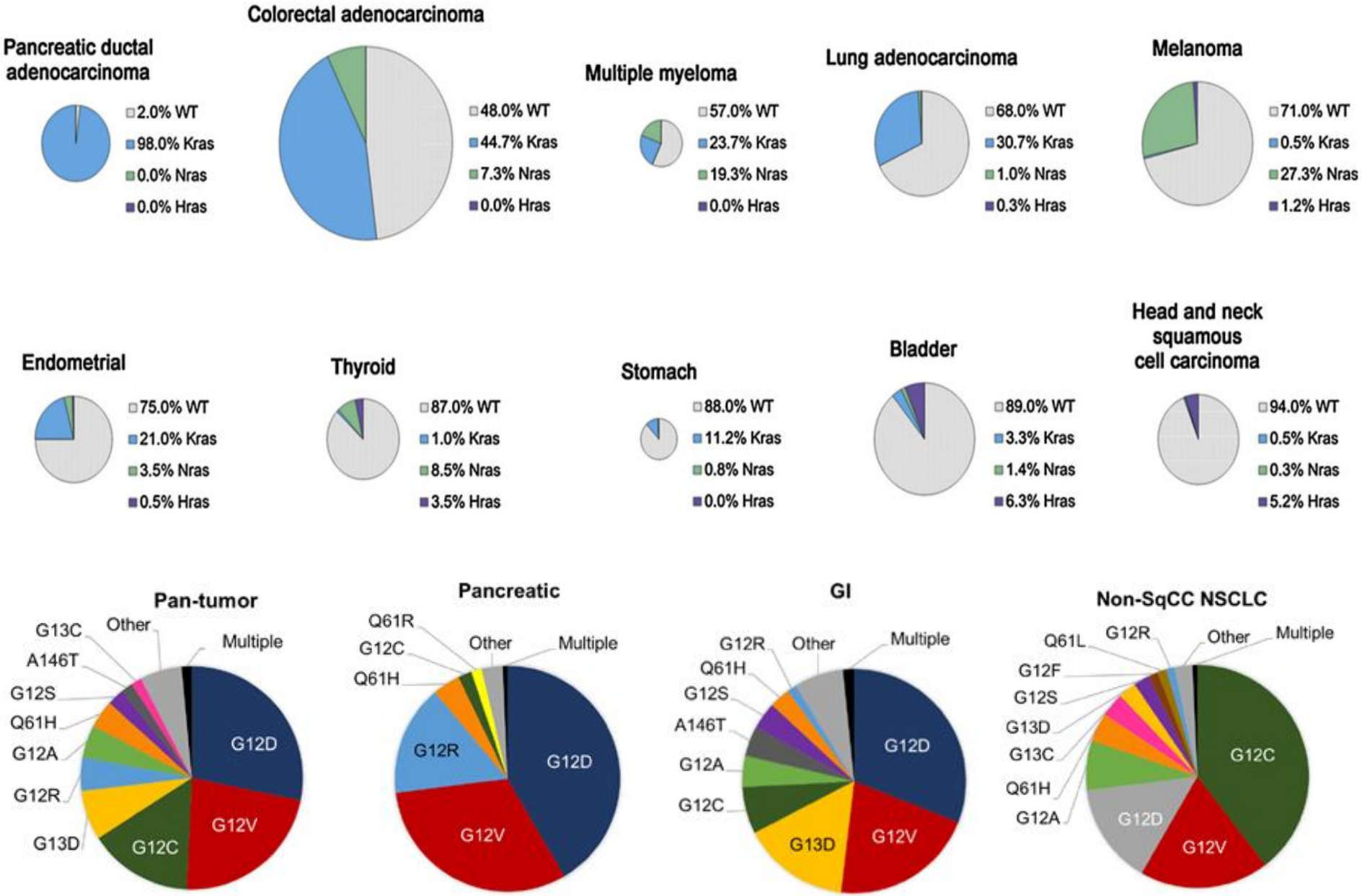
	n=34
ORR (95% CI)	85% (69%–95%)*
CR	3%
PR	82%
SD	9%
PD	3%
NE	3%

Selpercatinib is a highly effective oncogene-targeted therapy for RET gene fusions

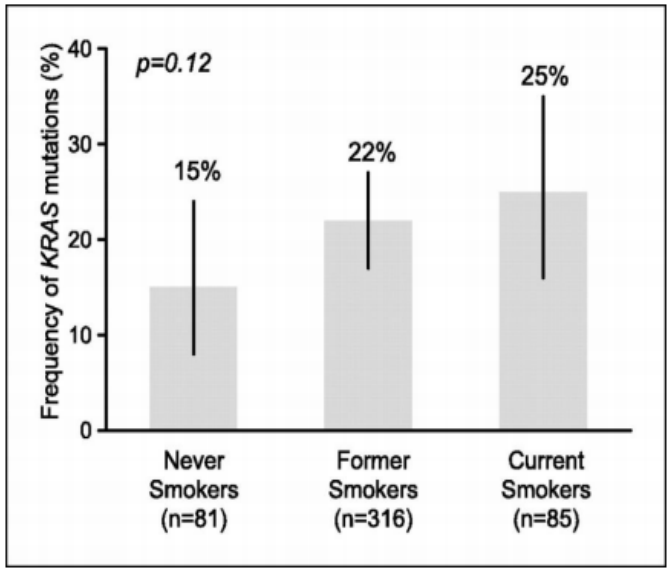


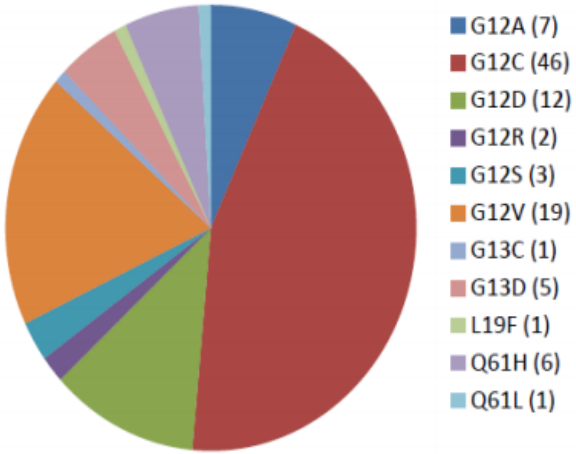
- Excellent ORR and PFS
  - Differential KIF5B vs. non-KIF5B?
- Excellent CNS activity
  - Await IC-PFS/DoR
- Safety data suggests no concerns
  - Low discontinuation rate
- Likely achieved efficacy and safety through selective kinase approach
  - Over VEGFR2 and other kinases
- Awaiting resistance data

RAS

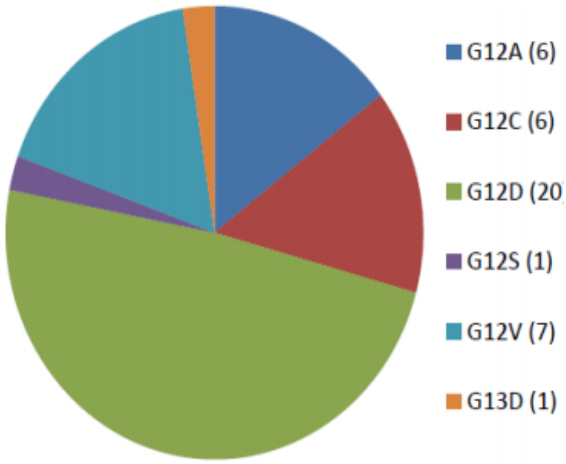

Pancreatic ductal adenocarcinoma
2.0% WT
98.0% Kras
0.0% Nras
0.0% Hras
Colorectal adenocarcinoma
48.0% WT
44.7% Kras
7.3% Nras
0.0% Hras
Multiple myeloma
57.0% WT
23.7% Kras
19.3% Nras
0.0% Hras
Lung adenocarcinoma
68.0% WT
30.7% Kras
1.0% Nras
0.3% Hras
Melanoma
71.0% WT
0.5% Kras
27.3% Nras
1.2% Hras
Endometrial
75.0% WT
21.0% Kras
3.5% Nras
0.5% Hras
Thyroid
87.0% WT
1.0% Kras
8.5% Nras
3.5% Hras
Stomach
88.0% WT
11.2% Kras
0.8% Nras
0.0% Hras
Bladder
89.0% WT
3.3% Kras
1.4% Nras
6.3% Hras
Head and neck squamous cell carcinoma
94.0% WT
0.5% Kras
0.3% Nras
5.2% Hras
Pan-tumor
G13C
Other
Multiple
A146T
G12S
Q61H
G12A
G12R
G13D
G12C
G12V
G12D
Pancreatic
Q61R
G12C
Q61H
Other
Multiple
G12R
G12V
G12D
GI
G12R
Other
Multiple
Q61H
G12S
A146T
G12A
G12C
G13D
G12V
G12D
Non-SqCC NSCLC
Q61L
G12R
Other
Multiple
G12F
G12S
G13D
G13C
Q61H
G12A
G12C
G12D
G12V

