OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

UNIVERSITÀ DEGLI STUDI
DI GENOVA

RICADUTE PRATICHE DELLA CARATTERIZZAZIONE MOLECOLARE MULTIGENICA IN ONCOLOGIA

24/11/2021

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- Astra Zeneca, Bristol-Myers-Squibb, Merck-Sharp-Dohme, Roche, Takeda

Research grants:

- Bristol-Myers-Squibb; Ministero della Salute

EVOLUTION OF THE THERAPEUTIC APPROACH

Traditional medicine

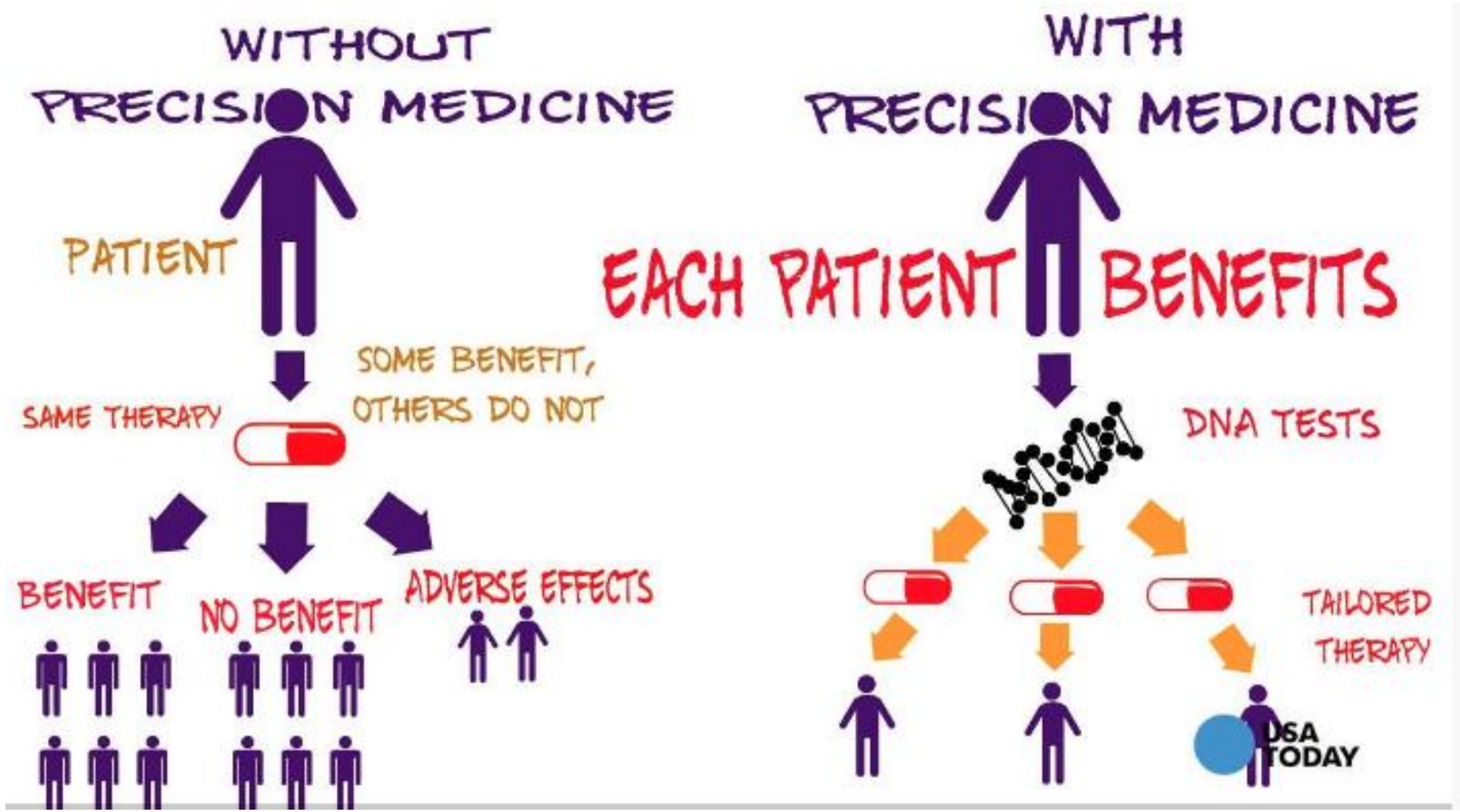
- «one drug fits all (?)»

Stratified medicine

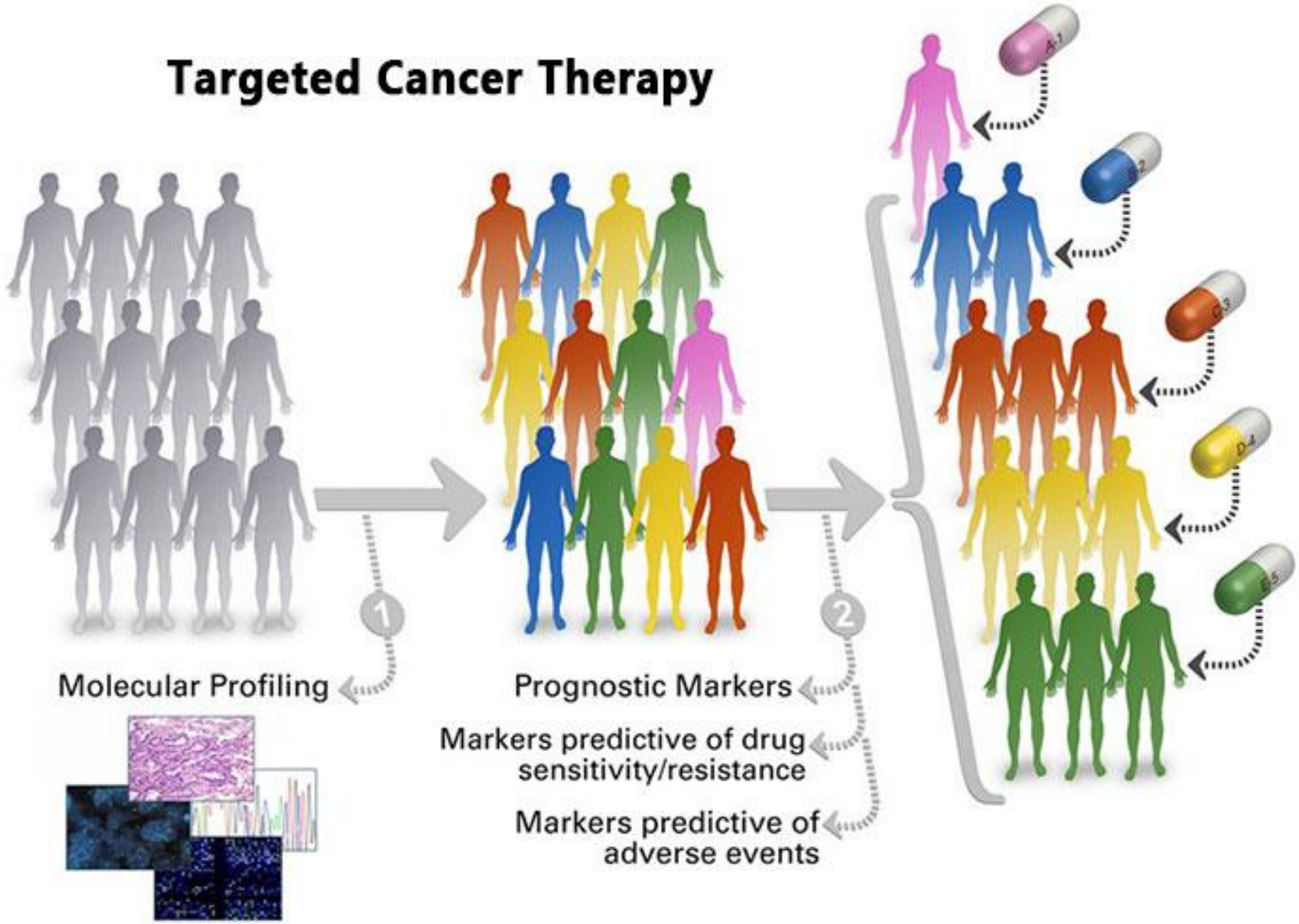
- Disease sub-types; risk stratification; biomarkers

Precision medicine

- «-omics»; compliance; exogeneous factors; molecular diagnostics



https://cancerx.co.in/blog/2018/09/28/understanding-precision-medicine-for-cancer/



http://puhuahospital.com/treatments/cancer/targeted

TARGETED AGENTS 2001

MABS

- Rituximab
- Trastuzumab

Small molecules

- Imatinib

TARGETED AGENTS 2020

MABS

- Rituximab
- Trastuzumab
- Bevacizumab
- Ramucirumab
- Cetuximab
- Panitumumab
- Pertuzumab
- Trastuzumab-DM1 (T-DM1)*
- Aflibercept

Small molecules

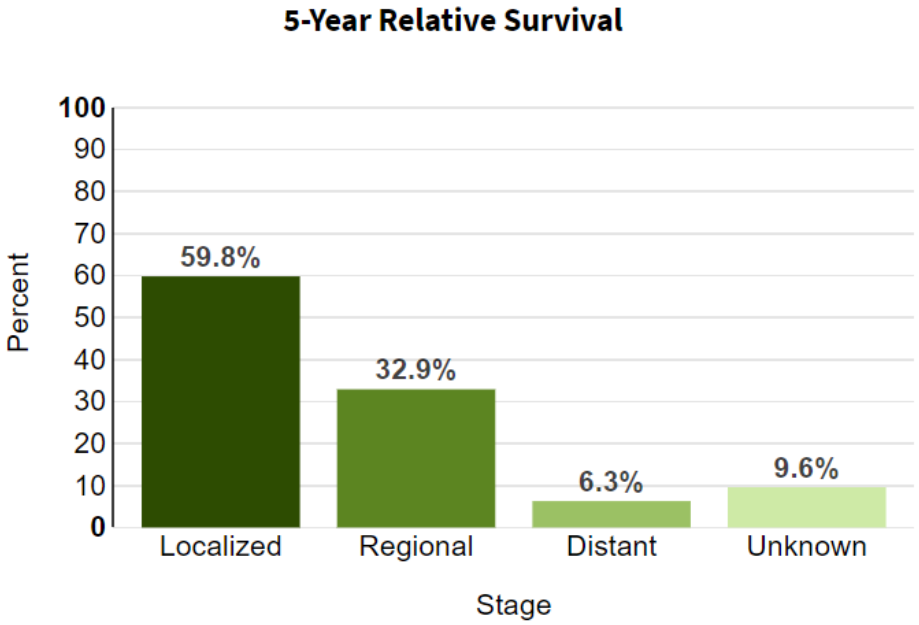
- Imatinib
- Erlotinib
- Gefitinib
- Sorafenib
- Sunitinib
- Lapatinib
- Neratinib
- Pazopanib
- Regorafenib
- Axitinib
- Cabozantinib
- Osimertinib
- Dabrafenib
- Trametinib
- Cobimetinib
- Nintedanib
- Vismodegib
- Vemurafenib
- Crizotinib
- Ceritinib
- Alectinib
- Palbociclib
- Ribociclib
- Abemaciclib
- Everolimus
- Temsirolimus
- Olaparib
- Talazoparib
- Rucaparib
- Niraparib
- Afatinib
- Vandetanib
- Lenvatinib

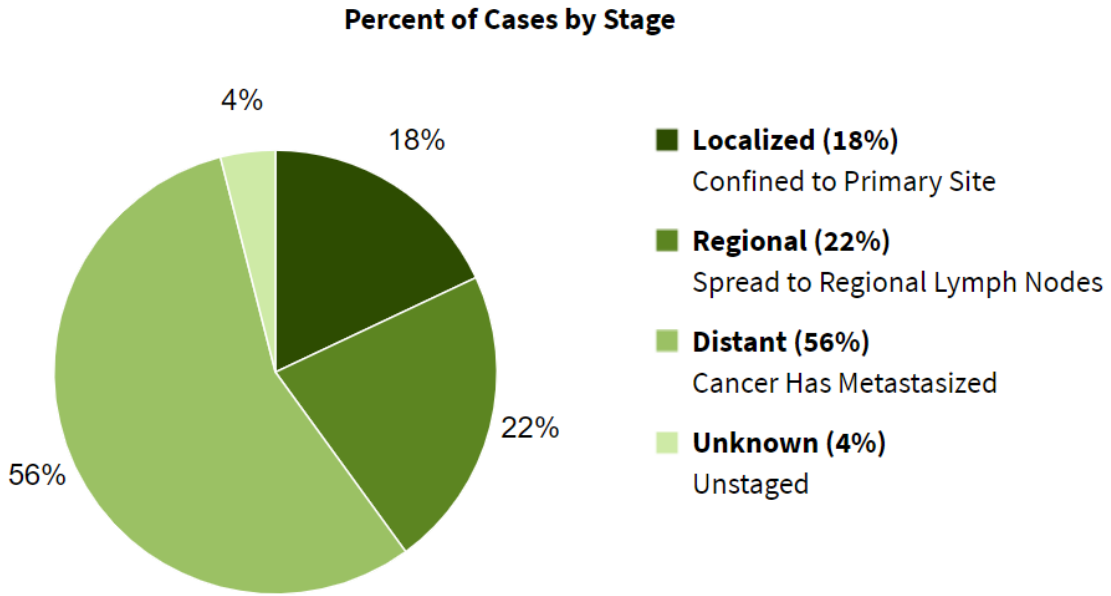
*** Indicates chemio-immuno conjugates**

PRECISION MEDICINE MODEL: NON-SMALL CELL LUNG CANCER

- I Numeri del Cancro in Italia (2020)
- SEER Database (2021)

POLMONE	
Incidenza	Nel 2020, sono attese circa 41.000 nuove diagnosi (maschi = 27.550; femmine = 13.300). È la seconda neoplasia più frequente nei maschi (15%) e la terza nelle femmine (6%)
Mortalità	Nel 2020, sono stimati 34.000 decessi per tumori del polmone (maschi = 23.400; femmine = 10.600)
Sopravvivenza netta a 5 anni dalla diagnosi	15% nei maschi e 19% nelle femmine
Sopravvivenza di ulteriori 5 anni condizionata ad aver superato il primo anno dopo la diagnosi	33% nei maschi e 40% nelle femmine
Prevalenza	Sono 117.800 le persone viventi in Italia dopo una diagnosi di tumore del polmone (maschi = 77.200; femmine = 40.600)



