Mechanism of Resistance to Osimertinib in EGFR Mutated Lung Cancer

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Current Indications

- Adjuvant therapy after tumor resection in adult patients with NSCLC whose tumors *have EGFR* ***exon 19 deletions or exon 21 L858R*** mutations, as detected by an FDA-approved test.
- 1L Rx of adult patients with metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- Treatment of adult patients with metastatic ***EGFR T790M*** mutation positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy

Osimertinib resistance mechanisms

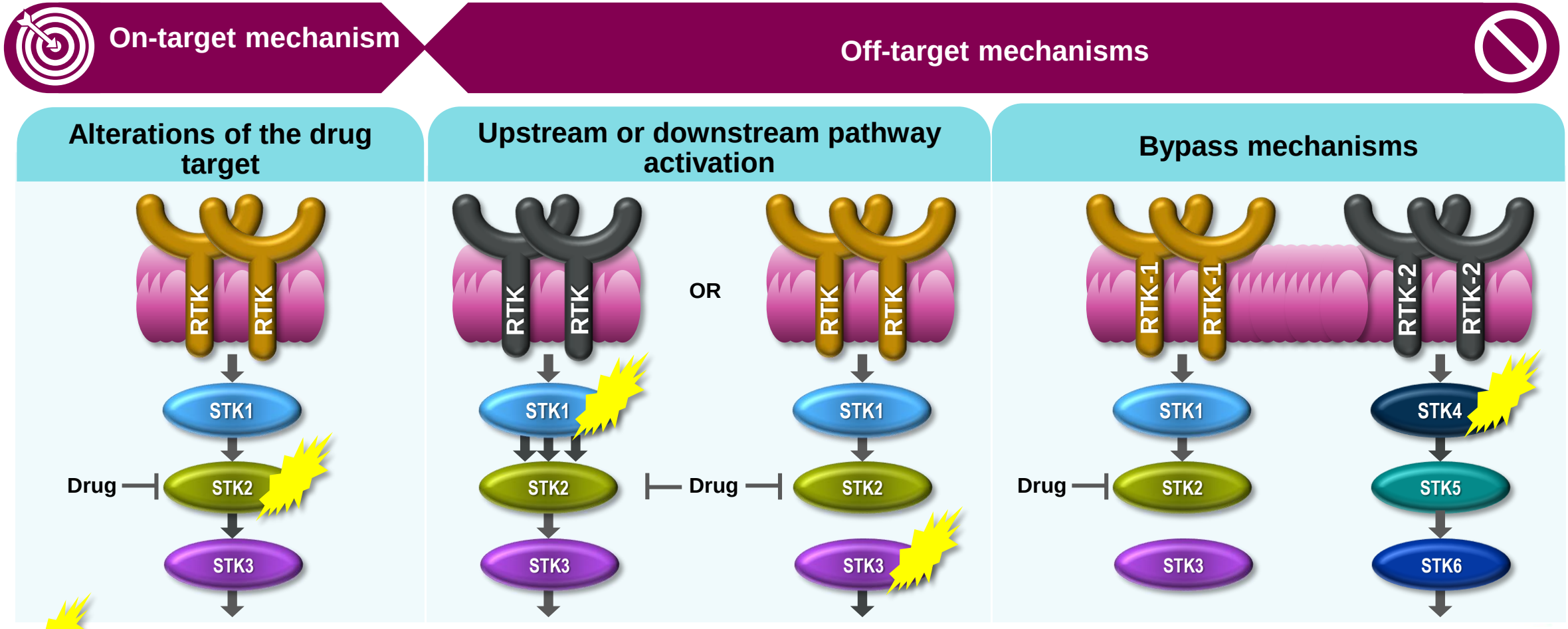
Mechanisms of Resistance to EGFR-TKIs:

- Despite the often initial dramatic responses and substantial PFS to EGFR-TKI observed in various clinical trials, most patients develop acquired resistance and experience subsequent disease progression[1]
- Several molecular mechanisms of acquired resistance have been reported[2]:
  - Development secondary Mutation in EGFR eceptor
  - Alternative EGFR Pathway Transformation
  - Phenotypic Transformation
- Secondary resistance to EGFR-TKIs occurs more frequently than primary resistance

1) Lin L, Bivona T. Chemother Res Pract 2012;2012:817297
2) Cortot AB, Janne PA. Eur Respir Rev 2014;23:356–66.

