Treatment of Driver Alterations other than EGFR

SEMINAR

30 SEP 2023

Dr. Sandeep Sharma

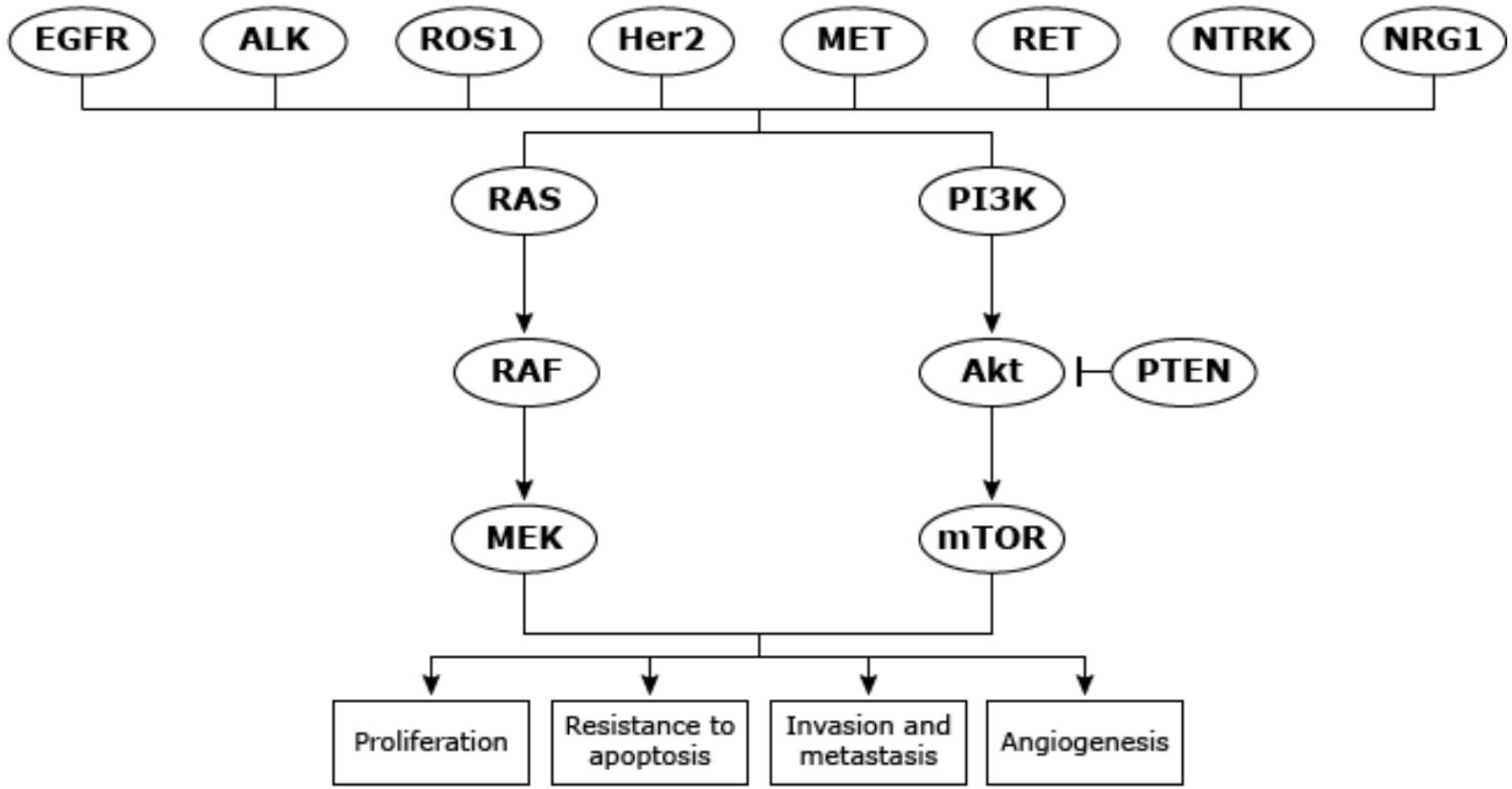
Oncogenic driver alterations

- Oncogenic driver alterations refer to mutations that are responsible for both the initiation and maintenance of the cancer
- Driver alterations lead to gain of function of oncogenes or loss of function of tumor suppressor genes
- These alterations are often found in genes that encode for signaling proteins that are critical for maintaining normal cellular proliferation and survival
- Some lung cancers harbor specific somatic alterations that are essential for malignant growth

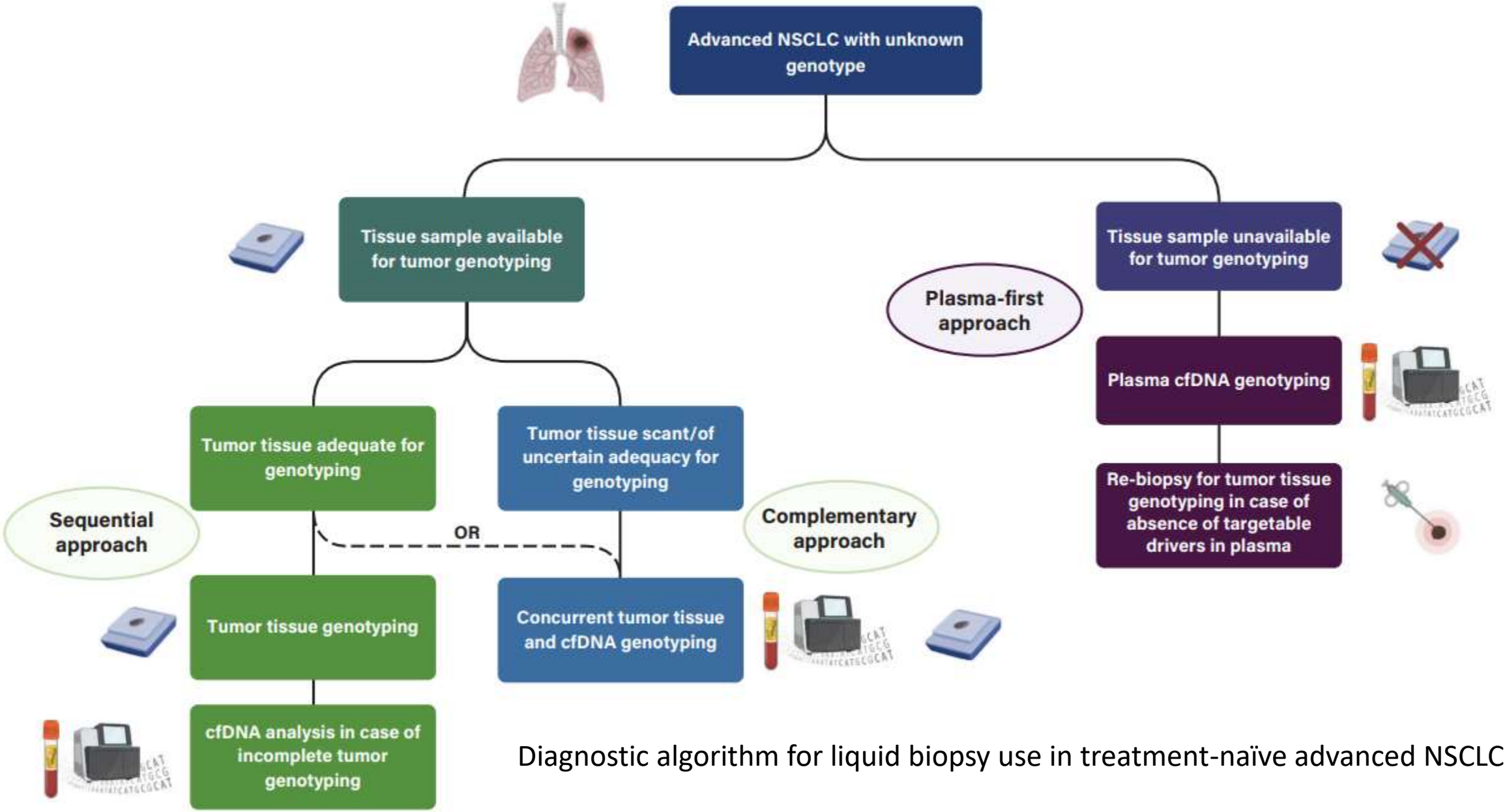
Table 1. Recurrent Molecular Alterations in Lung Adenocarcinoma, Squamous-Cell Carcinoma, and Small-Cell Carcinoma.*

Type of Alteration	Adenocarcinoma	Squamous-Cell Carcinoma	Small-Cell Carcinoma
Cell-cycle mutations	*TP53* (46%), *CDKN2A*(4%)	*TP53* (91%), *CDKN2A* (17%), *RB1* (7%)	*TP53* (92%), *RB1* (75%)
	RTK/PI3K-MTOR signaling	*RTK/PI3K-MTOR* signaling	*RTK/PI3K-MTOR* signaling: *PTEN* (5%)
	KRAS (33%), *EGFR* (14%), *BRAF* (10%), *STK11* (17%), *MET* (8%), *NF1* (11%), *PIK3CA* (7%), *RIT1* (2%)	*PIK3CA* (16%), *PTEN* (8%), *HRAS* (3%)	
Other mutations	Oxidative stress response: *KEAP1* (17%), *MYC* pathway; *MGA* (8%)	Oxidative stress response: *CUL3* (6%), *KEAP1* (12%), *NFE2L2* (15%)	Epigenetic deregulation: *EP300* (11%), *CREBBP* (10%)
	Aberrant splicing: *U2AF1* (3%), *RBM10* (8%)	Squamous differentiation: *NOTCH1* (8%), *ASCL4* (3%), *NOTCH2* (5%)	Neuroendocrine differentiation: *NOTCH1* (15%), *NOTCH2* (5%), and *NOTCH3* (9%)
Rearrangements	*ALK* (3–8%), *ROS1* (2%), *RET* (1%), *NTRK1* (3%), *NRG1* (2%), *BRAF* (3% in those who never smoked), *ERBB4* (1%)	*FGFRs* (rare)	*RB1* (13%), *TP73* (7%), *CREBBP* (4%), *PTEN* (4%), *RBL1* (3%)
Amplifications	*TTF1* (14%), *TERT* (18%), *EGFR* (7%), *MET* (4%), *KRAS* (6%), *ERBB2* (3%), *MDM2* (8%)	Chr3q: *SOX2* (43%), *TP63* (29%), *PIK3CA* (38%), *HES1* (26%)†	*MYC* family members (16%): *MYC, MYCN, MYCL1, SOX2* (27%), *FGFR1* (8%), *IRS2* (2%)
Deletions	*CDKN2A* (20%)	*CDKN2A* (27%), *PTEN* (3%)	*TP53, RB1, CDKN2A,* Chr3p (e.g., *FHIT, ROBO1*)†
Commonly altered pathways	MAPK and PI3K signaling, oxidative stress response, cell-cycle progression, RNA splicing and processing, nucleosome remodeling	Squamous-cell differentiation, oxidative stress response, MAPK and PI3K signaling	Cell-cycle regulation, PI3K signaling, regulation of nucleosome transcriptional and remodeling, NOTCH signaling and neuroendocrine differentiation

N Engl J Med 2016;374:1864-73



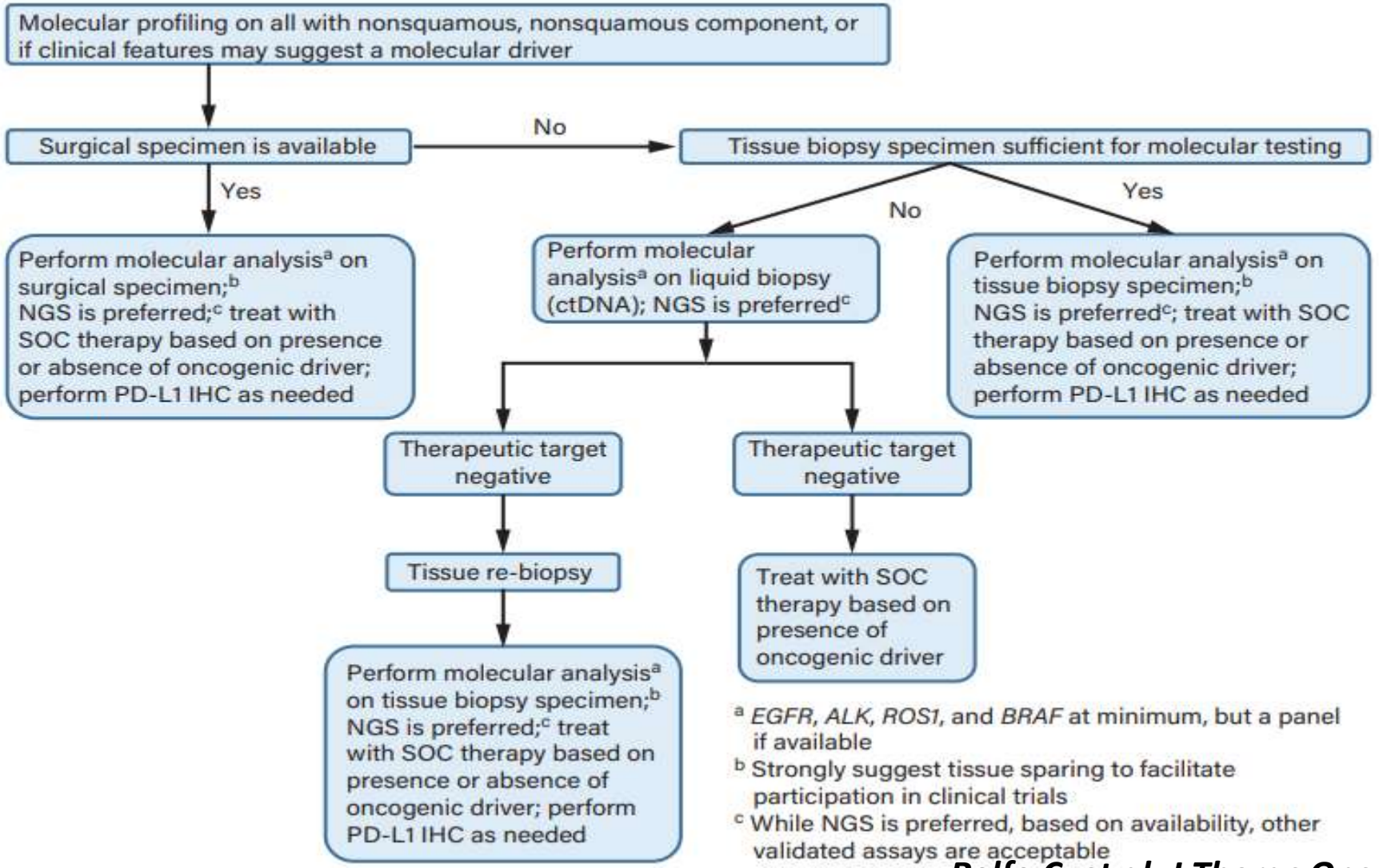
Oncogenic driver mutations lead to ligand-independent activation of downstream signaling pathways, leading to cellular survival, proliferation, and metastasis



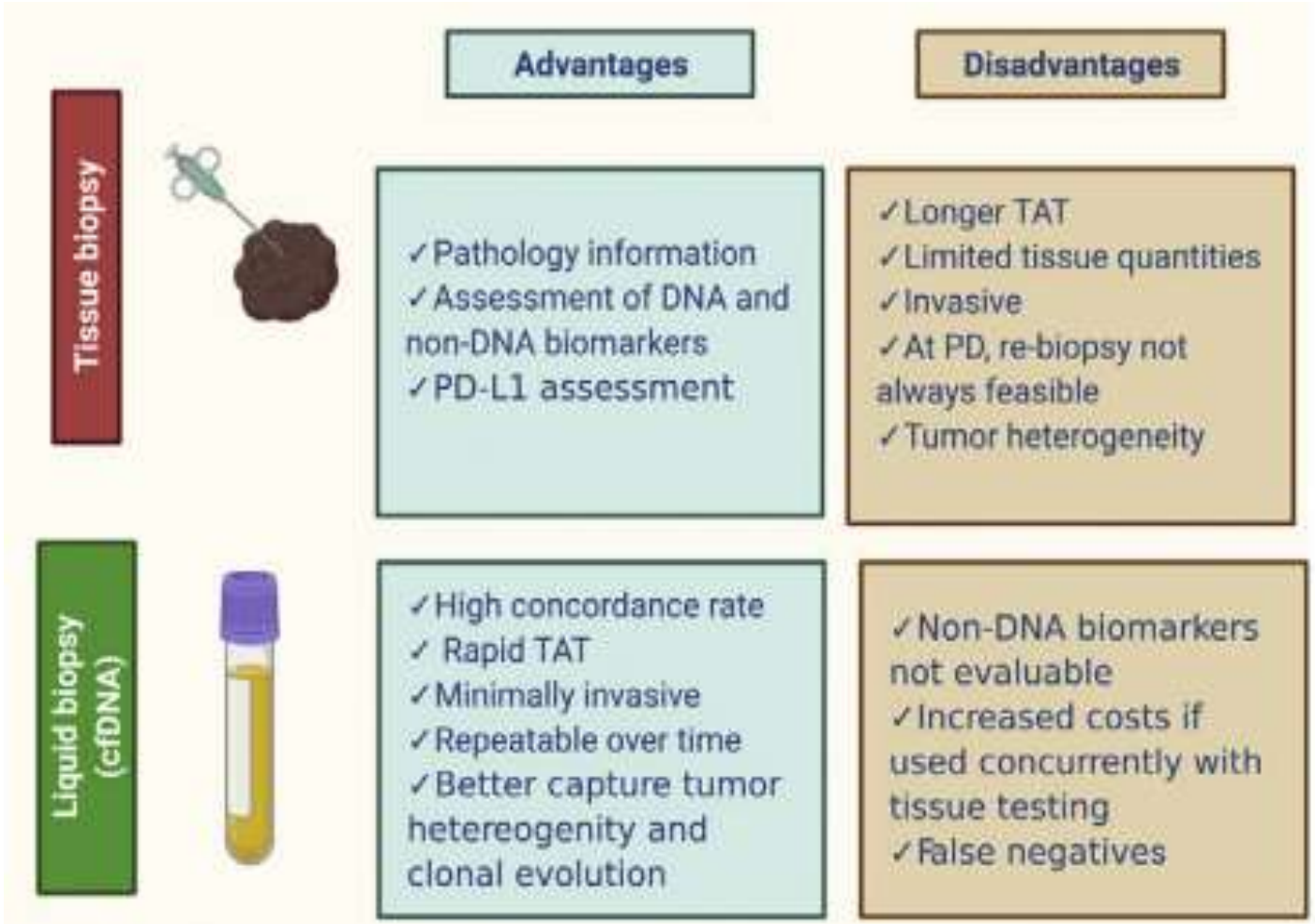
Diagnostic algorithm for liquid biopsy use in treatment-naïve advanced NSCLC

Rolfo C, et al. Liquid biopsy for advanced NSCLC: a consensus statement from the International Association for the Study of Lung Cancer. J Thorac Oncol. 2021;16(10):1647-1662

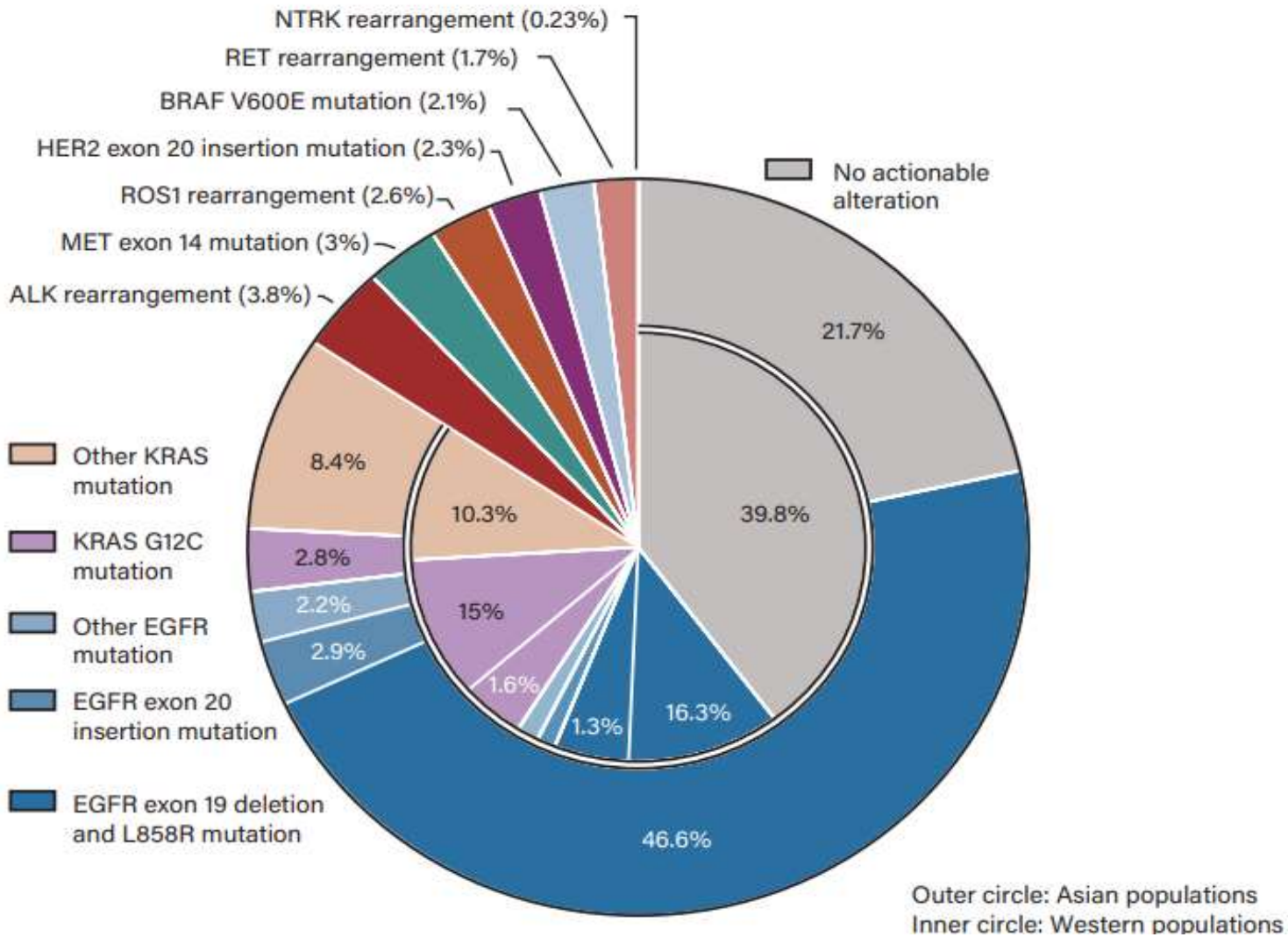
Patient with NSCLC progressive or recurrent disease during treatment with TKI



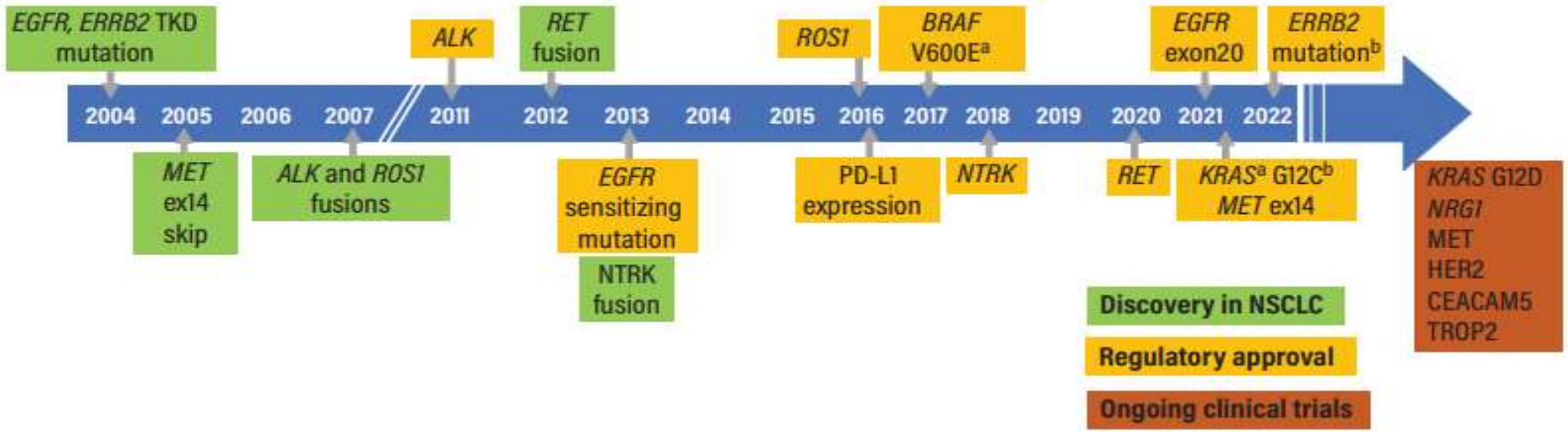
Rolfo C, et al. J Thorac Oncol. 2021;16(10):1647-1662