Prevalence and type of KRAS mutation in NSCLC





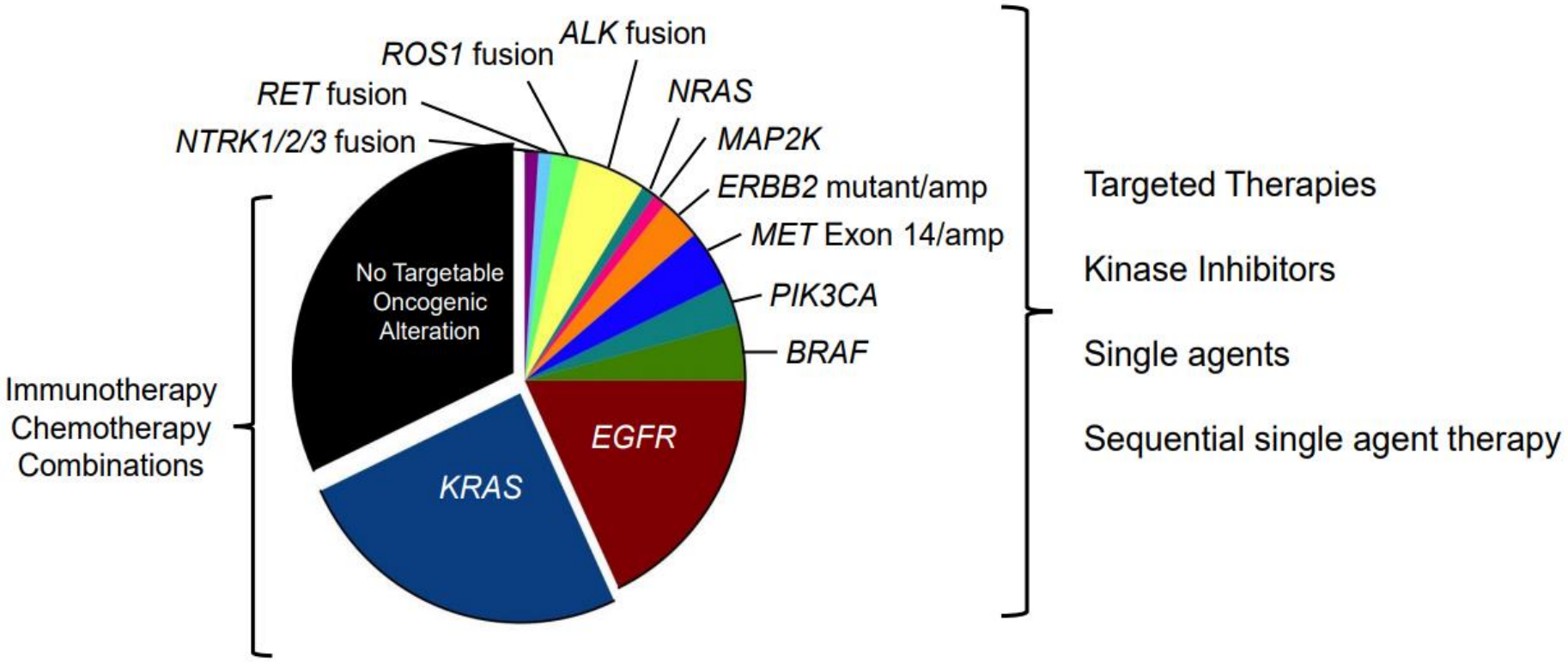
Current/Former Smokers



Never Smokers

Riely et al. CCR 2008; Redig et al. ASCO 2016

Precision Therapy for Lung Adenocarcinoma in 2019



Nature | Vol 575 | 7 November 2019 | 217

Article

The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity

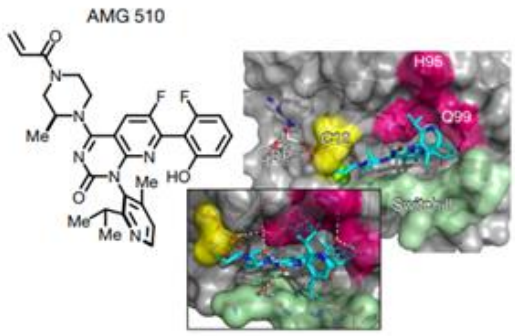
https://doi.org/10.1038/s41586-019-1694-1

Received: 29 March 2019

Accepted: 18 September 2019

Published online: 30 October 2019

Jude Canon[1*], Karen Rex[1,17], Anne Y. Saiki[1,17], Christopher Mohr[1], Keegan Cooke[1], Dhanashri Bagal[2], Kevin Gaida[1], Tyler Holt[1], Charles G. Knutson[3], Neelima Koppada[3], Brian A. Lanman[1], Jonathan Werner[1], Aaron S. Rapaport[2], Tisha San Miguel[1], Roberto Ortiz[3,14], Tao Osgood[1], Ji-Rong Sun[1], Xiaochun Zhu[3,15], John D. McCarter[1], Laurie P. Volak[3,16], Brett E. Houk[4], Marwan G. Fakih[5], Bert H. O'Neil[6], Timothy J. Price[7,8], Gerald S. Falchook[9], Jayesh Desai[10], James Kuo[11], Ramaswamy Govindan[12], David S. Hong[13], Wenjun Ouyang[2], Haby Henary[4], Tara Arvedson[2], Victor J. Cee[1] & J. Russell Lipford[1*]



AMG 510 is a First in Class *KRAS*^{G12C} Inhibitor, by locking it in an inactive GDP-bound state

AMG 510 First in Human Study Design

This is a multicenter, open-label, phase 1, first in human study (NCT 03600883) in adult patients with locally advanced or metastatic *KRAS*^{G12C} mutant solid tumors

Key Eligibility Criteria

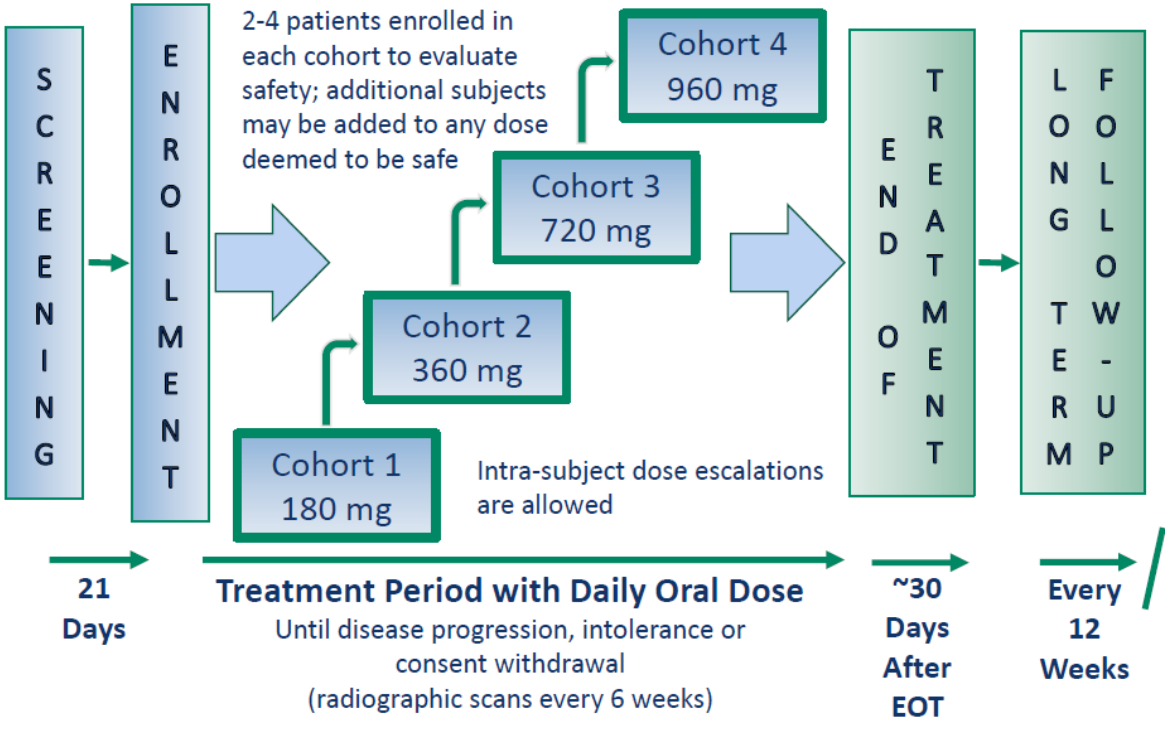
- Documented locally-advanced or metastatic *KRAS*^{G12C} measurable or evaluable solid tumors
- Received prior standard therapy appropriate for tumor type and stage of disease
- No active brain metastases

Primary Endpoints

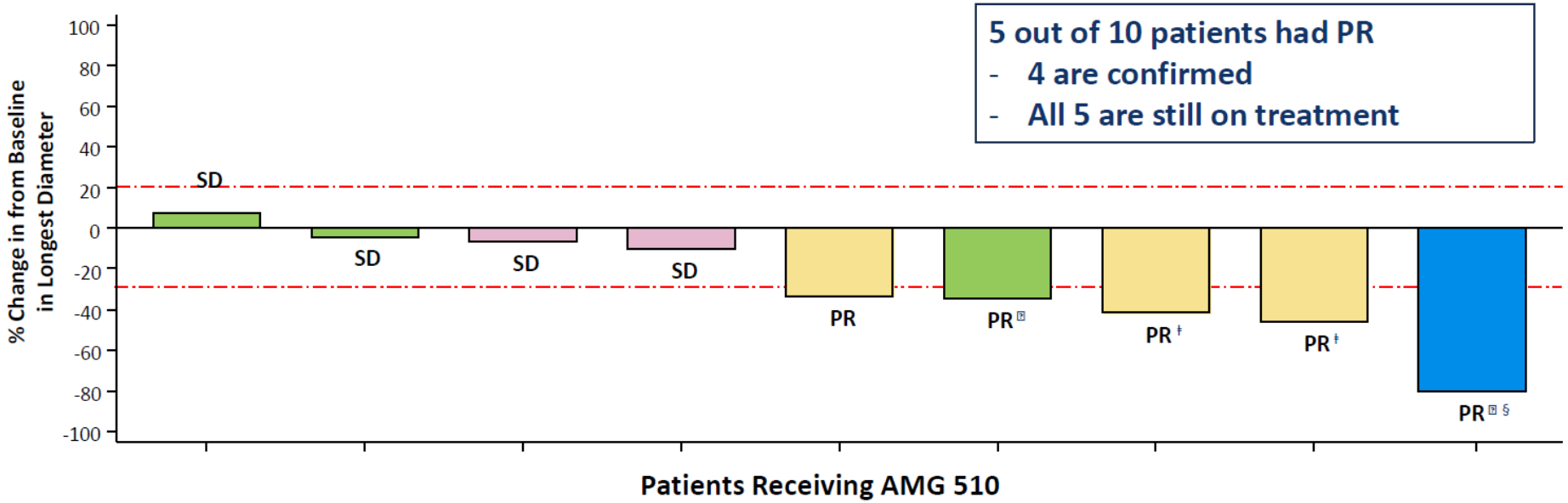
- Safety and tolerability including the incidence of AEs and DLTs

Key Secondary Endpoints

- PK, best response, duration of response and duration of stable disease,
- Objective response rate and PFS