Oncogene-driven cancers, such as EGFR mutation-positive NSCLC, inevitably develop resistance to targeted therapies

Mechanisms of Acquired Resistance[1,3,4]



Adapted from Groenendijk FH et al. *Mol Oncol.* 2014;8:1067-1083.

EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; RTK = receptor tyrosine kinase; STK = serine/threonine kinase.

1. Berns K et al. *Drug Resist Updat.* 2012;15:268-275. 2. Workman P et al. *Curr Opin Pharmacol.* 2013;13:486-496. 3. Arbour KC et al. *Cancer.* 2018;124:2272-2275. 4. Groenendijk FH et al. *Mol Oncol.* 2014;8:1067-1083.

Resistance mechanisms to Osimertinib can be grouped into 3 categories

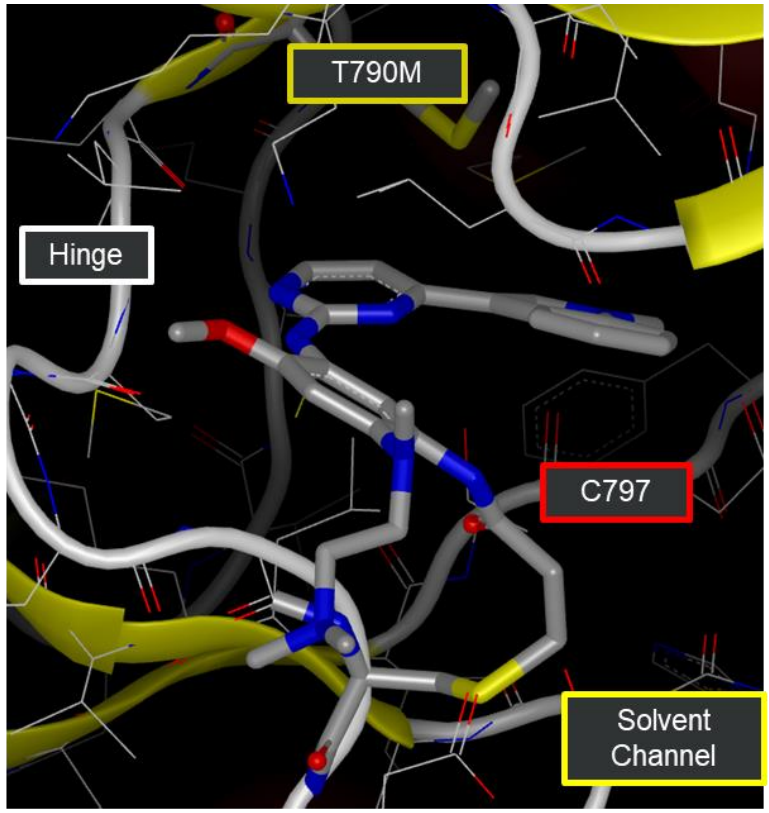
Secondary mutations in the EGFR gene	Bypass signalling	Phenotypic alteration
EGFR C797S	*MET* amplification	SCLC transformation
	HER2 amplification	

- **In some cases, these mechanisms may co-occur**

EGFR-Dependent Resistance Mechanisms

Mutations in EGFR C797

- The cysteine to serine (C797S) mutation in EGFR causes resistance by preventing covalent bond formation at that position, thereby reducing inhibitor binding and efficacy[1]
  - 2L osimertinib: 10-26%
  - 1L osimertinib: 7%