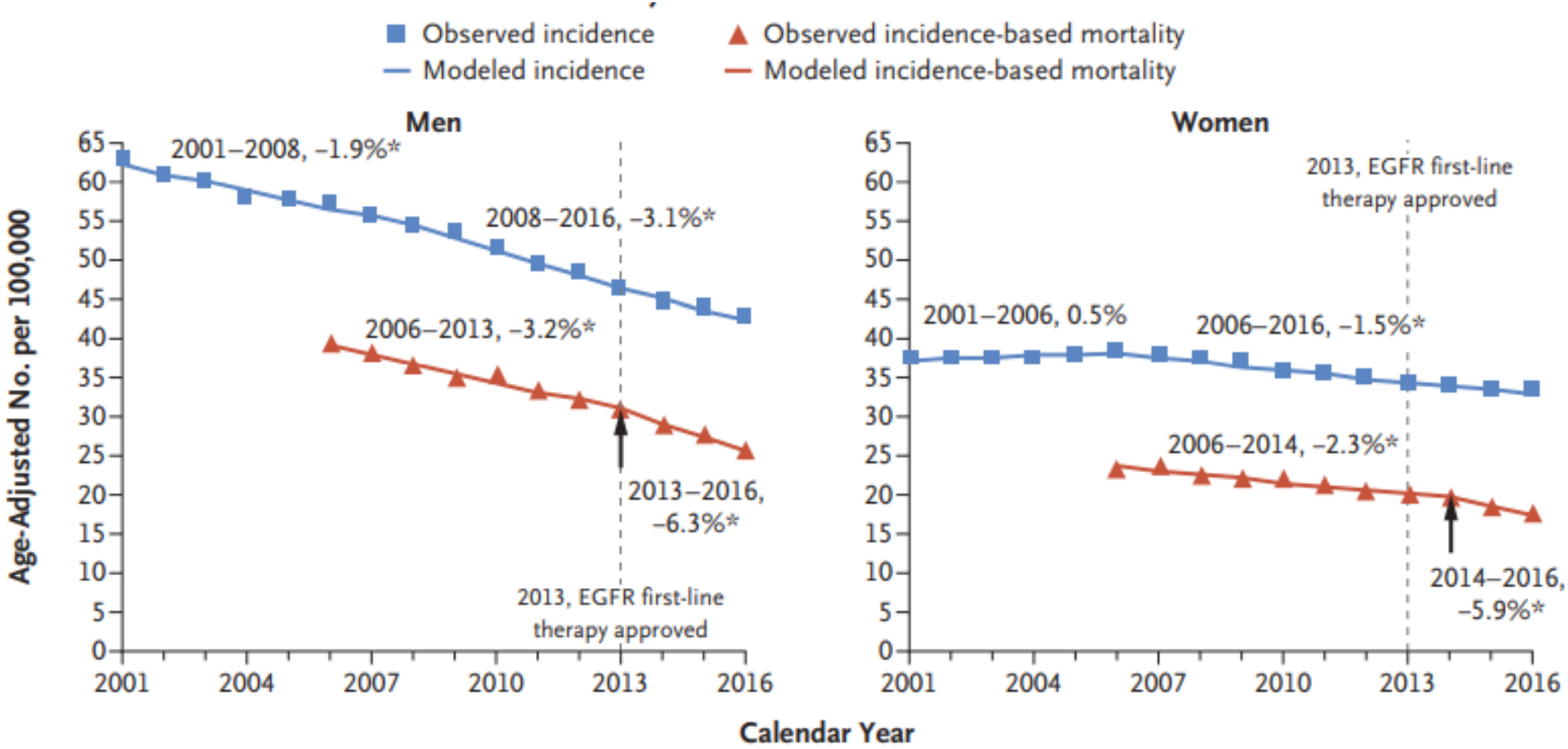


ORIGINAL ARTICLE

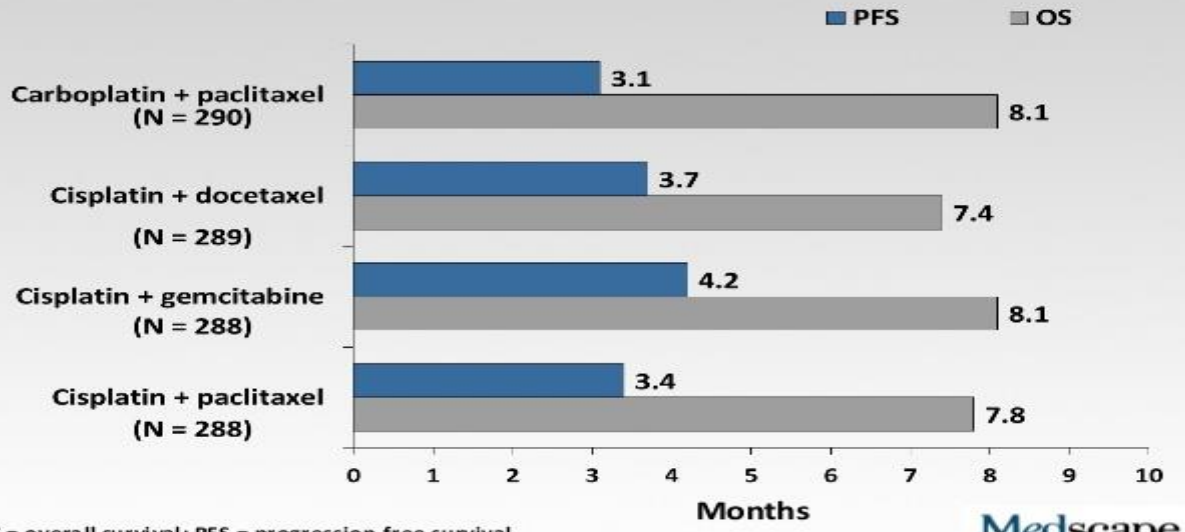
The Effect of Advances in Lung-Cancer Treatment on Population Mortality

Nadia Howlader, Ph.D., Gonçalo Forjaz, D.V.M., Meghan J. Mooradian, M.D., Rafael Meza, Ph.D., Chung Yin Kong, Ph.D., Kathleen A. Cronin, Ph.D., Angela B. Mariotto, Ph.D., Douglas R. Lowy, M.D., and Eric J. Feuer, Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE



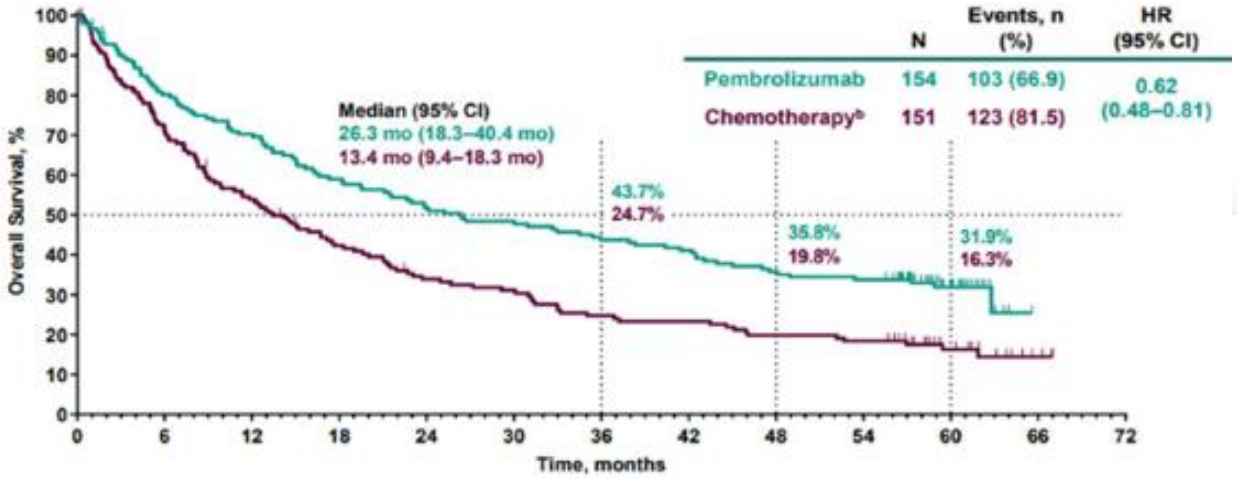
Outcomes With First-Line Doublet Therapy: ECOG 1594



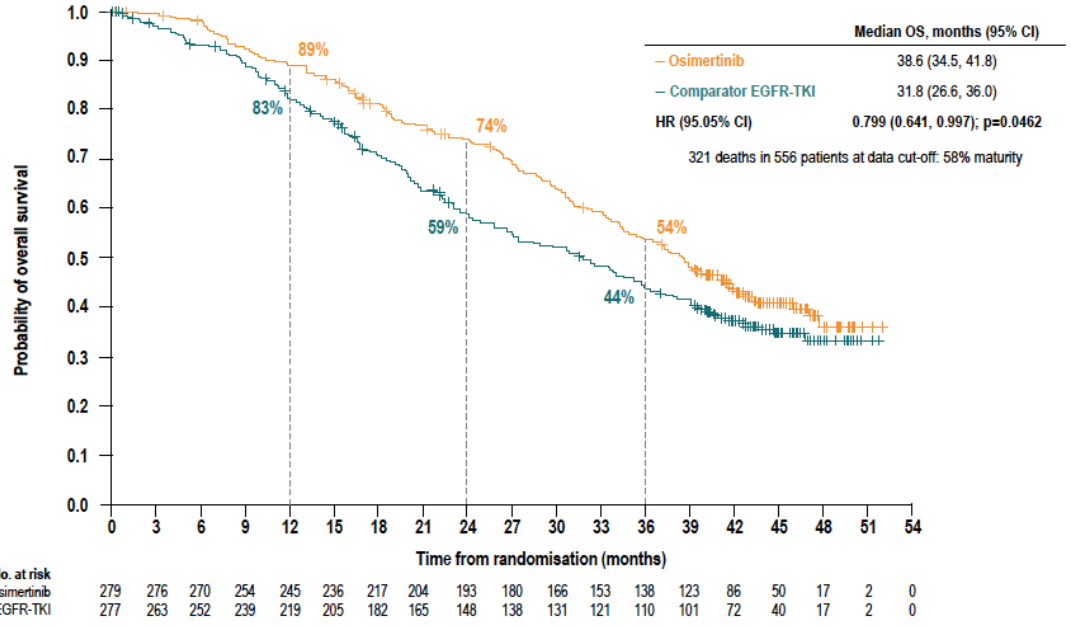
OS = overall survival; PFS = progression-free survival

Schiller JH, et al. *New Engl J Med*. 2002;346:92-98.

Medscape EDUCATION



FINAL ANALYSIS: OVERALL SURVIVAL

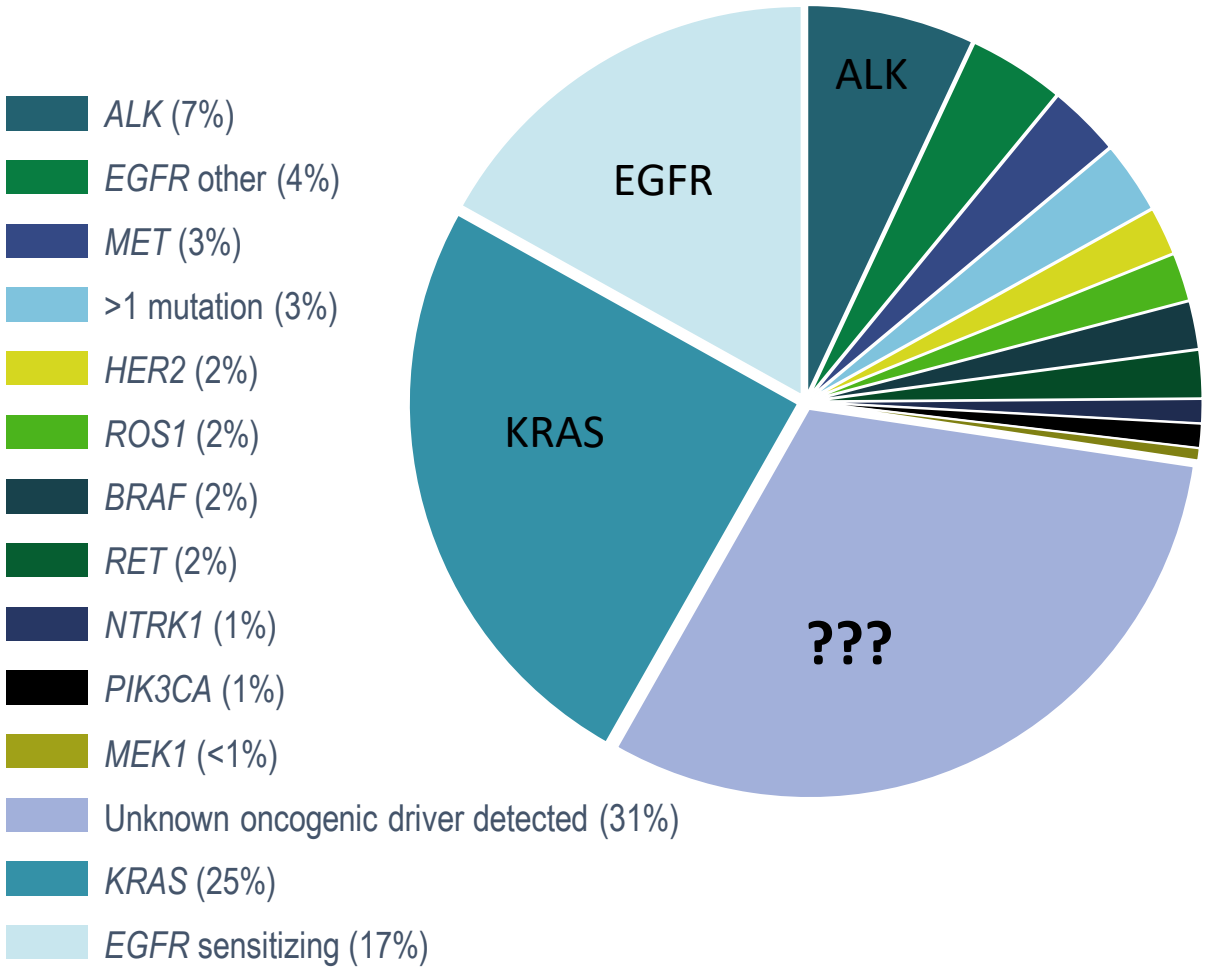


BARCELONA 2019 ESMO congress

Data cut-off: 25 June 2019

For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required

ONCOGENIC DRIVERS IN NSCLC



***EGFR* sensitizing**
Gefitinib; Erlotinib; Afatinib; Osimertinib; Dacomitinib

ALK
Crizotinib; Alectinib; Ceritinib; Lorlatinib; Brigatinib

ROS1
Crizotinib; Cabozantinib; Ceritinib; Lorlatinib; Entrectinib; Repotrectinib, DS-6051b

BRAF
Vemurafenib; Dabrafenib; Dabrafenib + Trametinib

MET
Crizotinib; Cabozantinib; Capmatinib; Savolitinib; Tepotinib; Merestinib; Glesatinib

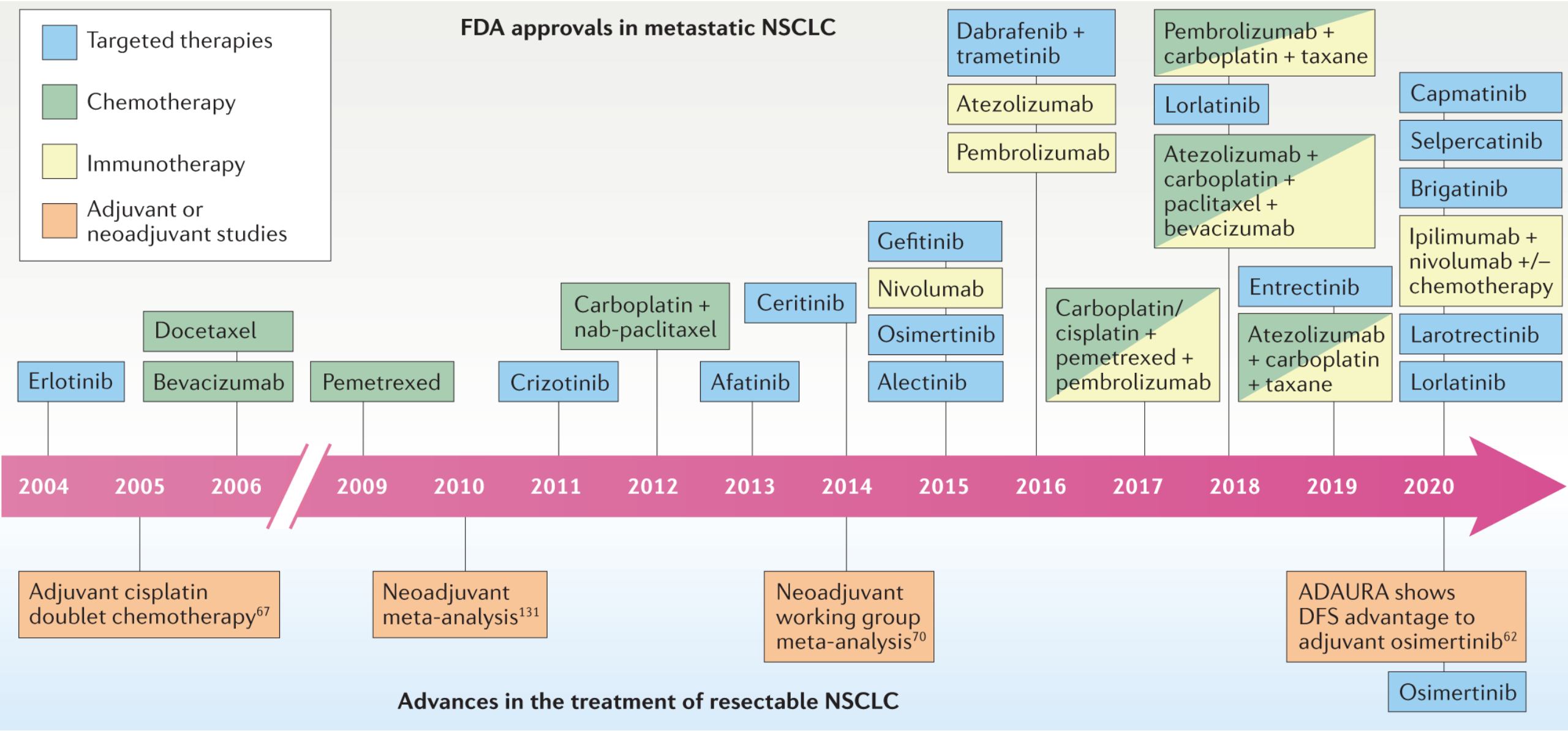
HER2
Trastuzumab emtansine; Afatinib; Neratinib-temsirolimus; Dacomitinib; Poziotinib; XMT-1522; TAK-788; DS-8201a,

RET
Cabozantinib; Alectinib; Apatinib; Vandetanib; sunitinib; Ponatinib; Lenvatinib; BLU-667; LOXO-292