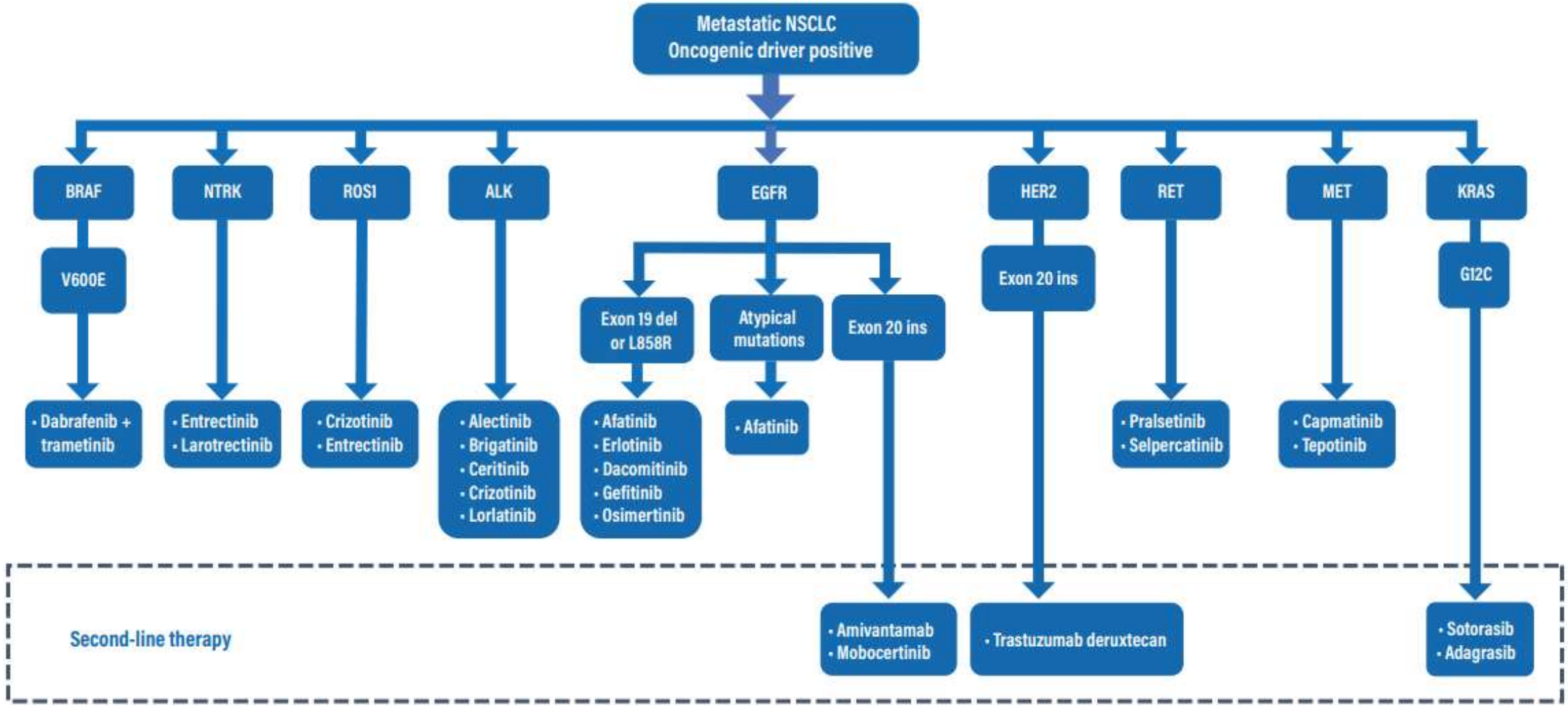
Rolfo C, et al. Liquid biopsy for advanced NSCLC: a consensus statement from the International Association for the Study of Lung Cancer. J Thorac Oncol. 2021;16(10):1647-1662



Aaron C. Tan and Daniel S.W. Tan , Journal of Clinical Oncology 2022 40:6, 611-625



The timeline of biomarker-dependent US Food and Drug Administration (FDA) drug approvals in the first-line setting for patients with advanced NSCLC


Metastatic NSCLC
Oncogenic driver positive
BRAF
V600E
• Dabrafenib + trametinib
NTRK
• Entrectinib
• Larotrectinib
ROS1
• Crizotinib
• Entrectinib
ALK
• Alectinib
• Brigatinib
• Ceritinib
• Crizotinib
• Lorlatinib
EGFR
Exon 19 del or L858R
• Afatinib
• Erlotinib
• Dacomitinib
• Gefitinib
• Osimertinib
Atypical mutations
• Afatinib
Exon 20 ins
• Amivantamab
• Mobocertinib
HER2
Exon 20 ins
• Trastuzumab deruxtecan
RET
• Pralsetinib
• Selpercatinib
MET
• Capmatinib
• Tepotinib
KRAS
G12C
• Sotorasib
• Adagrasib
Second-line therapy

Clinical endpoints

- **Progression-free survival** -the time from randomization until disease progression or death from any cause, whichever occurred first
- **Time to progression** (**TTP**) -the time from randomization until first evidence of disease progression
- **Disease free survival (DFS) -**the time from randomization until evidence of disease recurrence
- **Event-free survival (EFS)** - the time from randomization to an event which may include disease progression, discontinuation of the treatment for any reason, or death
- **Overall survival** - the time from randomization to death from any cause
- **Overall response rate** -as the sum of the confirmed complete response rate and confirmed partial response rate by BICR/RESIST
- **Duration of response** was measured from the first complete or partial response until progressive disease or death, whichever occurred first

Delgado A, Guddati AK. Clinical endpoints in oncology - a primer. Am J Cancer Res. 2021 Apr 15;11(4):1121-1131

Clinical endpoints

- **Time-to-treatment failure (TTF)** is the time from the initiation of chemotherapy treatment/intervention to its early discontinuation
- **Time to next treatment (TTNT**) is defined as the time from initiating treatment to initiating the next line of therapy
- **Duration of clinical benefit (DoCB)** is defined as the time from randomization to disease progression or death in patients who achieve complete response, partial response, or stable disease for 24 weeks or longer
- **Duration of response (DoR)** is defined as the time from randomization to disease progression or death in patients who achieve complete or partial response
- **Disease control rate (DCR)** describes the percentage of patients with advanced cancer whose therapeutic intervention has led to a complete response, partial response, or stable disease
- **Clinical benefit rate (CBR**) is defined as the percentage of advanced cancer patients who achieve complete response, partial response, or at least six months of stable disease as a result of therapy

Delgado A, Guddati AK. Clinical endpoints in oncology - a primer. Am J Cancer Res. 2021 Apr 15;11(4):1121-1131

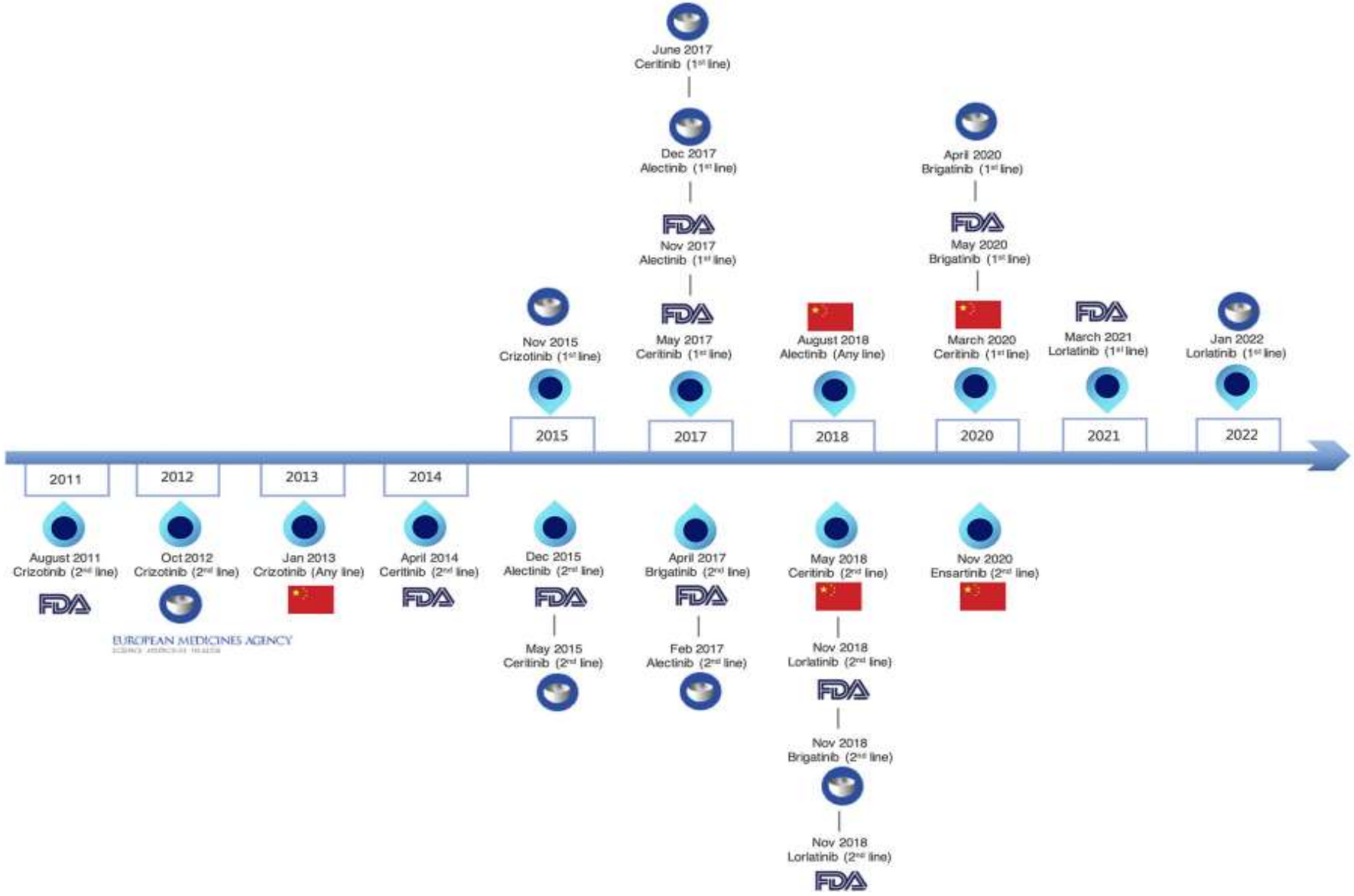
ANAPLASTIC LYMPHOMA KINASE (ALK) IN NSCLC

- Younger, with no smoking history, and have adenocarcinoma as the most common histological
- ALK+ NSCLC accounting for **3%–7%**
- Increased incidence of thromboembolism in ALK+ NSCLC patients as compared to non-ALK+ patients
- Often presents with central tumor location, large pleural effusion, and absence of a pleural tail
- ALK+ tumors are also prone to nodal metastasis and lymphangitic carcinomatosis

Peng L, Zhu L, Sun Y, Stebbing J, Selvaggi G, Zhang Y and Yu Z (2022) Targeting ALK Rearrangements in NSCLC: Current State of the Art. Front. Oncol. 12:86346

ALK

- Crizotinib
- Alectinib
- Ceritinib
- Ensartinib
- Brigatinib
- Lorlatinib



Peng L, Zhu L, Sun Y, Stebbing J, Selvaggi G, Zhang Y and Yu Z (2022) Targeting ALK Rearrangements in NSCLC: Current State of the Art. Front. Oncol. 12:86346

[Intervention Review]

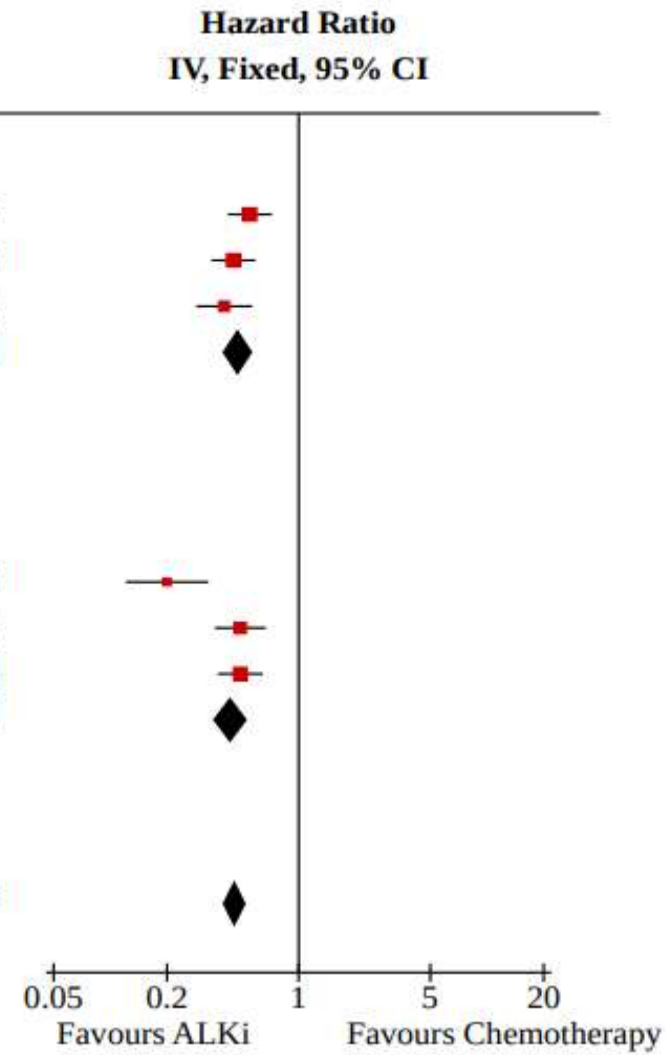
Targeted therapy for advanced anaplastic lymphoma kinase (*ALK*)-rearranged non-small cell lung cancer

- **Aim**-To evaluate the **safety and efficacy** of ALK inhibitors given as monotherapy to treat advanced ALK-rearranged NSCLC
- **RCTs** comparing **ALK inhibitors** with **cytotoxic chemotherapy** or **another ALK inhibitor** in individuals with incurable locally advanced or metastatic pathologically confirmed ALK-rearranged NSCLC
- 11 studies , **N=2874** participants
- **Primary outcomes** - progression-free survival (PFS) and adverse events (AE)
- **Secondary outcomes** - overall survival (OS), OS at one year, overall response rate (ORR) by RECIST (Response Evaluation Criteria in Solid Tumours) criteria, and health-related quality of life (HRQoL).

Cameron LB et al,. Cochrane Database of Systematic Reviews 2022, Issue 1. Art. No.: CD013453

Figure 4. Forest plot of comparison: 1 ALK inhibitor versus chemotherapy, outcome: 1.1 Progression-free survival subgrouped by line of treatment.

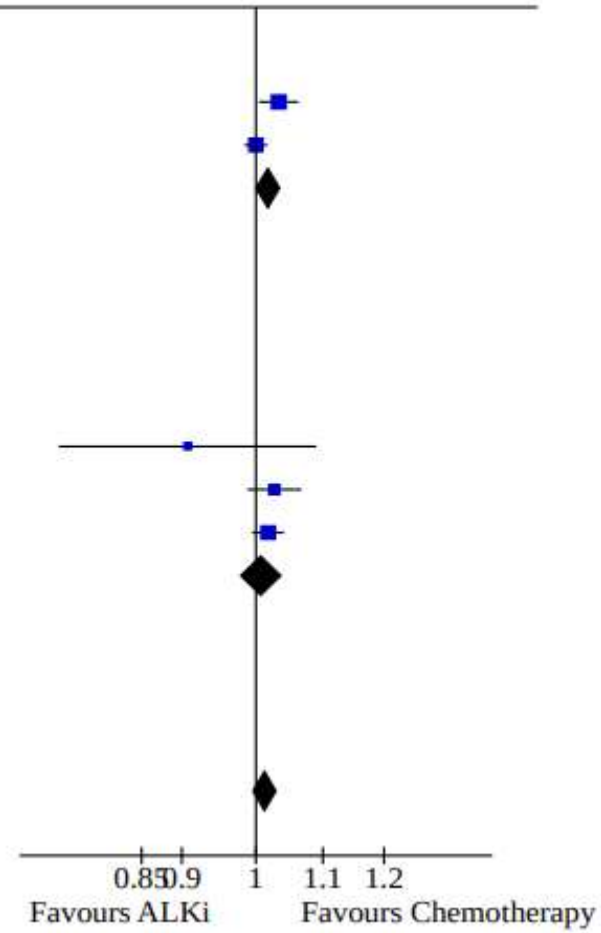
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
1.1.1 1st line				
ASCEND-4 2017	-0.5978	0.1376	21.6%	0.55 [0.42 , 0.72]
PROFILE 1014 2014	-0.798508	0.137502	21.6%	0.45 [0.34 , 0.59]
PROFILE 1029 2018	-0.911303	0.173685	13.5%	0.40 [0.29 , 0.57]
Subtotal (95% CI)			**56.7%**	**0.47 [0.40 , 0.56]**
Heterogeneity: Chi² = 2.21, df = 2 (P = 0.33); I² = 10%				
Test for overall effect: Z = 8.83 (P < 0.00001)				
1.1.2 2nd or subsequent line				
ALUR 2018	-1.609438	0.258066	6.1%	0.20 [0.12 , 0.33]
ASCEND-5 2017	-0.71335	0.158466	16.3%	0.49 [0.36 , 0.67]
PROFILE 1007 2013	-0.71335	0.13979	20.9%	0.49 [0.37 , 0.64]
Subtotal (95% CI)			**43.3%**	**0.43 [0.36 , 0.52]**
Heterogeneity: Chi² = 10.35, df = 2 (P = 0.006); I² = 81%				
Test for overall effect: Z = 8.65 (P < 0.00001)				
Total (95% CI)			**100.0%**	**0.45 [0.40 , 0.52]**
Heterogeneity: Chi² = 13.06, df = 5 (P = 0.02); I² = 62%				
Test for overall effect: Z = 12.34 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.50, df = 1 (P = 0.48), I² = 0%				



Cameron LB et al,. Cochrane Database of Systematic Reviews 2022, Issue 1. Art. No.: CD013453

Figure 5. Forest plot of comparison: 1 ALK inhibitor versus chemotherapy, outcome: 1.4 Overall adverse events subgrouped by line of treatment.

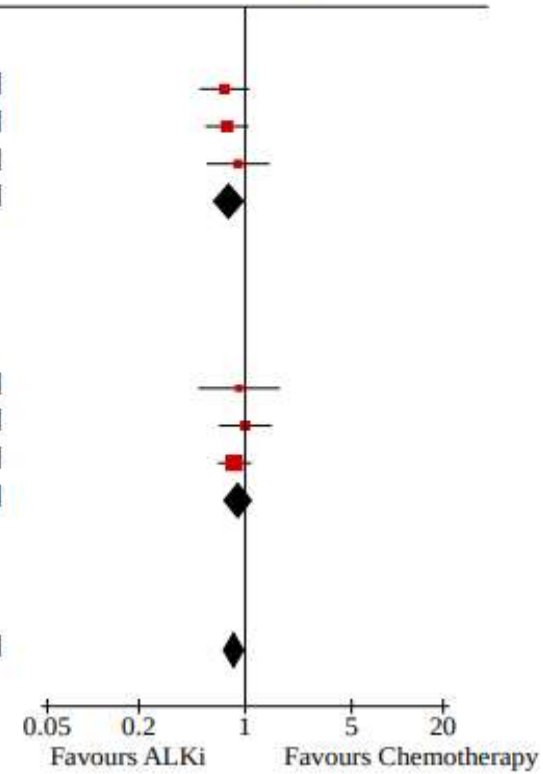
Study or Subgroup	ALK inhibitor Events	ALK inhibitor Total	Chemotherapy Events	Chemotherapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 1st line						
ASCEND-4 2017	189	189	181	187	27.0%	1.03 [1.00 , 1.06]
PROFILE 1014 2014	171	172	170	171	25.2%	1.00 [0.98 , 1.02]
Subtotal (95% CI)		**361**		**358**	**52.2%**	**1.02 [1.00 , 1.03]**
Total events:	360		351			
Heterogeneity: Chi² = 5.38, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 2.01 (P = 0.04)						
1.4.2 2nd or subsequent line						
ALUR 2018	56	72	30	35	6.0%	0.91 [0.76 , 1.09]
ASCEND-5 2017	114	115	112	116	16.5%	1.03 [0.99 , 1.07]
PROFILE 1007 2013	173	173	171	174	25.3%	1.02 [0.99 , 1.04]
Subtotal (95% CI)		**360**		**325**	**47.8%**	**1.01 [0.98 , 1.04]**
Total events:	343		313			
Heterogeneity: Chi² = 3.05, df = 2 (P = 0.22); I² = 34%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		**721**		**683**	**100.0%**	**1.01 [1.00 , 1.03]**
Total events:	703		664			
Heterogeneity: Chi² = 6.28, df = 4 (P = 0.18); I² = 36%						
Test for overall effect: Z = 1.49 (P = 0.14)						
Test for subgroup differences: Chi² = 0.37, df = 1 (P = 0.55), I² = 0%						



Cameron LB et al,. Cochrane Database of Systematic Reviews 2022, Issue 1. Art. No.: CD013453

Figure 7. Forest plot of comparison: 1 ALK inhibitor versus chemotherapy, outcome: 1.16 Overall survival subgrouped by line of treatment.

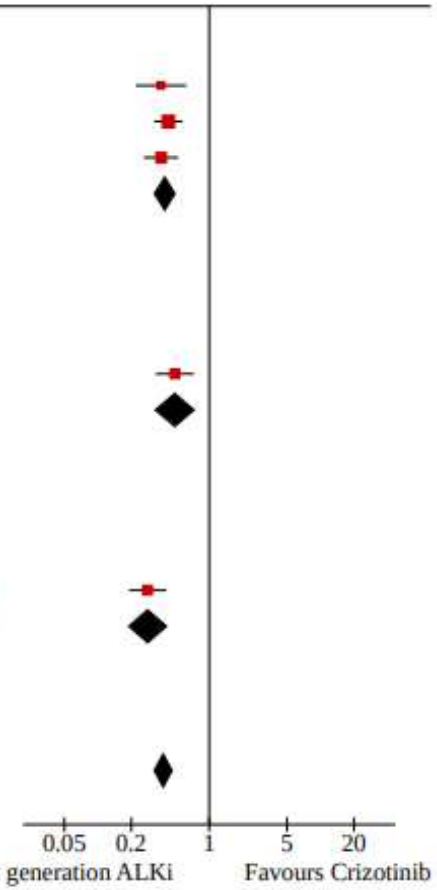
Study or Subgroup	log[Hazard Ratio]	SE	ALK inhibitor Total	Chemotherapy Total	Weight	Hazard Ratio IV, Fixed, 95% CI
1.16.1 1st line						
ASCEND-4 2017	-0.3147	0.1931	189	187	15.5%	0.73 [0.50 , 1.07]
PROFILE 1014 2014	-0.2744	0.1669	172	171	20.7%	0.76 [0.55 , 1.05]
PROFILE 1029 2018	-0.1087	0.244	104	103	9.7%	0.90 [0.56 , 1.45]
Subtotal (95% CI)			**465**	**461**	**45.8%**	**0.78 [0.62 , 0.97]**
Heterogeneity: Chi² = 0.47, df = 2 (P = 0.79); I² = 0%						
Test for overall effect: Z = 2.26 (P = 0.02)						
1.16.2 2nd or subsequent line						
ALUR 2018	-0.0943	0.3158	72	35	5.8%	0.91 [0.49 , 1.69]
ASCEND-5 2017	0	0.2043	115	116	13.8%	1.00 [0.67 , 1.49]
PROFILE 1007 2013	-0.1625	0.1291	173	174	34.6%	0.85 [0.66 , 1.09]
Subtotal (95% CI)			**360**	**325**	**54.2%**	**0.89 [0.73 , 1.09]**
Heterogeneity: Chi² = 0.46, df = 2 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.10 (P = 0.27)						
Total (95% CI)			**825**	**786**	**100.0%**	**0.84 [0.72 , 0.97]**
Heterogeneity: Chi² = 1.76, df = 5 (P = 0.88); I² = 0%						
Test for overall effect: Z = 2.34 (P = 0.02)						
Test for subgroup differences: Chi² = 0.83, df = 1 (P = 0.36), I² = 0%						



Cameron LB et al,. Cochrane Database of Systematic Reviews 2022, Issue 1. Art. No.: CD013453

Figure 8. Forest plot of comparison: 2 Next-generation ALK inhibitor versus crizotinib, outcome: 2.1 Progression-free survival subgrouped by type of ALK inhibitor.

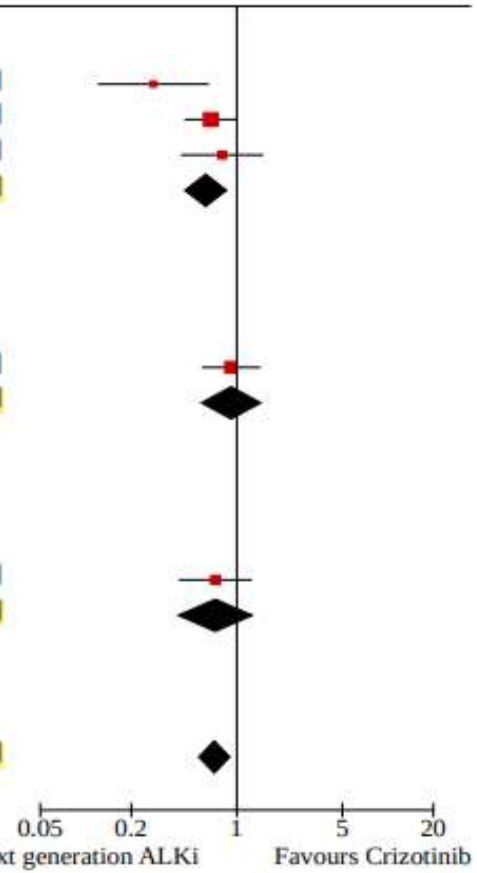
Study or Subgroup	log[Hazard Ratio]	SE	Next generation ALK inhibitor Total	Crizotinib Total	Weight	Hazard Ratio IV, Random, 95% CI
2.1.1 Alectinib						
ALESIA 2019	-0.9943	0.2652	125	62	11.2%	0.37 [0.22 , 0.62]
ALEX 2017	-0.84397	0.151714	152	151	29.3%	0.43 [0.32 , 0.58]
J-ALEX 2017	-0.9943	0.18	103	104	22.2%	0.37 [0.26 , 0.53]
Subtotal (95% CI)			**380**	**317**	**62.6%**	**0.40 [0.32 , 0.49]**
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 2 (P = 0.78); I² = 0%						
Test for overall effect: Z = 8.66 (P < 0.00001)						
2.1.2 Brigatinib						
ALTA-1L 2019	-0.7133	0.2017	137	138	18.2%	0.49 [0.33 , 0.73]
Subtotal (95% CI)			**137**	**138**	**18.2%**	**0.49 [0.33 , 0.73]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.54 (P = 0.0004)						
2.1.3 Lorlatinib						
CROWN 2020	-1.272966	0.196211	149	142	19.1%	0.28 [0.19 , 0.41]
Subtotal (95% CI)			**149**	**142**	**19.1%**	**0.28 [0.19 , 0.41]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.49 (P < 0.00001)						
Total (95% CI)			**666**	**597**	**100.0%**	**0.39 [0.32 , 0.46]**
Heterogeneity: Tau² = 0.01; Chi² = 4.66, df = 4 (P = 0.32); I² = 14%						
Test for overall effect: Z = 10.30 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.16, df = 2 (P = 0.12), I² = 52.0%						



Cameron LB et al,. Cochrane Database of Systematic Reviews 2022, Issue 1. Art. No.: CD013453

Figure 11. Forest plot of comparison: 2 Next-generation ALK inhibitor versus crizotinib, outcome: 2.11 Overall survival subgrouped by type of ALK inhibitor.