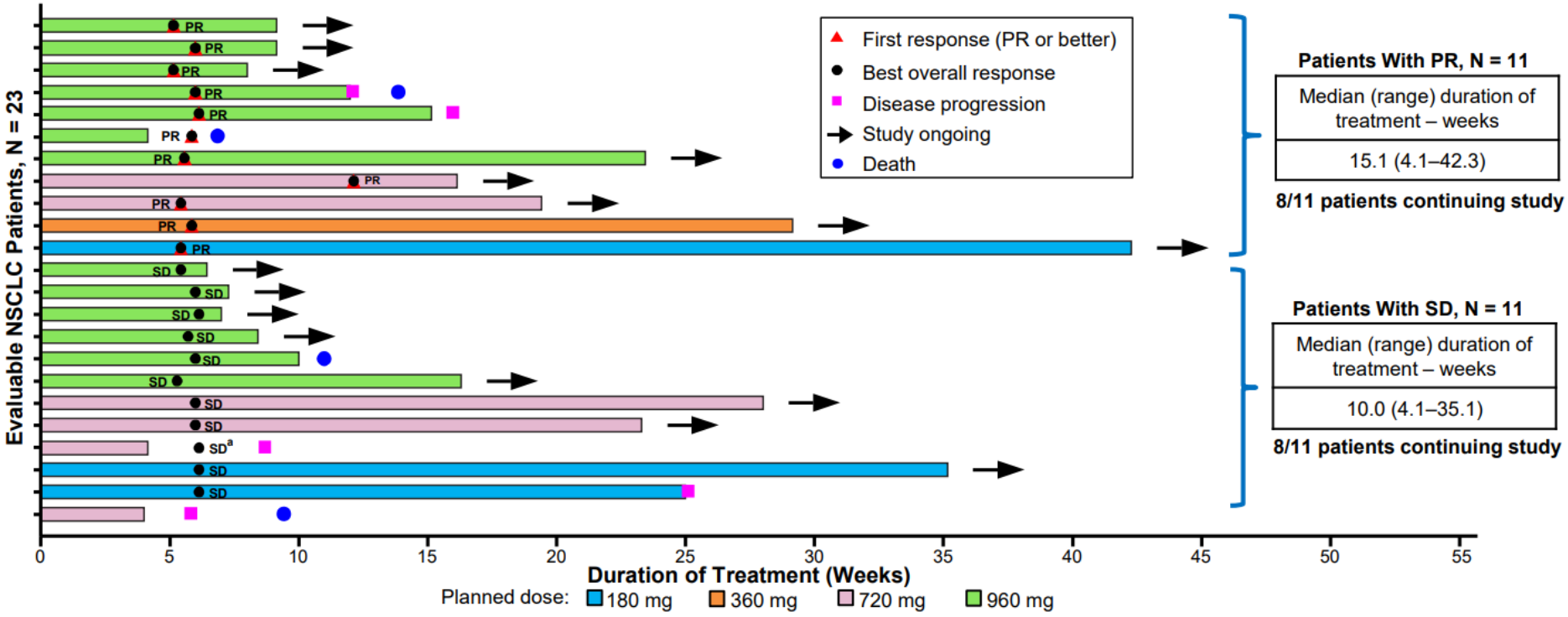
NSCLC: Best Tumor Response* (n=10)



* Based on local radiographic scans every 6 weeks using RESIST 1.1 criteria
1 patient had clinical progression prior to week 6 and is not on this graph
⍰ Confirmed response
ǂ 2 additional patients had confirmed PR post data cutoff
§Patient had a CR of the target lesions at week 18, post data cutoff

Planned Dose: 180 mg | 360 mg | 720 mg | 960 mg

Time to Response and Duration of Treatment for All Dose Levels



Patients With PR, N = 11

Median (range) duration of treatment – weeks
15.1 (4.1–42.3)

8/11 patients continuing study

Patients With SD, N = 11

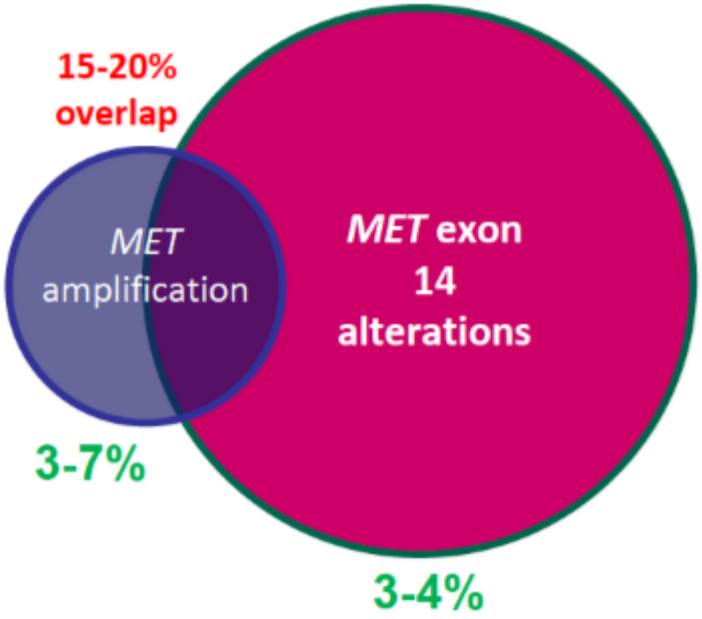
Median (range) duration of treatment – weeks
10.0 (4.1–35.1)

8/11 patients continuing study

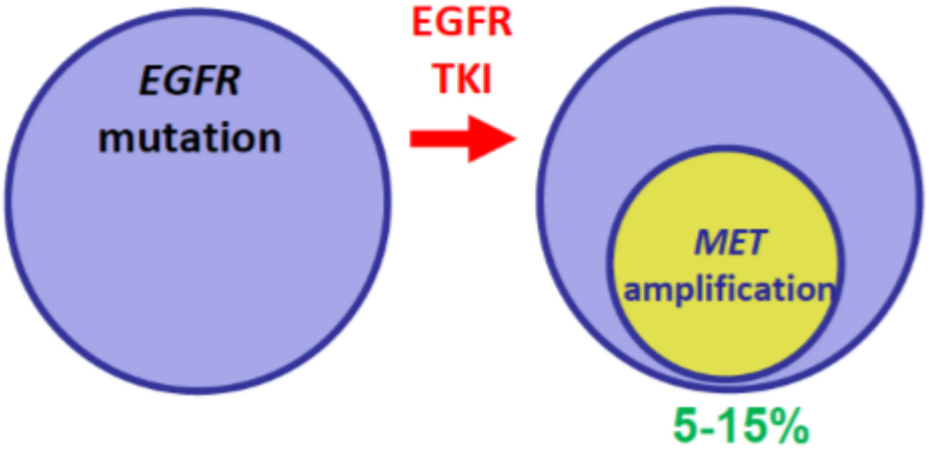
he graph was plotted based on the data received from the participating sites as of the data cutoff; duration of treatment data for this patient might be missing from the study site. PR: partial response; SD: stable disease.

Activation of MET pathway in lung cancer

MET as a primary driver



Acquired resistance to EGFR-TKI



Comoglio et al, Nar Rev Cancer 2018

MET Inhibitors in Drug Development

	Capmatinib	Savolitinib	Tepotinib	Crizotinib
IC 50 (nM)	0.6	2.1	3.0	22.5

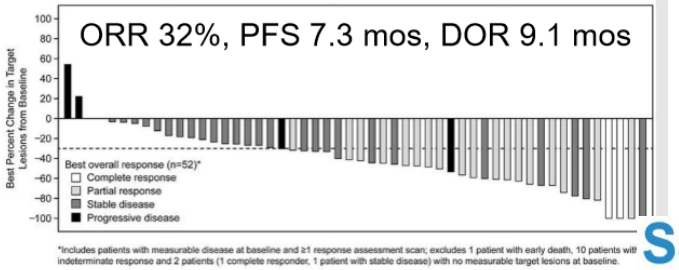
Fujino et al. WCLC 2018

Crizotinib in MET exon 14 skipping (PROFILE 1001)

n=69

84% adenoca
9% sarcomatoid

61% former smoker



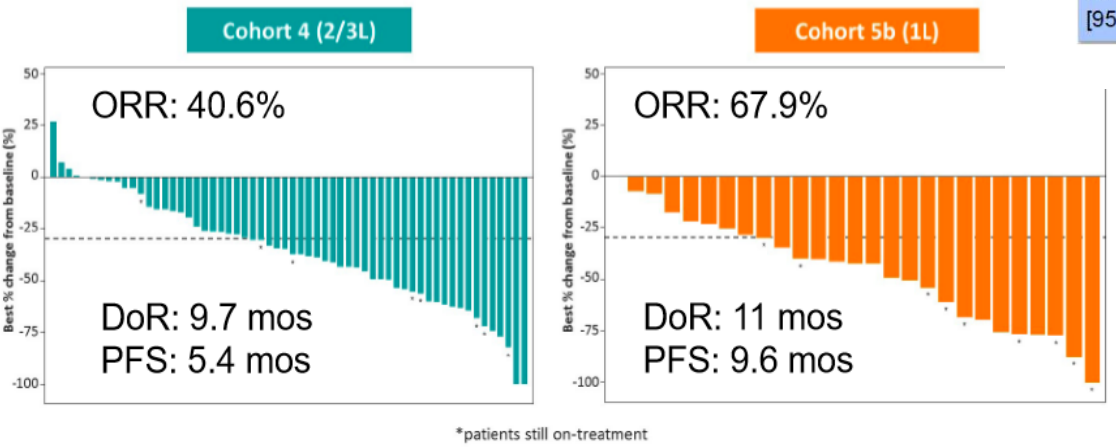
Drilon et al. WCLC 2018

Savolitinib in MET exon 14 skipping

Investigator assessment	PSC (n=11)	Other NSCLC (n=20)	Total (n=31)
BOR by RECIST 1.1, n (%)			
PR	6 (54.5)	11 (55.0)*	17 (54.8)*
SD	4 (36.4)	8 (40.0)	12 (38.7)
PD	1 (9.1)	1 (5.0)	2 (6.5)
Interim ORR † in EES, n (%) [95% CI]	6 (54.5) [23.4,83.3]	10 (50.0) [27.2, 72.8]	16 (51.6) [33.1, 69.8]
Interim DCR † in EES, n (%) [95% CI]	10 (90.9) [58.7, 99.8]	19 (95.0) [75.1, 99.9]	29 (93.5) [78.6, 99.2]