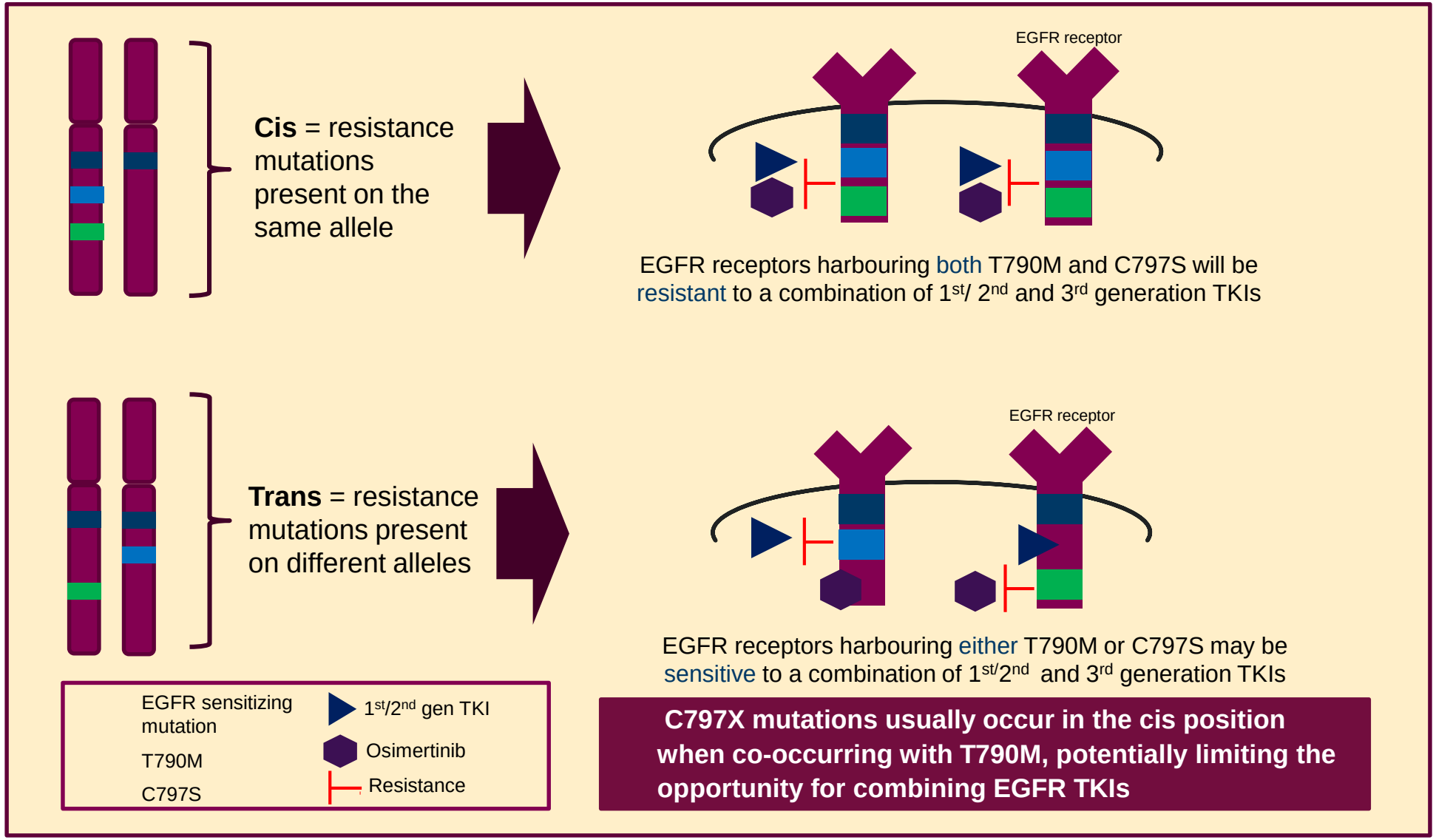


Osimertinib binds EGFR via an irreversible, covalent bond to the cysteine-797 residue[2]

EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor.