NTRK1
Entrectinib; LOXO-101 (larotrectinib); loxo-195; DS-6051b; repotrectinib

PIK3CA
LY3023414; PQR 309

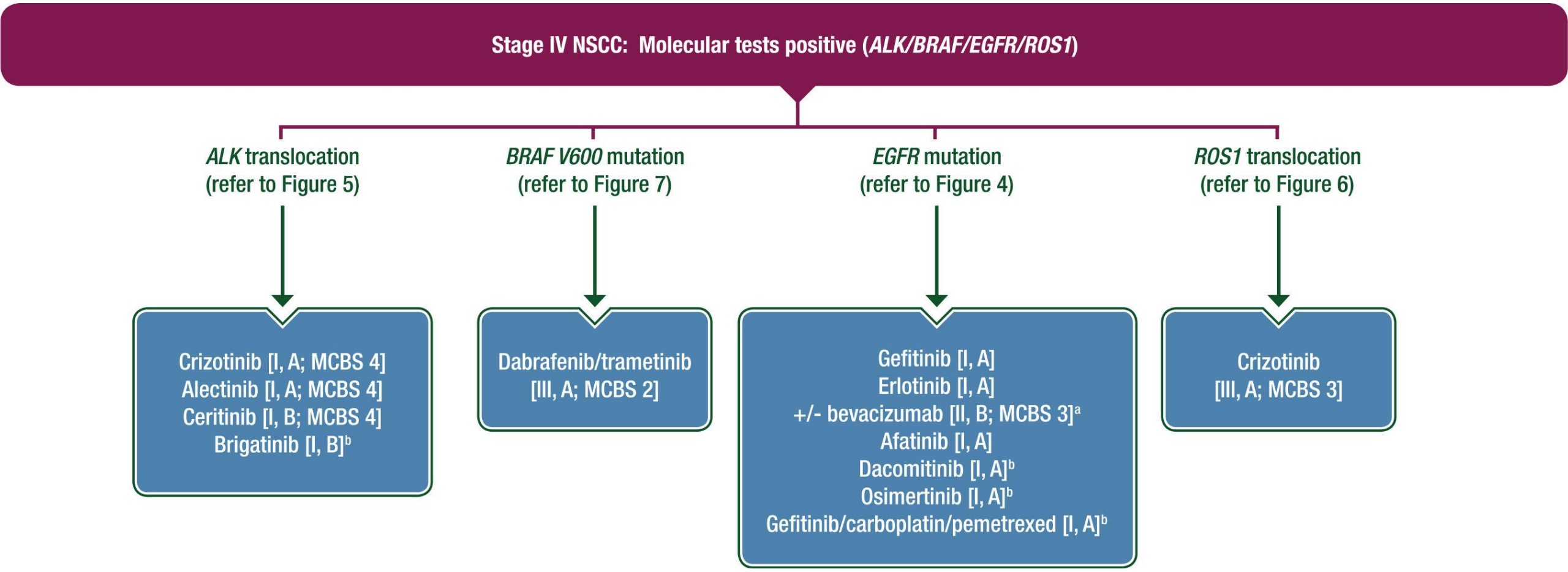
MEK1
Trametinib; Selumetinib; Cobimetinib



Chaft JE, et al. Nat Rev Clin Oncol. 2021

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Updated version published 15 September 2020 by the ESMO Guidelines Committee



National Comprehensive Cancer Network®

NCCN Guidelines Version 7.2021
Non-Small Cell Lung Cancer

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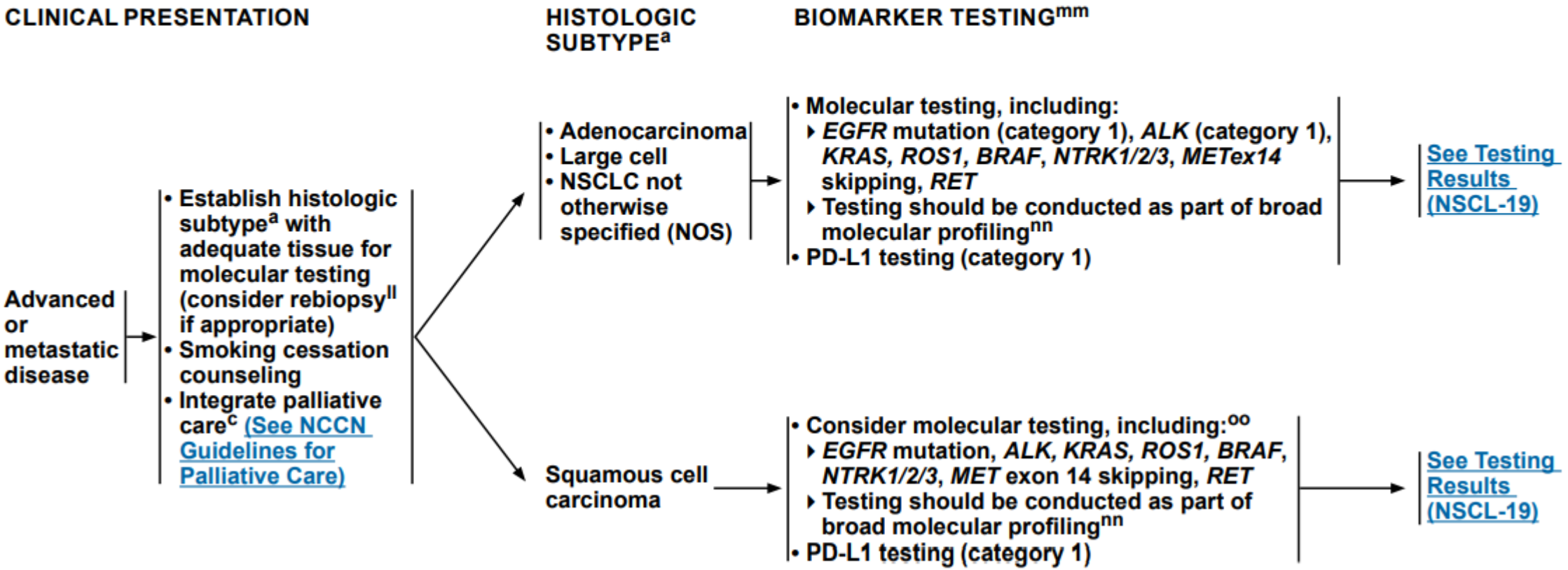
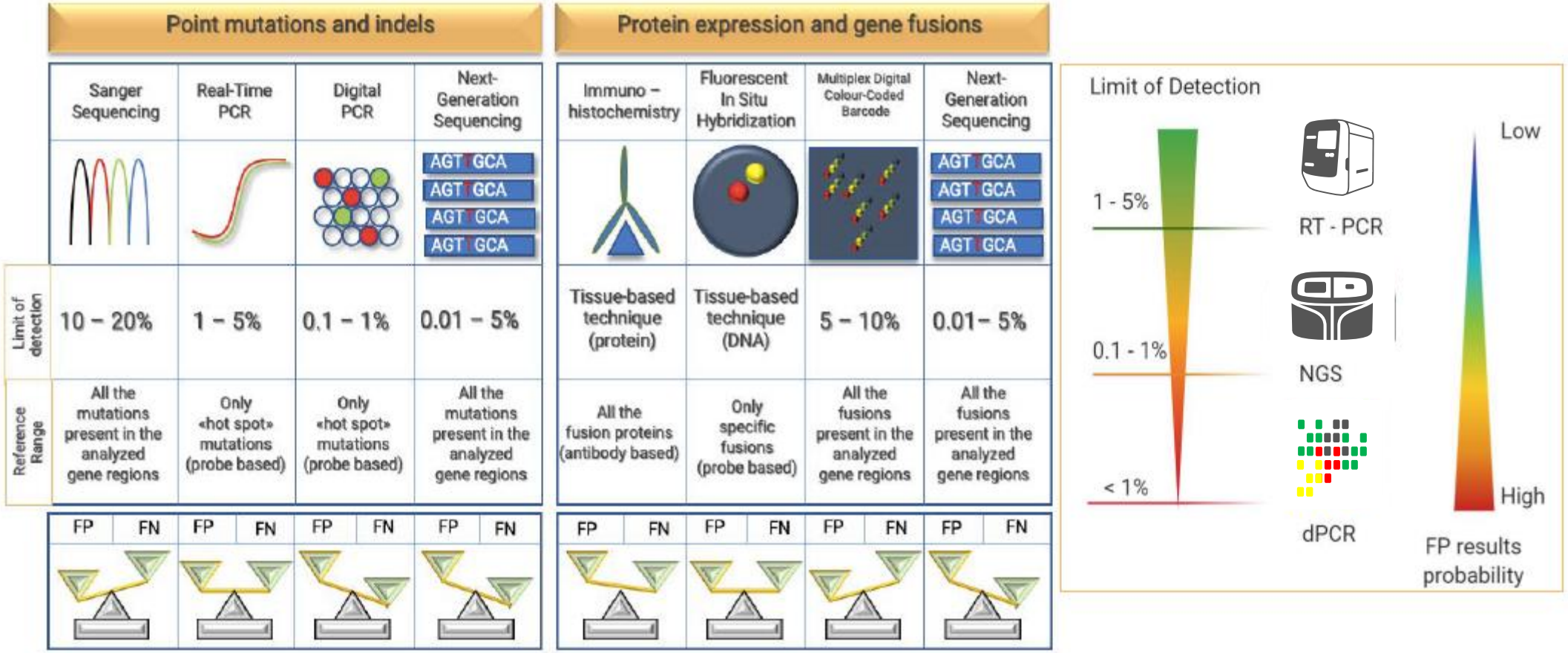
Discussion



Molecular Alterations[a]	Recommended Method of Detection	Role of IHC as a Surrogate Predictive Biomarker
EGFR mutations ("hot spot" mutations with ≥1% prevalence)	Any molecular method with ability to detect mutations in histology or cytology samples with ≥20% tumor cells within a turnaround time of 10 working days	Not appropriate for treatment selection
ALK rearrangements	Cytogenetic (FISH) or IHC[b]	Appropriate for treatment selection
ROS1 rearrangements	Molecular (RT-PCR or sequencing) or cytogenetic (FISH/ISH)	Appropriate for initial screening
BRAF (p.V600E and non-p.V600E mutations)	Molecular (sequencing with evaluation of at least exons 11 and 15)	Not defined as yet
MET alterations (exon 14 skipping mutations, amplification)	Molecular (RNA-based assay confirmatory); FISH is widely used for amplification but no specific cut-off validated	Not defined as yet
RET rearrangements	Molecular (sequencing preferable to targeted RT-PCR) or cytogenetic (FISH)	Not defined as yet
ERBB2/HER2 mutations	Molecular (sequencing, particularly for exon 20 alterations)	No role for IHC[c]
KRAS mutations[d]	Molecular (targeted analysis of hot spots in codons 12, 13, 61, and 146)	No role for IHC

	EGFR	ALK	ROS-1	BRAF	MET	PD-L1
 Excised during surgery	OK	OK	OK	OK	OK	OK
 Percutaneous Biopsy	OK	OK	OK	OK	OK	OK
 Bronchoscopic biopsy	OK	OK	OK	OK	OK	OK
 Cell-block	OK	OK	OK	OK	OK	OK if formalin fixed
 Cytology	OK	OK	OK	OK	OK	NO

Deepali J et al. ***Immunocytochemistry for Predictive Biomarker Testing in Lung Cancer Citology.*** Cancer Cytopahology 2019 May. – Lindeman NI et al. ***Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology.*** Journal of Thoracic Oncology 2018 Vol. 13;3: 323-358



dPCR; digital PCR; FN, false negative; FP, false positive; PCR, polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction.

Passiglia F, et al. J Thorac Oncol. 2019;14:2046-2052

EGFR

EGFR TKIs vs. CHEMOTHERAPY

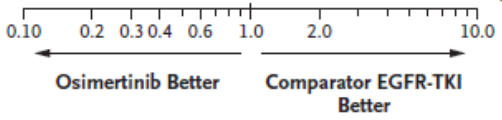
	Trial	EGFR TKI	Comparative therapy	N	EGFR mutaiton	ORR* (%)	PFS* (months)	OS* (months)
1st-Gen TKI	IPASS	Gefitinib	Car/Pac	1217	261	**71 vs 47** *P*<0.001	**9.5 vs 6.3** HR 0.48 (0.36-0.64)	**21.6 vs 21.9** HR 1.00 (0.76-1.33)
	NEJ002		Car/Pac	224	224	**74 vs 31** *P*<0.001	**10.8 vs 5.4** HR 0.32 (0.24-0.44)	**27.7 vs 26.6** HR 0.89 (0.63-1.24)
	WJTOG 3405		Cis/Doc	172	172	**62 vs 32** *P*<0.0001	**9.2 vs 6.3** HR 0.0.5 (0.34-0.71)	**36 vs 39** HR 1.19 (0.77-1.83)
	EURTAC	Erlotinib	Cis/Doc or Cis/Gem	173	173	**58 vs 15** *P*-value NR	**9.7 vs 5.2** HR 0.37 (0.25-0.54)	**22.9 vs 19.6** HR 0.92 (0.63-1.35)
	OPTIMAL		Gem/Car	165	154	**83 vs 36** *P*<0.0001	**13.1 vs 4.6** HR 0.16 (0.10-0.26)	**22.8 vs 27.2** HR 1.19 (0.83-1.71)
	ENSURE		Gem/Cis	217	216	**63 vs 34** *P*=0.0001	**11.0 vs 5.6** HR 0.42 (0.27-0.66)	**26.3 vs 25.5** HR 0.91 (0.61-1.31)
2nd-Gen TKI	LUX-Lung 3	Afatinib	Pem/Cis	345	308	**69 vs 44** *P*=0.001	**13.6 vs 6.9** HR 0.41 (0.31-0.56)	**31.6 vs 28.2** HR 0.78 (0.58-1.06)
	LUX-Lung 6		Gem/Cis	364	324	**74 vs 31** *P*<0.0001	**13.7 vs 5.6** HR 0.26 (0.19-0.36)	**23.6 vs 23.5** HR 0.83 (0.62-1.09)
	LUX-Lung 7		Gefitinib	319	319	**70 vs 56** *P*=0.0083	**11.0 vs 10.9** HR 0.73 (0.57-0.95	**27..9 vs 24.5** HR 0.86 (0.66-1.12)
	ARCHER 1050	Dacomatinib	Gefitinib	452	452	**75 vs 72** *P*=0.423	**14.7 vs 9.2** HR 0.59 (0.47-0.74)	**34.1 vs 26.8** HR 0.76 (0.58-0.99)
3rd-Gen TKI	FLAURA	Osimertinib	Gefitinib or Erlotinib	556	500	**80 vs 76** *P*=0.24	**18.9 vs 10.2** HR 0.46 (0.37-0.57)	**NC vs NC** HR 0.63 (0.45-0.88)

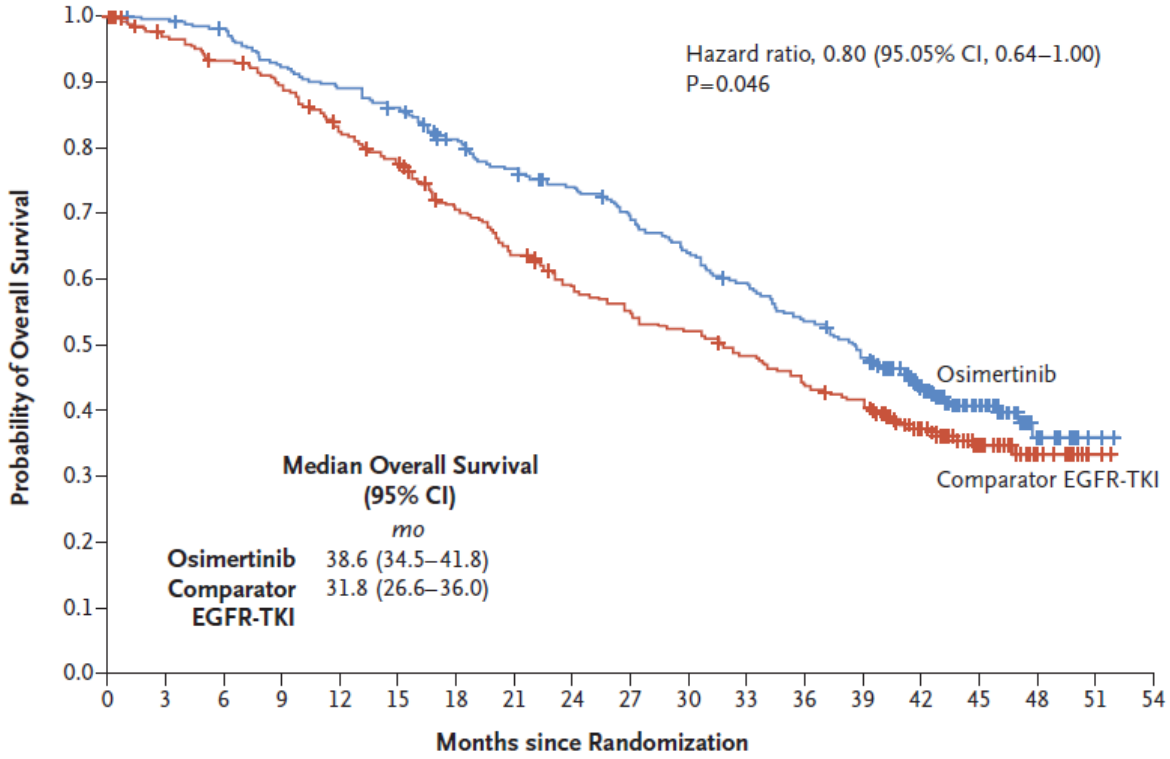
N Engl J Med. 2009;361:947-57; J Clin Oncol. 2011;29:2866-74; N Engl J Med. 2010;362:2380-98; Lancet Oncol. 2010;11:121-8; J Clin Oncol. 2014;32(suppl):abstract 8117; Lancet Oncol. 2012;13:239-46; ESMO 2014. Abstract 1273P; Lancet Oncol. 2011;12:735-42; J Clin Oncol. 2012;30(suppl):abstract 7520; Ann Oncol. 2015;26:1883-9; J Clin Oncol. 2013;31:3327-34; Lancet Oncol. 2014;15:213-22; Lancet Oncol 2015;16:141-51; Lancet Oncol. 2016;17(5):577-89; Ann Oncol 2017;28(2):270-7; Lancet Oncol. 2017;18(11):1454-66; J Clin Oncol. 2018;36(22):2244-50; N Engl J Med. 2018;378(2):113-25.