Lun S et al. AACR 2019

GEOMETRY mono-1



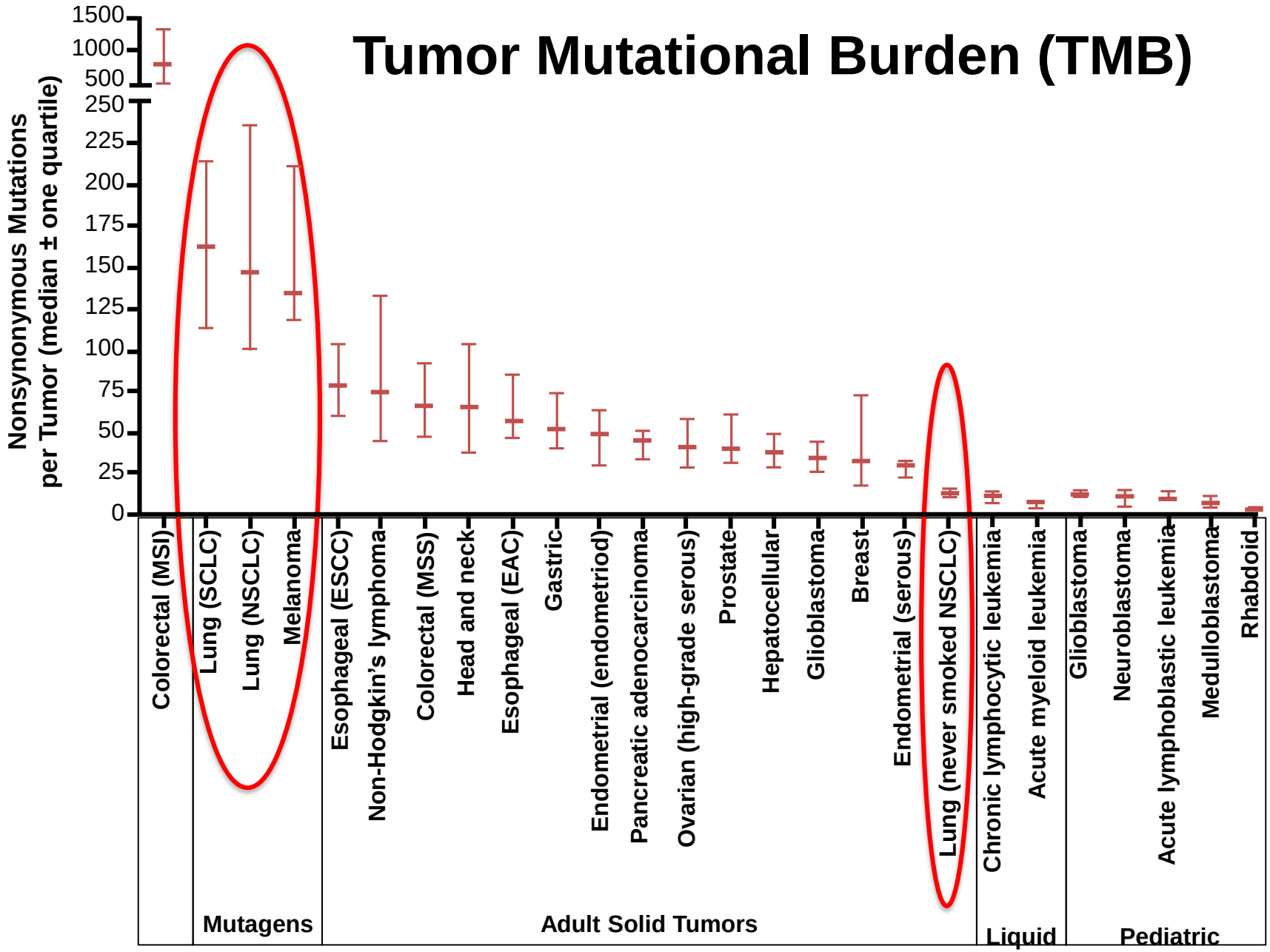
*patients still on-treatment

Responses were observed independently on the type of mutation or co-presence of Amplification

Wolf et al, ASCO 2019

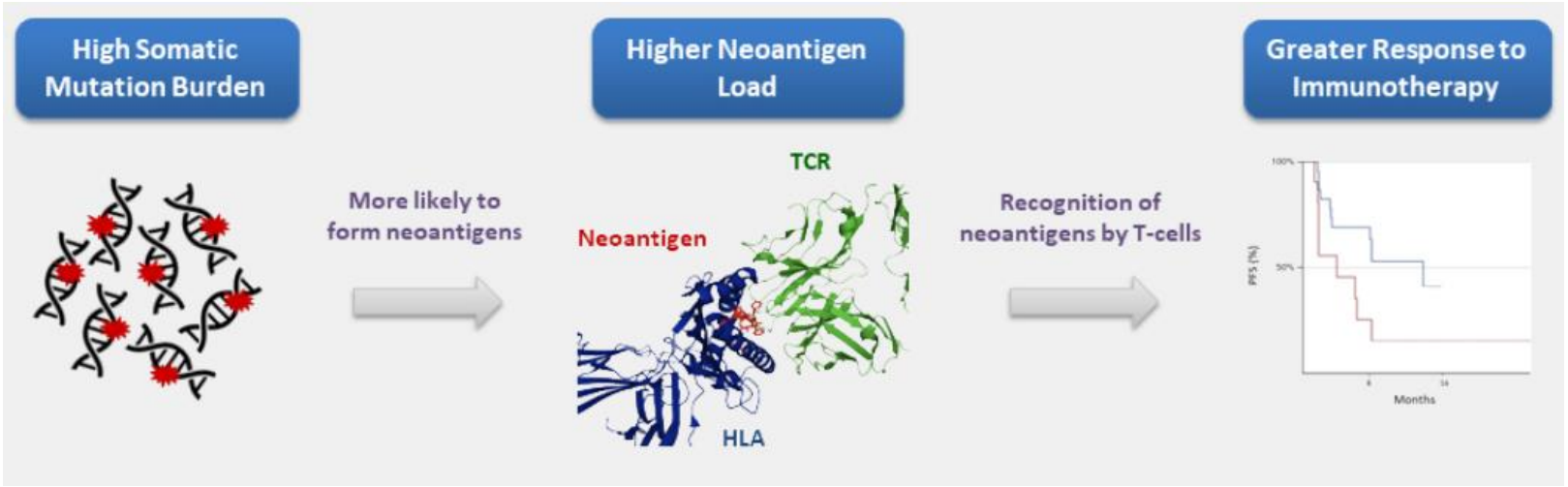
Biomarcatori utilizzati in pratica clinica per il trattamento con immunocheckpoint inhibitor

Patologia	Farmaco	Target del farmaco	Marcatore predittivo	Positività del marcatore
NSCLC	Pembrolizumab (KEYTRUDA)	PD1	PD-L1 expression > 50%	30%
All tumors	Pembrolizumab (KEYTRUDA)	PD1	MSI-DMMR	10%

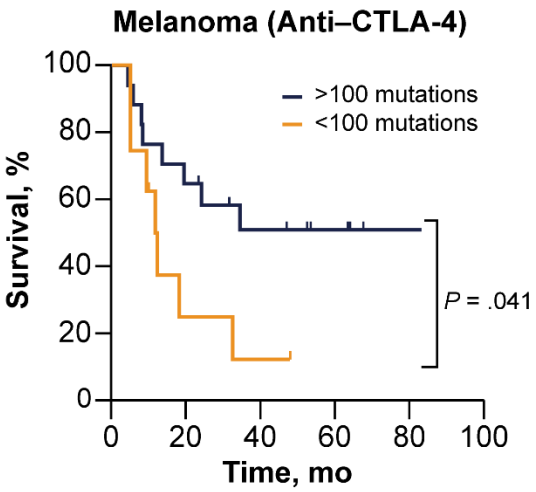


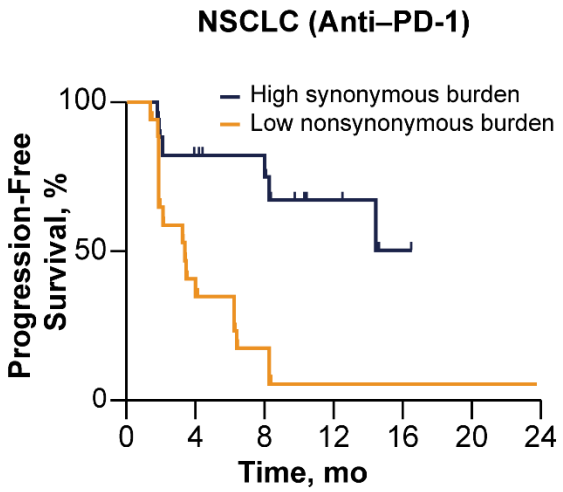
Vogelstein B, et al. *Science*. 2013

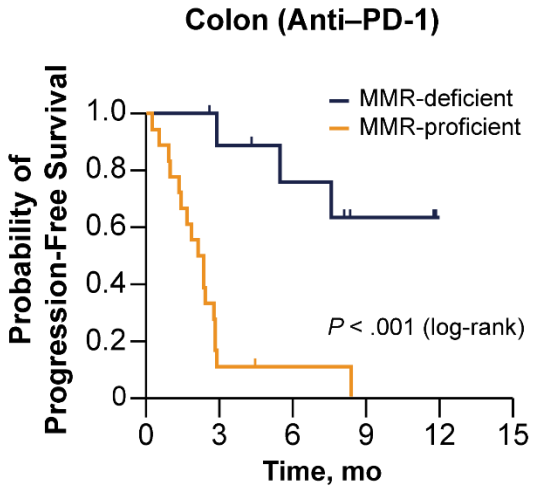
TMB is a surrogate of tumor neoantigenic load

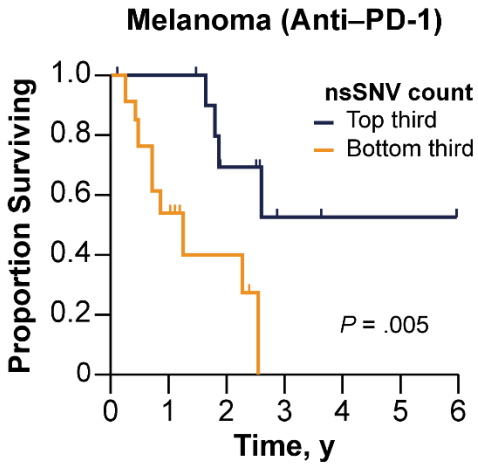


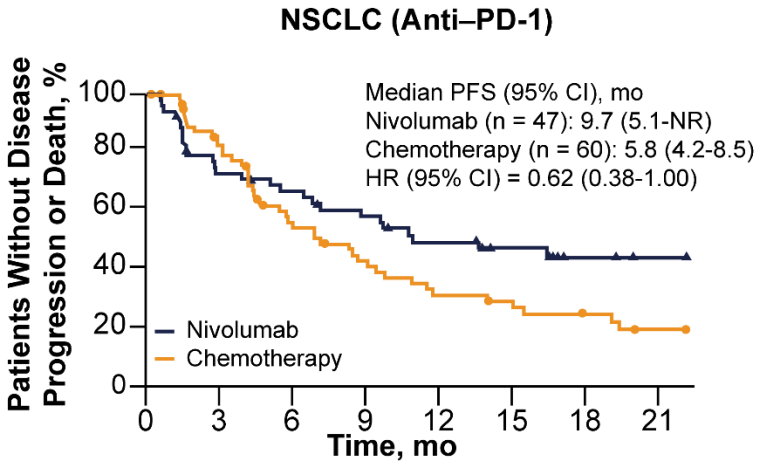
ELEVATO MUTATIONAL LOAD → EFFICACE RISPOSTA











1. Snyder A et al. *N Engl J Med*. 2014;371:2189-2199. 2. Rizvi NA et al. *Science*. 2015;348:124-128. 3. Le DT et al. *N Engl J Med*. 2015;372:2509-2520. 4. Van Allen EM et al. *Science*. 2015;350:207-211. 5. Hugo W et al. *Cell*. 2016;165:35-44. 6. Carbone DP et al. *N Engl J Med*. 2017;376:2415-2426.