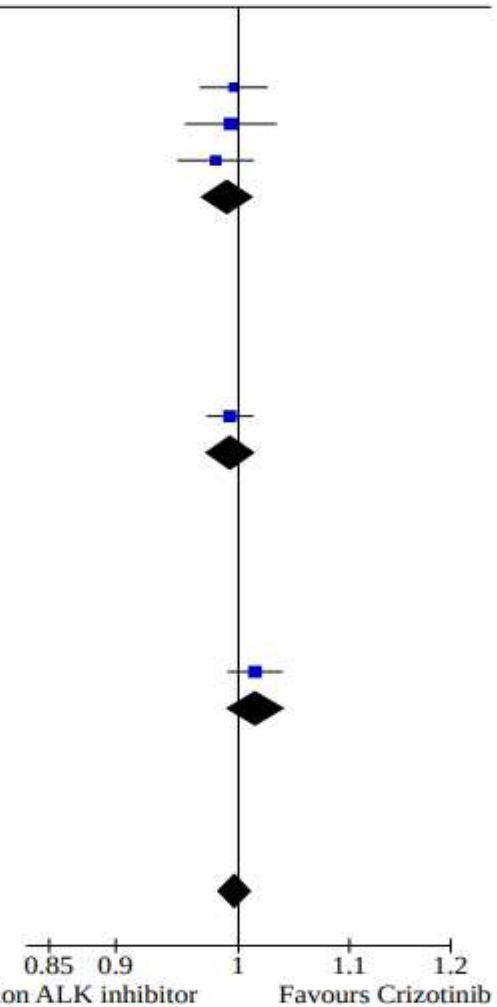
Study or Subgroup	log[Hazard Ratio]	SE	Next generation ALK inhibitor Total	Crizotinib Total	Weight	Hazard Ratio IV, Fixed, 95% CI
2.11.1 Alectinib						
ALESIA 2019	-1.273	0.4323	125	62	7.6%	0.28 [0.12 , 0.65]
ALEX 2017	-0.398366	0.2043	152	151	33.9%	0.67 [0.45 , 1.00]
J-ALEX 2017	-0.2231	0.3209	103	104	13.8%	0.80 [0.43 , 1.50]
Subtotal (95% CI)			**380**	**317**	**55.3%**	**0.62 [0.45 , 0.85]**
Heterogeneity: Chi² = 4.16, df = 2 (P = 0.12); I² = 52%						
Test for overall effect: Z = 2.97 (P = 0.003)						
2.11.2 Brigatinib						
ALTA-1L 2019	-0.087739	0.228065	137	138	27.2%	0.92 [0.59 , 1.43]
Subtotal (95% CI)			**137**	**138**	**27.2%**	**0.92 [0.59 , 1.43]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.70)						
2.11.3 Lorlatinib						
CROWN 2020	-0.328504	0.284378	149	142	17.5%	0.72 [0.41 , 1.26]
Subtotal (95% CI)			**149**	**142**	**17.5%**	**0.72 [0.41 , 1.26]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.16 (P = 0.25)						
Total (95% CI)			**666**	**597**	**100.0%**	**0.71 [0.56 , 0.90]**
Heterogeneity: Chi² = 6.10, df = 4 (P = 0.19); I² = 34%						
Test for overall effect: Z = 2.89 (P = 0.004)						
Test for subgroup differences: Chi² = 1.93, df = 2 (P = 0.38), I² = 0%						



Cameron LB et al,. Cochrane Database of Systematic Reviews 2022, Issue 1. Art. No.: CD013453

Figure 9. Forest plot of comparison: 2 Next-generation ALK inhibitor versus crizotinib, outcome: 2.3 Overall adverse events subgrouped by type of ALK inhibitor.

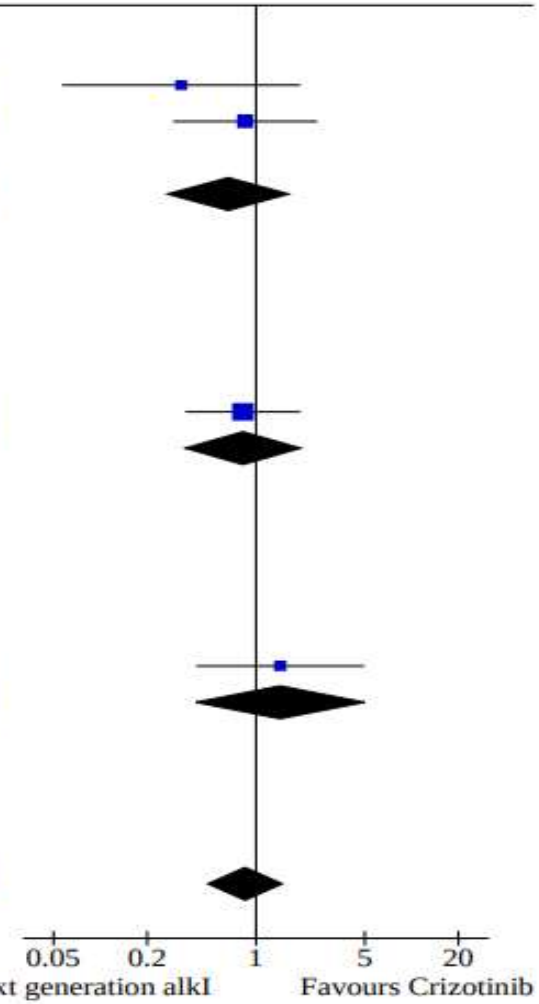
Study or Subgroup	Next generation ALK inhibitor Events	Total	Crizotinib Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Alectinib						
ALESIA 2019	124	125	62	62	13.5%	1.00 [0.97 , 1.03]
ALEX 2017	147	152	147	151	23.9%	0.99 [0.96 , 1.03]
J-ALEX 2017	101	103	104	104	16.9%	0.98 [0.95 , 1.01]
Subtotal (95% CI)		**380**		**317**	**54.3%**	**0.99 [0.97 , 1.01]**
Total events:	372		313			
Heterogeneity: Chi² = 0.51, df = 2 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
2.3.2 Brigatinib						
ALTA-1L 2019	136	137	138	138	22.4%	0.99 [0.97 , 1.01]
Subtotal (95% CI)		**137**		**138**	**22.4%**	**0.99 [0.97 , 1.01]**
Total events:	136		138			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
2.3.3 Lorlatinib						
CROWN 2020	149	149	140	142	23.3%	1.01 [0.99 , 1.04]
Subtotal (95% CI)		**149**		**142**	**23.3%**	**1.01 [0.99 , 1.04]**
Total events:	149		140			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
Total (95% CI)		**666**		**597**	**100.0%**	**1.00 [0.98 , 1.01]**
Total events:	657		591			
Heterogeneity: Chi² = 3.24, df = 4 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.60)						
Test for subgroup differences: Chi² = 2.61, df = 2 (P = 0.27), I² = 23.3%						



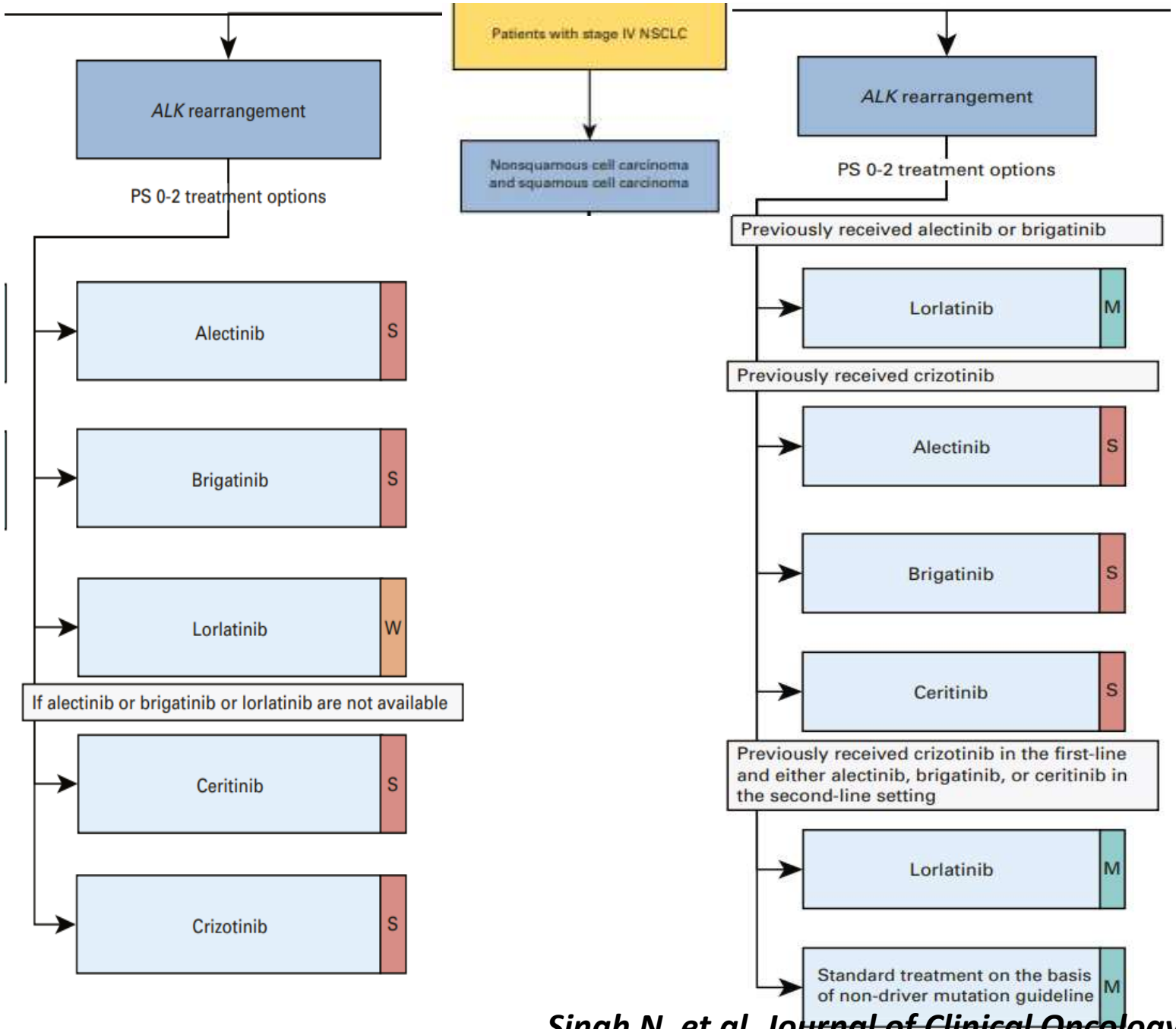
Cameron LB et al,. Cochrane Database of Systematic Reviews 2022, Issue 1. Art. No.: CD013453

Figure 10. Forest plot of comparison: 2 Next-generation ALK inhibitor versus crizotinib, outcome: 2.5 Grade 5 adverse events (excluding progressive disease) subgrouped by type of ALK inhibitor.

Study or Subgroup	Next generation ALK inhibitor Events	Total	Crizotinib Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 Alectinib						
ALESIA 2019	2	125	3	62	15.4%	0.33 [0.06 , 1.93]
ALEX 2017	6	152	7	151	26.9%	0.85 [0.29 , 2.47]
J-ALEX 2017	0	103	0	104		Not estimable
Subtotal (95% CI)		**380**		**317**	**42.3%**	**0.66 [0.27 , 1.62]**
Total events:	8		10			
Heterogeneity: Chi² = 0.81, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
2.5.2 Brigatinib						
ALTA-1L 2019	9	137	11	138	42.0%	0.82 [0.35 , 1.93]
Subtotal (95% CI)		**137**		**138**	**42.0%**	**0.82 [0.35 , 1.93]**
Total events:	9		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.66)						
2.5.3 Lorlatinib						
CROWN 2020	6	149	4	142	15.7%	1.43 [0.41 , 4.96]
Subtotal (95% CI)		**149**		**142**	**15.7%**	**1.43 [0.41 , 4.96]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.57)						
Total (95% CI)		**666**		**597**	**100.0%**	**0.85 [0.49 , 1.47]**
Total events:	23		25			
Heterogeneity: Chi² = 1.78, df = 3 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
Test for subgroup differences: Chi² = 0.98, df = 2 (P = 0.61), I² = 0%						



Cameron LB et al,. Cochrane Database of Systematic Reviews 2022, Issue 1. Art. No.: CD013453



Singh N, et al. Journal of Clinical Oncology 2022 40:28, 3310-3322

ROS1

- ROS1 gene fusions account for **1% - 2%** of NSCLC
- ROS-1-positive NSCLCs are predominantly lepidic, acinar, or solid adenocarcinomas, with more than 90% expressing TTF1
- Diagnosed at an advanced stage (stage III–IV), with a higher frequency of brain metastases
- The TK domains of ALK and ROS1 share **77%** amino acid identity within the ATP-binding sites
- Asian ethnicity, young age (median 49.8 years), never-smokers, and adenocarcinoma histology

Gendarme S, Bylicki O, Chouaid C, Guisier F. ROS-1 Fusions in Non-Small-Cell Lung Cancer: Evidence to Date. Curr Oncol. 2022 Jan 28;29(2):641-658

ROS1

- About 36% of ROS-1-positive NSCLCs have oncogenic co-mutations
- For metastatic squamous-cell tumors, ROS-1 status can be assessed for never-smokers
- IHC is used as a screening technique but positive or questionable results require confirmation by FISH /NGS
- IHC ROS-1-labelling high sensitivity (90–100%), compared to FISH and NGS
- IHC ROS-1 specificity is variable, ranging from 70% to 90%

ROS1

- Crizotinib (limited BBB penetration)
- Entrectinib
- Ceritinib
- Brigatinib
- Lorlatinib
- Repotrectinib
- Taletrectinib

Current Oncology

MDPI

Review

ROS-1 Fusions in Non-Small-Cell Lung Cancer: Evidence to Date

Sébastien Gendarme [1,2,*], Olivier Bylicki [3], Christos Chouaid [1,2] and Florian Guisier [4,5]

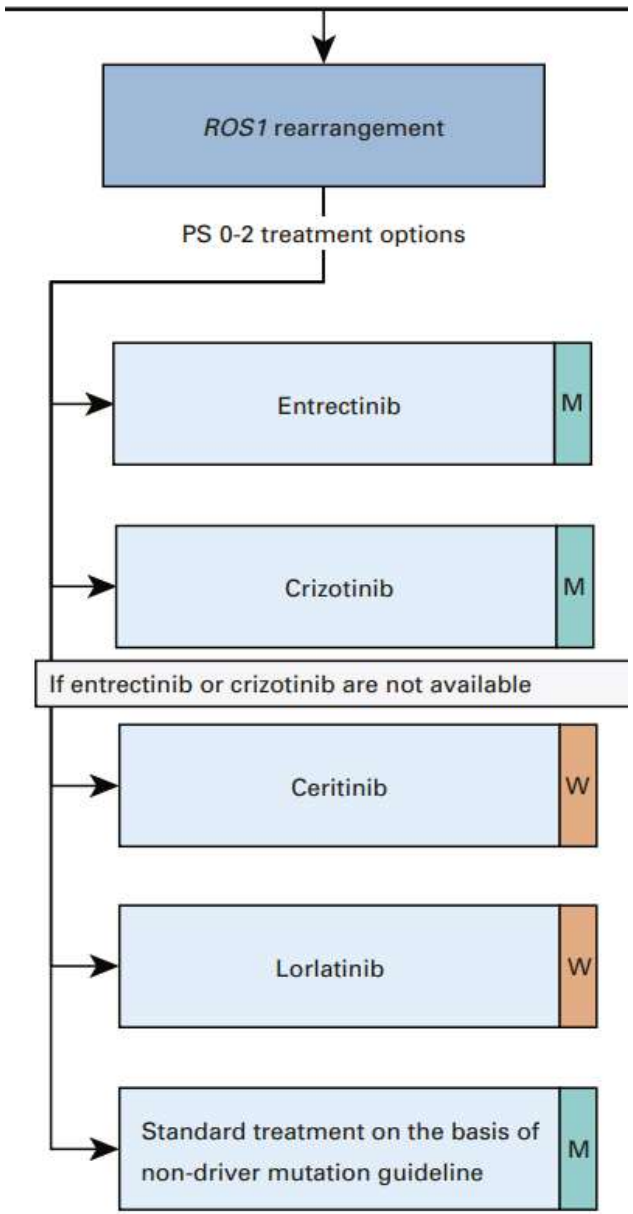
Table 2. Summary of clinical trials on tyrosine-kinase inhibitors (TKIs) targeting ROS-1 in patients with *ROS-1*-positive non-small-cell lung cancers.

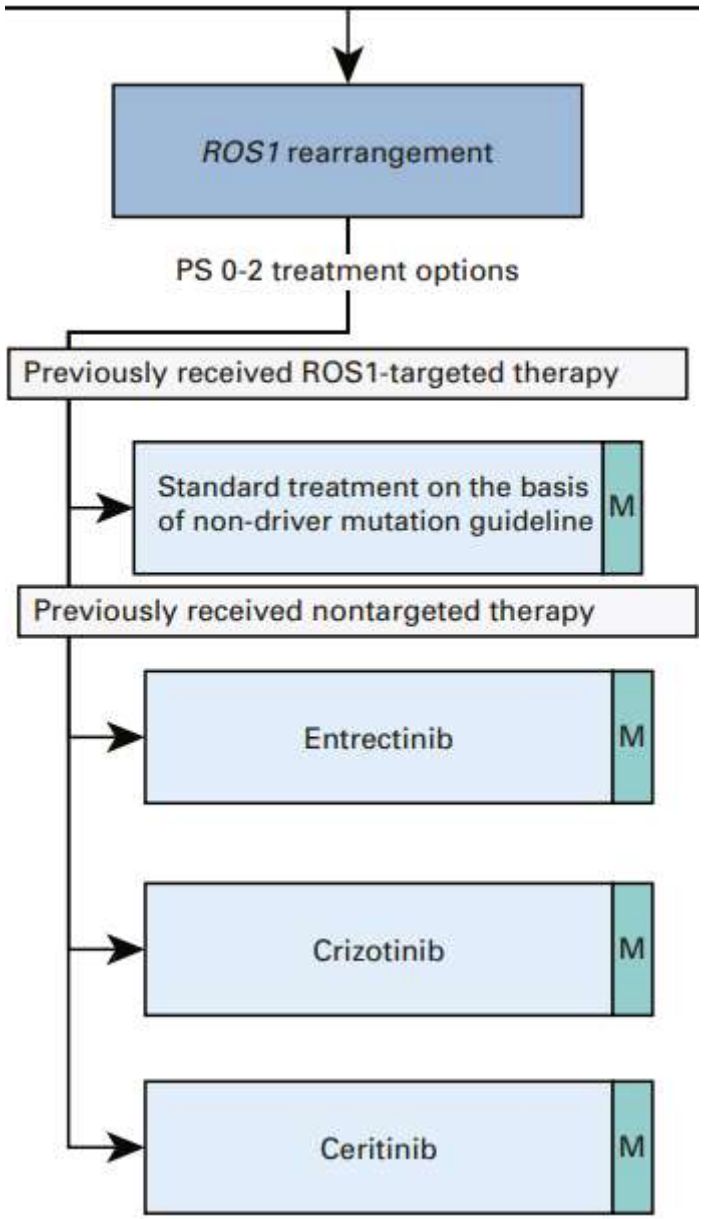
TKI	Clinical Trial	Phase	*N*	ORR (95% CI)	mPFS (mo) (95% CI)	mOS (mo) [95% CI]	1-Year OS	Grade-3/4 Adverse Events (%)
Crizotinib	PROFILE 1001	Prospective I/II	53	72% (58–83)	19 (15–39)	51 (29–NR)		36%
	EUROS-1	Retrospective	31	80%	9	—	—	—
	AcSé	Prospective I/II	36	47% (30–65)	6 (4–9)	17 (9–33)	—	—
	EUCROSS	Prospective II	34	70% (51–85)	20 [8–NR]	Not reached	83%	24%
	METROS	Prospective II	26	65% (44–82)	23 (15–30)	NR	—	27%
	East Asian	Prospective II	127	72% (63–79)	16 (13–24)	33	83%	25%
	Shanghai	Retrospective	30	87% (73–97)	18 (6–30)	NR	81%	23%
	Beijing	Retrospective	56	84%	15 (11–19)	NR	—	—
	China	Retrospective	168	86%	18	—	—	—
Entrectinib	ALKA-372-001/STRATRK-1/ STARTRK-2	Prospective I/II	161	67% (59–74)	16 (11–21)	NR	81%	31% [a]
Lorlatinib	NCT01970865	Prospective I/II	69	62% (38–82) [b] 35% (21–52) [c]	21 (4–32) [b] 9 (5–15) [c]	—	—	43%
Ceretinib	NCT01964157	Prospective II	32	62% (45–77)	9 (0–22) [d] 19 (1–37) [b]	24 (5–43)	—	37%
Ensartinib	NCT03608007	Prospective II	59	27% (14–41)	—	—	—	25%
Cabozantinib	NCT01639508	Prospective II	—	—	—	—	—	—
Repotrectinib	TRIDENT	Prospective I	—	—	—	—	—	—
Taletrectinib	United States	Prospective I	6	33% [c] 58% [d]	4 (1–14) [c]	—	—	26%
	Japan	Prospective I	15	67% [b] 33% [c]	—	—	—	—

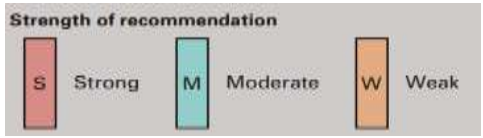
[a] Preliminary results based on 53 patients, [b] Results for crizotinib-naïve patients, [c] Results for crizotinib-resistant patients, [d] Results for crizotinib-naïve and -resistant patients.