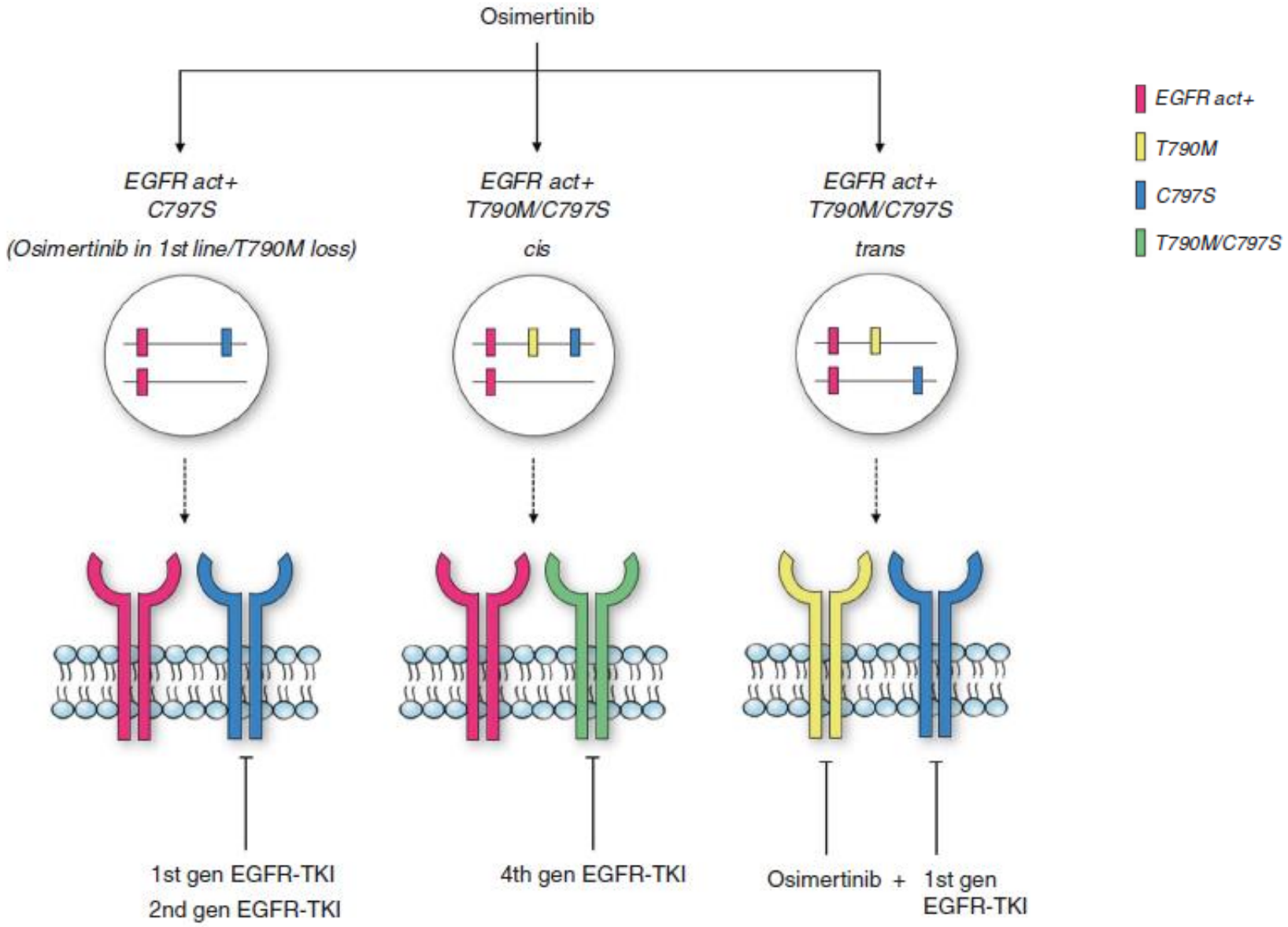
1. Tran PN, Klempner SJ. *Lung Cancer (Auckl)*. 2016;7:91-97. 2. Cross DA, et al. *Cancer Discov*. 2014;4(9):1046-1061.

C797S as mechanism of Resistance



1. Niederst MJ, et al. *Clin Cancer Res*. 2015;21(17):3924-3933. 2. Costa DB. *Transl Lung Cancer Res*. 2016;5(3):331-337.