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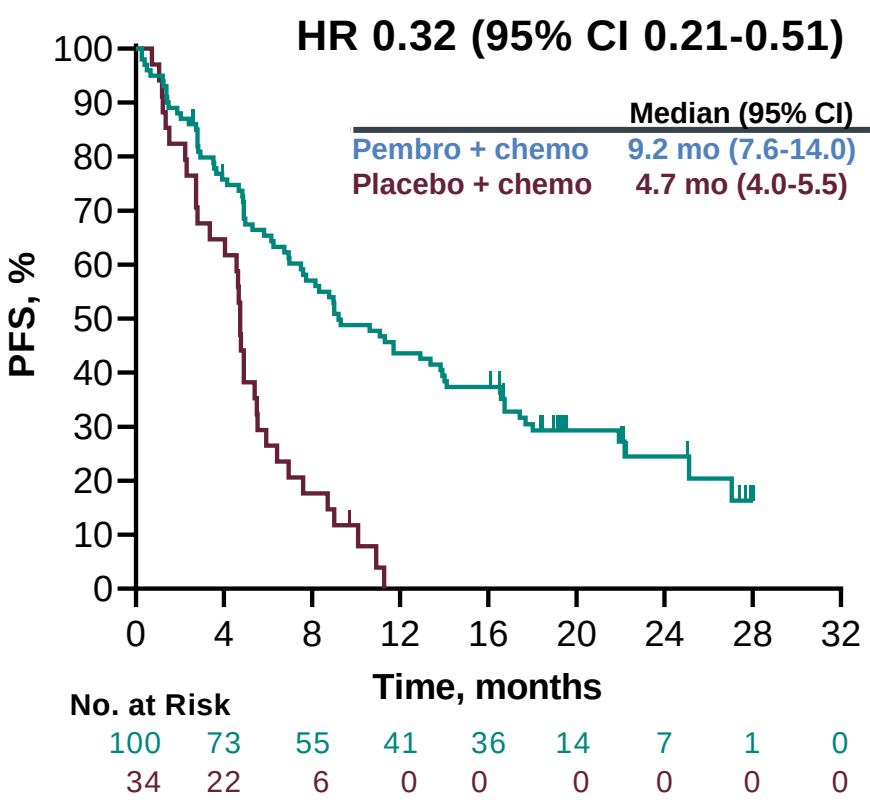
Evaluation of TMB in KEYNOTE-189: Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy for Nonsquamous NSCLC

Marina C. Garassino,[1] Delvys Rodriguez-Abreu,[2] Shirish M. Gadgeel,[3] Emilio Esteban,[4] Enriqueta Felip,[5] Giovanna Speranza,[6] Martin Reck,[7] Rina Hui,[8] Michael Boyer,[9] Razvan Cristescu,[10] Deepti Aurora-Garg,[10] Andrew Albright,[10] Andrey Loboda,[10] Julie Kobie,[10] Jared Lunceford,[10] Mark Ayers,[10] Gregory M. Lubiniecki,[10] Bilal Piperdi,[10] M. Catherine Pietanza,[10] Edward B. Garon[11]

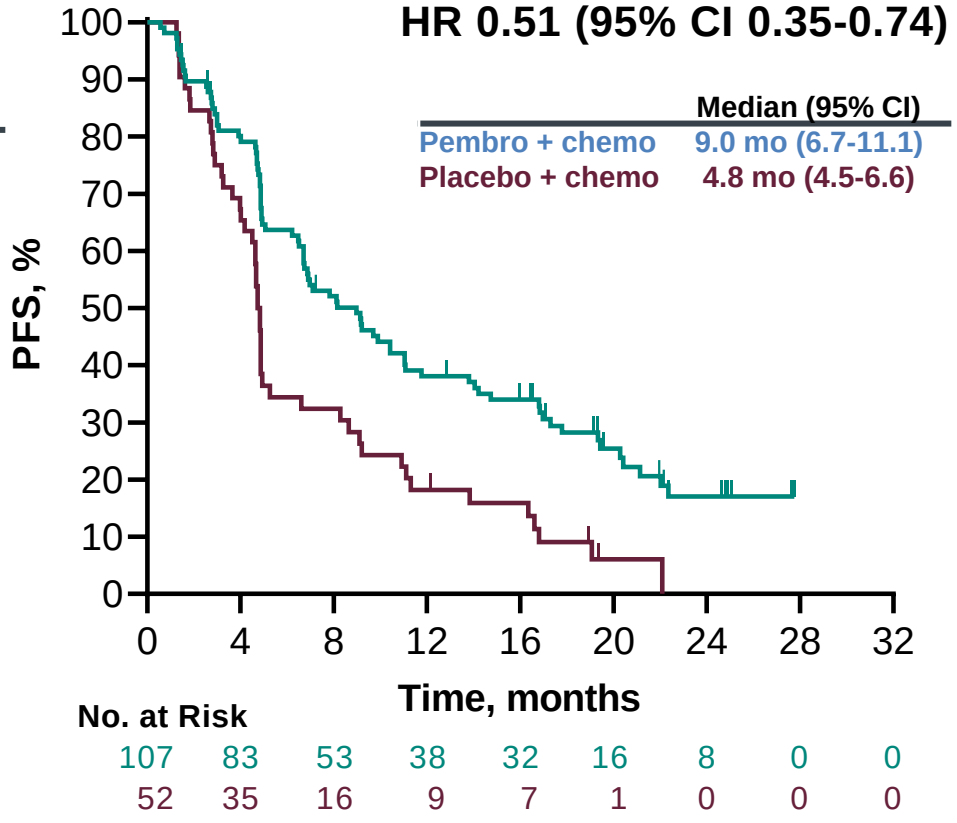
[1]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [2]Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain; [3]Karmanos Cancer Institute, Detroit, MI, USA (currently at University of Michigan, Ann Arbor, MI, USA); [4]Hospital Universitario Central de Asturias, Oviedo, Spain; [5]Vall d'Hebron University, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [6]Centre integré de cancérologie de la Montérégie, Université de Sherbrooke, Greenfield Park, QC, Canada; [7]LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [8]Westmead Hospital and University of Sydney, Sydney, NSW, Australia; [9]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [10]Merck & Co., Inc., Kenilworth, NJ, USA; [11]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