Gendarme, S.; Bylicki, O.; Chouaid, C.; Guisier, F. ROS-1 Fusions in Non-Small-Cell Lung Cancer: Evidence to Date. Curr. Oncol. 2022, 29, 641–658

ROS1







Singh N, et al. Journal of Clinical Oncology 2022 40:28, 3310-3322

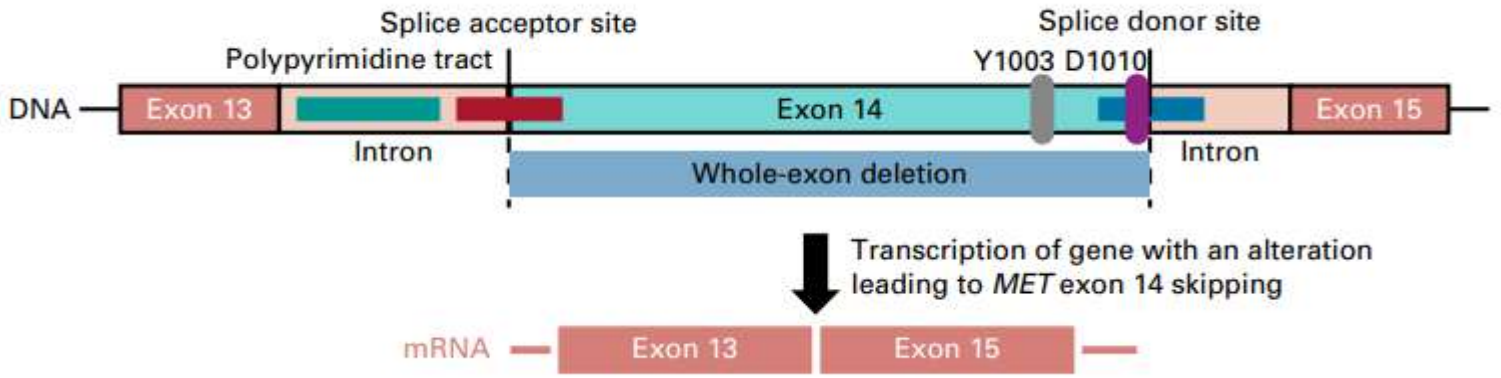
MET exon 14 skipping mutations (METex14)

- **Mutations** (alterations leading to exon 14 skipping), gene **amplification**, and **protein overexpression** may all lead to oncogenic activation of MET mediated signaling
- METex14 is observed in approximately **3%- 4%** of NSCLC
- Generally older (median age, **65-76 years**), more often **female**, and less likely to have a history of smoking compared with those without METex14
- Histology: approximately **2%** in adenocarcinoma, approximately **1%** in squamous cell carcinoma, approximately **6%** in adenosquamous cell carcinoma, and approximately **13%** in pulmonary sarcomatoid carcinoma

Mark A. Socinski, Nathan A. Pennell, and Kurtis D. Davies
JCO Precision Oncology 2021 :5, 653-663

MET exon 14 skipping mutations (METex14)

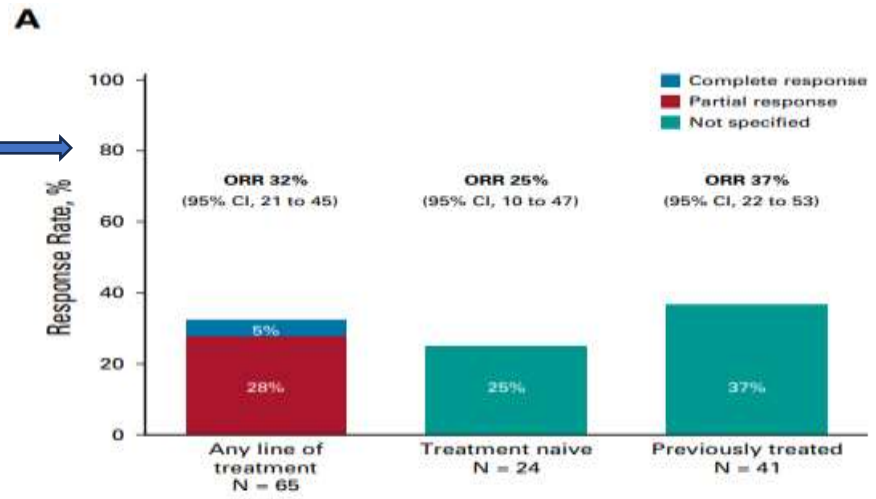
- Crizotinib
- Tepotinib
- Capmatinib
- Savolitinib
- Cabozantinib
- Gumarontinib

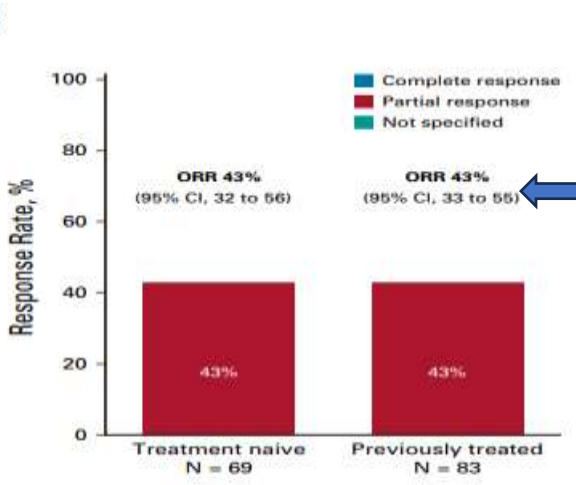


Mark A. Socinski, Nathan A. Pennell, and Kurtis D. Davies
JCO Precision Oncology 2021 :5, 653-663

MET exon 14 skipping mutations (METex14)

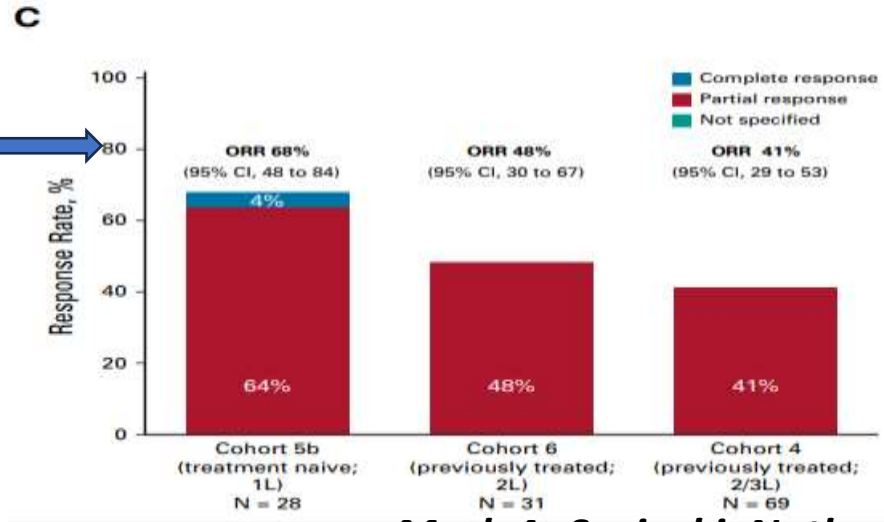
Crizotinib
PROFILE 1001 trial

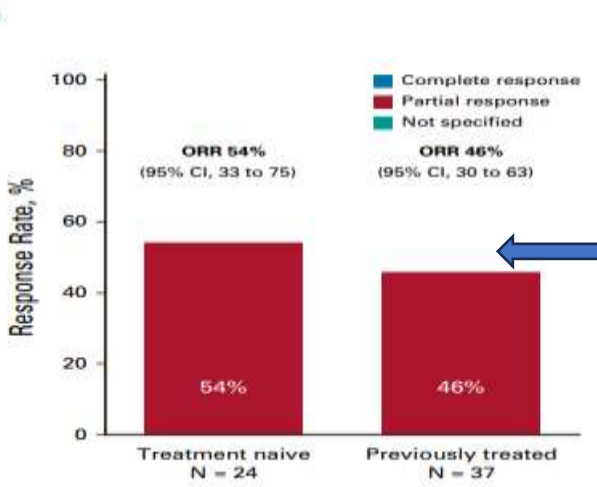




Tepotinib
VISION trial

Capmatinib
GEOMETRY mono-1 trial





Savolitinib
NCT02897479

Mark A. Socinski, Nathan A. Pennell, and Kurtis D. Davies ,JCO Precision Oncology 2021 :5, 653-663

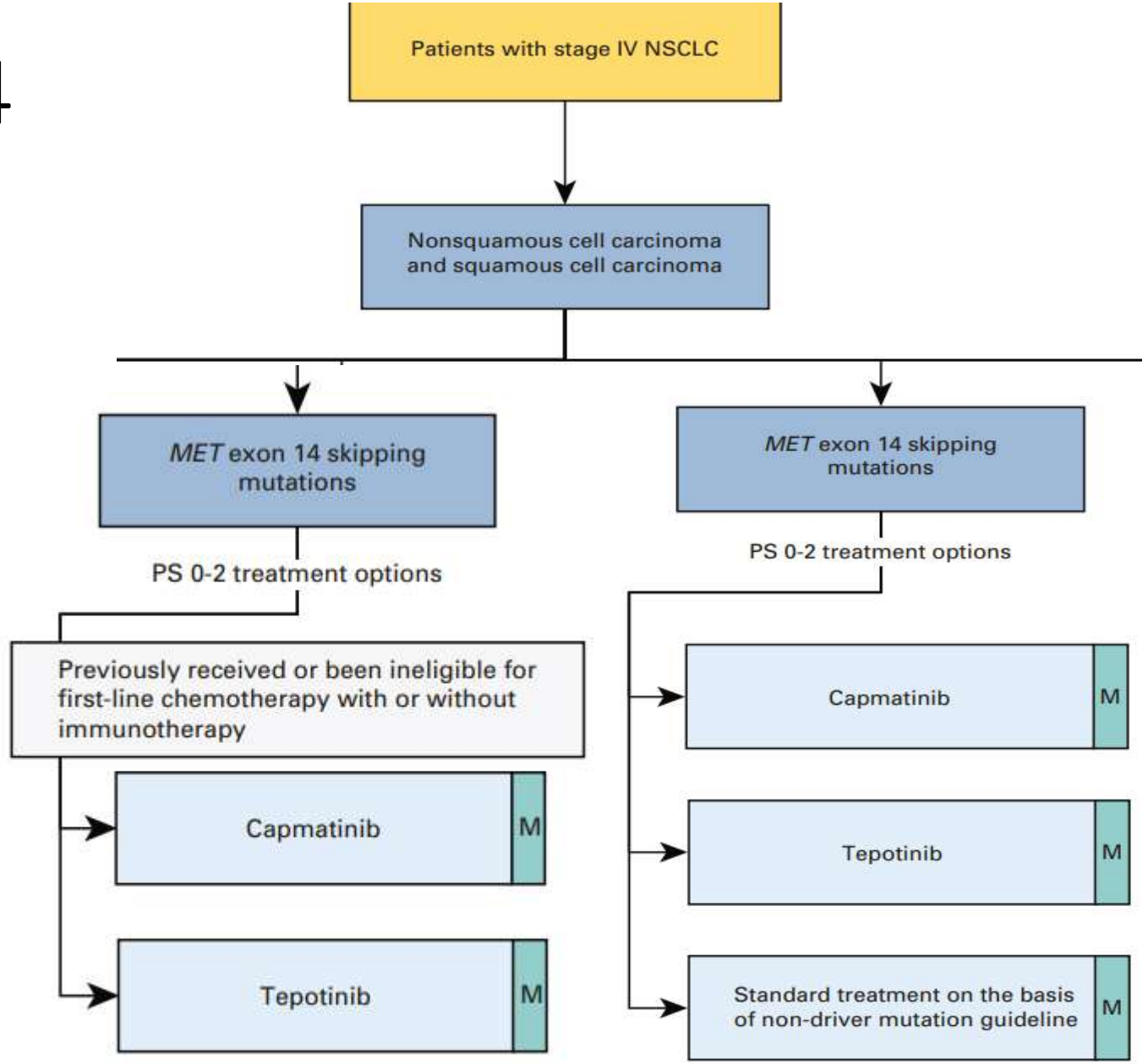
Gumarontinib in patients with non-small-cell lung cancer harbouring *MET* exon 14 skipping mutations: a multicentre, single-arm, open-label, phase 1b/2 trial

Yongfeng Yu,[a,ae] Jianya Zhou,[b,ae] Xingya Li,[c,ae] Koichi Goto,[d,ae] Xuhong Min,[e,ae] Kazumi Nishino,[f,ae] Jiuwei Cui,[g,ae] Lin Wu,[h,ae] Jun Sakakibara,[i,ae]

- **GLORY study -**Single-arm, multicentre, open-label, phase 2 stage
- Locally advanced or metastatic METex14-positive NSCLC
- **Gumarontinib** 300 mg once daily in continuous 21-day cycles
- N=78
- ORR **66%** (95% CI 54–76) **overall** (n = 79), **71%** (95% CI 55–83) in **treatment-naïve patients** (n = 44), and **60%** (95% CI 42–76) in **previously-treated patients** (n = 35)
- Treatment-related adverse events (any grade) were oedema (67/84 patients, 80%) and hypoalbuminuria (32/84, 38%)
- **Grade ≥3 TRAEs** occurred in 45 (54%) patients. TRAEs leading to permanent discontinuation occurred in 8% (7/84) of patients.

eClinicalMedicine 2023;59: 101952

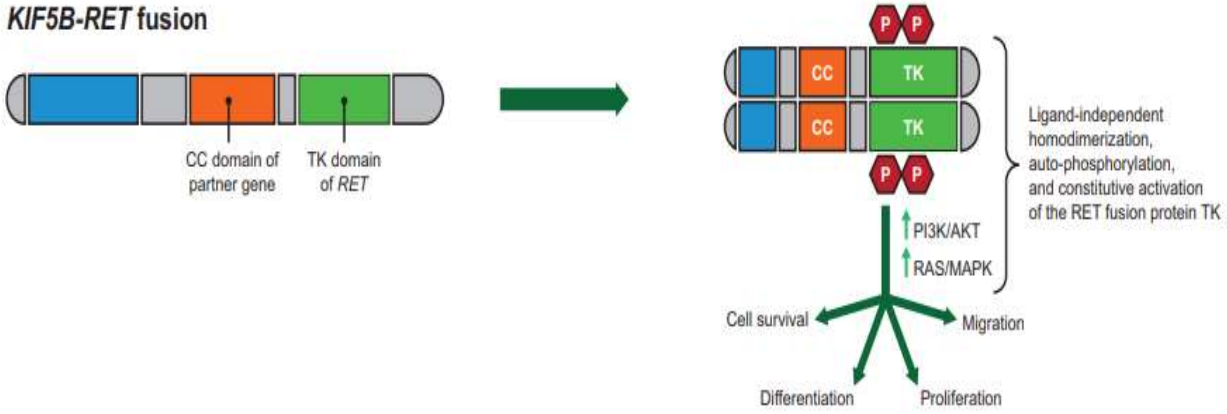
METex14



Singh N, et al. Journal of Clinical Oncology 2022 40:28, 3310-3322

REarranged during Transfection (RET)

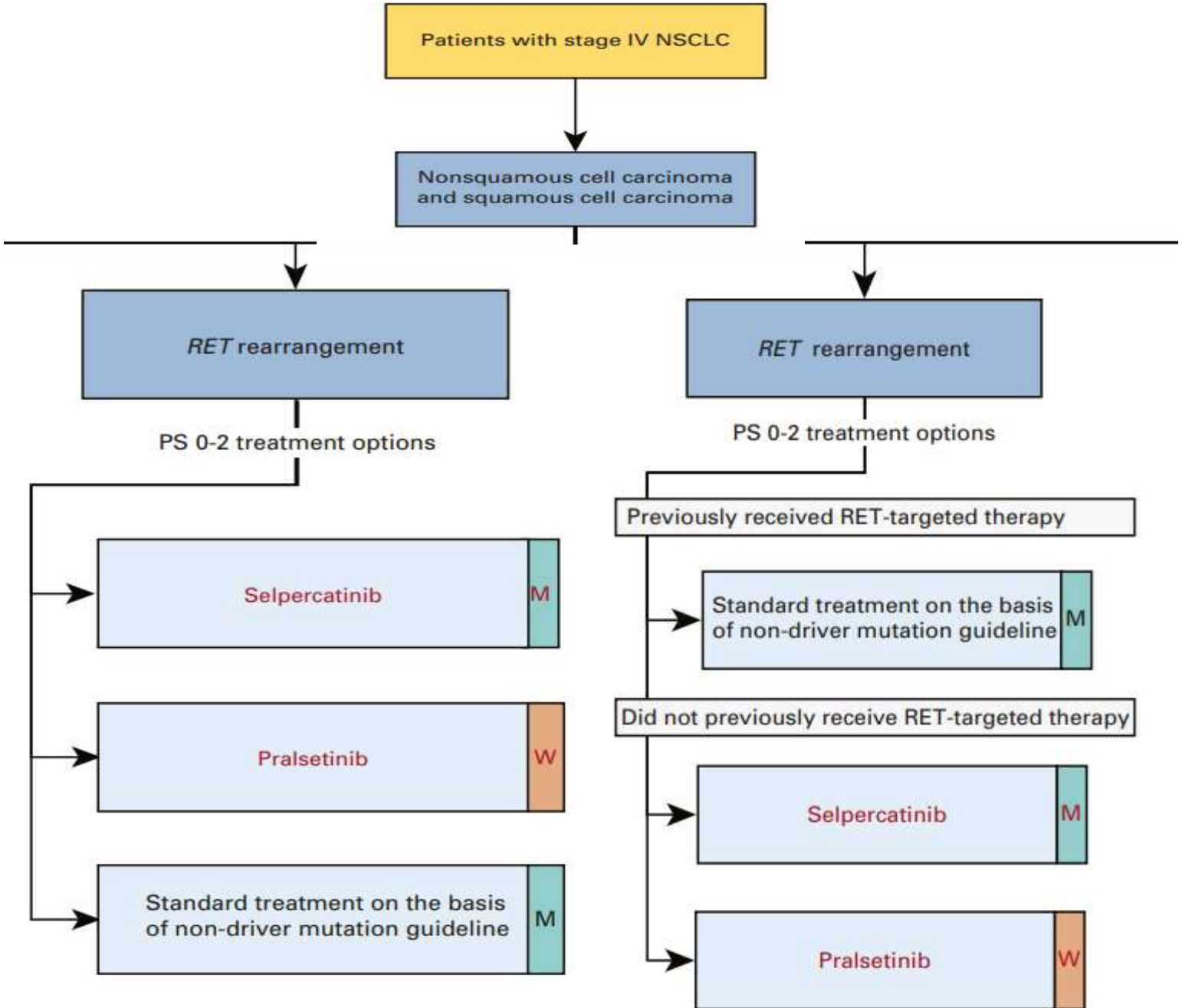
- RET have been identified in **1% - 2%** of all lung cancers
- **46%** of patients develop **brain metastases** over their lifetime
- Higher incidence in **never-smokers**, **females**, **adenocarcinoma**, and **poorly differentiated tumors**, potentially may confer higher chemosensitivity (particularly to pemetrexed-based regimens)
- **Selpercatinib**
- **Pralsetinib**



Novello S, Califano R, Reinmuth N, Tamma A, Puri T. RET Fusion-Positive Non-small Cell Lung Cancer: The Evolving Treatment Landscape. Oncologist. 2023 May 8;28(5):402-413

Study	Patient population RET fusion-positive	Results	Common grade 3 or worse TRAEs
Selpercatinib LIBRETTO-001 Phase I/II, open-label trial	Pts with RET fusion-positive advanced NSCLC had previously received at least platinum-based chemotherapy **(n = 247**) or were previously untreated **(n = 69)**	**Previous platinum-based chemotherapy**: **ORR = 61%** (95% CI 55-67**), PFS** = 24.9 months (95% CI 19.3- NR), **2-year OS** = 69% (95% CI 62-75), **Treatment-naïve pts**: ORR = 84% (95% CI 73-92), PFS = 22.0 months (95% CI 13.8-NR), 2-year OS = 69% (95% CI 55-80)	Hypertension (13%), Increased ALT (9%), Increased AST (6%)
Pralsetinib ARROW Phase I/II, multi-cohort, open-label trial	Pts with RET fusion-positive NSCLC who had previously received at least platinum-based chemotherapy **(n = 130)** or were previously untreated (**n = 107**)	**Pts with previous platinum-based chemotherapy**: ORR = 63.1% (95% CI 54.2-71.4); PFS = 16.4 months (95% CI 11.4-22.3); OS = 44.3 months (95% CI 26.9-44.3), **Treatment-naïve pts**: ORR = 77.6% (95% CI 68.5-85.1), PFS = 12.6 months (95% CI 9.2-16.6), OS = NR (95% CI 31.9, NR)	Neutropenia (20%), Anemia (12%), and Hypertension (12%)

Novello S, Califano R, Reinmuth N, Tamma A, Puri T. RET Fusion-Positive Non-small Cell Lung Cancer: The Evolving Treatment Landscape. Oncologist. 2023 May 8;28(5):402-413



Singh N, et al. Journal of Clinical Oncology 2022 40:28, 3310-3322

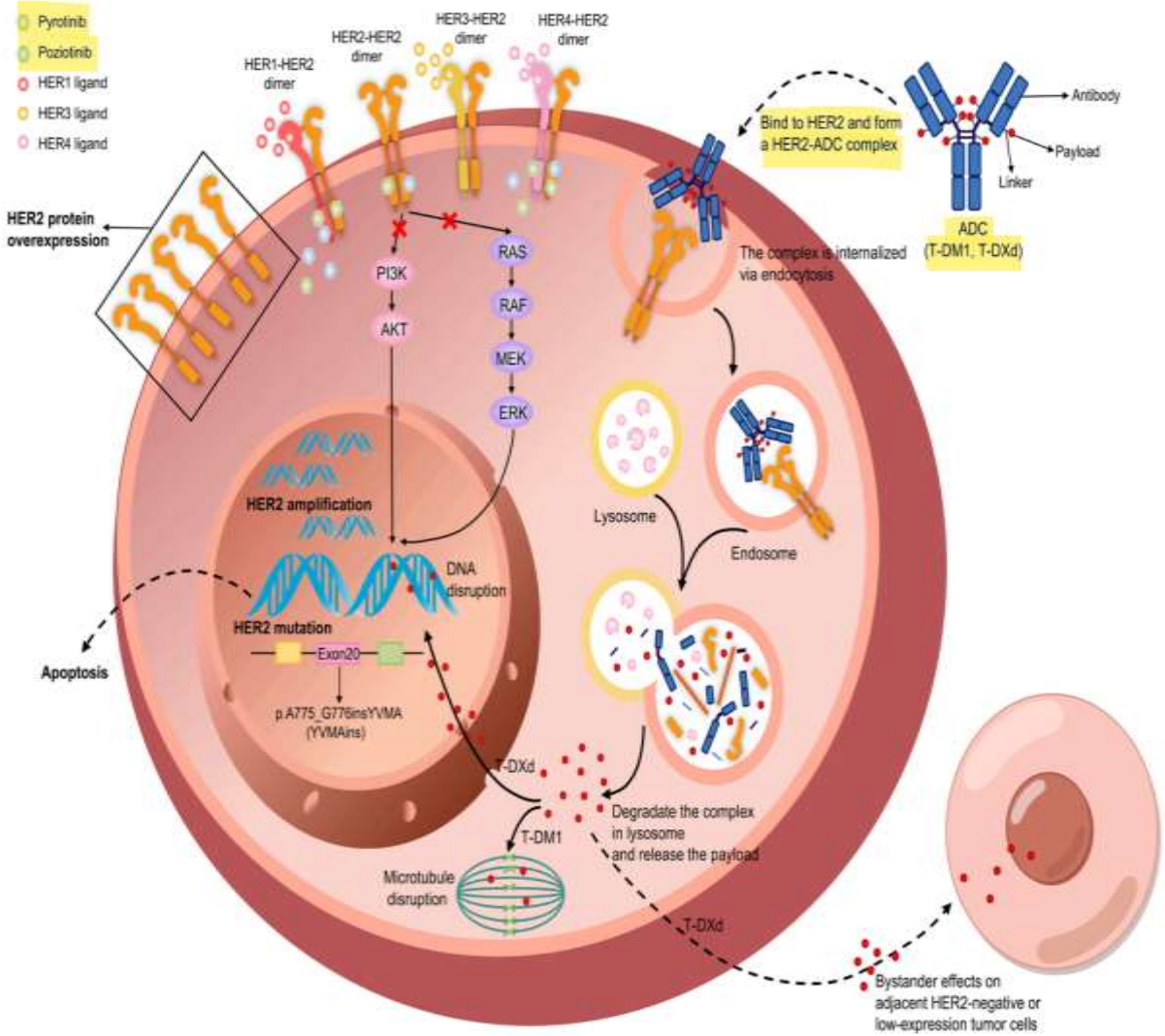
Human epidermal growth factor receptor 2 (HER2/ERBB2)

- HER2 protein product is a member of the HER/ErbB family of **tyrosine kinases receptors**
- HER2 gene **mutation** (1%-4% of cases), gene **amplification** (2%-5%) and protein **overexpression** (2%-30%)
- HER2 mutations and amplifications have been associated with **female** sex, **Asian** ethnicity, **non-smoking** status as well as moderate to poorly differentiated **adenocarcinoma** histology
- Pleural invasion is commonly seen in HER2-amplified and HER2-overexpressing NSCLC while CNS involvement has been reported in up to 47% of patients with HER2-mutant NSCLC
- HER2 overexpression has been found to be associated with poor outcomes in NSCLC

Riudavets M, et al, ESMO Open. 2021 Oct;6(5):100260

HER2/ERBB2

- Pan-HER TKIs-
  - Afatinib
  - Neratinib
  - Dacomitinib
- Selective HER2 TKIs-
  - Pyrotinib
  - Poziotinib
- Antibody-drug conjugates-
  - Trastuzumab emtansine
  - Trastuzumab Deruxtecan

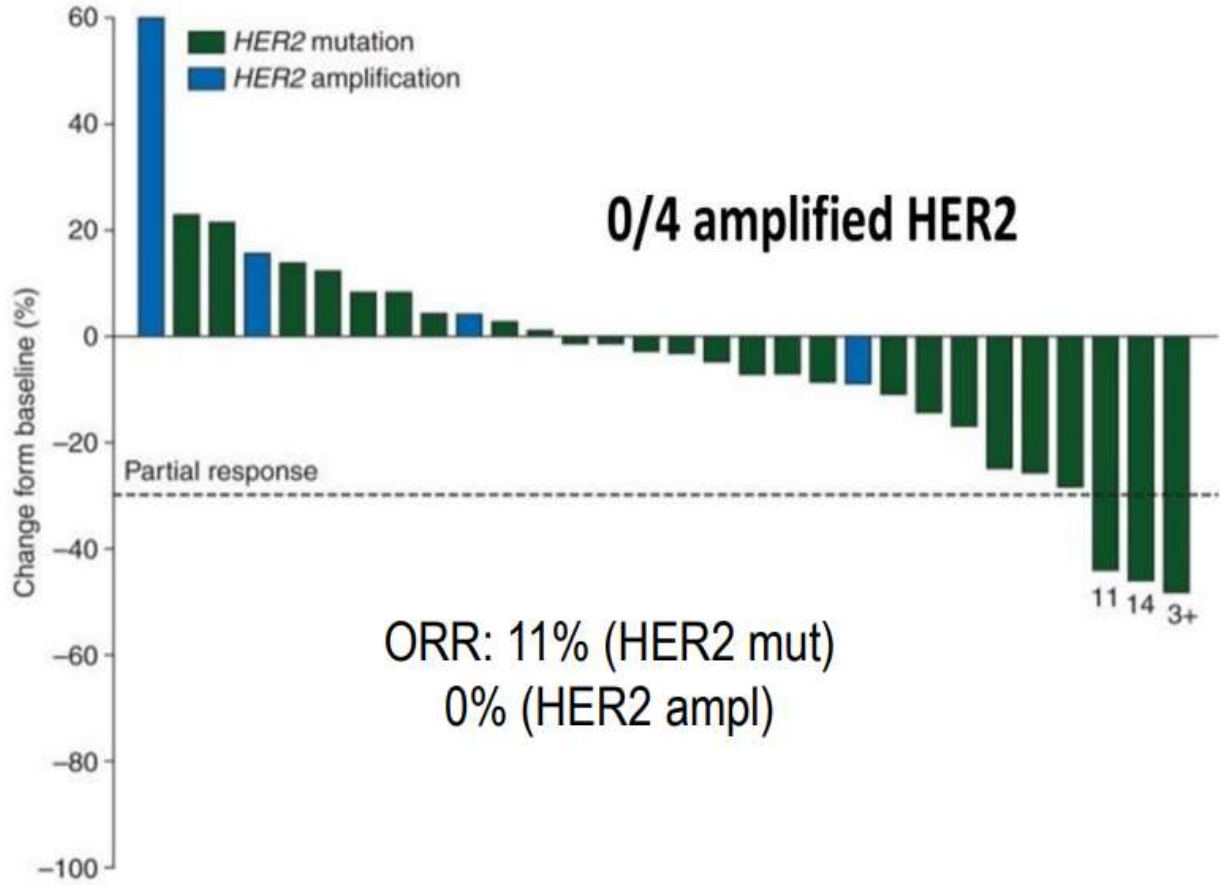


Y. Yu et al. Cancer Treatment Reviews 114 (2023) 102520

Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with *HER2*-mutant or amplified tumors