C797S-mediated resistance: clinical implications



Leonetti et al. Br J Cancer 2019;121:725

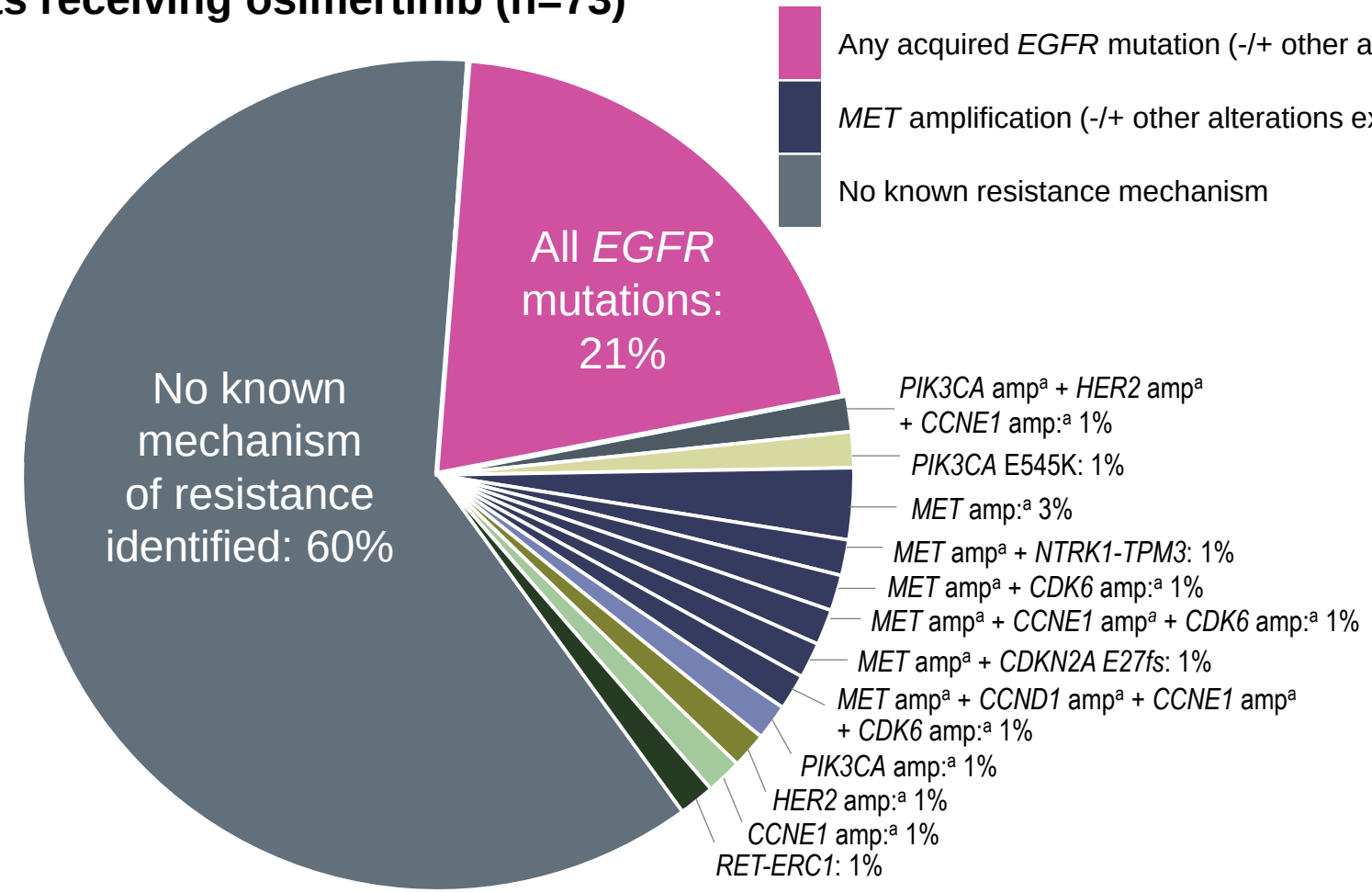
Other EGFR mutation:

- G796 R
- G796 D
- G796 S
- L792

EGFR-Independent Resistance Mechanisms

The Most Common Acquired Resistance Mechanisms After Osimertinib in AURA3 Were Acquired EGFR Mutations And MET Amplifications

Patients receiving osimertinib (n=73)



Acquired Alterations

- Acquired *EGFR* mutations: 21%
- *MET* amp:[b] 19%
- Cell-cycle gene alterations: 12%
- *HER2* amp:[a] 5%
- *PIK3CA* amp[a]/mutation: 5%
- Oncogenic fusion: 4%
- *BRAF* V600E: 3%

aPlasma samples were analyzed by next-generation sequencing (NGS; Guardant Health, Guardant360, 73 gene panel); bAmplification events may be underrepresented in plasma analyses.

Amp = amplification; BRAF = v-Raf murine sarcoma viral oncogene homolog B; CAST = calpastatin; CCND1 = cyclin-D1; CCNE1 = cyclin-E1; CDK6 = cyclin-dependent kinase 6; CDKN2A = cyclin-dependent kinase inhibitor 2A; EGFR = epidermal growth factor receptor; ERC1 = ELKS/Rab6-interacting/CAST family member 1; fs = frameshift; HER2 = human epidermal growth factor receptor 2; MET = MET proto-oncogene receptor tyrosine kinase; NTRK1 = neurotrophic tyrosine kinase receptor 1; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; RET = rearranged during transfection proto-oncogene; TPM3 = tropomyosin 3;

First-line[a] And Second-line[†] Osimertinib Resistance Mechanisms Were Similar

First-line resistance mechanisms to osimertinib[1,a]

- **Acquired EGFR C797S**
- ***EGFR* amplification**
- ***MET* amplification**
- ***HER2***
- **Exon 20 insertion**
- ***PIK3CA* mutation**
- ***KRAS* mutation** or ***KRAS*** amplification
- Acquired MEK1 G128V variant
- *JAK2* V617F