CLINICAL UTILITY FOR PFS: TTMB CUTPOINT OF 175 MUT/EXOME

tTMB ≥175 mut/exome

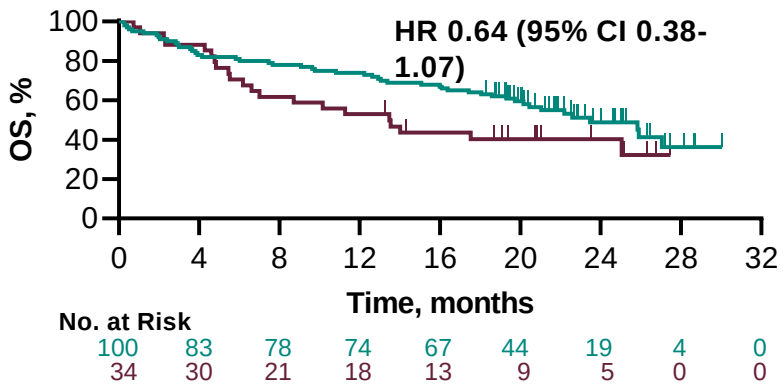


tTMB <175 mut/exome

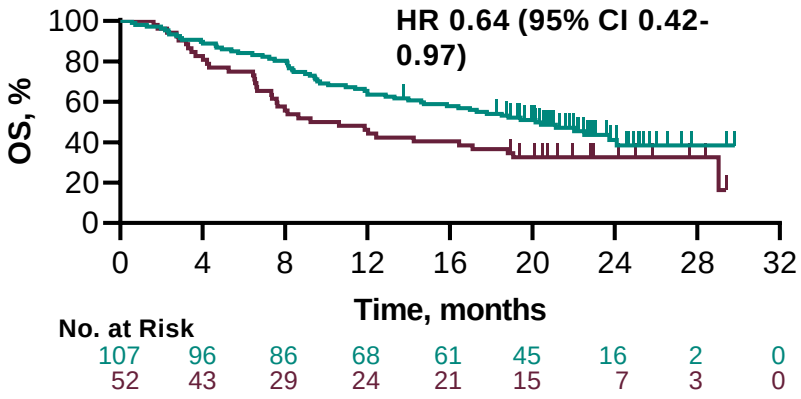


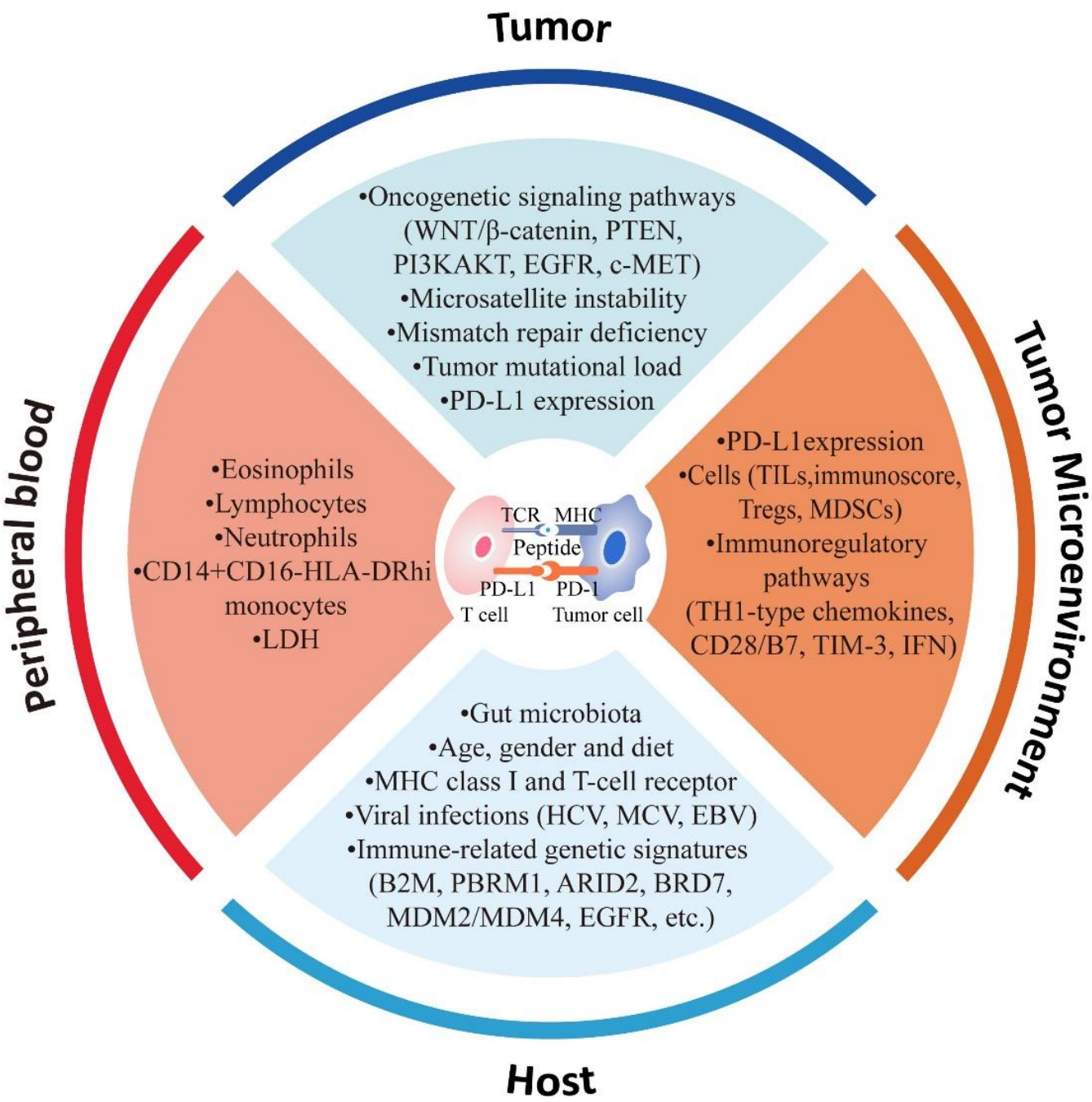
CLINICAL UTILITY FOR OS: TTMB CUTPOINTS OF 175 AND 150 MUT/EXOME

tTMB ≥175 mut/exome



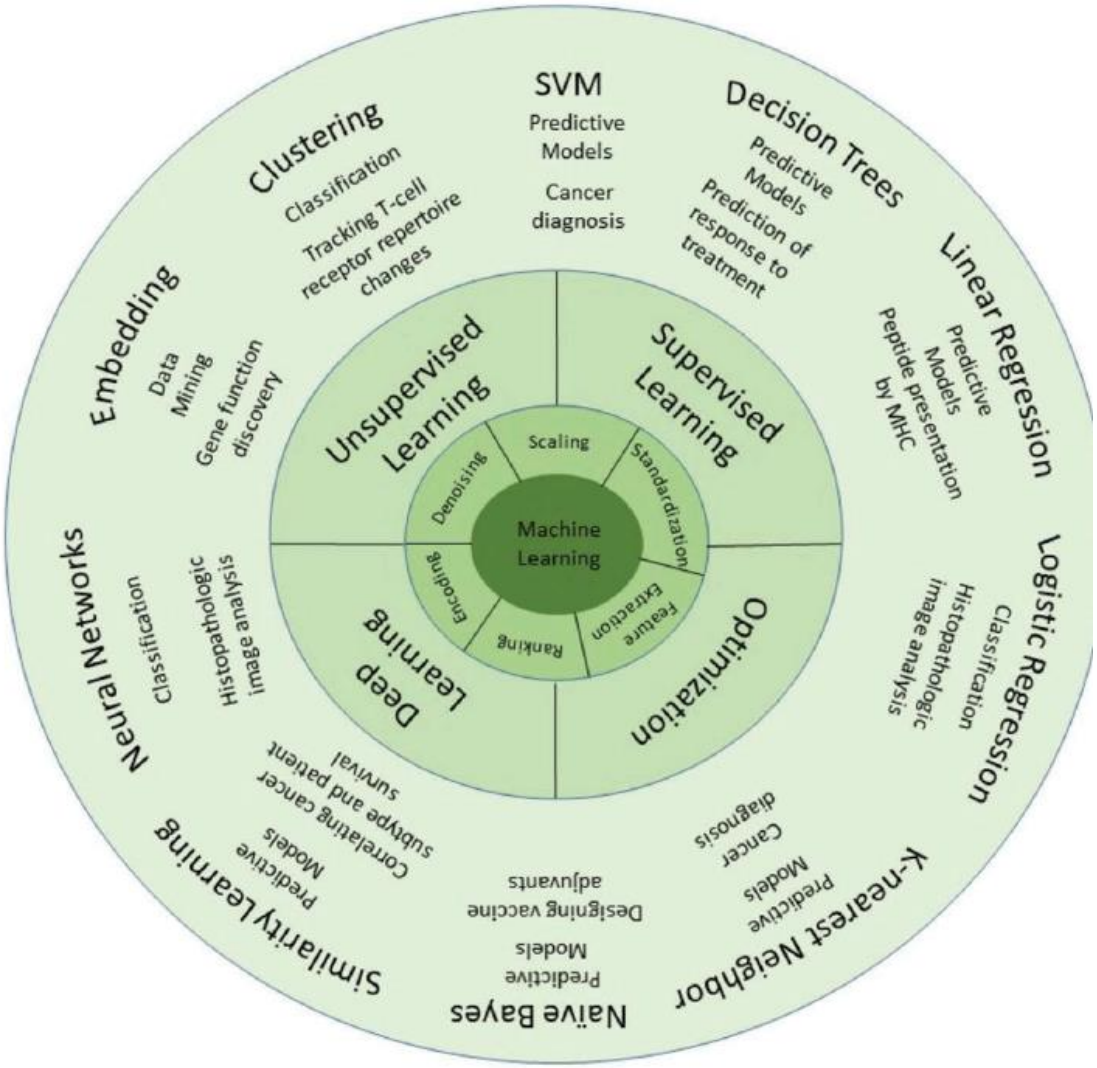
tTMB <175 mut/exome





Yan X et al, Front. Pharmacol., September 2018

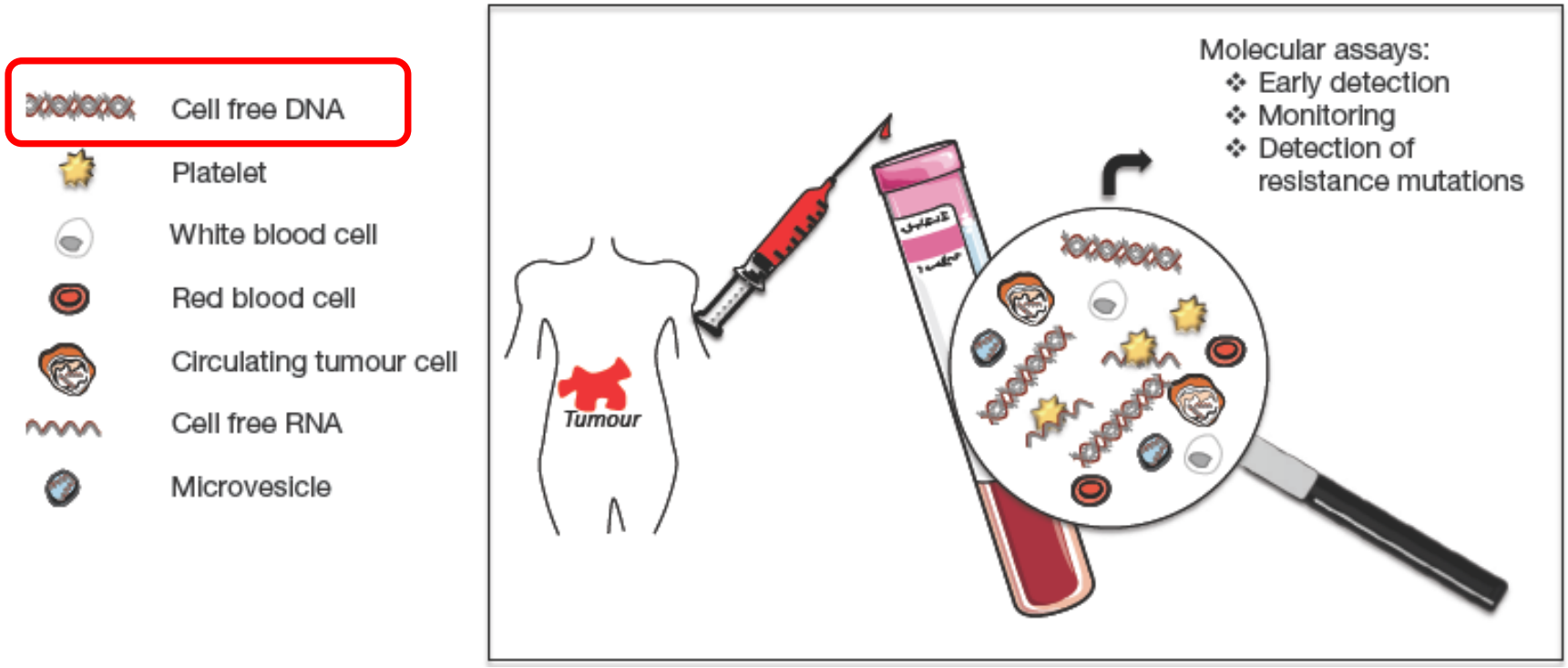
Approcci di intelligenza artificiale per la definizione delle predizione di risposta all'immunoterapia