EGFR - FLAURA

OSIMERTINIB

Subgroup	No. of Patients	Hazard Ratio (95% CI)
Overall	556	0.79 (0.63–0.98)
Sex		
Male	206	0.79 (0.55–1.14)
Female	350	0.79 (0.60–1.04)
Age		
<65 yr	298	0.72 (0.54–0.97)
≥65 yr	258	0.87 (0.63–1.22)
Race		
Asian	347	1.00 (0.75–1.32)
Non-Asian	209	0.54 (0.38–0.77)
Smoking history		
Yes	199	0.70 (0.49–1.00)
No	357	0.85 (0.64–1.12)
CNS metastases at trial entry		
Yes	116	0.83 (0.53–1.30)
No	440	0.79 (0.61–1.01)
WHO performance status		
0	228	0.93 (0.63–1.37)
1	327	0.70 (0.54–0.91)
EGFR mutation at randomization		
Exon 19 deletion	349	0.68 (0.51–0.90)
L858R	207	1.00 (0.71–1.40)
EGFR mutation detected by DNA in blood		
Positive	359	0.77 (0.60–0.99)
Negative	124	0.72 (0.37–1.36)
Centrally confirmed *EGFR* mutation		
Positive	500	0.75 (0.60–0.95)
Negative	6	NC (NC–NC)





No. at Risk

Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

ADAURA Phase III double-blind study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
- ≥18 years (Japan / Taiwan: ≥20)
- WHO performance status 0 / 1
- Confirmed primary non-squamous NSCLC Ex19del / L858R‡
- Brain imaging, if not completed pre-operatively
- Complete resection with negative margins§
- Max. interval between surgery and randomization:
  - 10 weeks without adjuvant chemotherapy
  - 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Randomization 1:1 (N=682)

- Osimertinib 80 mg, once daily
- Placebo, once daily

Planned treatment duration: 3 years

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

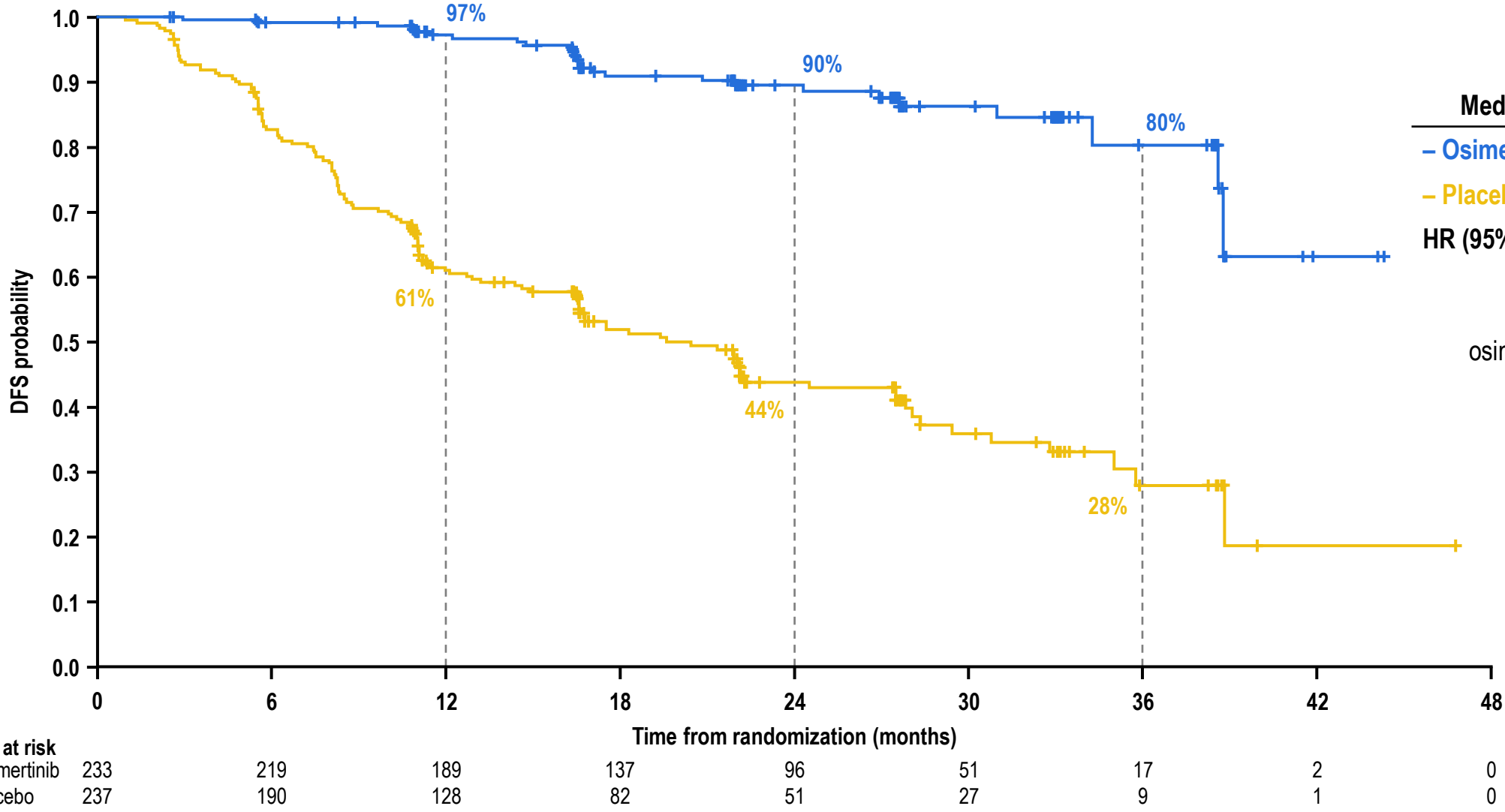
Follow up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Endpoints

- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

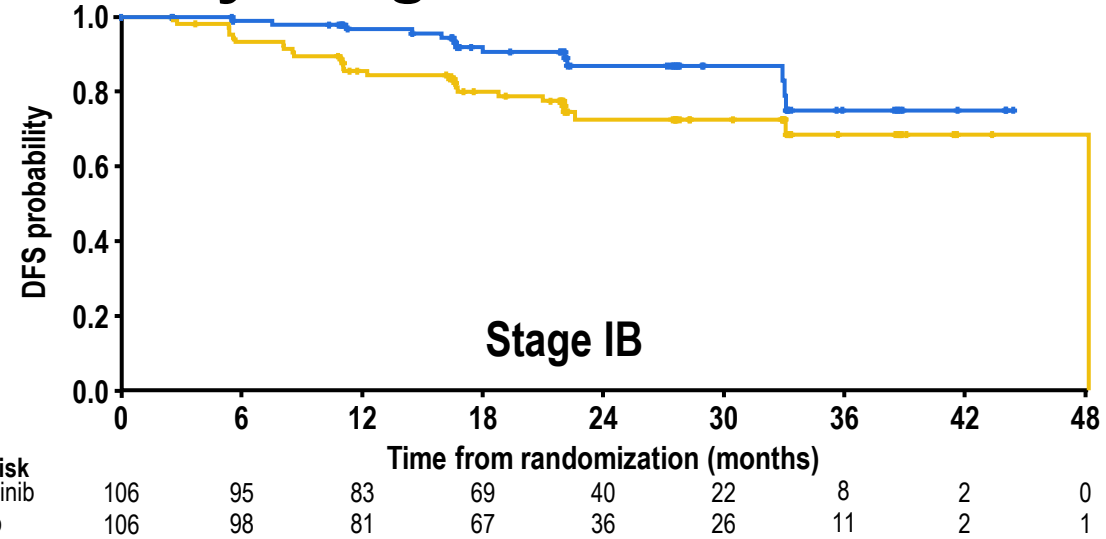
Primary endpoint: DFS in patients with stage II/IIIA disease



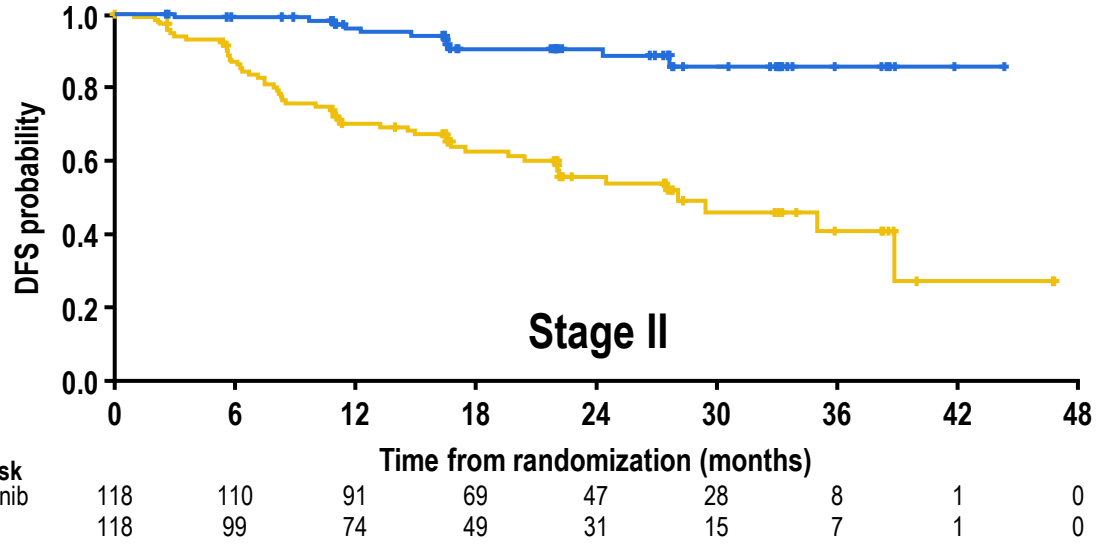
Median DFS, months (95% CI)	
– Osimertinib	NR (38.8, NC)
– Placebo	20.4 (16.6, 24.5)
HR (95% CI)	**0.17 (0.12, 0.23); p<0.0001**

Maturity 33%:
osimertinib 11%, placebo 55%

DFS by stage

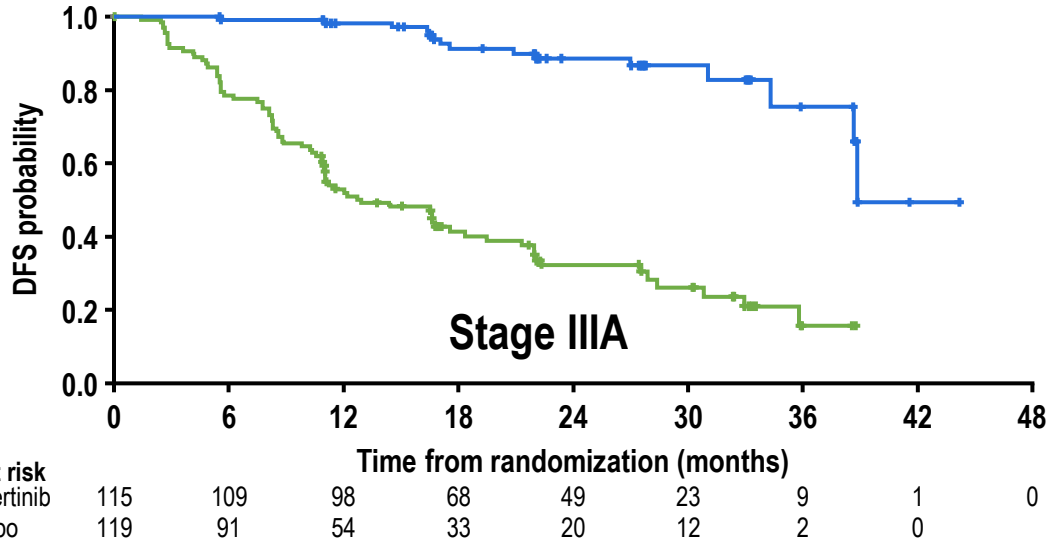


No. at risk									
Osimertinib	106	95	83	69	40	22	8	2	0
Placebo	106	98	81	67	36	26	11	2	1



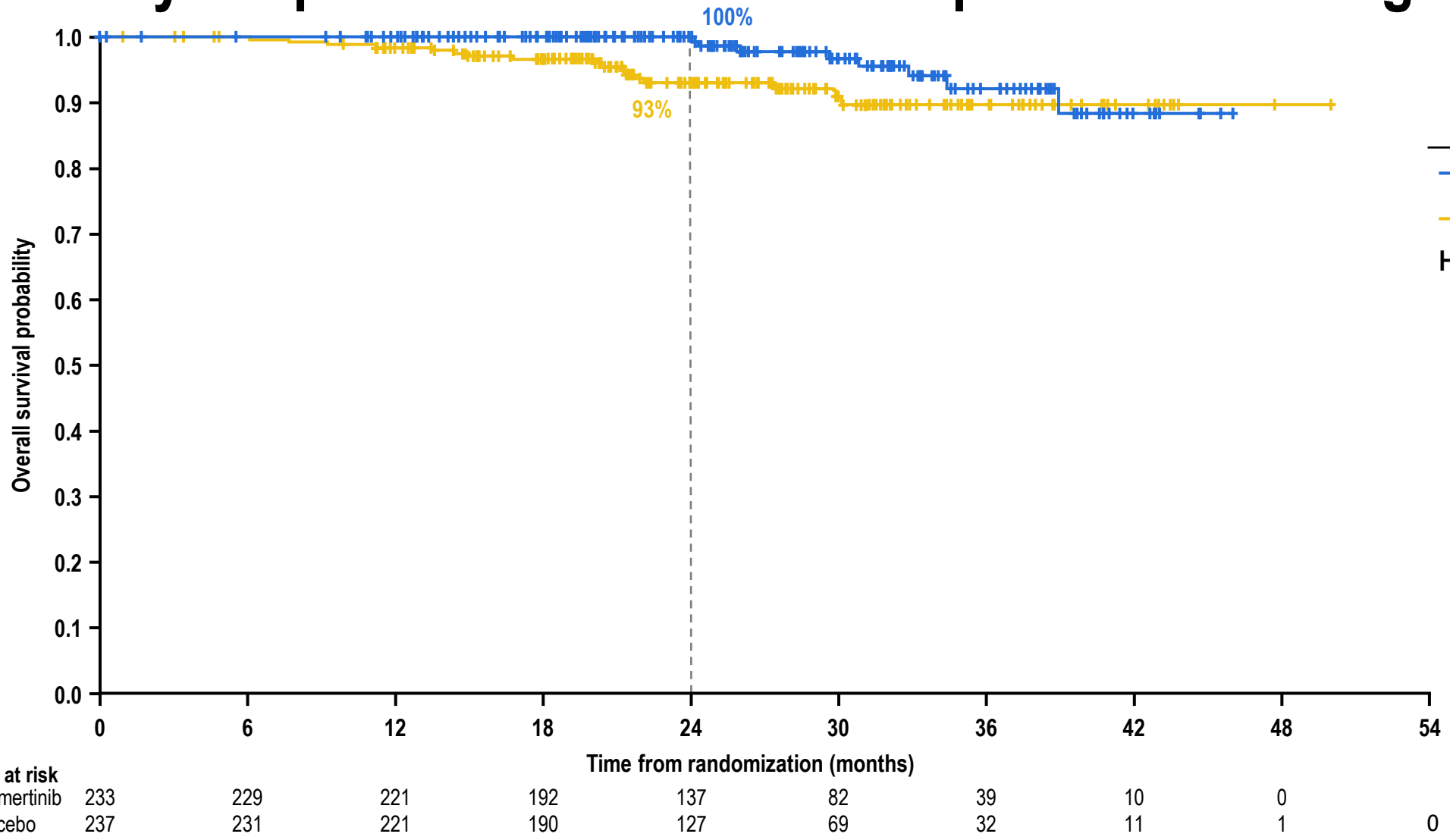
No. at risk									
Osimertinib	118	110	91	69	47	28	8	1	0
Placebo	118	99	74	49	31	15	7	1	0

	Stage IB	Stage II	Stage IIIA
2 year DFS rate, % (95% CI)			
– Osimertinib	87 (77, 93)	91 (82, 95)	88 (79, 94)
– Placebo	73 (62, 81)	56 (45, 65)	32 (23, 42)
Overall HR (95% CI)	**0.50 (0.25, 0.96)**	**0.17 (0.08, 0.31)**	**0.12 (0.07, 0.20)**



No. at risk									
Osimertinib	115	109	98	68	49	23	9	1	0
Placebo	119	91	54	33	20	12	2	0	