30 patients

Dacomitinib

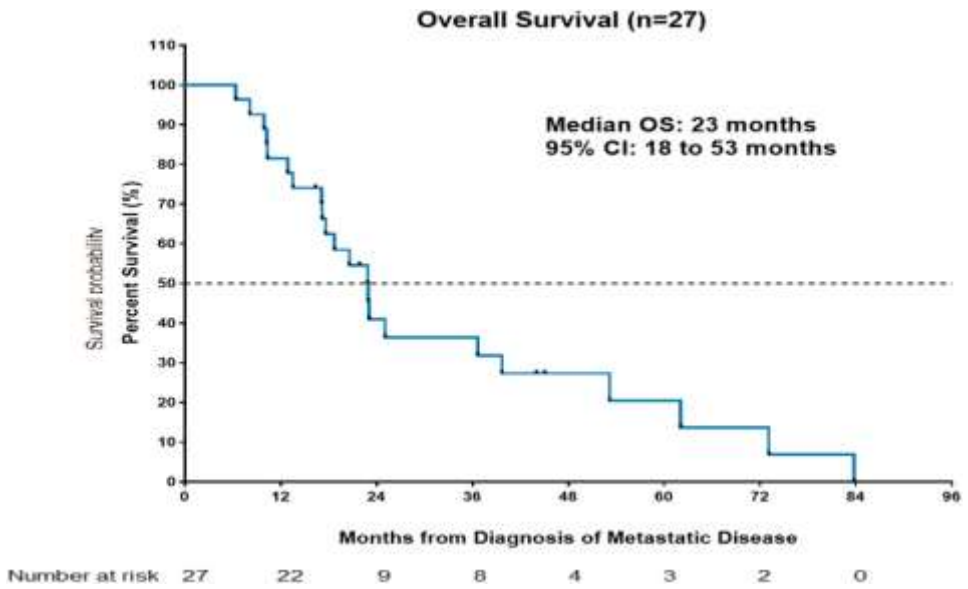


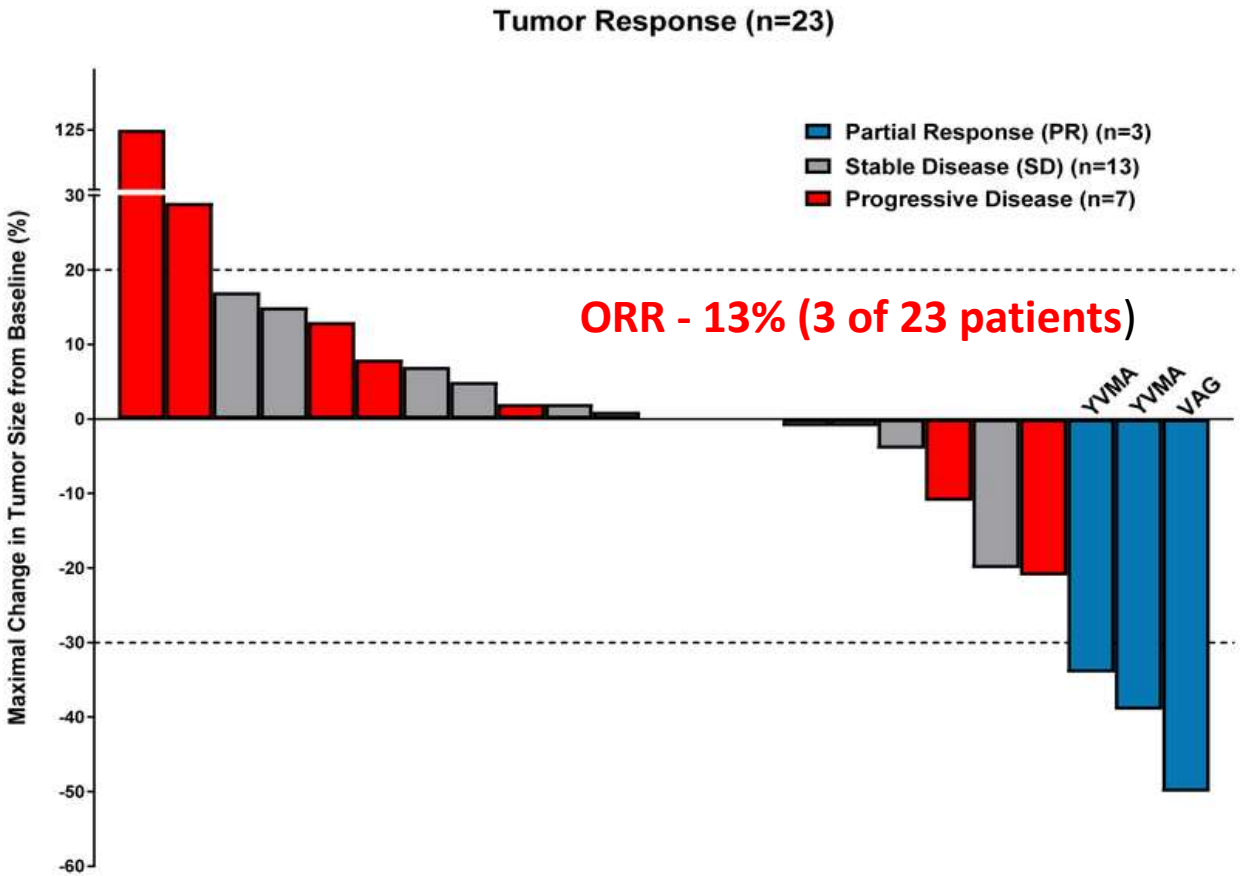
Kris M et al.Official Journal of the European Society for Medical Oncology. 2015 Jul;26(7):1421-1427.

Original Research

Afatinib in patients with metastatic or recurrent *HER2*-mutant lung cancers: a retrospective international multicentre study☆

- **27 patients** with stage IV or recurrent HER2-mutant lung adenocarcinomas treated with afatinib
- Median duration of response to afatinib was **6 months** (range 5-10)
- Median time on treatment **was 3 months** (range 1-30)





Lai WV et al. Afatinib in patients with metastatic or recurrent HER2-mutant lung cancers: a retrospective international multicentre study. Eur J Cancer. 2019 Mar;109:28-35.

HER2 in NSCLC

Relevant studies assessing selective TKIs in NSCLC with HER2 mutations.

Trial	Phase	N	Drug	Line	Efficacy				Safety				
					ORR (%)	mPFS (months)	mDoR (months)	mOS (months)	TRAEs (%)	Grade 3–5 TRAEs (%)	Dose reduction (%)	Dose interruptions (%)	Discontinuations (%)
NCT02834936	II	60	Pyrotinib	≥ 2L	30.0	6.9	–	14.4	98.3	28.3	–	21.7	1.7
ChiCTR 1800020262	II	78	Pyrotinib	≥ 1L	19.2	5.6	9.9	10.5	91.0	20.5	2.6	–	5.1
ChiCTR 1900021684	II	33	Pyrotinib + Apatinib	≥ 2L	51.5	6.9	6.0	14.8	100.0	12.1	30.3		15.2
NCT03318939 (ZENITH20)	II (Cohort 2)	90	Poziotinib 16 mg QD	≥ 2L	27.8	5.5	5.1	–	97.8	84.4	76.7	–	13.3
	II (Cohort 4)	48	Poziotinib 16 mg QD	1L	41.0	5.6	5.7	–	–	79	90	90	–
		22	Poziotinib 8 mg BID						–	68	64	68	–
NCT04447118	III	150	Pyrotinib vs Docetaxel	2L	Estimated study completion date is October 31, 2023								
NCT05378763	III	268	Poziotinib vs Docetaxel	≥ 2L	Estimated study completion date is December 25, 2028								
NCT04706949	II	26	Pyrotinib + Pemetrexed + Carboplatin	1L	Estimated study completion date is December 31, 2022								
NCT04144569	II	30	Pyrotinib + PD-1 inhibitors	≥ 2L	Estimated study completion date is December 31, 2024								
NCT05016544	Ib	48	Pyrotinib + Inetetamab	≥ 1L	Estimated study completion date is February 1, 2025								

Y. Yu et al. Cancer Treatment Reviews 114 (2023) 102520

Outcomes of studies assessing ADCs in NSCLC with HER2 alterations.

Trial	Phase	N	HER2 alterations type	Drug	Line	Efficacy				Toxicity
						ORR (%)	mPFS (months)	mDoR (months)	mOS (months)	
NA	II	15	HER2 mutation (7); HER2 IHC/FISH + (8)	T-DM1	≥ 2L	6.7	2.0	–	10.9	Thrombocytopenia (40 %), Hypokalemia (7 %), Hyperuricemia (7 %)
NCT02675829	II	18	HER2 mutations	T-DM1	≥ 1L	44.0	5.0	6.0	–	Elevated AST or ALT (44 %), Thrombocytopenia(33 %), Fatigue (33 %), Nausea (33 %)
NCT02289833	II	29	HER2 IHC 2 +	T-DM1	≥ 2L	0.0	2.6	–	12.2	Any grade TRAEs (92 %), grade 3 TRAEs (20 %), grade 4 TRAEs (2 %), no grade 5 TRAEs
		20	HER2 IHC 3 +			20.0	2.7	–	15.3	
NCT03505710 (DESTINY-Lung01)	II	91	(cohort 2) HER2 mutations	*T*-DXd 6.4 mg/kg	≥ 2L	55.0	8.2	9.3	17.8	All grade TRAEs (97 %), grade ≥ 3 TRAEs (46 %), 31 dose reductions, 29 dose interruptions and 23 discontinuations; ILD (26 %) and leading to 2 deaths
		49	(cohort 1) HER2 IHC 2/3 +			24.5	5.4	6.0	11.3	Any grade TRAEs (100 %), grade ≥ 3 TRAEs (73.5 %); dose interruptions (53.1 %), dose reductions (34.7 %), and discontinuations in (22.4 %); ILD (16.3 %)
NCT04644237 (DESTINY-Lung02)	II	52	HER2 mutations	*T*-DXd 5.4 mg/kg	≥ 2L	53.8	–	–	–	The dose of 5.4 mg/kg led to a lower incidence of grade ≥ 3 TRAEs (31.7 % vs 58 %) and ILD (5.9 % vs 14 %) than the dose of 6.4 mg/kg
		28	HER2 mutations	*T*-DXd 6.4 mg/kg		42.9	–	–	–	
NCT05048797 (DESTINY-Lung04)	III	264	HER2 exon 19 or 20 mutations	*T*-DXd vs pembrolizumab + ChT	1L	Estimated study completion date is March 1, 2027				

Y. Yu et al. Cancer Treatment Reviews 114 (2023) 102520

HER2/ERBB2

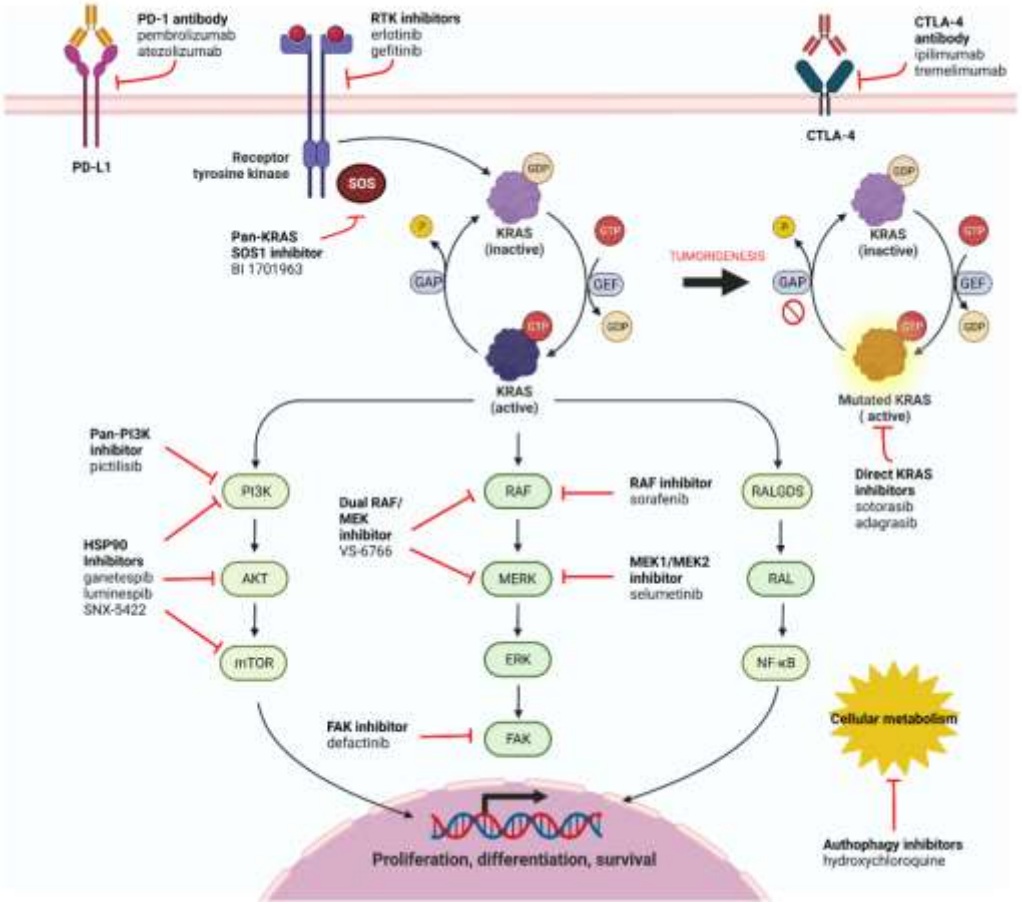
Drugs	ORR
Dacomitinib	11%
Neratinib-temsirolimus	21%
Afatinib	14%
Poziotinib	35.1% preTxt 43.8% 1st line
Pyrotinib	30%
Tarloxotinib	22%
Trastuzumab emtansine	51 %
Trastuzumab-deruxtecan	54.9%

RAS/MAPK Pathway

- MAPK pathway can be activated by multiple mechanisms, including activation of RTKs in response to extracellular stimuli and mutations that lead to constitutive TK activity (e.g., EGFR mutations, EML4-ALK rearrangements)
- The canonic MAPK cascade is composed of three successive serine/ threonine kinases: RAF, MEK, and ERK.

RAS

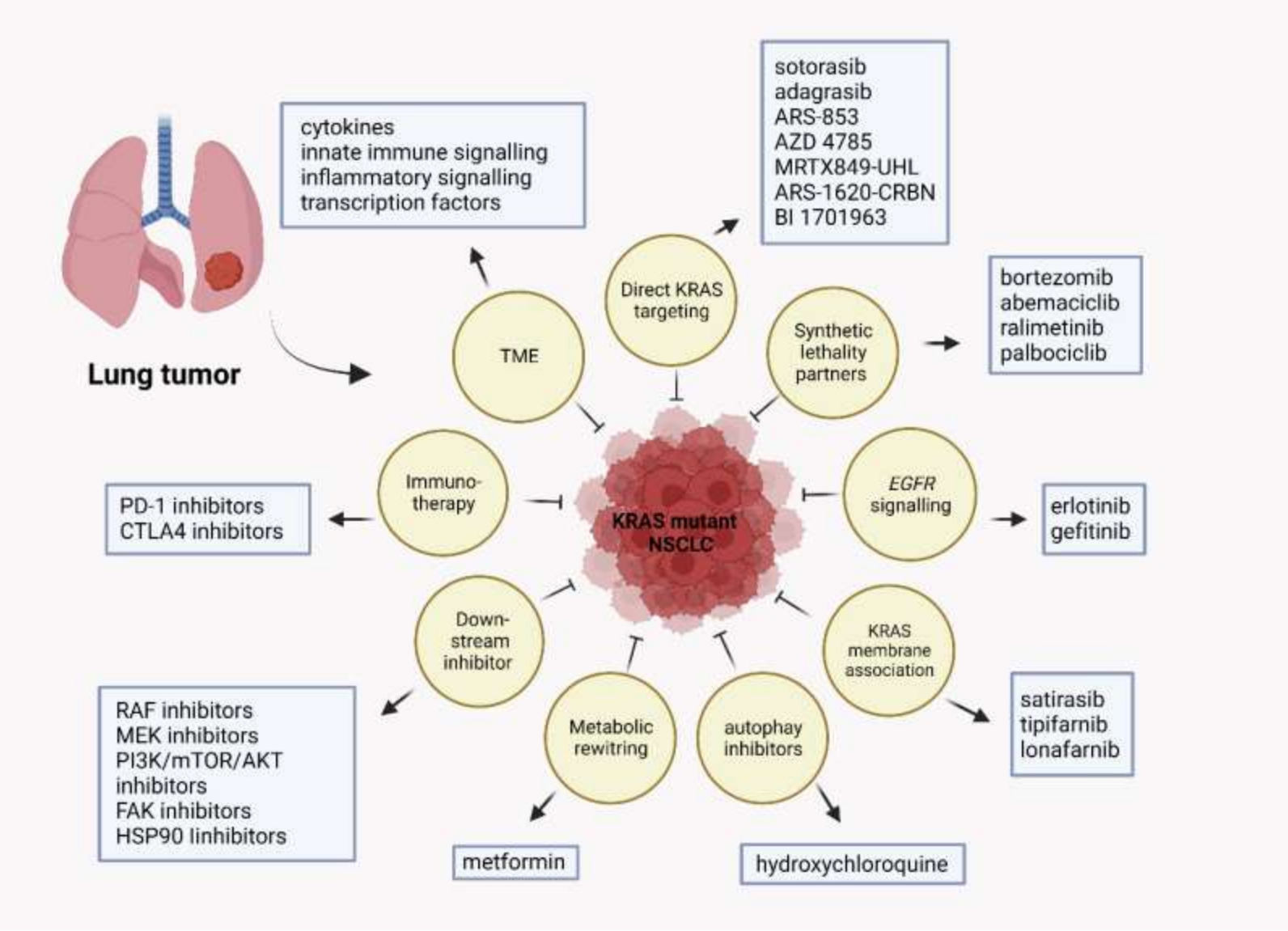
- RAS mutations are the **most common** oncogenic mutations in human cancers
- **KRAS** has the highest frequency among other members of the RAS family in NSCLC
- **30%** of NSCLC cases in **western countries** are KRAS mutated
- **10%** positive **Asian** patients
- RAS mutations specifically in codons **12, 13, and 61**
- G12D mutation in non smoker , G12C and G12V in smokers
- Worse survival for NSCLC with KRAS mutations compared to non-KRAS-mutant NSCLC



Karimi, N et al. Cells 2023, 12, 749

RAS

- Salirasib
- Sotorasib
- Adagrasib

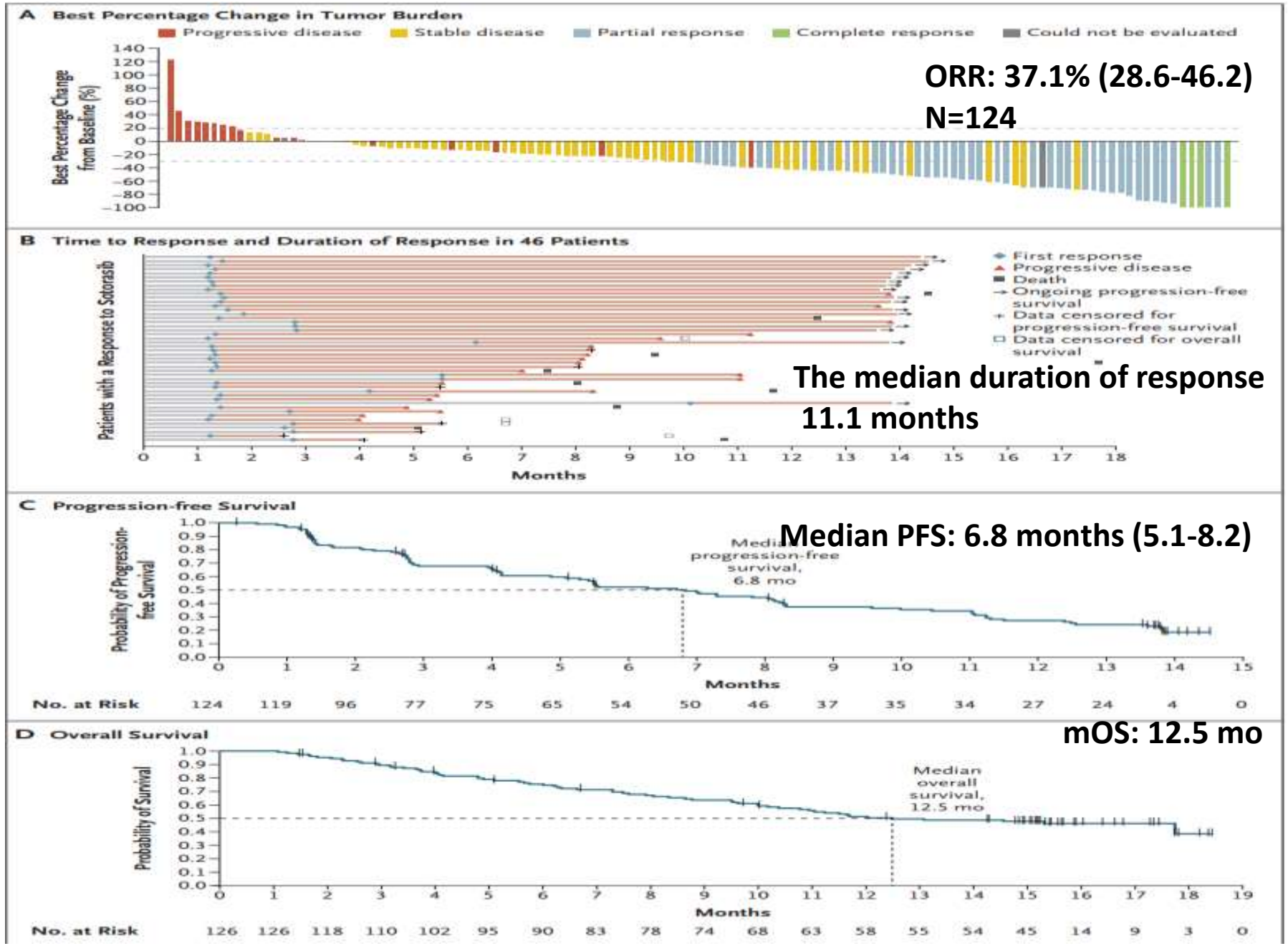


Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation

F. Skoulidis, B.T. Li, G.K. Dy, T.J. Price, G.S. Falchook, J. Wolf, A. Italiano, M. Schuler, H. Borghaei, F. Barlesi, T. Kato, A. Curioni-Fontecedro, A. Sacher, A. Spira, S.S. Ramalingam, T. Takahashi, B. Besse, A. Anderson, A. Ang, Q. Tran, O. Mather, H. Henary, G. Ngarmchamnanrith, G. Friberg, V. Velcheti, and R. Govindan

- Code Break 100: NCT03600883
- Single-group, phase 2 trial
- Orally at a dose of 960 mg OD until disease progression
- **KRAS p.G12C**– mutated advanced NSCLC previously treated with standard therapies
- **N=126**
- **ORR -(37.1%;** 95% CI, 28.6 to 46.2) including in 4 (3.2%) who had a completes and in 42 (33.9%) who had a partial response
- Median duration of response - 11.1 months
- The median OS was 12.5 months with DCR of 80.6%
- TRAEs were reported in 69.8% of patients, with 19.8% grade 3 events

N Engl J Med 2021;384:2371-81.



N Engl J Med 2021;384:2371-81.

Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with *KRAS*^{G12C} mutation: a randomised, open-label, phase 3 trial

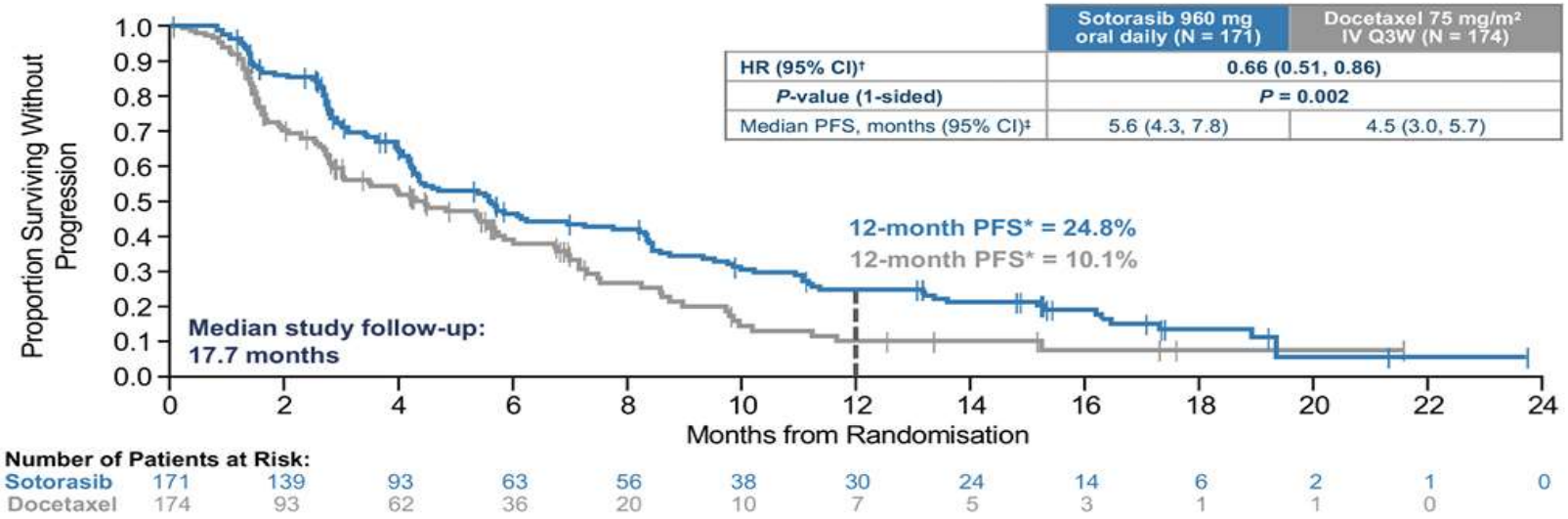
Study	Intervetion	Results	Adverse events
• Randomised, open-label phase 3 trial • *KRAS*^{G12C}-mutated advanced NSCLC, who progressed after **previous** platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor • **345 patients** ,sotorasib (n=171 [50%]) or docetaxel (n=174 [50%])	• 1:1 • **oral sotorasib (960 mg once daily)** or • **intravenous docetaxel (75 mg/m^2 once every 3 weeks)** • Treatment continued until an independent central confirmation of disease progression, intolerance, initiation of another anticancer therapy, withdrawal of consent, or death, whichever occurred first	• Median follow-up of 17·7 months (IQR 16·4–20·1) • **PFS** for sotorasib, compared with docetaxel (median PFS **5·6 months** [95% CI 4·3–7·8] *vs* **4·5 months** [3·0–5·7]; • **hazard ratio 0·66** [0·51–0·86]; p=0·0017) • **ORR** for sotorasib vs docetaxel **(28.1**% [95% CI 21.5–35.4%] vs **13.2**% [95% CI: 8.6–19.2%], respectively; P<0.001). • **Overall survival** was not different between the treatment groups (HR 1·01 [95% CI 0·77–1·33] • **DCR** was 82.5% for sotorasib vs 60.3% for docetaxel	• Sotorasib-the most common TRAEs of grade 3 or worse were diarrhoea (n= 20 [12%]), ALT increase (n=13 [8%]), and AST increase (n=9 [5%]). • Docetaxel-the most common TRAEs of grade 3 or worse were neutropenia (n=13 [9%]), fatigue (n=9 [6%]), and febrile neutropenia (n=8 [5%])

de Langen AJ, et al. Lancet. 2023 Mar 4;401(10378):733-746.

Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with *KRAS*^{G12C} mutation: a randomised, open-label, phase 3 trial

CodeBreaK 200 trial

Primary endpoint: PFS by BICR



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)	*P* = 0.002	
Median PFS, months (95% CI)‡	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

Number of Patients at Risk:

Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

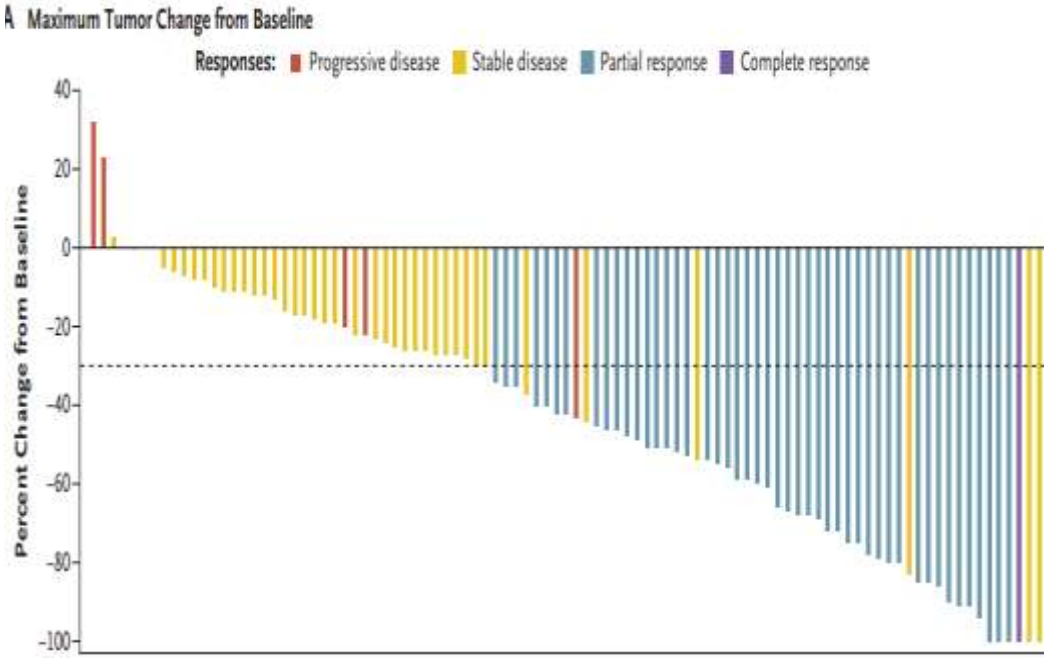
CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, P = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel
*PFS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model; P-value calculated using a stratified log-rank test.
‡Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

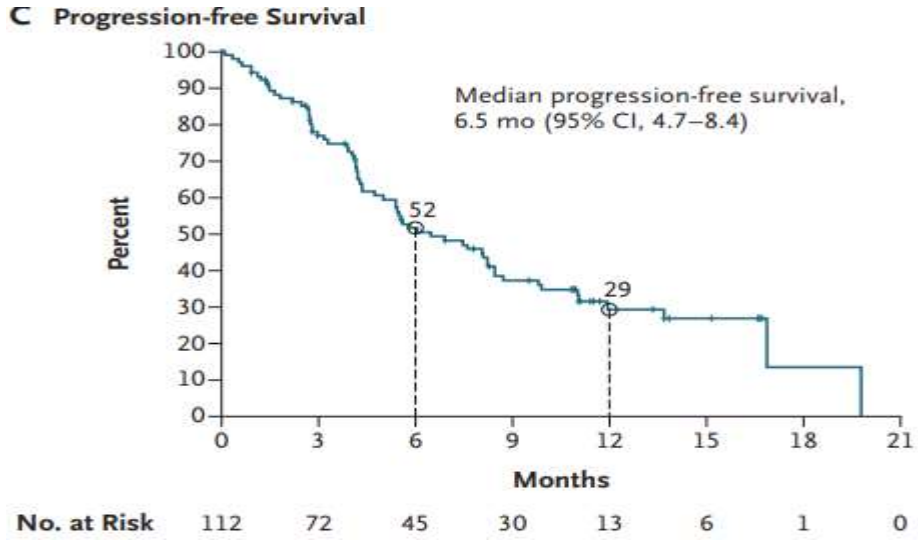
de Langen AJ, et al. Lancet. 2023 Mar 4;401(10378):733-746.

Adagrasib in Non–Small-Cell Lung Cancer Harboring a *KRAS*^{G12C} Mutation

- **KRYSTAL-1** (NCT03785249)
- Patients (n=116)
  - NSCLC with **KRASG12C** mutation
  - Unresectable or metastatic disease
  - Prior treatment with a PD-1/L1 inhibitor

  in combination or in sequence with chemotherapy
  - Treated, stable CNS metastases were allowed
- Adagrasib 600 mg BID capsule
- ORR 43% (95% CI, 33.5-52.6)
- Median PFS 6.5 months (95% CI, 4.7 to 8.4)
- Median OS 12.6 months (95% CI, 9.2 to 19.2)
- DCR was 80% (95% CI, 70.8-86.5)





N Engl J Med 2022;387:120-31

RAF

- RAF family of **serine/threonine kinases**, which includes ARAF, BRAF, and RAF-1 (also known as CRAF), plays a critical role in cellular growth, proliferation, and differentiation through the **MAPK signaling pathway**
- BRAF mutations divided into **three classes** based on mutation site
  - **Class I mutants** -including **V600**E/K/D/R, which occurs in the valine residue at amino acid position 600 of exon 15
  - **Class II mutants**-including K601, L597, G464, and G469 mutations, are located in the activation segment or Ploop and signal as RAS-independent dimer
  - **Class III mutants** - occur in the P-loop, catalytic loop, or DFG motif have impaired BRAF kinase activity; however, the activity of MAPK pathway signaling is enhanced via Raf-1 protooncogene CRAF activation
- All the class II and III mutations are **non-V600** mutations
- Approximately 50% of BRAF mutations in NSCLC are non-V600 mutations

Yan N, Guo S, Zhang H, Zhang Z, Shen S and Li X (2022) BRAF-Mutated Non-Small Cell Lung Cancer: Current Treatment Status and Future Perspective. Front. Oncol. 12:863043

RAF

- BRAF mutations are present in **3–5%** of NSCLC, almost exclusively in **adenocarcinoma** histology, though mutations in squamous cell carcinoma have been described
- The aggressive micropapillary architecture has been associated with V600E, whilst a mucinous pattern is common in non-V600 mutations
- Current or former smokers
- Smoking habits appear to be more common in class 2 and 3, whilst patients harbouring V600 mutations are more likely to be never smokers
- Class 2 and class 3 mutations were associated with a higher risk of brain metastasis at diagnoses, compared with class 1 alterations

Guaitoli G, Zullo L, Tiseo M, et al. Drugs Context. 2023;12:2022-11-3

RAF

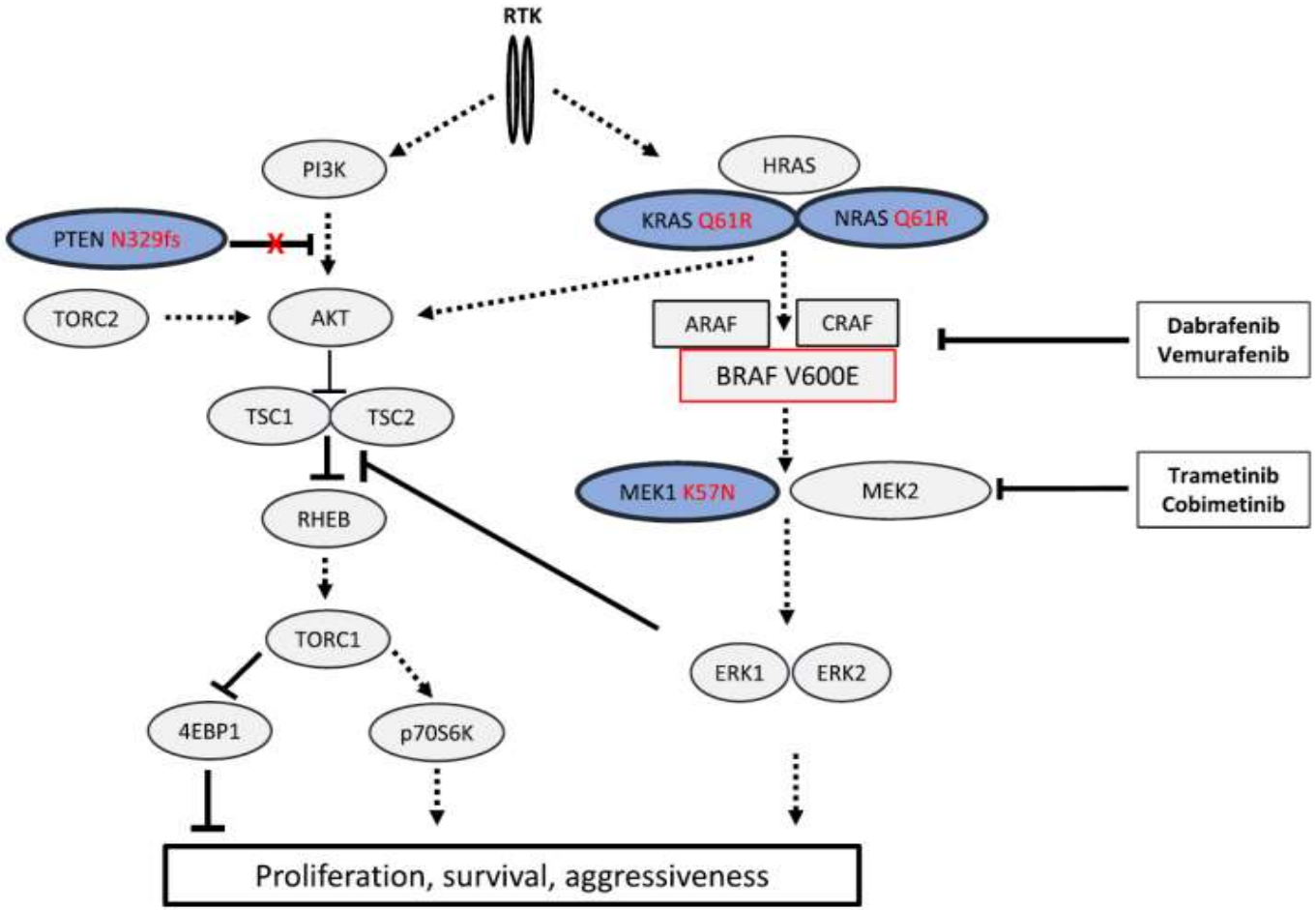

RTK
PI3K
HRAS
PTEN N329fs
KRAS Q61R
NRAS Q61R
TORC2
AKT
ARAF
CRAF
Dabrafenib
Vemurafenib
BRAF V600E
TSC1
TSC2
MEK1 K57N
MEK2
Trametinib
Cobimetinib
RHEB
TORC1
ERK1
ERK2
4EBP1
p70S6K
Proliferation, survival, aggressiveness

Table 2. Main studies of target therapies in advanced *BRAF*^{V600} NSCLC.

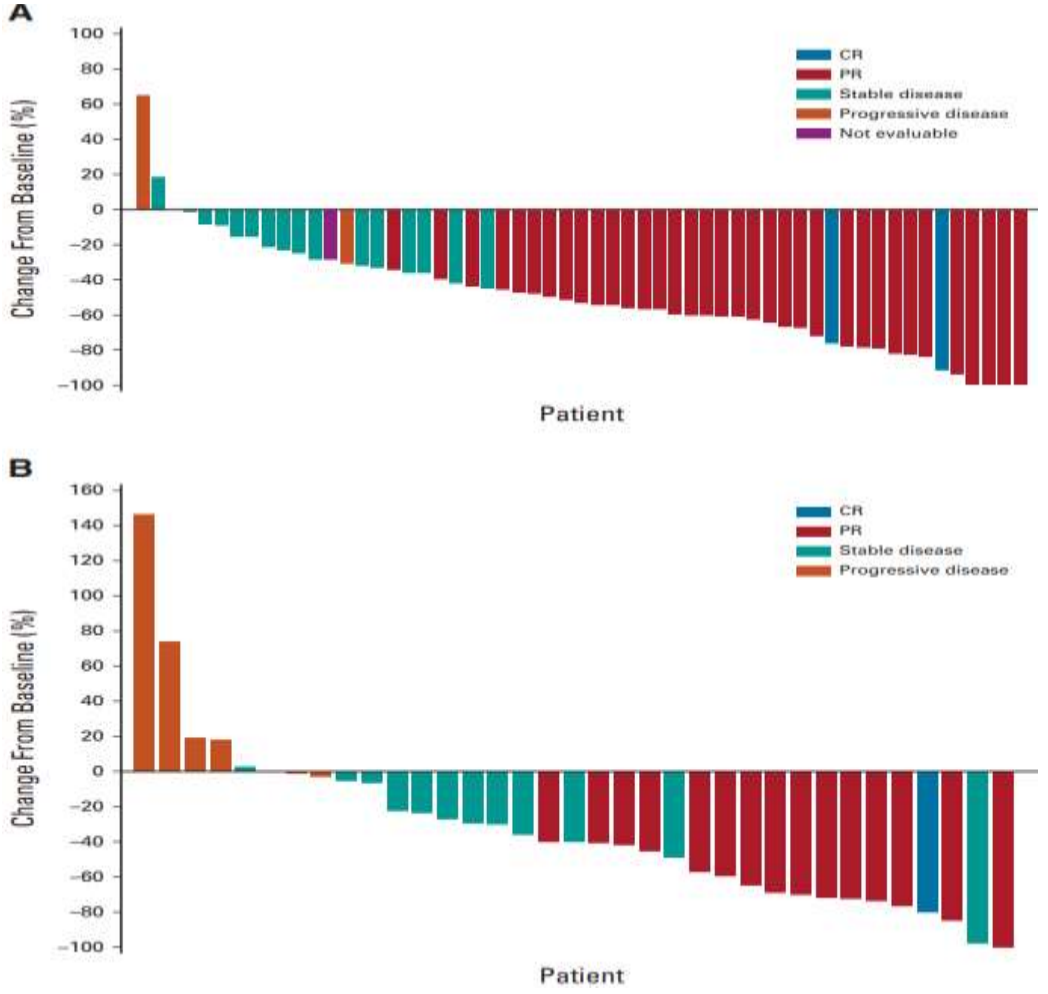
Study	Type	Drugs	Patients (*n*)	ORR (%)	DCR (%)	Median PFS, months (95% CI)	Median OS, months (95% CI)
NCT01336634-A[37]	Phase II	Dabrafenib	84	33	56	5.5 (2.8–7.3)	15.4 (7.3–NR)
NCT01336634-B[a,38]	Phase II	Dabrafenib + trametinib	57	68	81	10.2 (6.9–16.7)	18.2 (14.3–28.6)
NCT01336634-C[b,39]	Phase II	Dabrafenib + trametinib	36	64	75	10.8 (7.0–14.5)	17.3 (12.3–402)
NCI-MATCH (sub-protocol H)[42]	Phase II	Dabrafenib + trametinib	5	40	100	NA	NA
Auliac et al.[48]	Retrospective	Dabrafenib + trametinib	40	NA	NA	17.5 (7.1–23.0)	25.5 (16.6–NR)
EURAF cohort[49]	Retrospective	Dabrafenib	3	33	33	NA	NA
VE-BASKET (NSCLC cohort)[46]	Phase II	Vemurafenib	62	37.5[b] 37.0[a]	79	12.9[b] (4.0–NR) 6.1[a] (5.1–8.3)	NR[b] (6.0–NR) 15.4[a] (8.2–22.8)
AcSé (NSCLC cohort)[47]	Phase II	Vemurafenib	101	45	NA	5.3 (3.8–6.8)	10.0 (6.8–15.7)
EURAF cohort[49]	Retrospective	Vemurafenib	24[c]	54	96	NA	NA
EURAF cohort[49]	Retrospective	Sorafenib	1	100	100	NA	NA

[a]Previously treated patients; [b]Untreated patients; [c]V600E only.

Guaitoli G, Zullo L, Tiseo M, et al. Drugs Context.2023;12:2022-11-3

Phase II, Open-Label Study of Encorafenib Plus Binimetinib in Patients With *BRAF*^{V600}-Mutant Metastatic Non–Small-Cell Lung Cancer

- **98** patients (59 treatment-naıve and 39 previously treated)
- Oral Encorafenib 450 mg once daily plus Binimetinib 45 mg twice daily in 28-day cycles
- **ORR** of **75%** in treatment-naıve and **46%** in previously treated patients with BRAFV600E-mutant metastatic NSCLC
- The most frequently reported TRAEs (any grade) were gastrointestinal (nausea, diarrhea, and vomiting) and fatigue
- AEs led to permanent discontinuation dose, dose interruptions, dose reduction of both encorafenib and binimetinib in 15%, 44%, and 24% patients, respectively.



Riely GJ, Smit EF, Ahn M-J, et al: J Clin Oncol 41:3700-3711, 2023

Real-World Treatment Patterns and Effectiveness of Targeted and Immune Checkpoint Inhibitor-Based Systemic Therapy in *BRAF* Mutation-Positive NSCLC

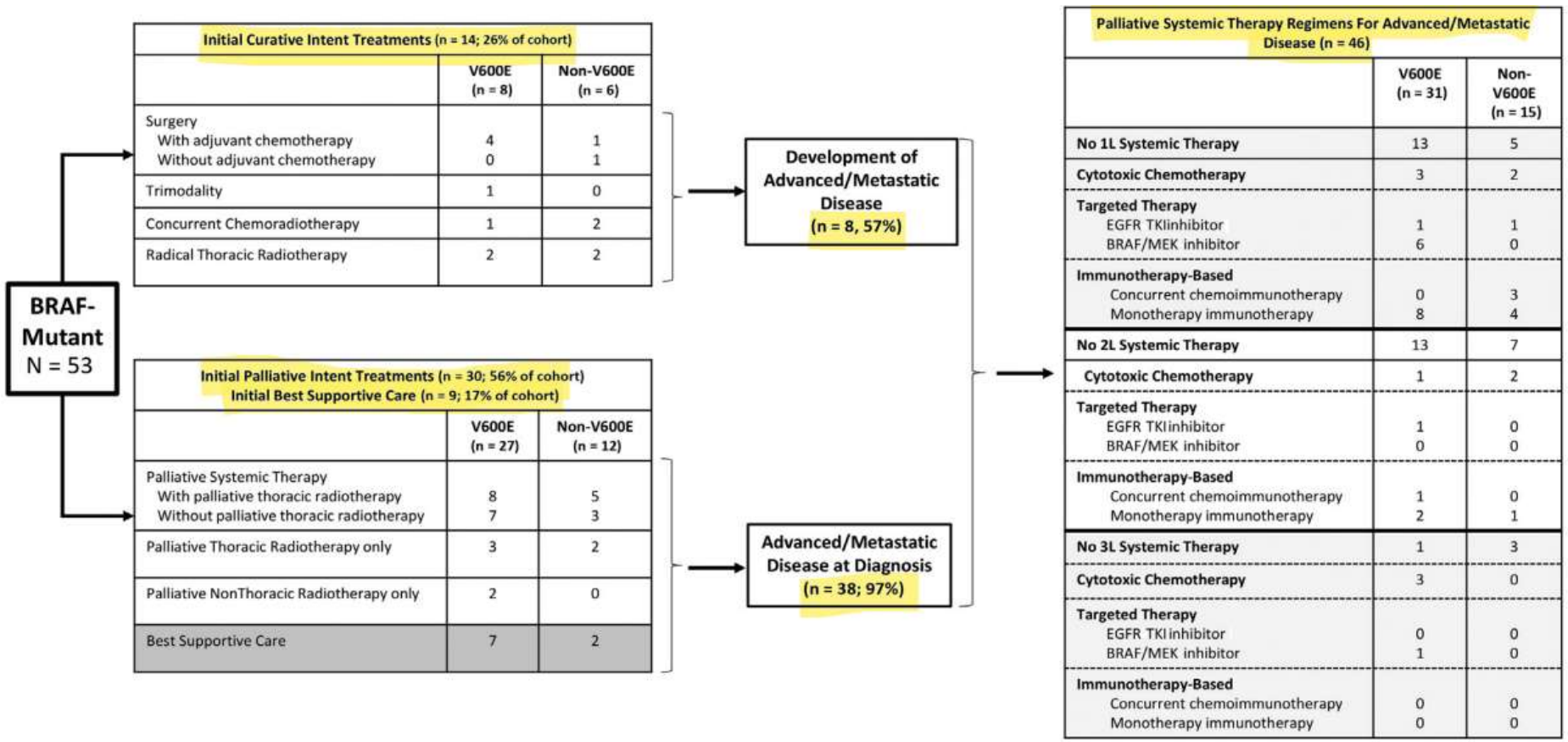
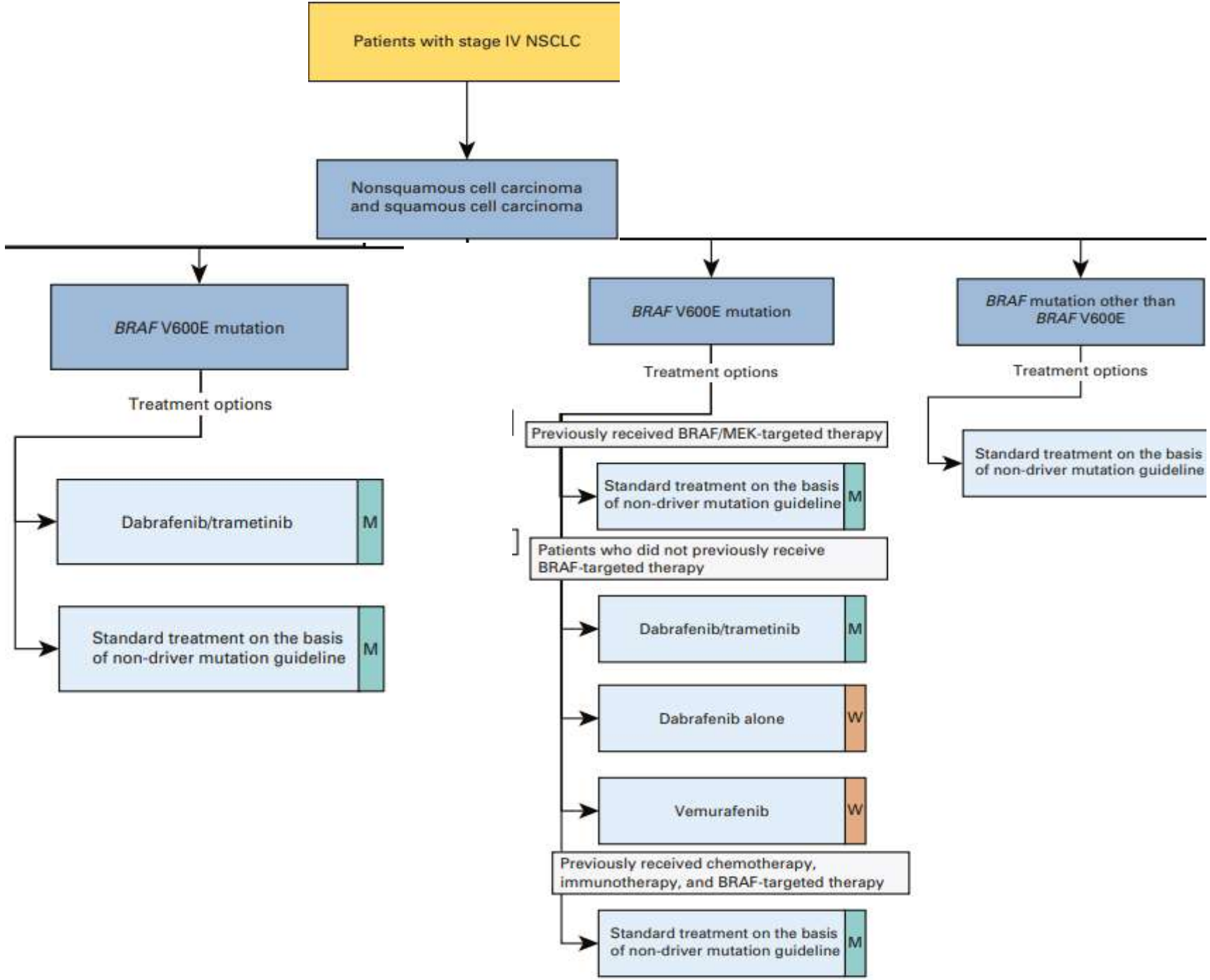


Figure 1. Initial treatment pathways and systemic therapy patterns. 1L, first line; 2L, second line; TKI, tyrosine kinase inhibitor.