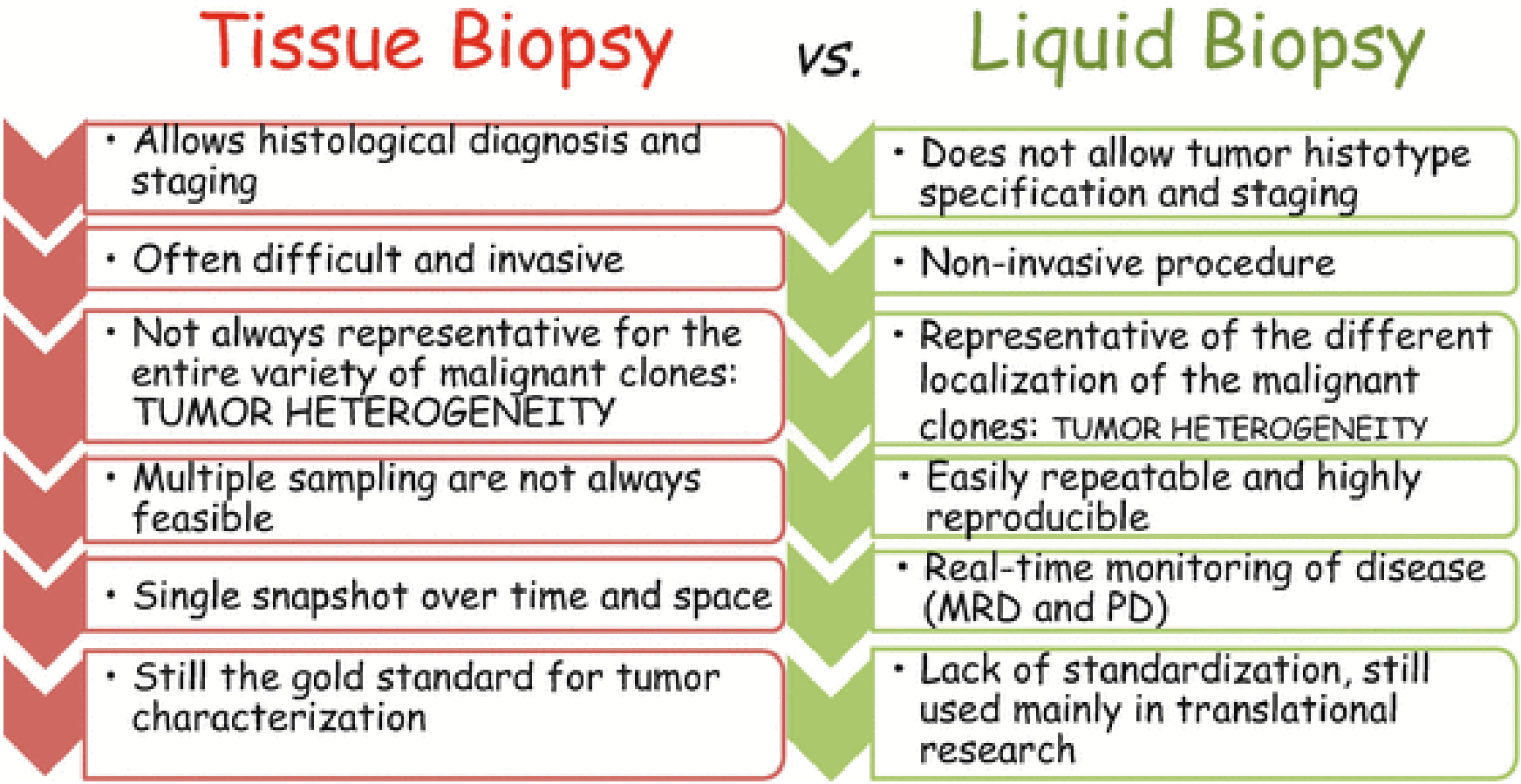


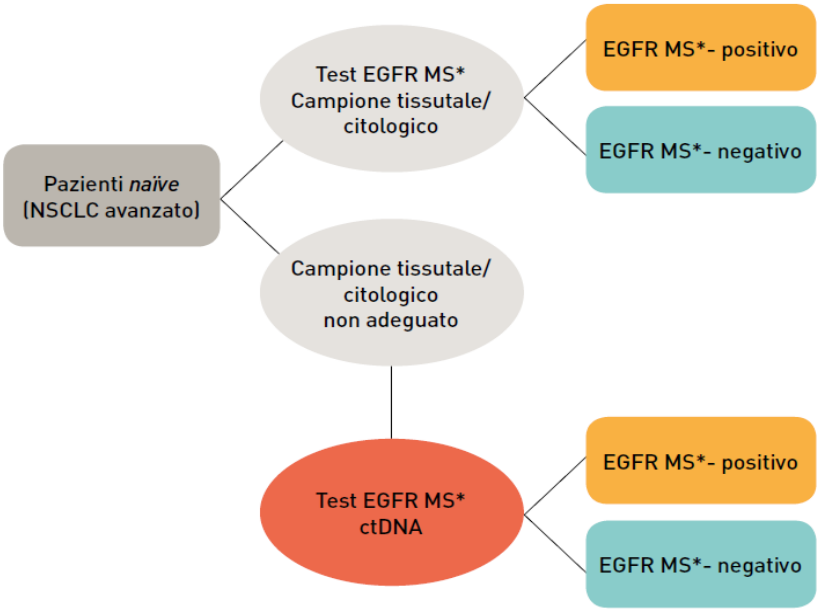
Jabbari P and Rezaei N, Exp Rev Clin Immunol 2019

Biopsia liquida

Test eseguito in un campione di sangue o di altro fluido biologico allo scopo di identificare materiale originato dal tumore




Tissue Biopsy
vs.
Liquid Biopsy
• Allows histological diagnosis and staging
• Often difficult and invasive
• Not always representative for the entire variety of malignant clones: TUMOR HETEROGENEITY
• Multiple sampling are not always feasible
• Single snapshot over time and space
• Still the gold standard for tumor characterization
• Does not allow tumor histotype specification and staging
• Non-invasive procedure
• Representative of the different localization of the malignant clones: TUMOR HETEROGENEITY
• Easily repeatable and highly reproducible
• Real-time monitoring of disease (MRD and PD)
• Lack of standardization, still used mainly in translational research

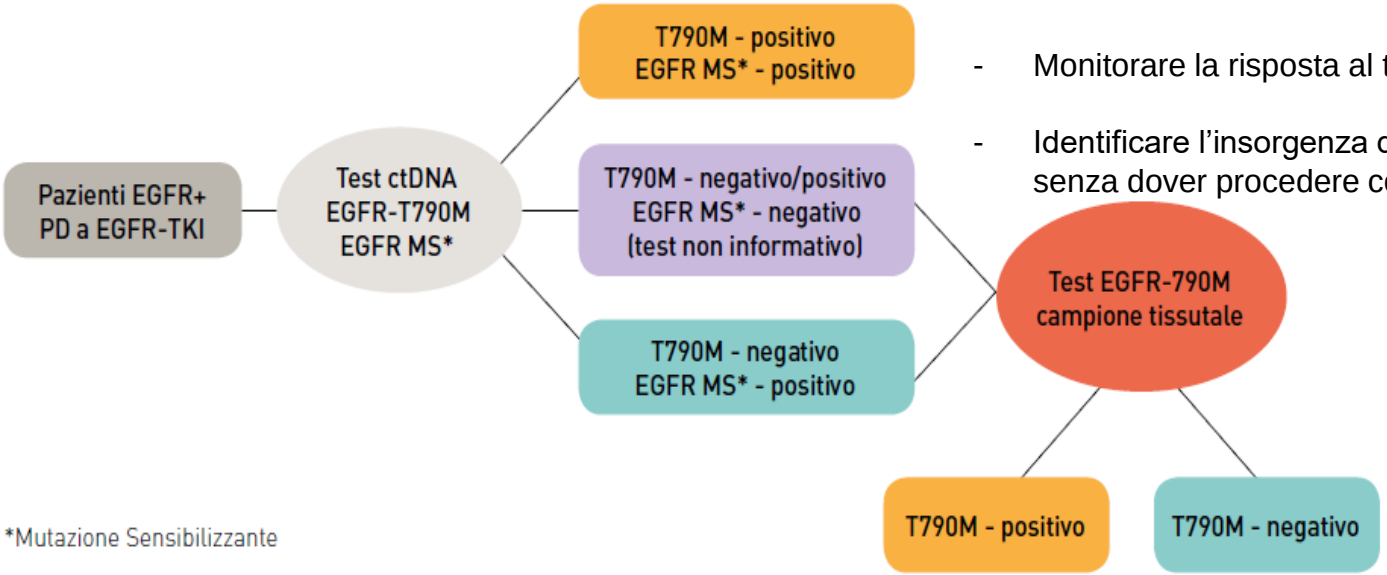


Pazienti naive, nei casi in cui:

- Non sia sufficiente il materiale citologico/istologico per l'analisi molecolare
- Il tumore non sia facilmente accessibile
- Il paziente sia in condizioni scadute tali da rendere problematica la procedura invasiva
- Biopsia ossea

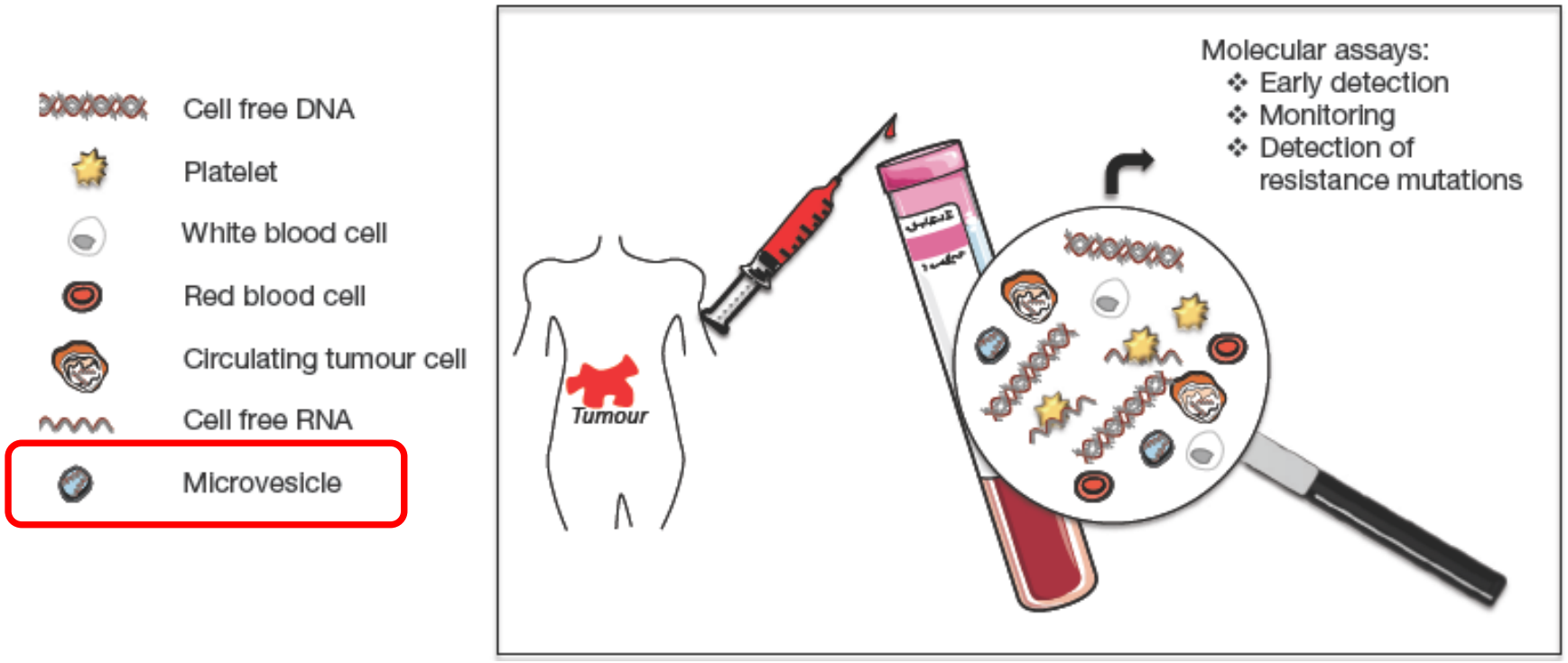
Pazienti EGFR mutati in corso di trattamento con TKI allo scopo di:

- Monitorare la risposta al trattamento
- Identificare l'insorgenza delle mutazioni di resistenza senza dover procedere con la rebiopsia tissutale