Early snapshot: overall survival in patients with stage II/IIIA disease

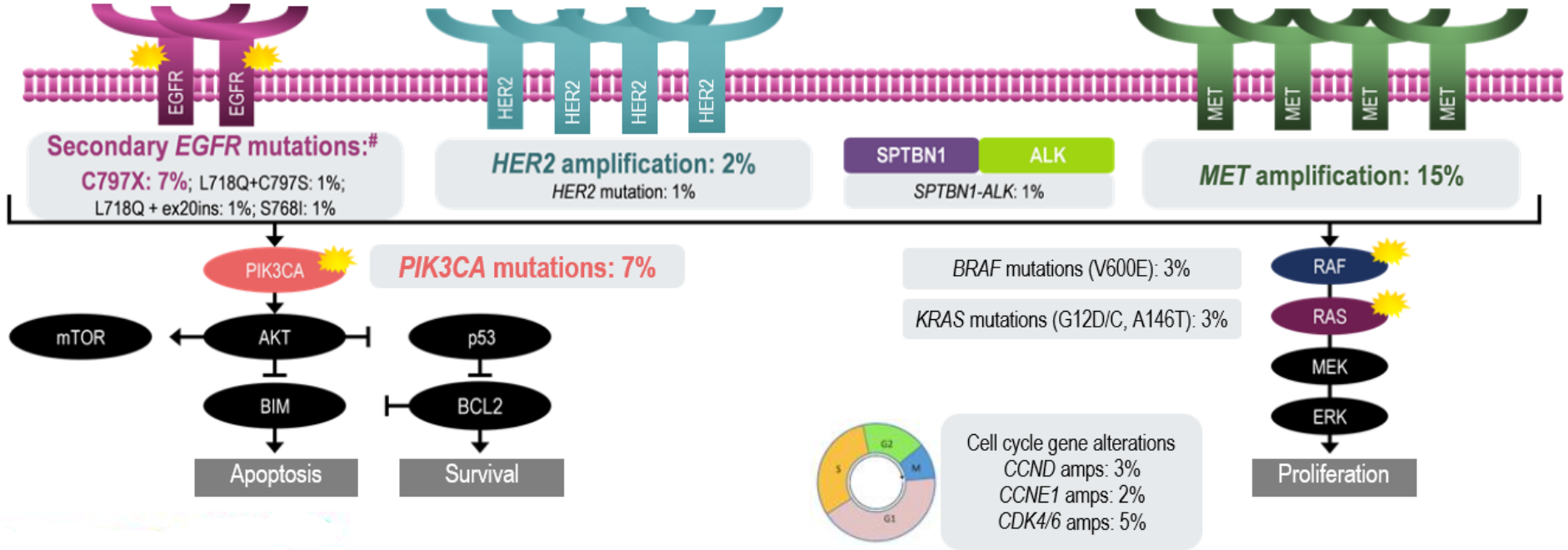


Median OS, months (95% CI)	
– Osimertinib	NR (NC, NC)
– Placebo	NR (NC, NC)
HR (95% CI)	**0.40 (0.18, 0.90)**

Maturity 5%:
osimertinib 3%, placebo 7%

CANDIDATE ACQUIRED ALTERATIONS WITH OSIMERTINIB

- No evidence of acquired EGFR T790M
- The most common resistance mechanisms were *MET* amplification and EGFR C797S mutation
  - Other mechanisms included *HER2* amplification, *PIK3CA* and *RAS* mutations



*Resistance mechanism reported may overlap with another; #Two patients had *de novo* T790M mutations at baseline of whom one acquired C797S at progression

Ramalingam SS, ESMO 2018

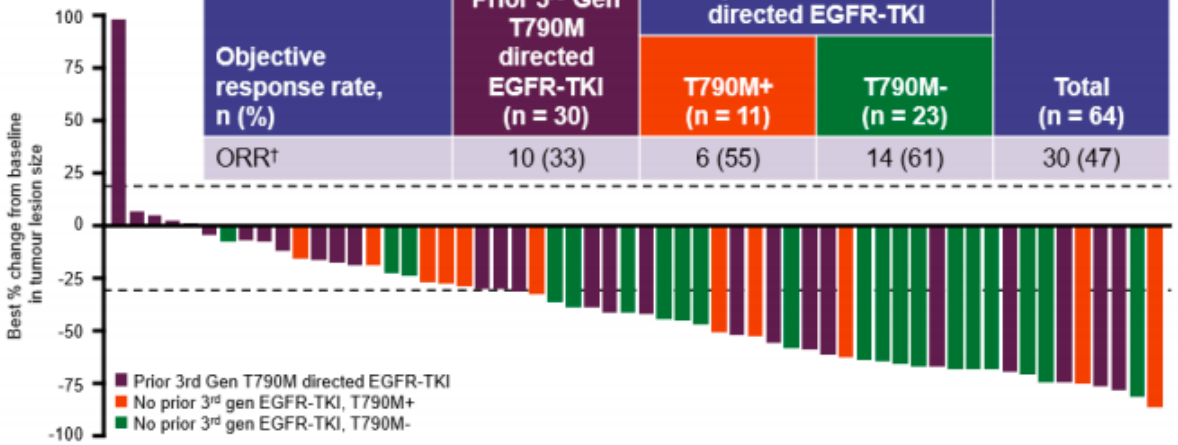
RESISTANCE TO OSIMERTINIB

Combination of TKIs

TATTON: savolitinib + osimertinib expansion cohort preliminary antitumour activity

Exhibit 1: Preliminary anti-tumour activity of the combination of savolitinib and Tagrisso in patients with centrally and locally confirmed MET-positive NSCLC

Objective response rate, n (%)	Prior 3rd Gen T790M directed EGFR-TKI (n = 30)	No prior 3rd Gen T790M directed EGFR-TKI		Total (n = 64)
		T790M+ (n = 11)	T790M- (n = 23)	
ORR†	10 (33)	6 (55)	14 (61)	30 (47)

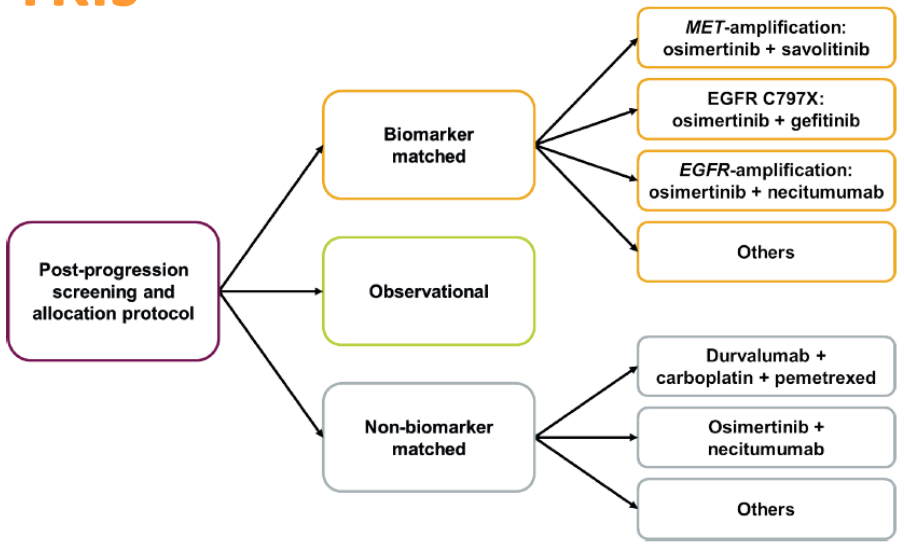


Waterfall plot based on evaluable patients (n = 64): all patients dosed and with on-treatment assessment or discontinuation prior to first tumour assessment
Data cut-off 31 Aug 2017
*17 patients did not have central FISH confirmation of MET-positive status (n = 6 MET-negative; n = 11 unknown by central lab); †Confirmed by a later scan performed at least 4 weeks after initial response observed

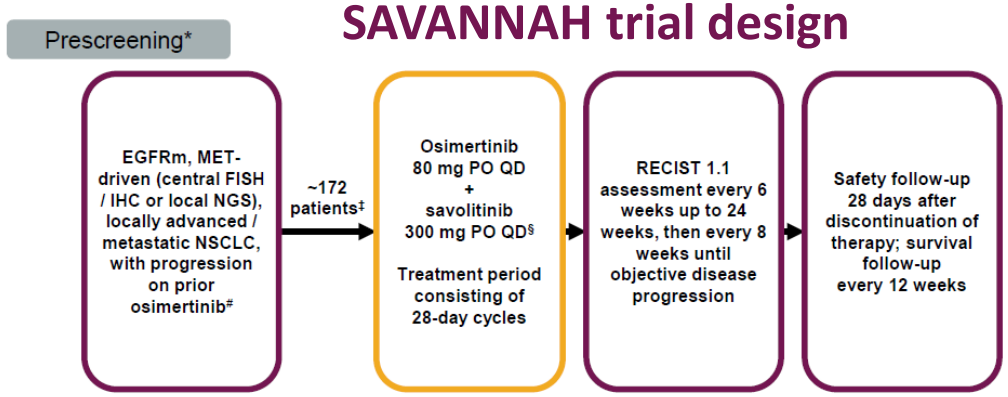
TATTON Part E
NCT02143466

Source: Ahn M-J, et al. TATTON Phase Ib Expansion Cohort: Osimertinib Plus Savolitinib for Patients with EGFR-mutant MET-amplified NSCLC After Progression on Prior EGFR-TKI. Abstract #8985. Presented at the World Lung Cancer Congress 2017, Yokohama, Japan, 15-18 October 2017.

ORCHARD trial design



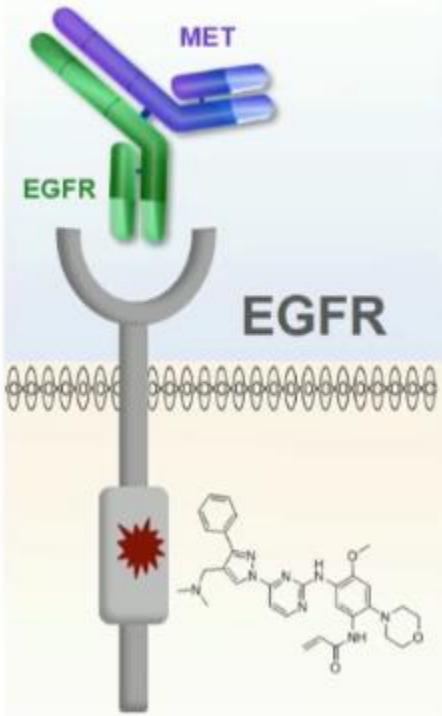
SAVANNAH trial design



SAVANNAH or ORCHARD based on pre-existing local NGS results, but must provide tissue samples for retrospective central *MET* FISH / MET IHC
NAH, or additional biomarker analyses if enrolled into ORCHARD
FISH, fluorescence *in situ* hybridisation; IHC, immunohistochemistry; MET, hepatocyte growth factor receptor; NGS, next-generation sequencing

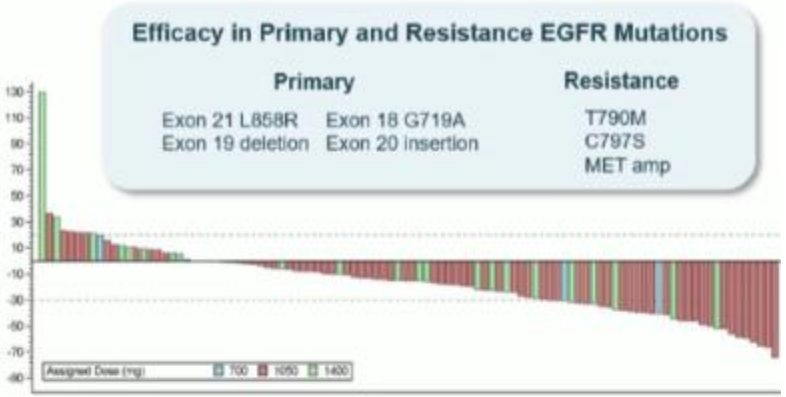
ClinicalTrials.gov identifier NCT03778229; NCT03944772

AMIVANTAMAB + LAZERTINIB



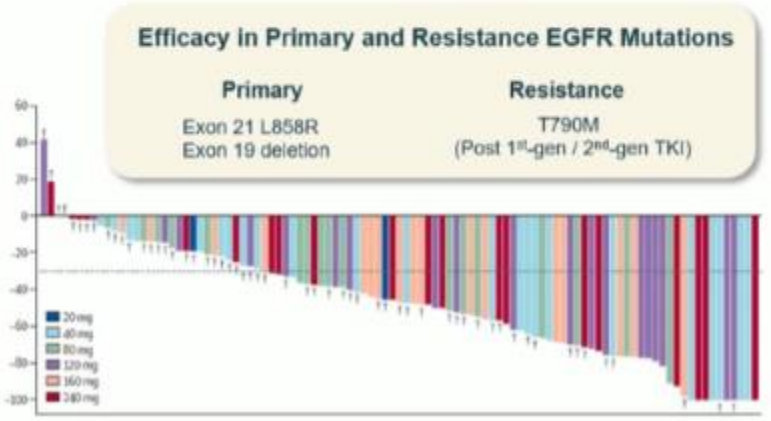
Amivantamab
(am-e-van-tuh-mab)

- Fully human bispecific (Duobody®) antibody that targets EGFR and MET
- Has immune cell-directing activity[1]
- Demonstrated clinical activity across diverse EGFRm NSCLC[2]
- Granted FDA Breakthrough Therapy Designation for EGFRm Exon20ins NSCLC post-chemotherapy

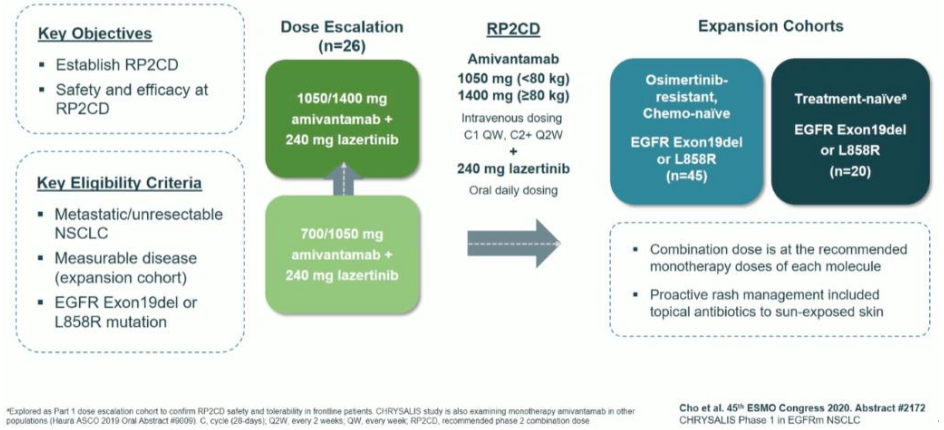


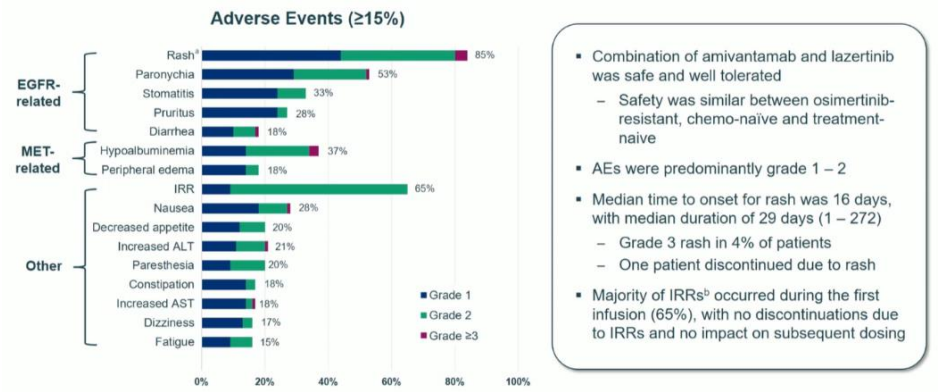
Lazertinib

- Potent 3rd-gen TKI with efficacy seen in activating EGFR mutations, T790M, and CNS disease[3-4]
- Low rates of EGFR-related toxicity such as rash and diarrhea[3]
- Safety profile that supports combination with other anti-EGFR molecules

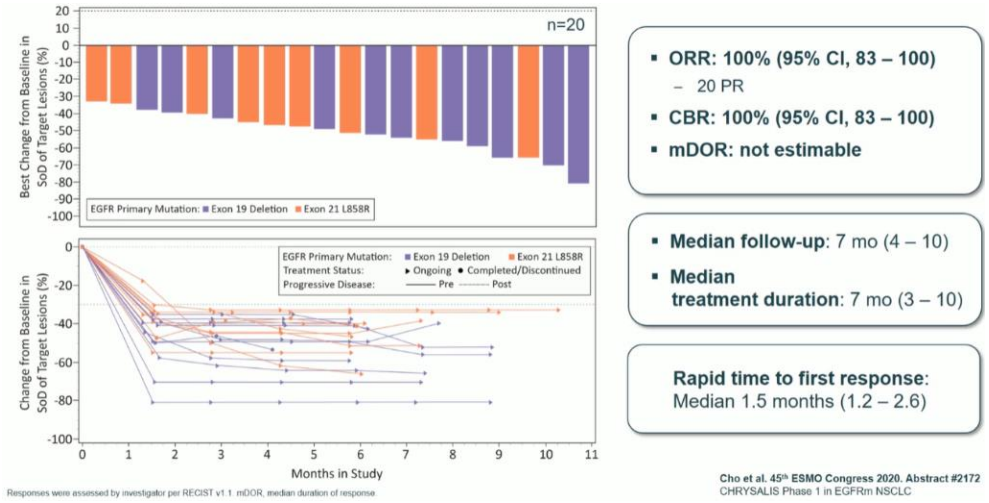


CHRYSALIS TRIAL: AMIVANTAMAB +LAZERTINIB

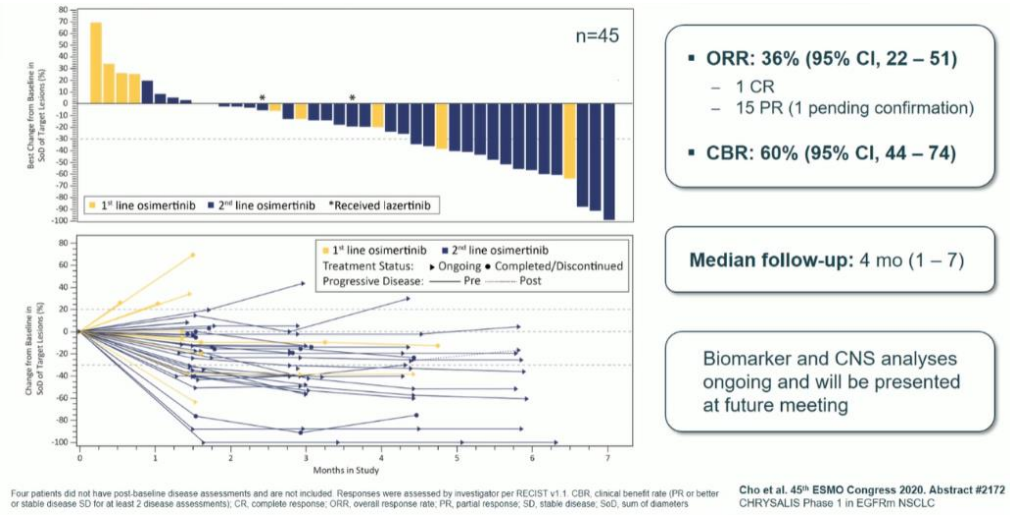




Treatment naïve



Osimertinib resistant

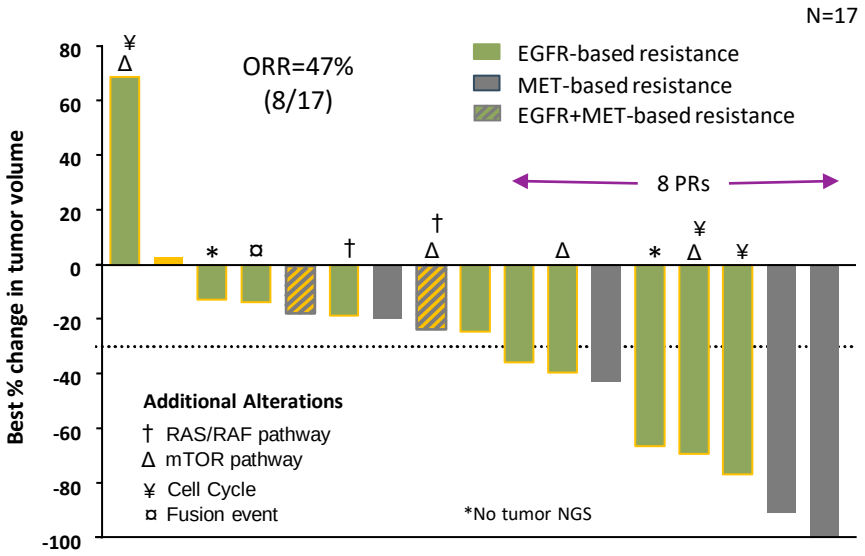


Cho BC, ESMO 2020

CHRYSALIS: Responders Among Patients with and without Identified EGFR/MET-based Resistance