Table 2. Response to Targeted and ICI-Based Systemic Therapies for BRAF-V600E Mutation-Positive Cohort

BRAF-V600E Patients Receiving Systemic Therapy (n = 17)

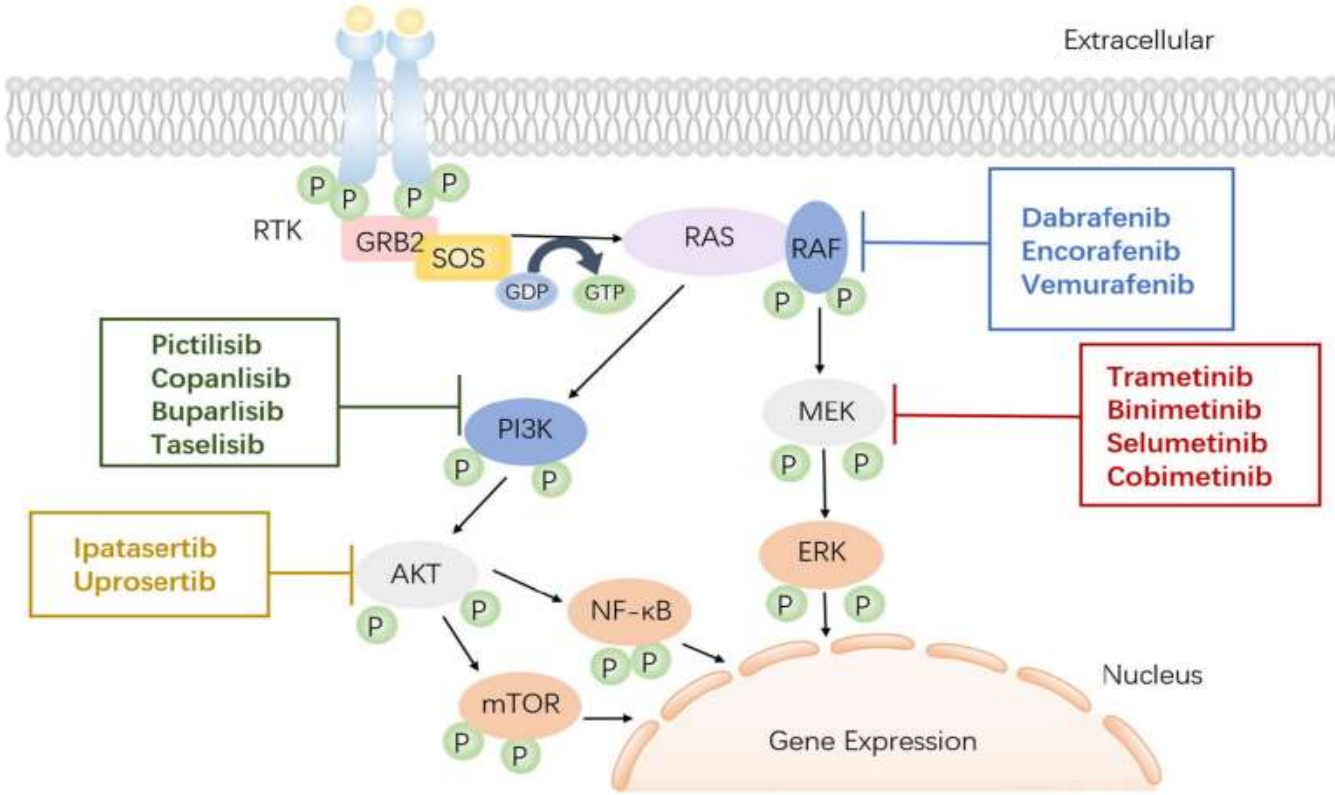
	1L Therapy			Any Line		
Clinical Data	1L Targeted BRAF/MEK Inhibitors (n = 6), n (%)	Nontargeted Systemic Therapy (n = 11), n (%)	*p* Value	Targeted BRAF/MEK Inhibitors (1L n = 6; 3L n = 1) (n = 7), n (%)	Immune Checkpoint Inhibitor (1L n = 8; 2L n = 2) (n = 10), n (%)	*P* Value
Systemic therapy type	Dabrafenib/trametinib	Cytotoxic chemotherapy (n = 3) Immunotherapy (n = 8)	-	Dabrafenib/trametinib	Monoimmunotherapy: Nivolumab (n = 1) Pembrolizumab (n = 9)	-
ECOG at initiation						
ECOG < 2	5 (83)	7 (64)	$\chi 2$, df(1) = 0.77 $p = 0.4$	6 (86)	6 (60)	$\chi 2$, df(1) = 1.4 $p = 0.2$
ECOG ≥ 2	1 (17)	4 (36)		1 (14)	4 (40)	
AJCC eighth edition M-stage at systemic therapy initiation						
M0	0 (0)	7 (64)	$\chi 2$, df(3) = 10.8 $p = 0.01$[a]	0 (0)	6 (60)	$\chi 2$, df(3) = 9.0 $p = 0.03$[a]
M1a	2 (34)	3 (27)		3 (43)	2 (20)	
M1b	3 (49)	1 (9)		3 (43)	1 (10)	
M1c	1 (17)	0 (0)		1 (14)	1 (10)	
PD-L1 status						
Negative (<1%)	0 (0)	1 (9)	$\chi 2$, df(3) = 3.8 $p = 0.3$	0 (0)	0 (0)	$\chi 2$, df(3) = 3.3 $p = 0.2$
Low (1%-49%)	2 (33)	1 (9)		3 (43)	1 (10)	
High (≥50%)	4 (67)	7 (64)		4 (66)	8 (80)	
Not tested/unknown	0 (0)	2 (18)		0 (0)	1 (10)	
Real-world ORR	33%	36%	$\chi 2$, df(1) = 0.02 $p = 0.9$	43%	50%	$\chi 2$, df(1) = 0.08 $p = 0.8$
Real-world DCR	67%	55%	$\chi 2$, df(1) = 0.2 $p = 0.6$	71%	60%	$\chi 2$, df(4) = 0.24 $p = 0.6$
Real-world primary resistance	33%	18%	$\chi 2$, df(1) = 0.5 $p = 0.5$	29%	20%	$\chi 2$, df(1) = 0.17 $p = 0.7$
Real-world PFS (mo) [95% CI]	15.2 [1.0-not reached]	30.9 [1.9-not reached]	Log-rank $p = 0.09$	16.0 [1.0-not reached]	10.4 [1.9-not reached]	Log-rank $p = 0.9$
6-mo PFS rate [95% CI]	67% [19%-90%]	79% [39%-94%]		71% [26%-92%]	67% [28%-88%]	
1-year survival rate [95% CI] (after detection of advanced/metastatic disease)	50% [11%-80%]	62% [28%-84%]	Log-rank $p = 0.45$	57% [17%-84%]	68% [31%-89%]	Log-rank $p = 0.4$
Reason for termination						
Progressive disease/ death	5 (83)	5 (45)	$\chi 2$, df(5) = 5.9 $p = 0.3$	5 (72)	4 (40)	$\chi 2$, df(4) = 6.0 $p = 0.2$



Singh N, et al. Journal of Clinical Oncology 2022 40:28, 3310-3322

MEK

- MEK1/2 are the downstream effectors of RAS and RAF
- MEK inhibitors have been developed as a strategy to treat NSCLC patients with KRAS or BRAF
- Trametinib
- Binimetinib
- Selumetinib
- Cobimetinib.



REVIEW Open Access

MEK inhibitors for the treatment of non-small cell lung cancer

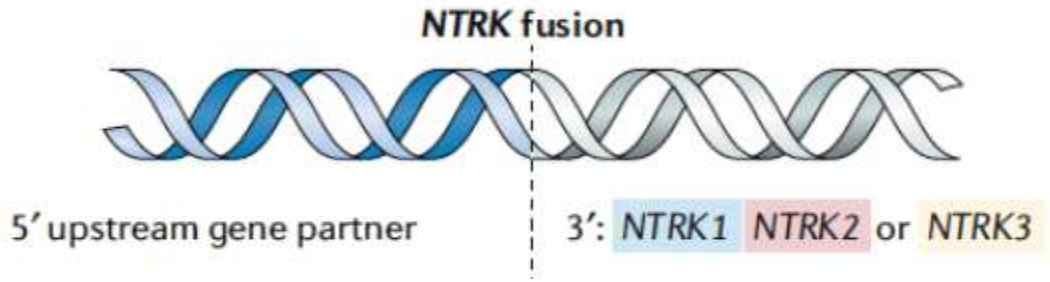
Table 2 Completed clinical trials of chemotherapy + MEK inhibitors in NSCLC

Study	Study design	Intervention	Comparation	Patient population	Patients (n)	Median OS (months)	Median PFS (months)	ORR (%)
Jänne et al. [43]	Phase2 (NCT00890825)	Selumetinib + docetaxel	Placebo + docetaxel	KRAS-mutant advanced NSCLC	87 (44 vs 43)	9.4 vs 5.2 (HR:0.8, 80% CI = 0.56–1.14, $P = 0.21$)	5.3 vs 2.1 (HR:0.58, 80%CI = 0.42–0.79, $P = 0.014$)	37% vs 0
Gandara et al. [46]	Phase1 (NCT01192165)	Trametinib + docetaxel	Trametinib + pemetrexed	NSCLC	95 (49 vs 46)	NA	KRAS wild-type:4.2 vs 5.8 KRAS-mutant type: 3.4 vs 4	KRAS wild-type:18% vs 11% KRAS-mutant type: 24% vs 17%
Jänne et al. [47]	Phase1 (NCT01933932)	Selumetinib + docetaxel	Placebo + docetaxel	KRAS-mutant NSCLC	510 (251 VS 254)	8.7 VS 7.9 (HR:1.05, 95% = 0.85–1.30, $P = 0.64$)	3.9 VS 2.8 (HR:0.93, 95%CI = 0.77–1.12, $P = 0.44$)	20.1% vs 13.7% (OR:1.61, 95%CI = 1–2.62, $P = 0.05$)
Soria et al. [49]	Phase2 (NCT01750281.)	Selumetinib + docetaxel	Placebo + docetaxel	NSCLC	212	5.7 vs 7.7 vs 11.5	3 vs 4.2 vs 4.3 (HR = 1.12,0.92)	33% vs 14% (OR:3.26, 95%CI = 1.47–7.95)
Greystoke et al. [50]	Phase1 (NCT01809210)	Selumetinib + gemcitabine/cisplatin or carboplatin	Selumetinib + pemetrexed/cisplatin or carboplatin	NSCLC	55	NA	NA	36% vs 33% vs 19% vs 13%
Seto et al. [51]	Phase1 (NCT01605916)	Selumetinib + docetaxel	Selumetinib	Solid tumor of NSCLC	25	NA	NA	NA
Melosky et al. [44]	phase2	Selumetinib + pemetrexed + cisplatin	No selumetinib	Non-squamous NSCLC	62	10 vs 10.1 vs 15.3 (HR = 1.56,1.72) ($P = 0.31$,0.2)	7.2 vs 6.9 vs 4 (HR = 0.82,0.77) ($P = 0.56$,0.44)	35% vs 62% vs 24%

Han, J., Liu, Y., Yang, S. et al. MEK inhibitors for the treatment of non-small cell lung cancer. J Hematol Oncol 14, 1 (2021)

Neurotrophic tropomyosin receptor kinase (NTRK) gene fusion

- NTRK genes involving NTRK1, NTRK2 and NTRK3, encode the proteins
- Tropomyosin receptor kinase (TRK) family TRKA, TRKB and TRKC respectively, which are **transmembrane receptor tyrosine kinases**
- **Prevalence** of **NTRK fusions** reported in multicontinental studies varies from **0.1% to 3.3%**
- NGS followed by IHC, FISH ,RT-PCR
- The first-generation NTRK-TKIs
  - **Larotrectinib**
  - **Entrectinib**



TRK inhibitor	Overall population					NSCLC		
	N	ORR	PFS	CNS ORR	CNS PFS	*N*	ORR	CNS ORR
Larotrectinib	159	79% (121/153)	28.3 (22.1–NE)	75% (9/12)	NA	12	75% (9/12)	NA
Entrectinib	54	57% (31/54)	11.2 (8.0–14.9)	50% (6/12)	7.7 (4.7–NE)	10	70% (7/10)	NA

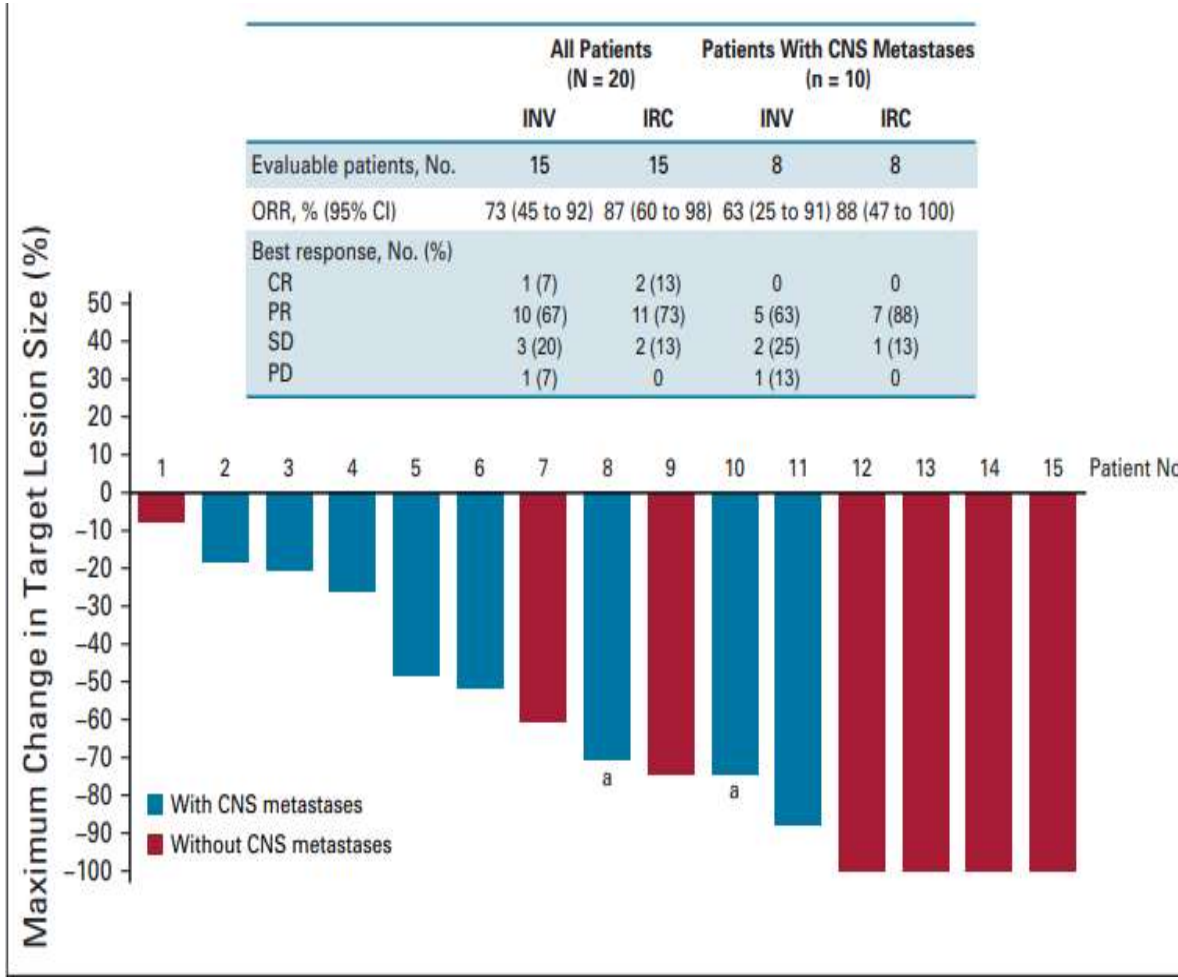
F Liu et al. Front Oncol. 2022 Mar 17;12:864666

PRECISION MEDICINE

Efficacy and Safety of Larotrectinib in Patients With Tropomyosin Receptor Kinase Fusion–Positive Lung Cancers

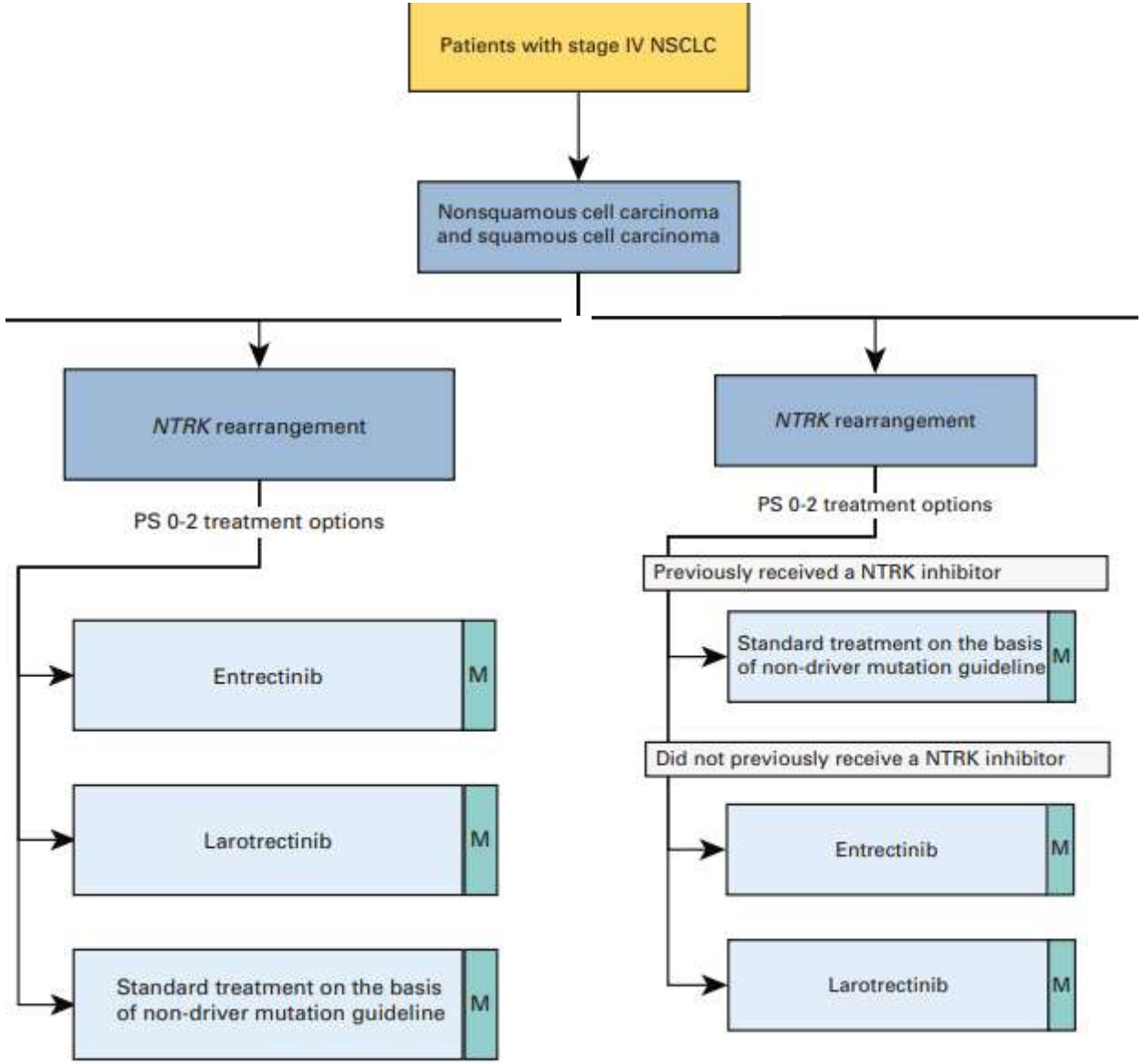
- Phase II
- N=20
- TRK fusion–positive lung cancer
- ORR -73% (95% CI,45 -92)
- DOR -33.9 months(95% CI,5.6 - 33.9)
- PFS -35.4 months(95% CI, 5.3 -35.4)
- OS- 35.4 months(95% CI, 5.3 -35.4)

	All Patients (N = 20)		Patients With CNS Metastases (n = 10)	
	INV	IRC	INV	IRC
Evaluable patients, No.	15	15	8	8
ORR, % (95% CI)	73 (45 to 92)	87 (60 to 98)	63 (25 to 91)	88 (47 to 100)
Best response, No. (%)				
CR	1 (7)	2 (13)	0	0
PR	10 (67)	11 (73)	5 (63)	7 (88)
SD	3 (20)	2 (13)	2 (25)	1 (13)
PD	1 (7)	0	1 (13)	0



A Drilon, et al. JCO Precis Oncol. 2022 Jan;6:e2100418.

NTRK



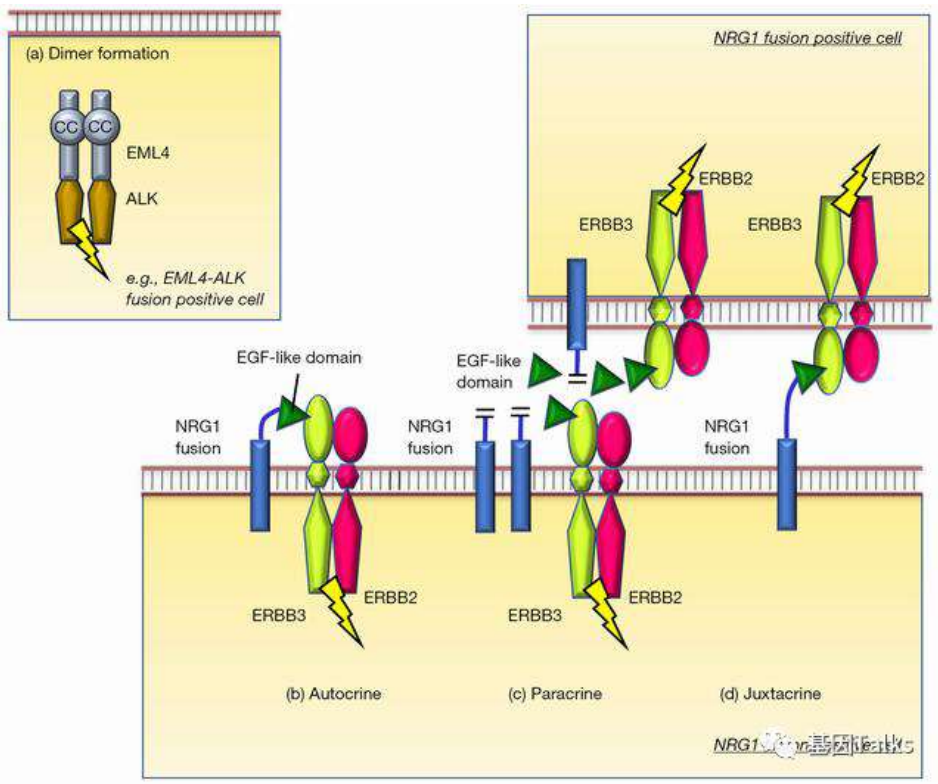
Singh N, et al. Journal of Clinical Oncology 2022 40:28, 3310-3322

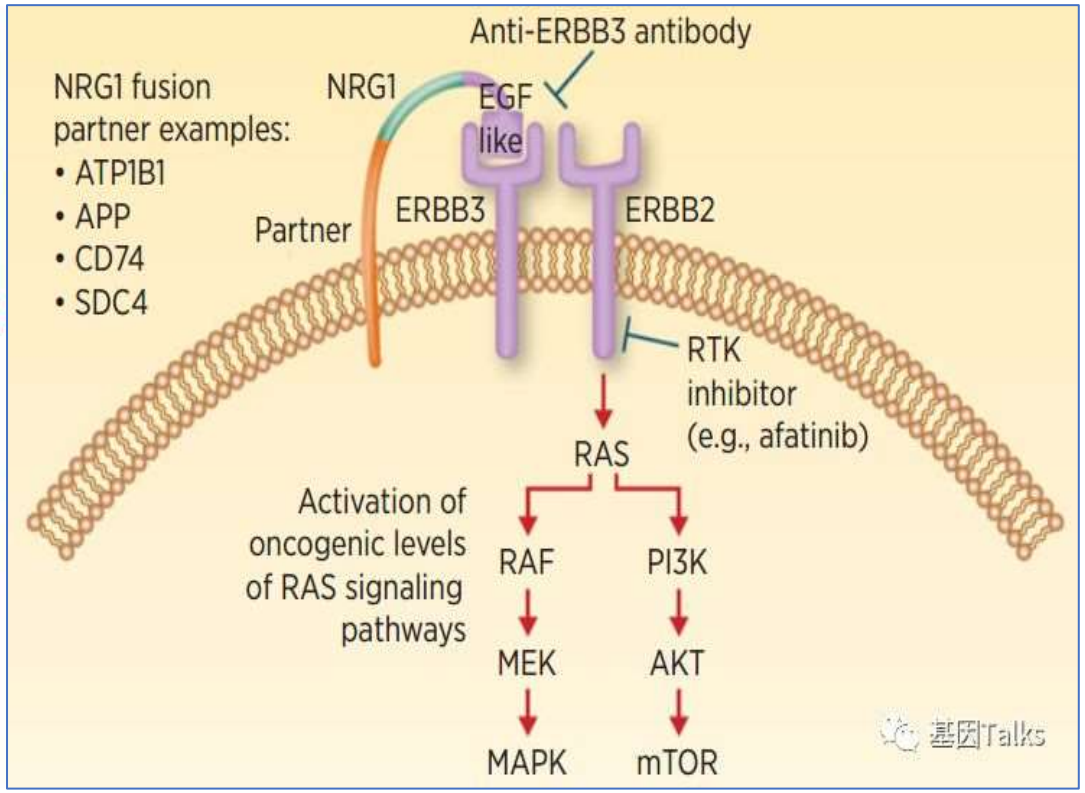
NRG1

- NRG1 (NeuReGulin 1, neuregulin 1) is a member of the epidermal growth factor (EGF) ligand family
- NRG1-receptor binding activates the **ERBB2-ERBB3 heterocomplex** and controls proliferation, differentiation, and survival in both normal and tumor cells through the predominant signaling cascades PI3K-AKT and MAP kinase
- Identified across a wide range of tumors including **NSCLC** (especially mucinous adenocarcinoma subtype), **gallbladder cancer, pancreatic cancer, renal cell carcinoma, ovarian cancer and hepatic cholangiocarcinoma**
- Detection of NRG1 gene fusions in solid tumors - **RNA NGS**