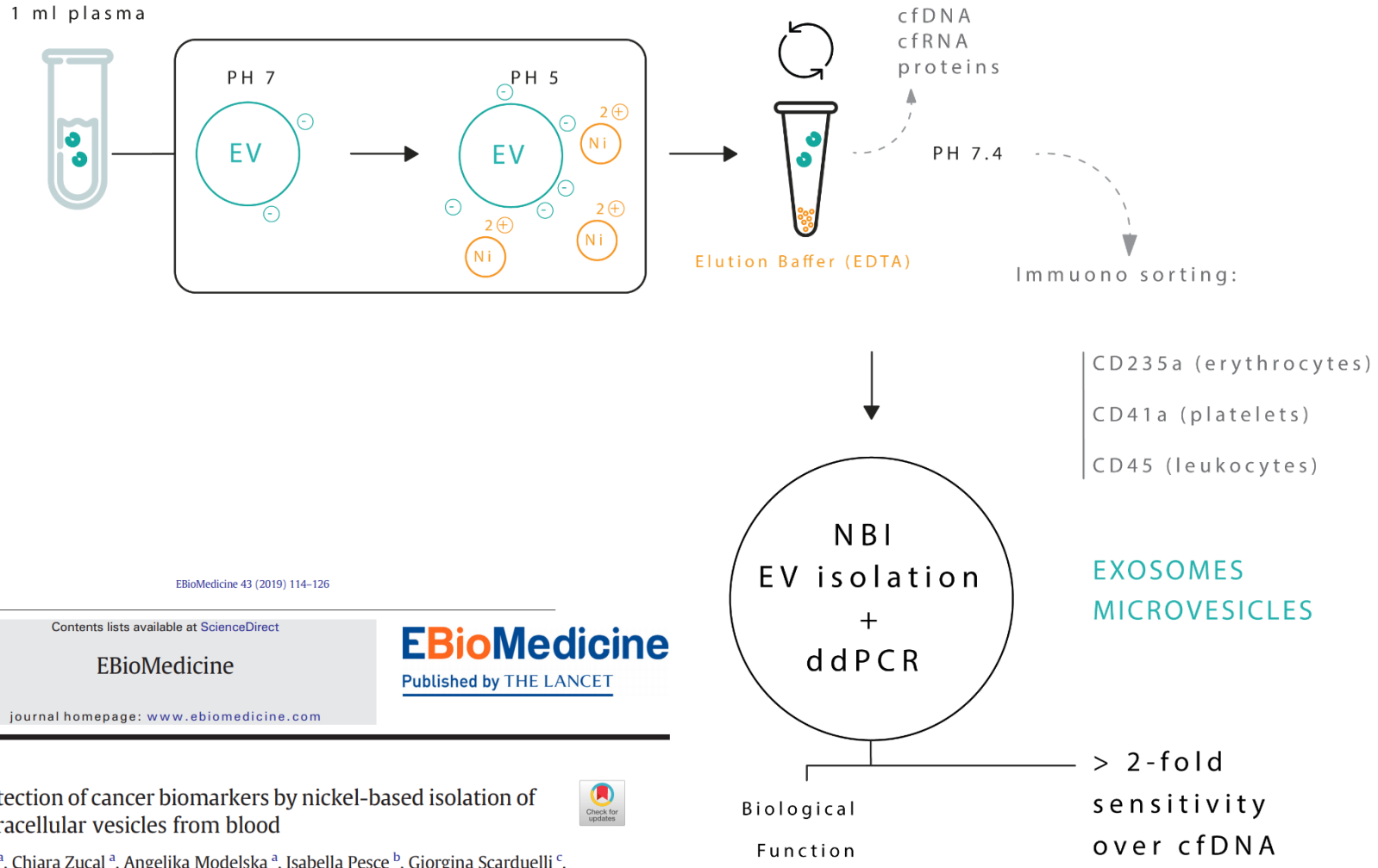


*Mutazione Sensibilizzante

Raccomandazioni AIOM-SIAPEC 2018


Cell free DNA
Platelet
White blood cell
Red blood cell
Circulating tumour cell
Cell free RNA
Microvesicle
Tumour
Molecular assays:
Early detection
Monitoring
Detection of resistance mutations

EV Nickel-Based Isolation (NBI) coupled ddPCR



EBioMedicine 43 (2019) 114–126

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

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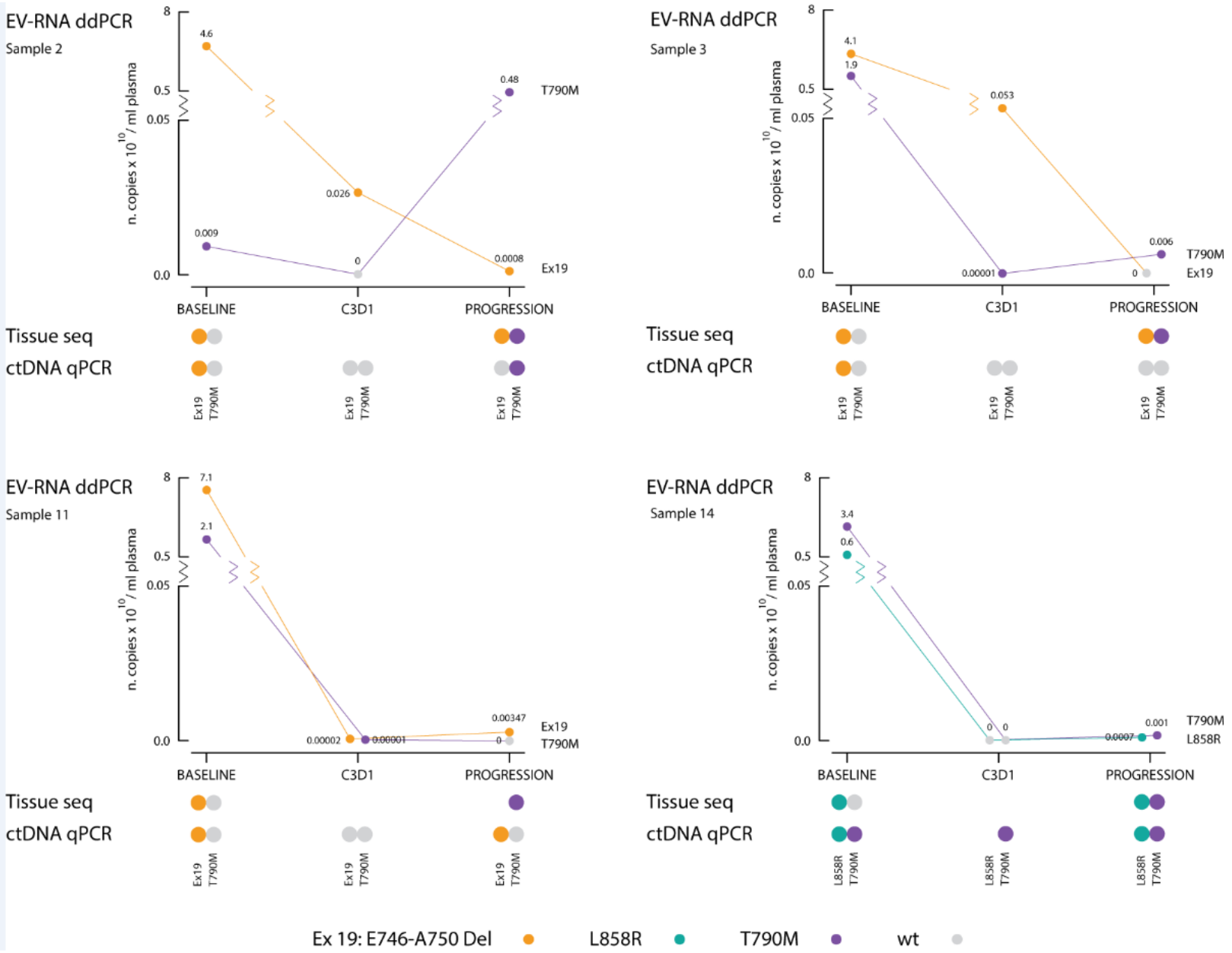
Ultrasensitive detection of cancer biomarkers by nickel-based isolation of polydisperse extracellular vesicles from blood

Michela Notarangelo [a], Chiara Zucal [a], Angelika Modelska [a], Isabella Pesce [b], Giorgina Scarduelli [c], Cristina Potrich [d], Lorenzo Lunelli [d], Cecilia Pederzolli [d], Paola Pavan [e], Giancarlo la Marca [f], Luigi Pasini [g], Paola Ulivi [g], Himisha Beltran [h], Francesca Demichelis [a], Alessandro Provenzani [a,1], Alessandro Quattrone [a,1], Vito G. D'Agostino [a,*,1]

NSCLC


EV-RNA ddPCR
Sample 2
n. copies x 10^10 / ml plasma
8
0.5
0.05
0.0
4.6
0.026
0.009
0
0.48
0.0008
T790M
Ex19
BASELINE
C3D1
PROGRESSION
Tissue seq
ctDNA qPCR
Ex19
T790M
EV-RNA ddPCR
Sample 3
4.1
1.9
0.053
0.00001
0.006
0
T790M
Ex19
EV-RNA ddPCR
Sample 11
7.1
2.1
0.00002
0.00001
0.00347
0
Ex19
T790M
EV-RNA ddPCR
Sample 14
3.4
0.6
0
0
0.0007
0.001
T790M
L858R
L858R
T790M
Ex 19: E746-A750 Del
L858R
T790M
wt

Carcinoma del colon-retto

Nessuna indicazione all'utilizzo nella pratica clinica della biopsia liquida

Pazienti non responsivi a terapia con mAb-anti EGFR

Pz	Sede tumore	Farmaco	Caratterizzazione molecolare tessuto al basale	Caratterizzazione molecolare biopsia liquida
1	Colon sinistro	panitumumab	RAS, BRAF wt	BRAF V600E
2	retto	cetuximab	RAS, BRAF wt	KRAS G13D
3	retto	panitumumab	RAS, BRAF wt	NRAS Q61K
4	Colon destro	panitumumab	RAS, BRAF wt	PIK3CA c.3073A>G, MAP2K1 c.607G>A

Conclusioni

Terapia target:

- Numerosi farmaci approvati in pratica clinica sulla base di un marcatore molecolare
- Promettenti risultati a riguardo di alcuni marcatori emergenti: RET, KRAS, MET

Immunocheckpoint inhibitors:

- Unici marcatori utilizzati in pratica clinica: PDL1, MSI
- Ridimensionato il ruolo del TMB
- Algoritmi e tools di intelligenza artificiale saranno probabilmente il futuro per la predizione di risposta a tali farmaci

Biopsia liquida:

- Crescente utilizzo per la caratterizzazione molecolare del tumore al basale e in corso di trattamento
- L'utilizzo di altre tipologie di materiale oltre al ctDNA potrebbe permettere di raggiungere più elevati valori di accuratezza diagnostica

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Thank you for your attention