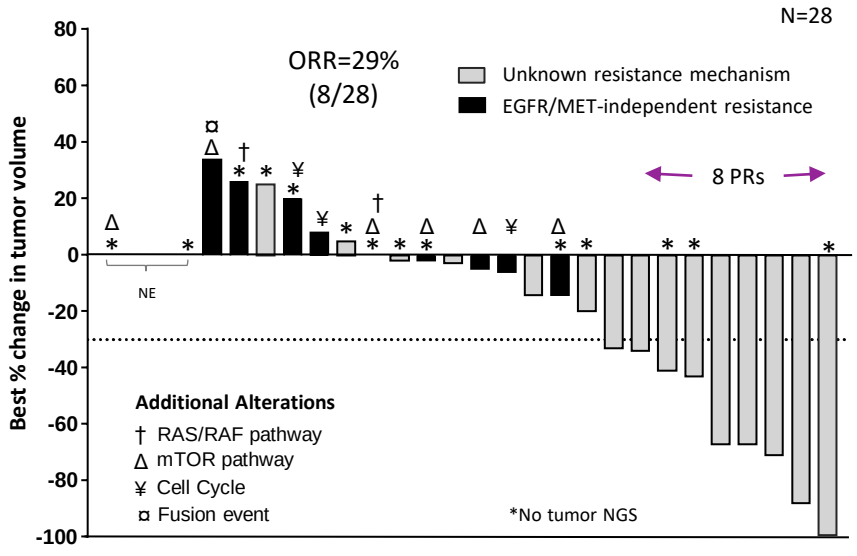
Bauml et al ASCO 2021

With Identified EGFR/MET-based Resistance



Resistance[b]	Alterations[c]	
EGFR-based	C797S (n=7) Amp (n=3) L718X (n=3) G724S (n=2)	L792H (n=1) G796S (n=1) E709K (n=1)
MET-based	Amp (n=5)	METex14 (n=1)

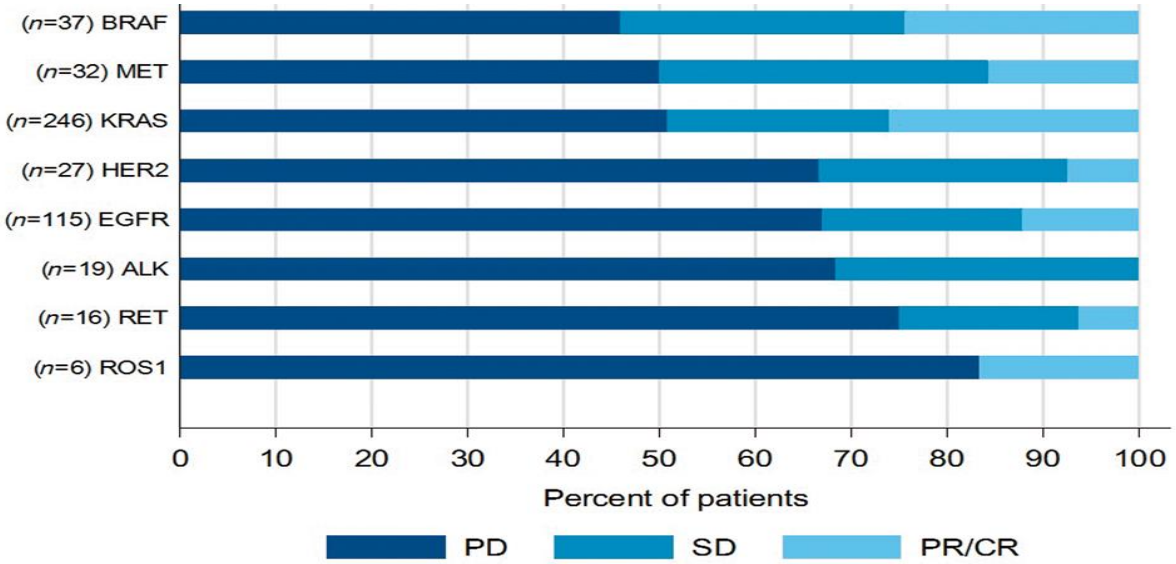
Without Identified EGFR/MET-based Resistance



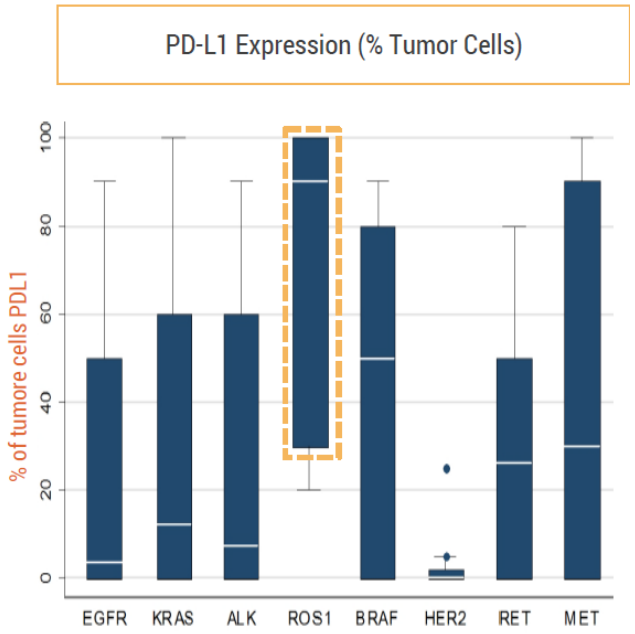
Resistance[b]	Alterations[c]	
Additional	PIK3CA E542X (n=2) CCNE1 Amp (n=1) PIK3CA Amp (n=1) CCND1 Amp (n=1) CDK4 (n=1)	KRAS Amp (n=1) FGFR3-TACC3 fusion (n=1) KRAS G12D (n=1) CDKN2A G101W (n=1)

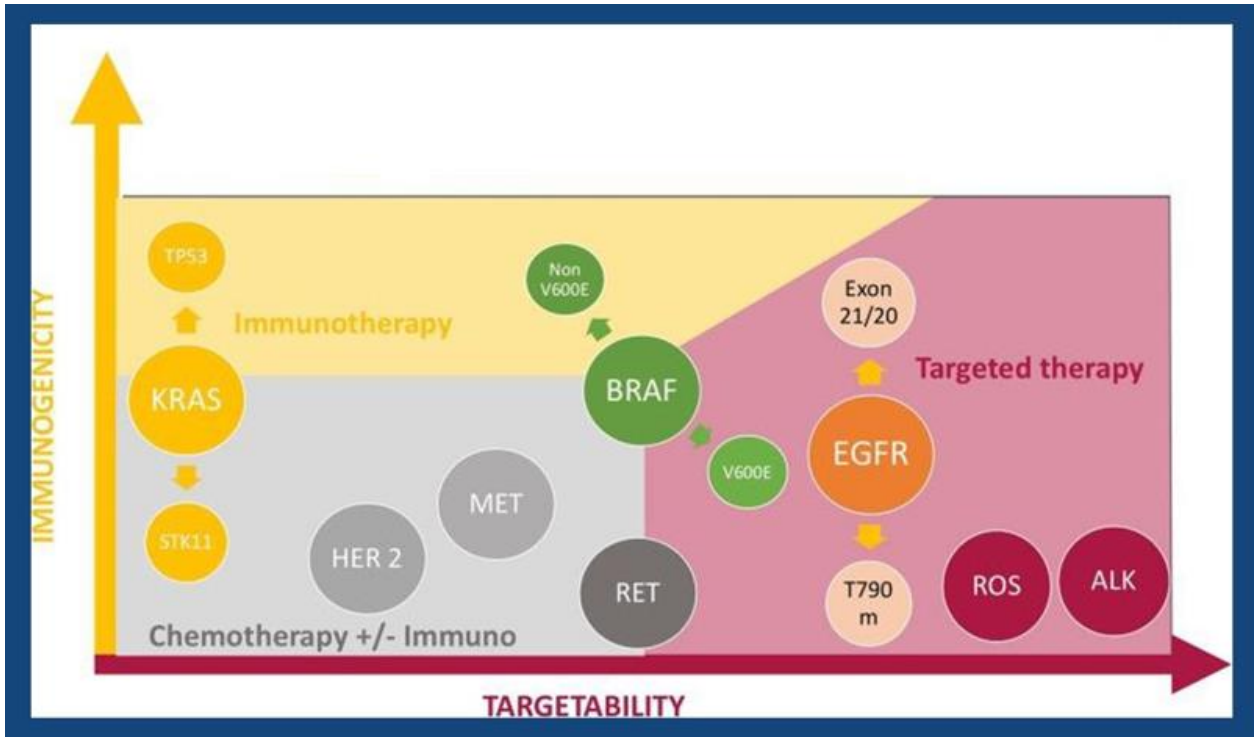
OTHER TARGETS

DRIVER MOLECOLARE	FARMACO	FASE DI TRIAL	DISPONIBILITÀ IN ITALIA
EGFR	Osimertinib	III	Rimborso AIFA (IV stadio); Expanded access program (adiuvante)
	Afatinib	III	Rimborso AIFA
	Gefitinib	III	Rimborso AIFA
EGFR (esone 20)	Mobocertinib	I/II	Expanded Access Program
ALK	Alectinib	III	Rimborso AIFA
	Brigatinib	III	Rimborso AIFA
	Lorlatinib	I/II	Rimborso AIFA
	Crizotinib	III	Rimborso AIFA
	Ceritinib	III	Rimborso AIFA
ROS1	Crizotinib	I	Rimborso AIFA
BRAF	Dabrafenib-trametinib	II	Rimborso AIFA
KRAS (G12C)	Sotorasib	II	Expanded Access Program
MET	Capmatinib	II	Expanded Access Program
	Tepotinib	II	Expanded Access Program
RET	Selpercatinib	I/II	CNN
	Pralsetinib	I/II	Expanded Access Program
NTRK	Entrectinib	I/II	Rimborso AIFA
	Larotrectinib	I/II	Rimborso AIFA



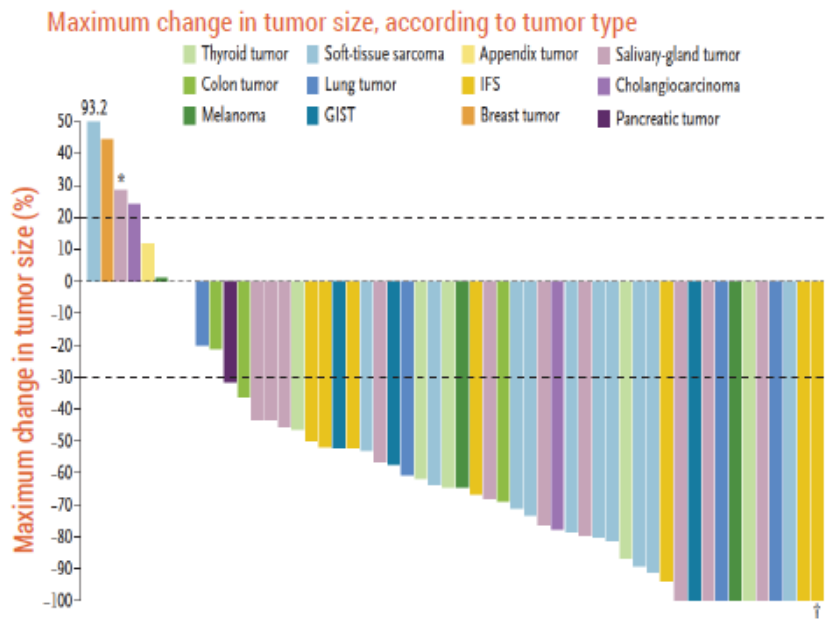
Mazieres et al. Annals Oncol e-pub May, 2019



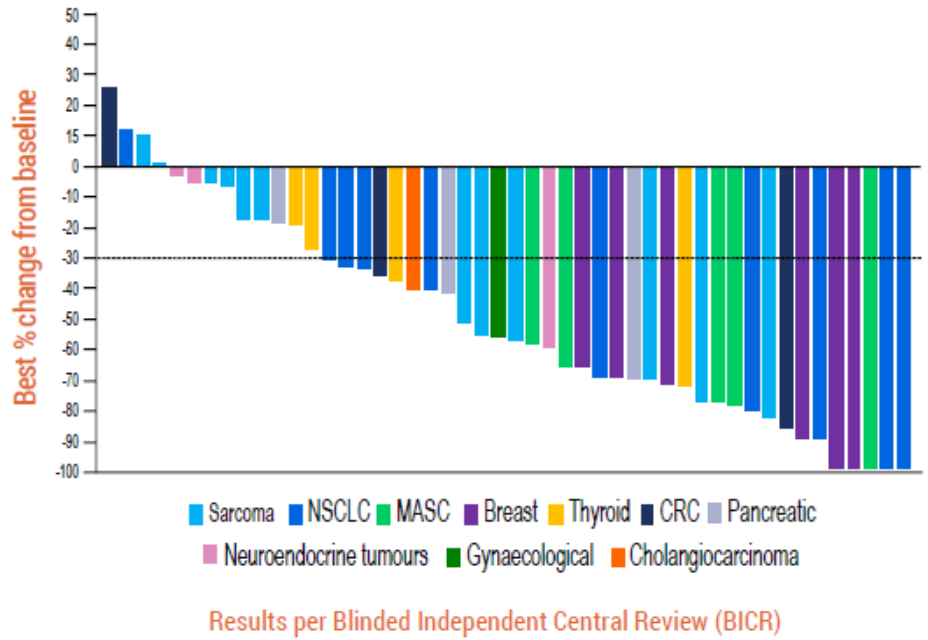


Clinical data demonstrated tumor activity regardless of tumor type for NTRK fusions

Larotrectinib in 12 tumor types[1]



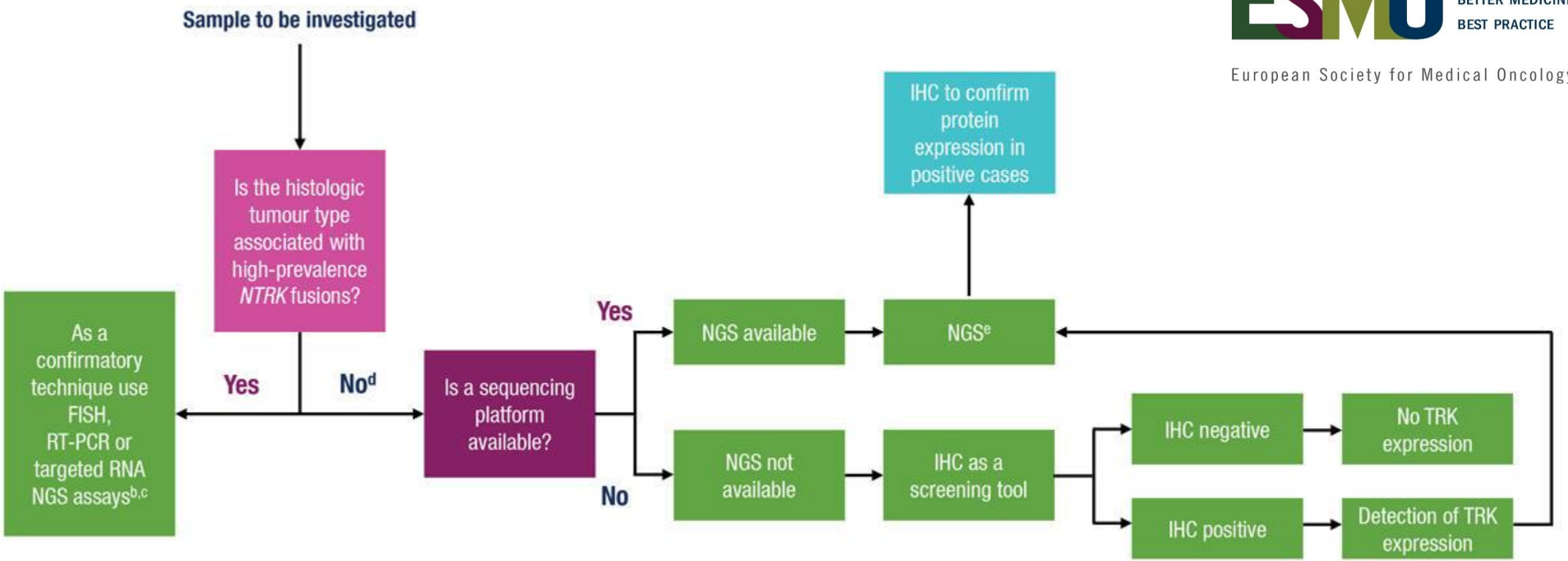
Entrectinib in 10 tumor types[2]



No clear evidence yet that a certain tumor type is refractory to TRK inhibitors

[1]Drilon A, et al. N Engl J Med. 2018;378:731-739

[2]Demetri G, et al. ESMO. 2018;Abstr5033



References

1. Mateo J, Chakravarty D, Dienstmann R et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol 2018; 29: 1895-1902.
2. Albert CM, Davis JL, Federman N et al. TRK Fusion Cancers in Children: A Clinical Review and Recommendations for Screening. J Clin Oncol 2019; 37: 513-524.
3. Marchio C, Scaltriti M, Ladanyi M et al. ESMO recommendations on the standard methods to detect NTRK fusions in daily practice and clinical research. Ann Oncol. 2019 Jul 3. pii: mdz204. doi: 10.1093/annonc/mdz204. [Epub ahead of print].