Chevallier M, et al.World J Clin Oncol 2021 April 24; 12(4): 217-237

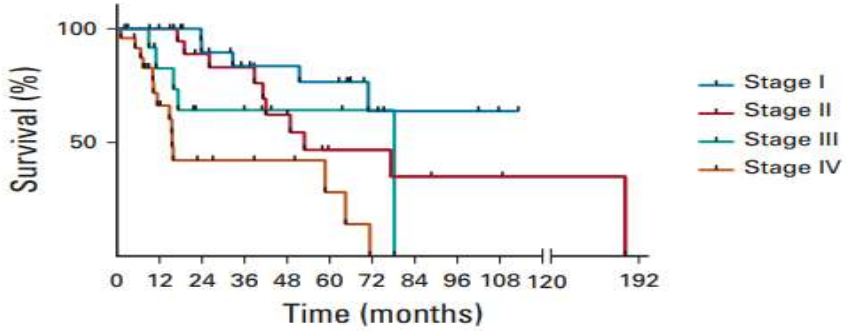
NRG1


(a) Dimer formation
CC CC
EML4
ALK
e.g., EML4-ALK fusion positive cell
NRG1 fusion positive cell
ERBB2
ERBB3
ERBB3
ERBB2
EGF-like domain
EGF-like domain
NRG1 fusion
NRG1 fusion
NRG1 fusion
ERBB3
ERBB2
ERBB3
ERBB2
(b) Autocrine
(c) Paracrine
(d) Juxtacrine


Anti-ERBB3 antibody
NRG1 fusion partner examples:
• ATP1B1
• APP
• CD74
• SDC4
NRG1
EGF like
Partner
ERBB3
ERBB2
RTK inhibitor (e.g., afatinib)
RAS
Activation of oncogenic levels of RAS signaling pathways
RAF
PI3K
MEK
AKT
MAPK
mTOR

Clinicopathologic Features and Response to Therapy of *NRG1* Fusion–Driven Lung Cancers: The eNRGy1 Global Multicenter Registry

- N=110 with *NRG1* fusion−positive
- 57 % never smoking
- 57 % mucinous adenocarcinoma
- 71 % nonmetastatic

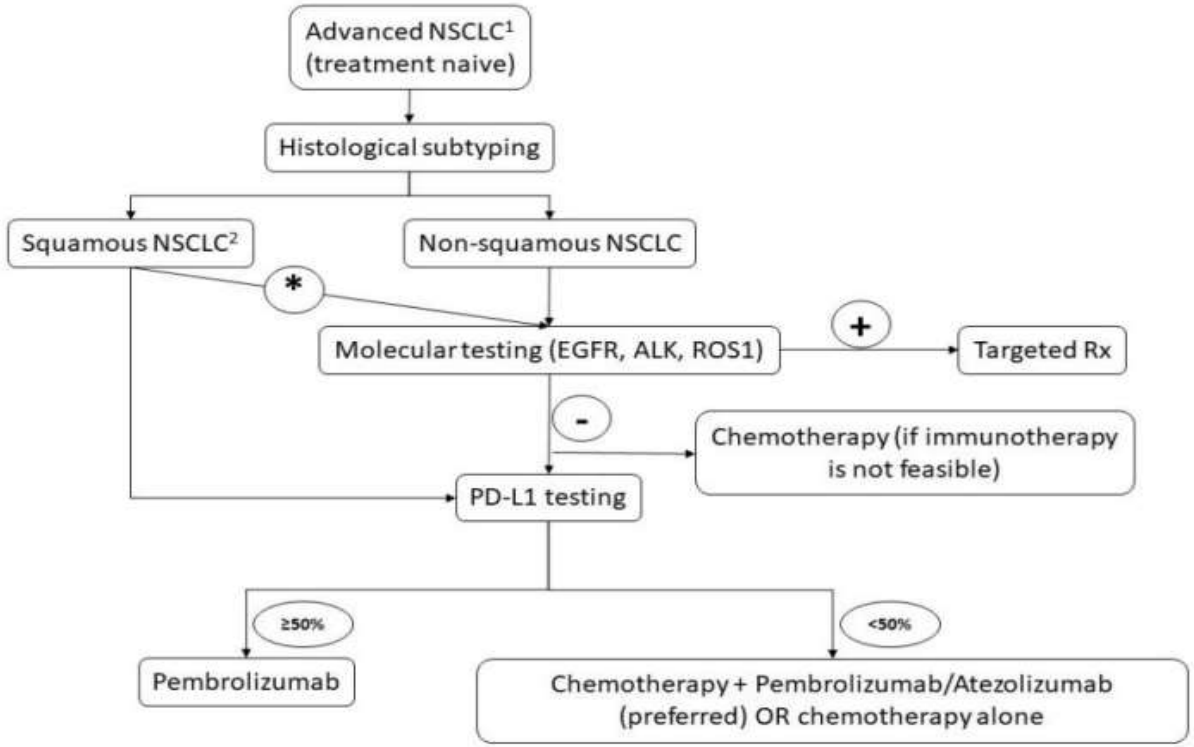


Stage at diagnosis	Stage I	Stage II	Stage III	Stage IV
Median OS (months)	NR	52.9	78.2	15.5
95% CI (months)	51.5 to U	38.8 to U	11.0 to U	10.3 to 64.5

Response	Platinum-Doublet–Based Chemotherapy	Taxane-Based Chemotherapy	Combined Chemotherapy and Immune Therapy	Single-Agent Immunotherapy	Targeted Therapy With Afatinib
Response rate, %	13	14	0	20	25
CR, % (n/N)	0 (0/15)	0 (0/7)	0 (0/9)	0 (0/5)	0 (0/20)
PR, % (n/N)	13 (2/15)	14 (1/7)	0 (0/9)	20 (1/5)	25 (5/20)
SD, % (n/N)	47 (7/15)	14 (1/7)	44 (4/9)	20 (1/5)	15 (3/20)
PD, % (n/N)	40 (6/15)	71 (5/7)	56 (5/9)	60 (3/5)	60 (12/20)
Median PFS (95% CI), range	5.8 months (2.2 to 9.8), 0.7-12.1	4.0 months (0.8 to 5.3), 0.8-5.5	3.3 months (1.4 to 6.3), 1.4-15.2	3.6 months (0.9 to undefined), 0.9-11.2	2.8 months (1.9 to 4.3), 0.3-25.3

Drilon, et al. J Clin Oncol 39:2791-2802.

Algorithm for treatment-naïve advanced NSCLC

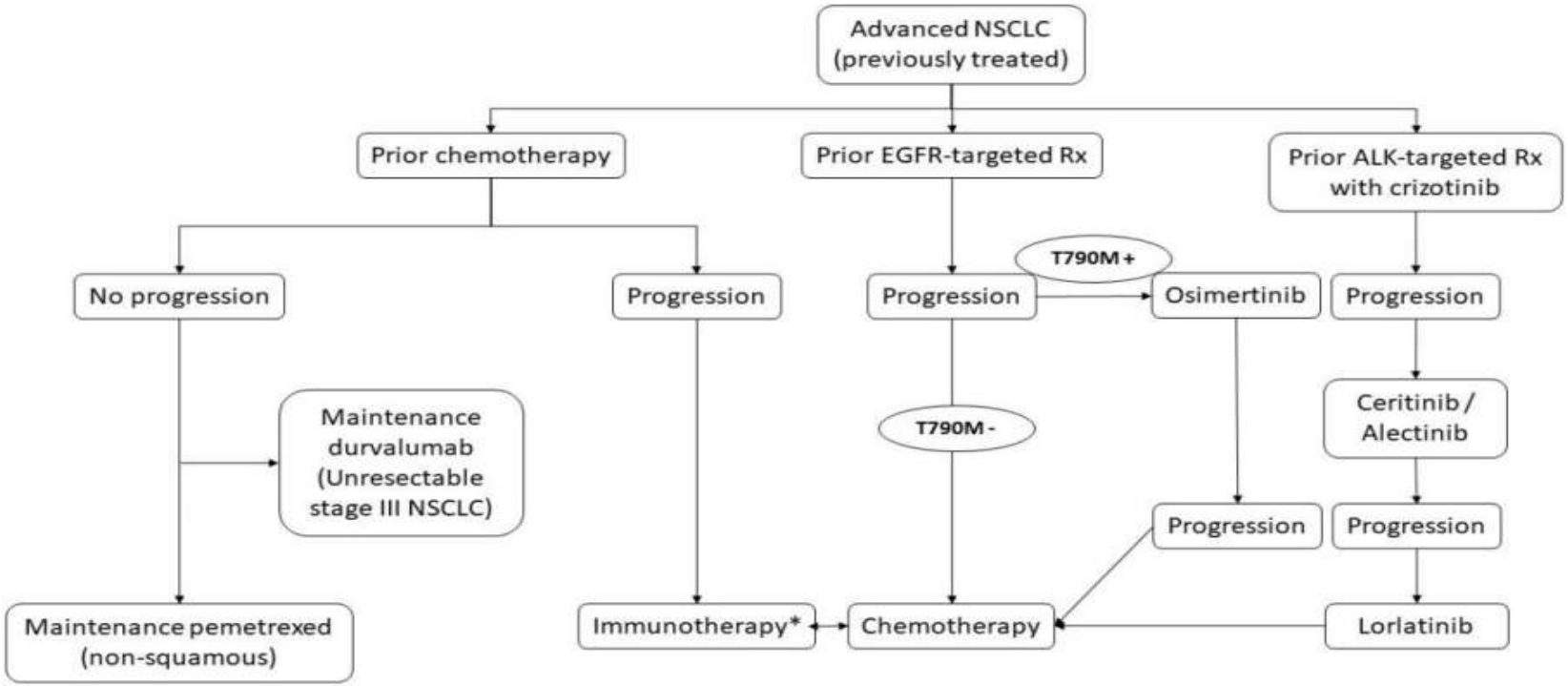


ALK anaplastic lymphoma kinase, EGFR epidermal growth factor receptor, NSCLC non-small cell lung cancer, PD-L1 programmed death-ligand 1

[1]Advanced NSCLC will include: Stage IV (excluding oligometastatic disease for which definitive therapy is feasible) and patients eligible for concurrent chemoradiotherapy, but unfit for it (Stage IIIC [T3N3, T4N3] and Stage IIIB [T1/T2N3, invasive T3N2, T4N2]).

[2]Non-smokers, females of relatively younger age.

Algorithm for previously-treated advanced NSCLC

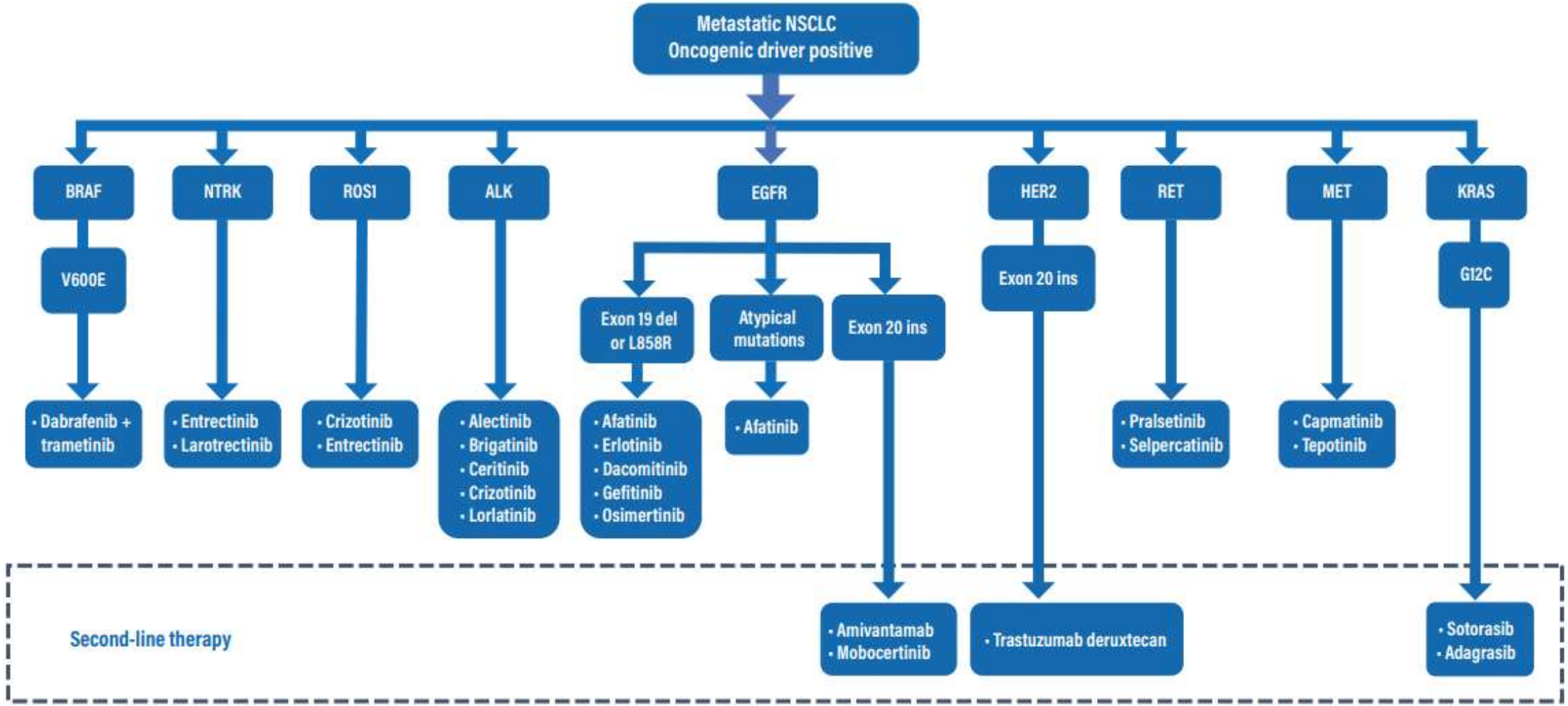


ALK anaplastic lymphoma kinase, EGFR epidermal growth factor receptor, NSCLC non-small cell lung cancer, PD-L1 programmed death-ligand 1

*Pembrolizumab (if PD-L1 ≥1%), or nivolumab/atezolizumab (regardless of PD-L1 status); second-line chemotherapy or docetaxel in combination with nintedanib/ramucirumab are also reasonable options.

Agent	Dose	Major treatment-related adverse events
Erlotinib	150 mg OD	Rash, diarrhoea
Gefitinib	250 mg OD	Rash, diarrhoea
Afatinib	40 mg OD	Diarrhoea, rash, stomatitis, paronychia
Osimertinib	80 mg OD	Rash/acne, diarrhoea, dry skin, paronychia, stomatitis
Crizotinib	250 mg BD	Vision disorder, nausea, edema, diarrhoea, vomiting, elevated transaminases, and constipation
Ceritinib	450 mg OD	Diarrhea, nausea, vomiting, and an increase in alanine aminotransferase
Alectinib	600 mg BD	Anemia, myalgia, increased bilirubin, increased weight, musculoskeletal pain, and photosensitivity reaction
Dabrafenib + Trametinib	152 mg OD 2 mg OD	Fever, nausea, vomiting, dry skin, peripheral edema, diarrhoea, decreased appetite, and cough, increase AST /ALT
Vemurafenib	960 mg BD	nausea (40%)
Adagrasib	600 mg BD	Diarrhea, nausea, vomiting, fatigue, increased ALT or AST, increased creatinine
Sotorasib	960 mg OD	diarrhoea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, and cough

Agent	Dose	Major treatment-related adverse events
Lorlatinib	100 mg OD	Hyperlipidemia, edema, increased weight, peripheral neuropathy, and cognitive effects
Brigatinib	180 mg OD	GI events (diarrhea, nausea, vomiting) increased blood CPK, cough, and increased aminotransferases
Entrectinib	600 mg OD	Dysgeusia, dizziness, constipation, fatigue, diarrhoea, weight gain, paresthesia
Selpercatinib	160 mg BD	Dry mouth, diarrhea, increased aspartate aminotransferase, increased alanine aminotransferase, hypertension
Pralsetinib	400 mg OD	Neutropenia, leukopenia, increased aspartate aminotransferase, anemia, increased alanine aminotransferase, constipation, fatigue, increased blood creatine phosphokinase
Larotrectinib	100 mg BD	Myalgias, dizziness, nausea, increased alanine aminotransferase
Dacomitinib	45 mg OD	Dermatitis, diarrhoea, elevated transaminase
Capmatinib	400 mg BD	edema, nausea, musculoskeletal pain, fatigue, vomiting, dyspnea, cough, and decreased appetite
Tepotinib	450mg OD	Peripheral edema, nausea, diarrhoea, blood creatinine increased, hypoalbuminemia
Trastuzumab deruxtecan	5.4 mg/kg or 6.4 mg/kg	Nausea, fatigue, alopecia, vomiting, neutropenia, anemia, diarrhoea , Drug-related ILD 14% with 6.4 mg/kg and 5.9% with 5.4 mg/kg

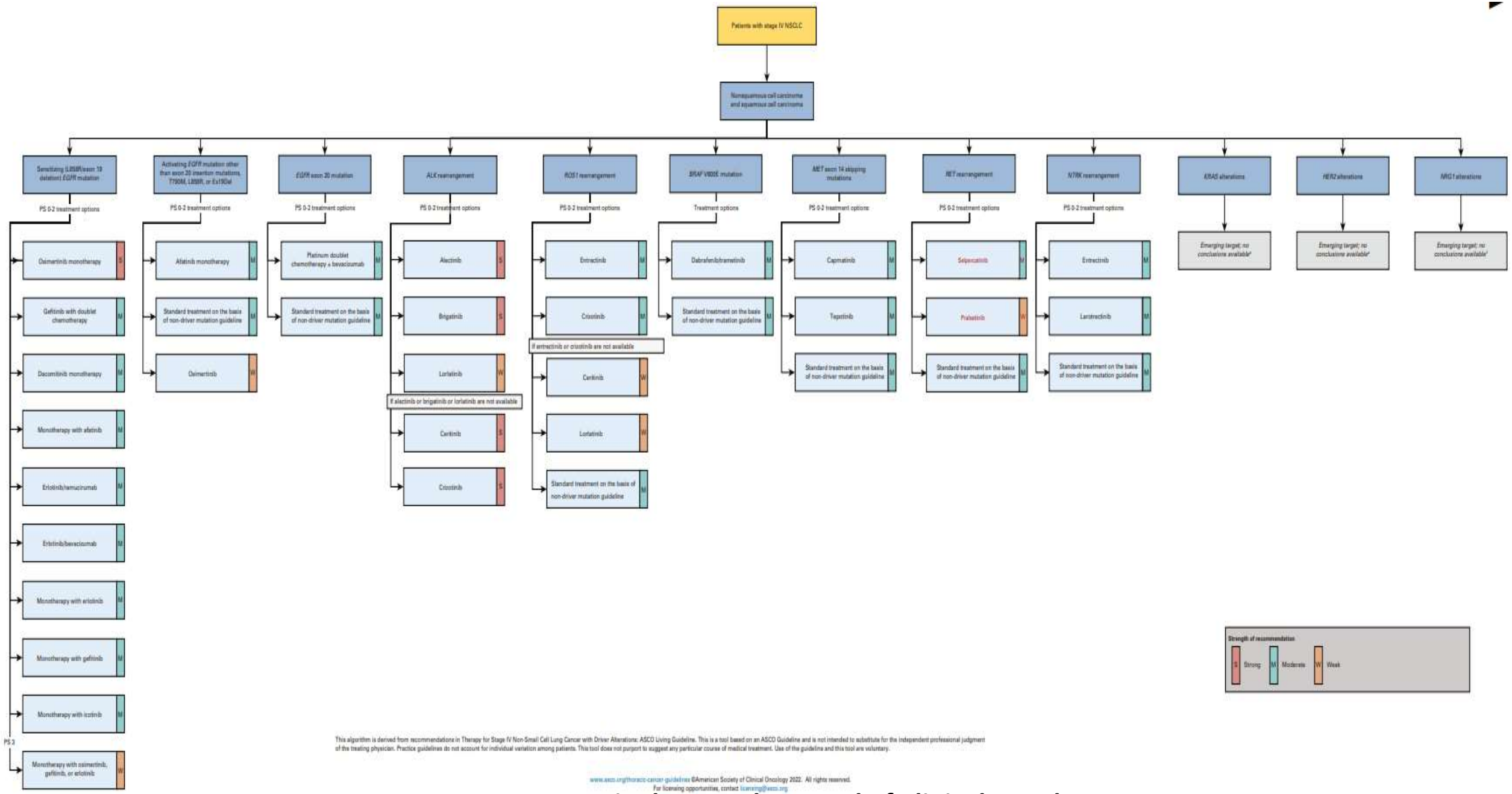

Metastatic NSCLC
Oncogenic driver positive
BRAF
V600E
• Dabrafenib + trametinib
NTRK
• Entrectinib
• Larotrectinib
ROS1
• Crizotinib
• Entrectinib
ALK
• Alectinib
• Brigatinib
• Ceritinib
• Crizotinib
• Lorlatinib
EGFR
Exon 19 del or L858R
• Afatinib
• Erlotinib
• Dacomitinib
• Gefitinib
• Osimertinib
Atypical mutations
• Afatinib
Exon 20 ins
• Amivantamab
• Mobocertinib
HER2
Exon 20 ins
• Trastuzumab deruxtecan
RET
• Pralsetinib
• Selpercatinib
MET
• Capmatinib
• Tepotinib
KRAS
G12C
• Sotorasib
• Adagrasib
Second-line therapy

	Targeted therapy	ORR	PFS	OS
ALK	Crizotinib 1L (vs chemo) **PROFILE 10141**	74% (vs 45%)	10.9 mo (vs 7.0 mo)	56.6% at 4y(vs 49.1%)
	Ceritinib 1L (vs chemo **ASCEND-4**	72.5% (vs 26.7%	16.6 mo (vs 8.1 mo)	NR
	Brigatinib 1L (vs crizotinib)	71% (vs 60%)	24.0 mo (vs 11.1 mo)	71% at 3 y (vs 68%)
	Alectinib 1L (vs crizotinib) **ALEX**	82.9% (vs 75.5%)	34.8 mo (vs 10.9 mo)	62.5% at 5 y (vs 45.5%)
	Lorlatinib 1L (vs crizotinib) **CROWN**	76% (vs 58%)	64% at 3 y (vs 19%)	NR
ROS1	Crizotinib **PROFILE 1001**	72%	19.3 mo	51.4 mo
	Lorlatinib (2L)	35%	DoR 13.8 mo	NR
	Entrectinib	68%	15.7 mo	47.8 mo
METex14	Crizotinib	32%	7.3 mo	NR
	Capmatinib **GEOMETRY mono-11**	1L 68%	1L 12.4 mo	1L 18.8 mo
	Tepotinib **VISION**	1L 61.3%	1L 13.8 mo	NR

Brea E, et al,Hematol Oncol Clin N Am 37 (2023) 575–594

	Targeted therapy	ORR	PFS	OS
HER2 mutations	Trastuzumab-deruxtecan **DESTINY-Lung01**	55%	8.2 mo	17.8 mo
KRAS G12 C	Sotorasib 2L vs chemo **CodeBreak 200**	28.1% (vs 13.2%)	5.6 mo (vs 4.5 mo)	10.6 mo (vs 11.3 mo)
	Adagrasib 2L + **KRYSTAL-18**	42.9%	6.5 mo	12.6 mo
NTRK	Entrectinib	57 %	11 mo	21 mo
	Larotrectinib	79	28.5	44.4
BRAF	Dabrafenib-trametinib 1L	1L 62.3%	1L 10.8 mo	1L 17.3 mo
RET	Selpercatinib **LIBRETTO-001**	84%	22	NR
	Pralsetinib **ARROW3**	72%	13	NR
NRG1	Afatinib	NR	NR	NR

Brea E, et al,Hematol Oncol Clin N Am 37 (2023) 575–594



This algorithm is derived from recommendations in Therapy for Stage IV Non-Small Cell Lung Cancer with Driver Alterations: ASCO Living Guideline. This is a tool based on an ASCO Guideline and is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients. This tool does not purport to suggest any particular course of medical treatment. Use of the guideline and this tool are voluntary.

Singh N, et al. Journal of Clinical Oncology 2022 40:28, 3310-3322

Conclusion

- All patients of advanced NSCLC (specially adenocarcinoma) should offered molecular testing for driver alterations
- At least EGFR, AKL, ROS1 to be tested
- Multiplex NGS testing should be standard practice if available
- Barring a therapeutic emergency, no patient should be started on systemic therapy before a comprehensive molecular analysis has been completed
- Treatment of driver mutations identified in metastatic NSCLC some leading to therapeutic success and some leading to failure
- More RCTs are required for efficacy and safety of targeted drug