PRACTICAL IMPLICATIONS OF MULTI-GENIC TESTING

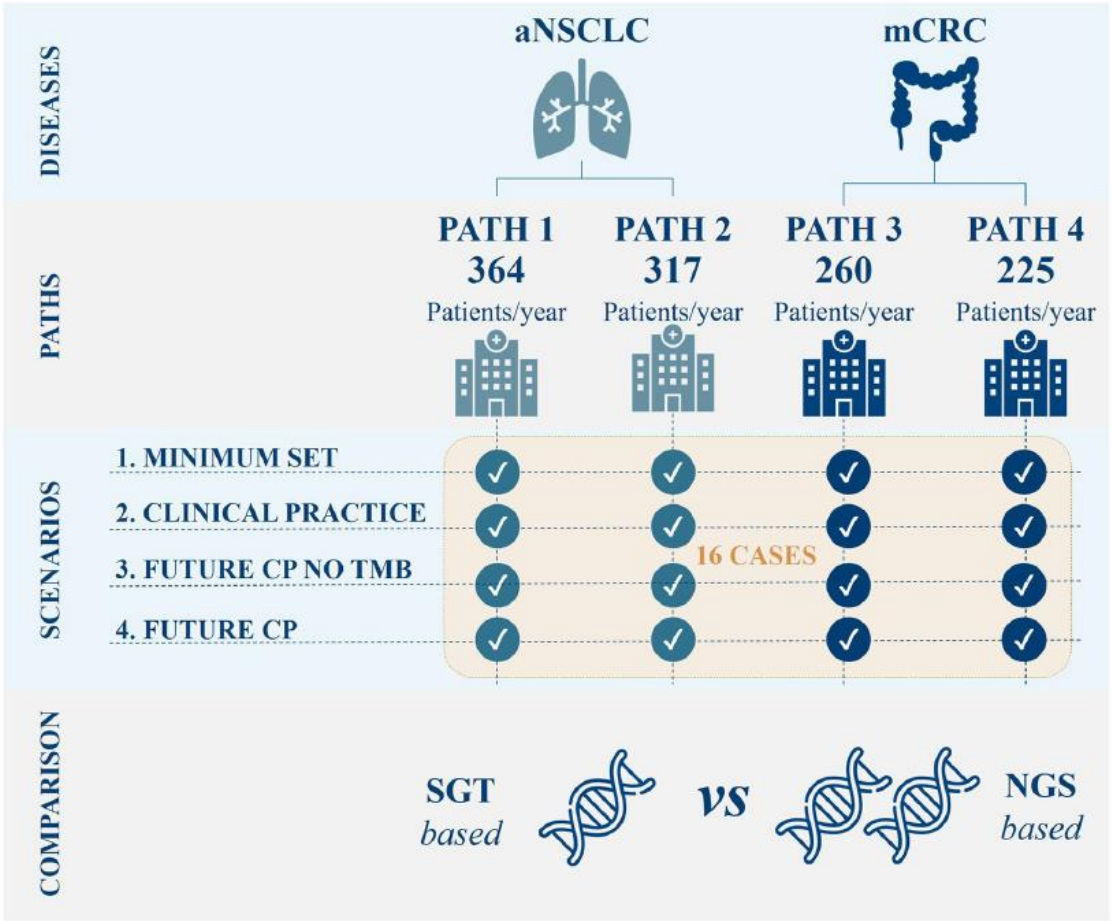
Next-Generation Sequencing in Clinical Practice: Is It a Cost-Saving Alternative to a Single-Gene Testing Approach?

PharmacoEconomics - Open
https://doi.org/10.1007/s41669-020-00249-0

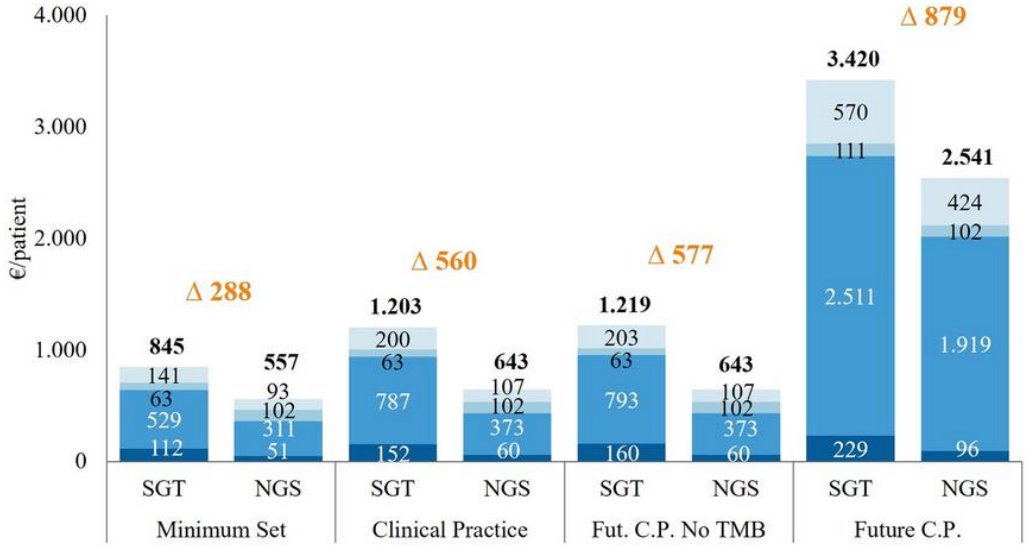
Giancarlo Pruneri[1,2] · Filippo De Braud[3,4] · Anna Sapino[5,6] · Massimo Aglietta[7,8] · Andrea Vecchione[9] · Raffaele Giusti[10] · Caterina Marchiò[5,6] · Stefania Scarpino[9] · Anna Baggi[11] · Giuseppe Bonetti[11] · Jean Marie Franzini[11] · Marco Volpe[11] · Claudio Jommi[12]

Original Research Article | Open Access | Published: 04 March 2021

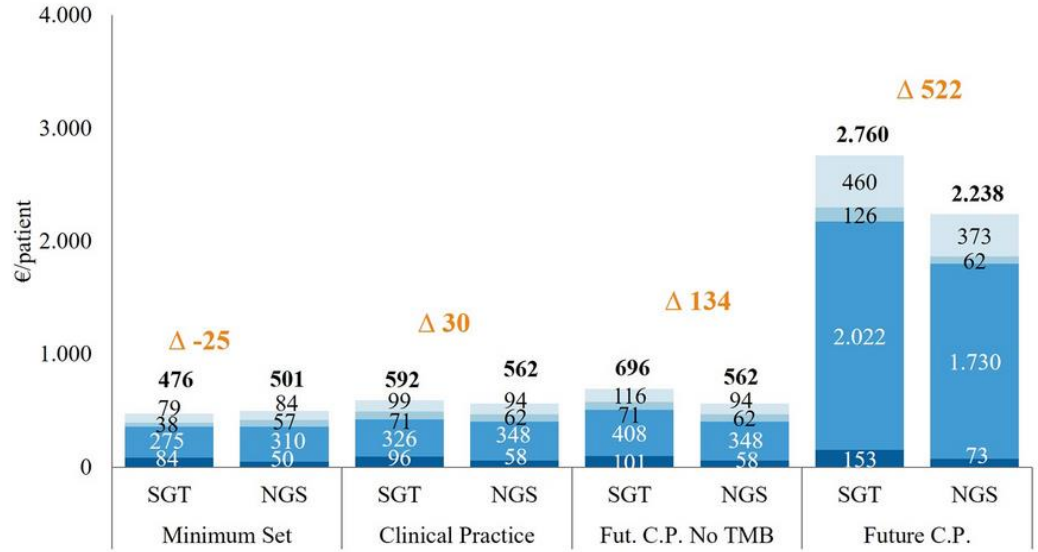
aNSCLC	EGFR, KRAS, BRAF, MET, ALK, ROS1, RET, HER2, MSI, TMB
mCRC	KRAS, NRAS, BRAF, MGMT, MLH1, MSH2,PMS2, MSI, RET, EGFR, HER2, NTRK1-3, FGFR2, TMB



Path 1 - aNSCLC

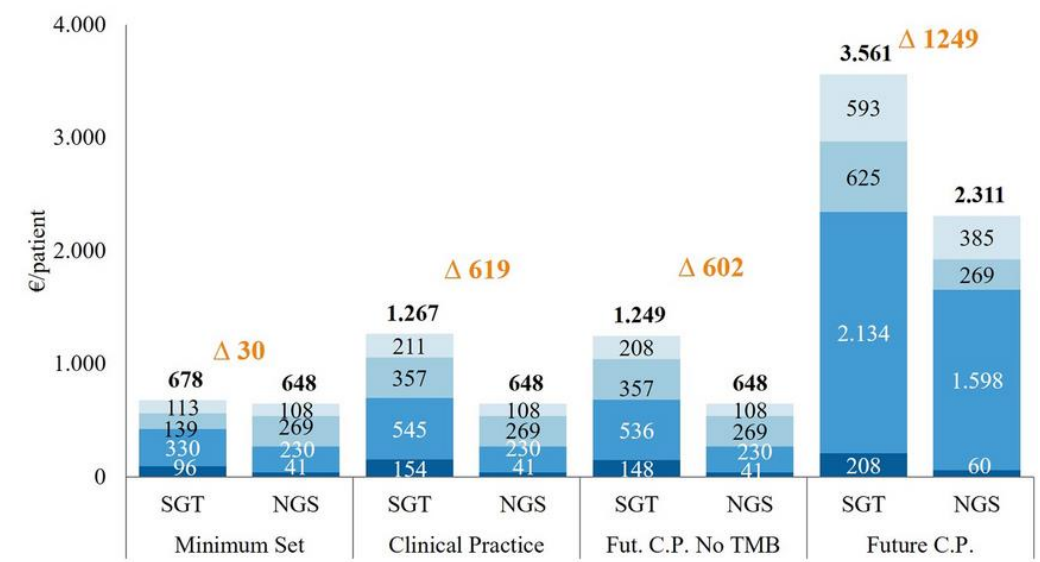


Path 2 - aNSCLC

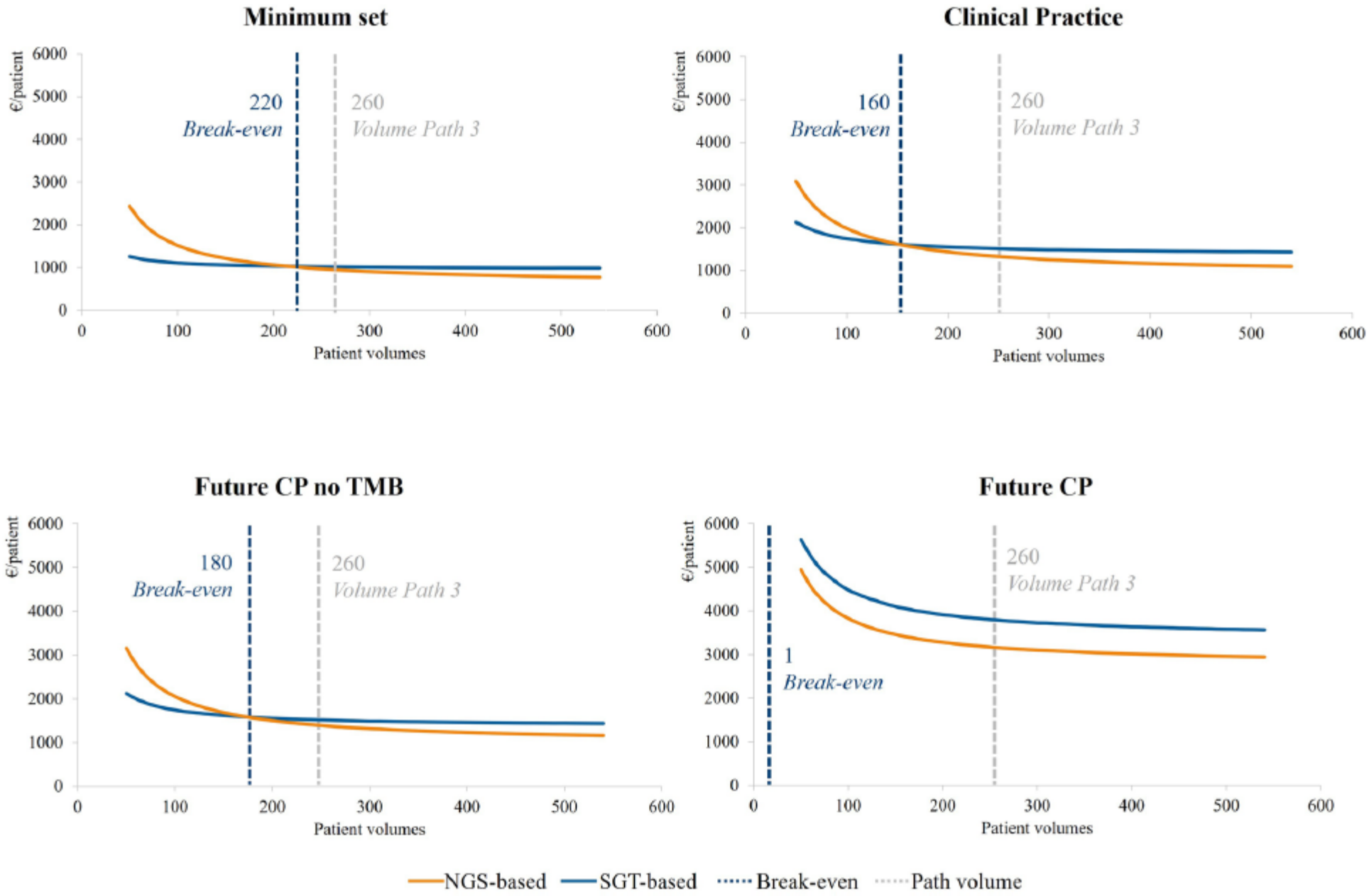


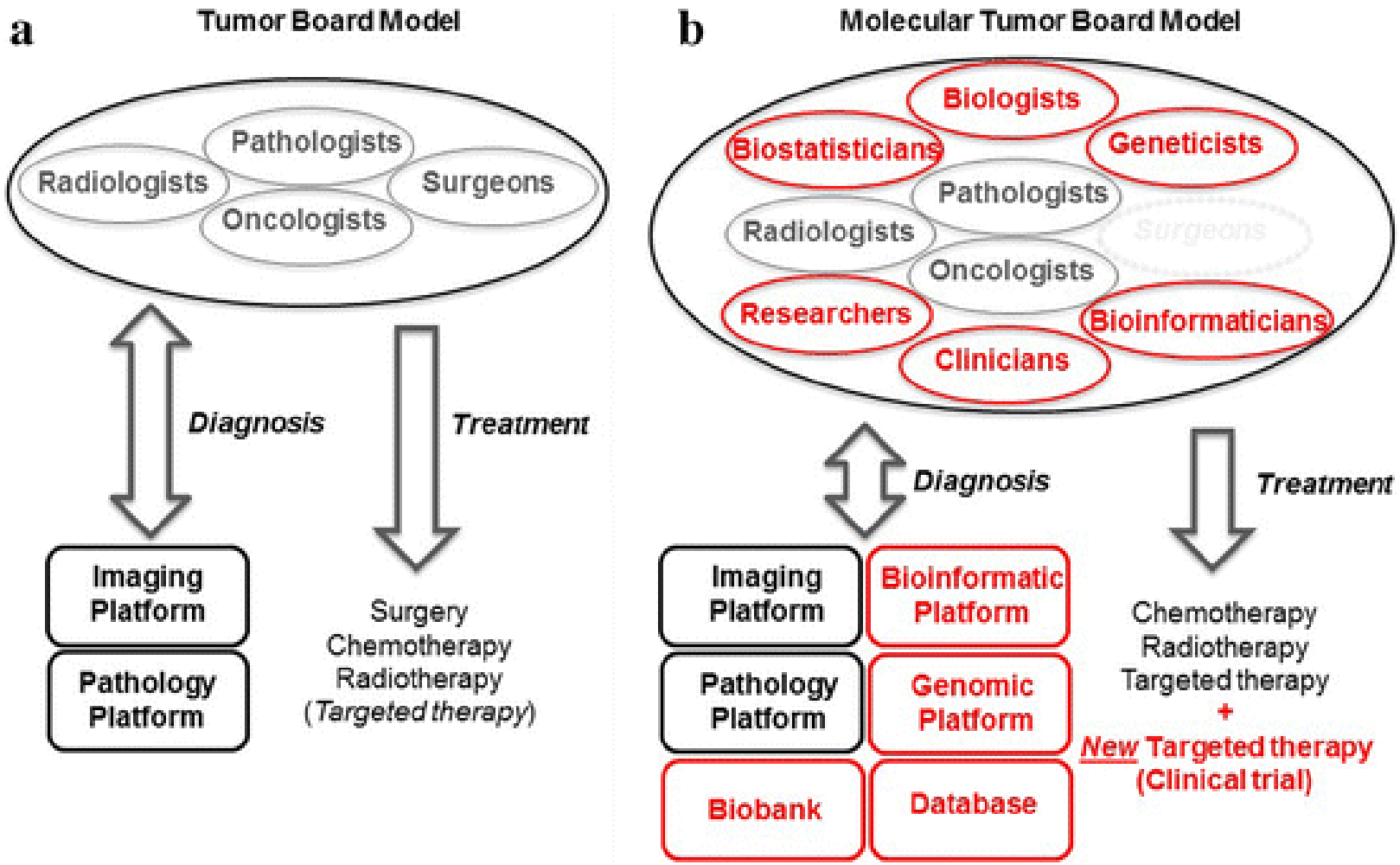
Path 3 - mCRC

Path 4 - mCRC



Personnel Consumables Equipment Overheads Δ Savings


Minimum set
€/patient
6000
5000
4000
3000
2000
1000
0
220
Break-even
260
Volume Path 3
0
100
200
300
400
500
600
Patient volumes
Clinical Practice
€/patient
160
Break-even
260
Volume Path 3
Patient volumes
Future CP no TMB
€/patient
180
Break-even
260
Volume Path 3
Patient volumes
Future CP
€/patient
1
Break-even
260
Volume Path 3
Patient volumes
NGS-based
SGT-based
Break-even
Path volume



Stoeklé, HC., Mamzer-Bruneel, MF., Frouart, CH. et al. Sci Eng Ethics (2018) 24: 307.

DEEP MOLECULAR CHARACTERIZATION OF NEVER SMOKER NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS

C. Dellepiane[1], G. De Luca[2], M. Tagliamento[3], S. Coco[1], G. Rossi[4], M.G. Dal Bello[1], M. Mora[5], L. Zullo[1], A. Alama[1], A. Bottini[1], G. Sacco[1], E. Cella[1], E. Bennicelli[1], R. Borea[1], V. Murianni[1], F. Parisi[1], S. Salvi[2], P. Pronzato[1], M. Dono[2], C. Genova[3,6],

1 U.O. Oncologia Medica 2, IRCCS Ospedale Policlinico San Martino, Genova, Italy, 2 UOS Diagnostica Molecolare, IRCCS Ospedale Policlinico San Martino, Genova, Italy, 3 Dipartimento di Medicina Interna e Specialità Mediche, Università degli Studi di Genova, Genova, Italy, 4 Dipartimento di Oncologia Medica, Ospedale Padre Antero Micone, Genova, Italy, 5 UOC Anatomia Patologica, IRCCS Ospedale Policlinico San Martino, Genova, Italy; 6 U.O.Clinica di Oncologia Medica IRCCS Ospedale Policlinico San Martino Genova Italy.

Poster 1276P

BACKGROUND

Patients (pts) with advanced NSCLC are eligible for treatments with immune checkpoint inhibitors (ICIs) as single agent or in combination with chemotherapy (ICI-CT), unless their tumor harbors actionable oncogenic drivers, which are more commonly observed in never-smokers.

Next generation sequencing (NGS) is being increasingly employed in clinical practice in place of traditional molecular techniques, such as Real Time PCR (RT-PCR), mass spectrometry (MS) and immunohistochemistry/fluorescence in situ hybridization (IHC/FISH), as offers high throughput and comprehensive testing and ensures optimal levels of sensitivity and specificity

AIMS

A more comprehensive molecular characterization of never smoker NSCLC pts, wild type for main standard of care biomarkers (EGFR, KRAS, BRAF and ALK) in tissue genotyping, was carried out in order to investigate low frequency alterations and/or variants present in other driver genes.

METHODS

276 patients diagnosed with stage IV NSCLC received ICIs between 2015 and 2020 in our department

Routine assessment for EGFR, KRAS, BRAF aberrations was tested by RT-PCR/MS and ALK rearrangements by IHC/FISH

A targeted amplicon based NGS panel of 52 genes has been used for tissue genotyping for detection of missense mutations, indels, copy number variations and gene fusions from DNA or RNA was performed on 16/276 never smoker NSCLC pts.

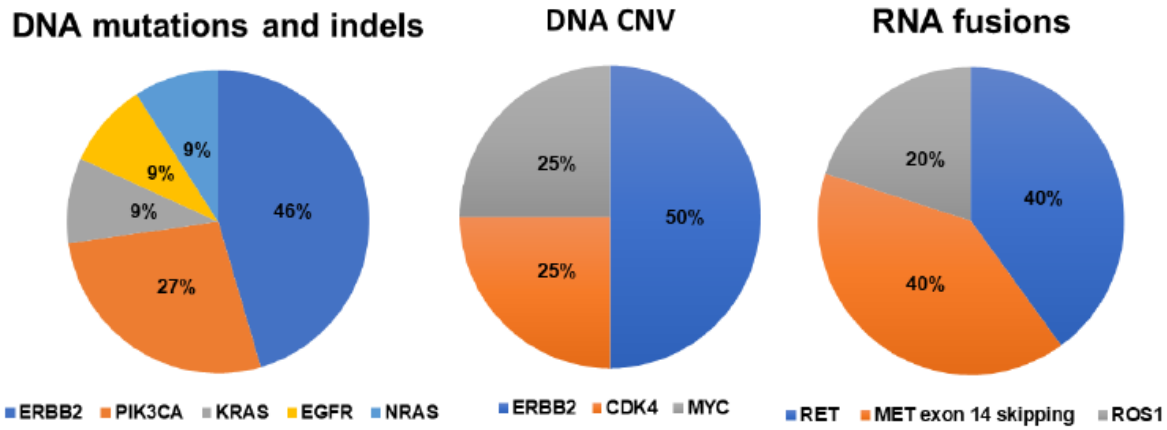
RESULTS

Clinical characteristics of n= 16 never smokers NSCLC patients	
Median Age	71.5 years (range 44-80)
Sex	Male: 5 Pts Famale: 11 Pts
Istotype	Squamous: 2 Pts Non-squamous: 14 Pts
Therapy received	ICI-CT First line: 6 Pts Single-agent ICI 1stline:2 Pts Single-agent ICI subsequent lines:8 Pts
Best Reponse to ICIs	Partial Responce: 5 Pts Stable Disease: 4 Pts Progressive Disease: 5 Pts Early Death: 2 Pts

All 16 patients were addressed to tissue NGS genotyping. 2 Pts samples were not suitable for analysis

DNA samples were successfully analyzed, otherwise RNA sequencing failed for 3/16 pts. A pt with RNA failed but available peripheral blood resulted positive for *ROS1* rearrangement.

NGS identified genetic alterations in 13/16 pts, including missense mutations, indels, copy number variations and gene fusions. Driver genes and corresponding mutations are shown in Figure 1.



CONCLUSIONS

Next generation sequencing should be implemented upfront in current NSCLC management, especially in specific patients subgroups more likely to harbor actionable oncogenic drivers, such as never smokers, with potential impact on therapeutic approaches.

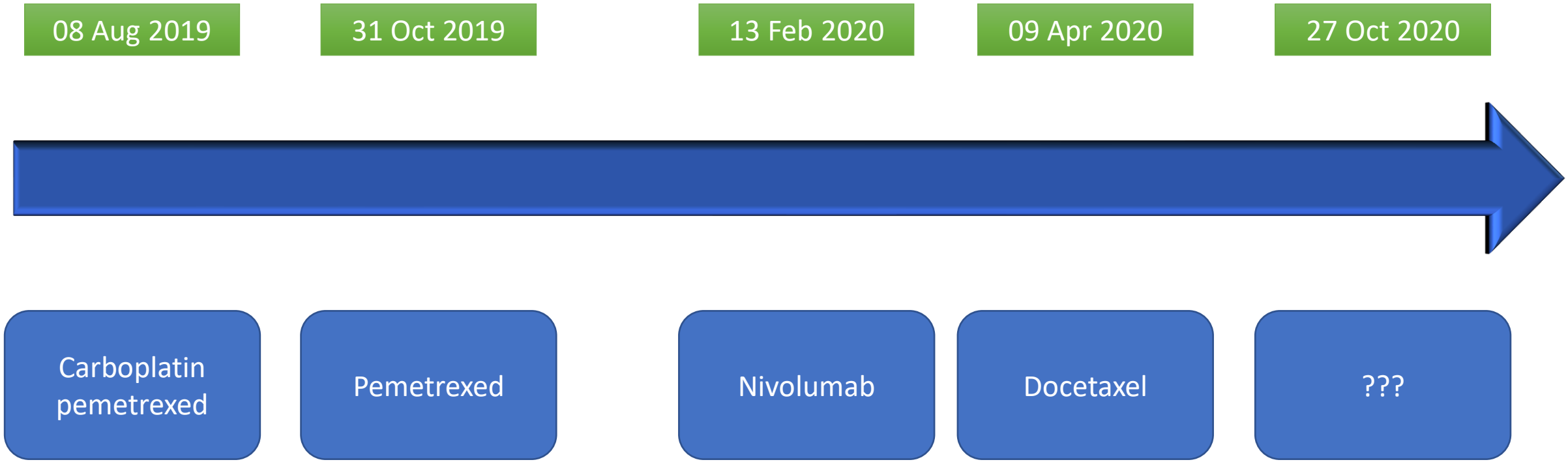
Currently, validation through an independent, customized, DNA-based NGS platform is ongoing on our study population. The results will be included in the full, finalized work.

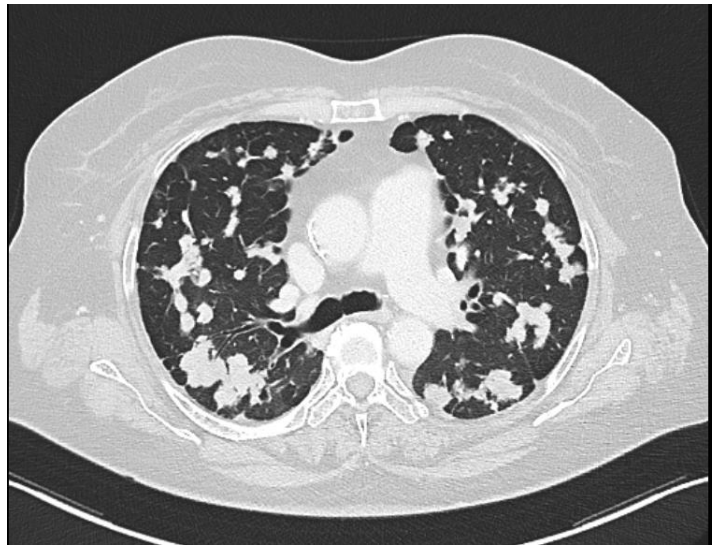
First Author (Chiara Dellepiane)'s conflicts of interest: honoraria from Astra Zeneca, BMS, Roche, MSD, Pfizer, Novartis.

Contacts: carlo.genova@hsanmartino.it chiara.dellepiane@hsanmartino.it

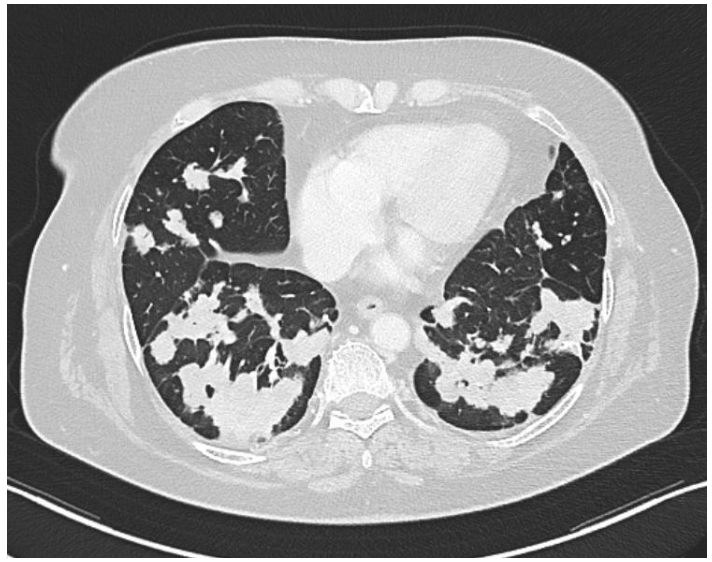
Acknowledgements, *Study sponsored by:*

Mass spectrometry	IHC	FISH
EGFR, K-RAS, BRAF	PD-L1, ALK	ROS-1
All wild type	PD-L1 10-20% ALK negative	Negative



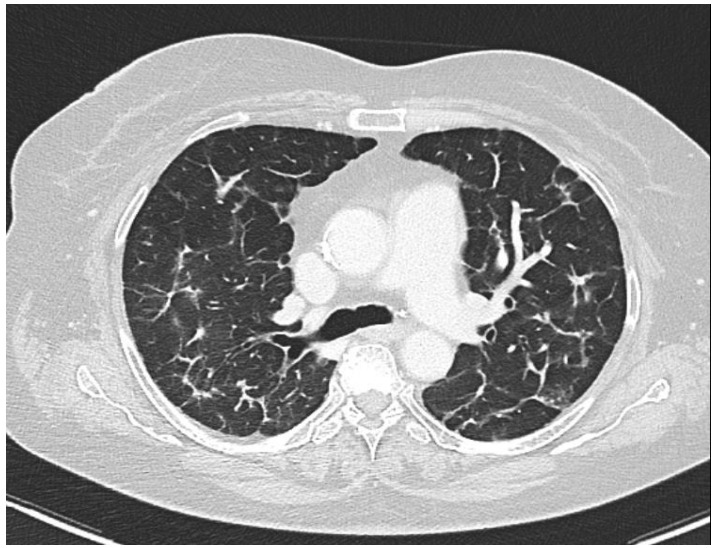


27 Oct 2020

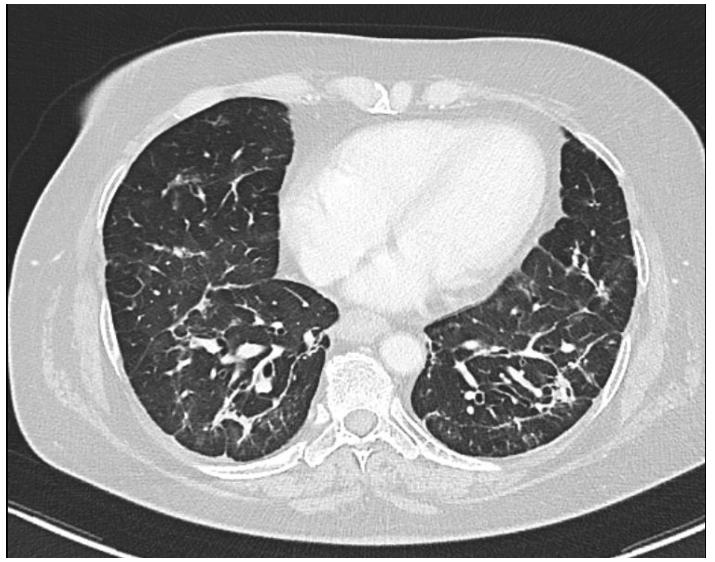


ROS1

CRIZOTINIB



07 Jan 2021




08 Aug 2019
31 Oct 2019
13 Feb 2020
09 Apr 2020
27 Oct 2020
11 Nov 2021
Carboplatin pemetrexed
Pemetrexed
Nivolumab
Docetaxel
Crizotinib
ONGOING

Take home messages

Tailored therapy based on pathological/molecular features (lack of «clinical» predictors)

Increasing need of multi-genic, tumor-specific panels

Strategies for improving testing governance and optimize clinical interpretation of molecular tests

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

UNIVERSITÀ DEGLI STUDI
DI GENOVA

THANK YOU FOR YOUR ATTENTION!

Carlo.genova@hsanmartino.it