- **To date, ctDNA from plasma has been used to study resistance to osimertinib in the first line, which will restrict identification of resistance mechanisms to genomic mechanisms. Nongenomic mechanisms of resistance, such as SCLC transformation, would not be identified[1]**

Second-line resistance mechanisms to osimertinib[b,c]

- **EGFR C797S[2-7] (~25%[2,3])**
- EGFR L718Q[8], C797G[9]
- ***EGFR* amplification[6,9]**
- ***MET* amplification[4-7,10,11]**
- ***HER2*** amplification[4,11]
- ***PIK3CA* mutation[5,6]** and/or amplification[6]
- ***KRAS* mutations[4,5,7]**
- *BRAF* mutations[5,7]
- *FGFR1* mutation[6] and/or amplification[6,12]
- *FGFR3-TACC* fusion[5,13]
- *CCDC6-RET* fusion[5]
- *FGF2* overexpression[12]
- *MAPK1* overexpression[12]
- *AKT3* overexpression[12]
- *PTEN* deletion[12]
- *AXL* upregulation[12]
- **SCLC transformation[5-7,14]**
- SqCC transformation[7]

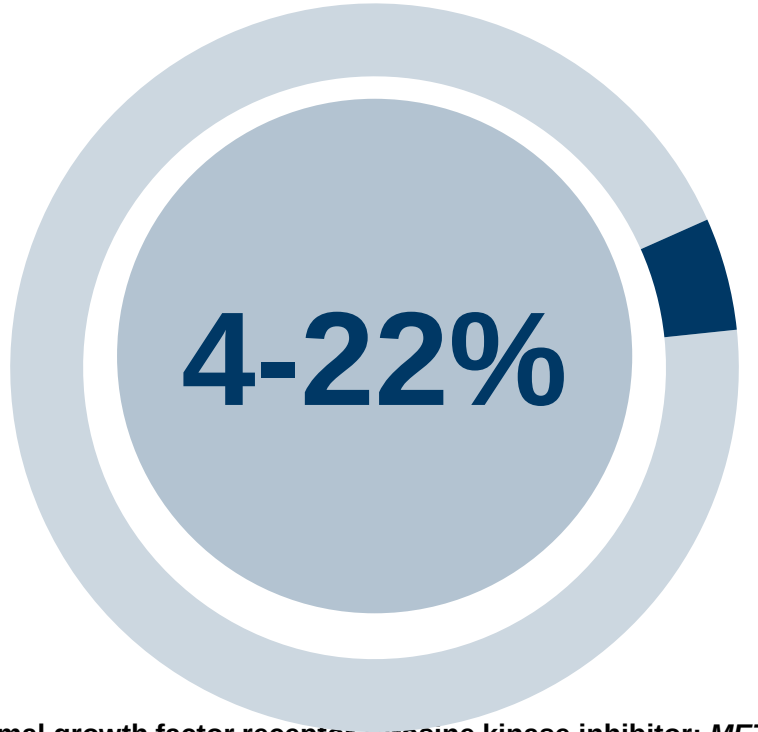
[a]Patients may have had more than one resistance mechanism identified; [b]Patients were T790M positive and may have received several previous therapies including an EGFR-TKI; [c]Patients may have had more than one resistance mechanism identified.[2-14]

1. Ramalingam SS et al. Article and supplementary appendix. *J Clin Oncol*. 2018;36:841-849. 2. Oxnard GR et al. Presented at: WCLC Congress; September 6-9, 2015; Denver, Colorado, USA. 3. Thress KS et al. *Nat Med*. 2015;21:560-562. 4. Ortiz-Cuaran S et al. *Clin Cancer Res*. 2016;22:4827-4847. 5. Oxnard GR et al. Presented at: World Conference on Lung Cancer; October 15-18, 2017; Yokohama, Japan. Abs OA 09.02. 6. Piotrowska Z et al. Poster presented at: AACR Annual Meeting; June 2-6, 2017; Chicago, IL. Abs 9020. 7. Lin CC et al. *Lancet Respir Med*. 2018;6:107-116. 8. Bersanelli M et al. *J Thorac Oncol*. 2016;11:e121-e123. 9. Menon R et al. *J Thorac Oncol*. 2016;11:e105-e107. 10. Ou SHI et al. *Lung Cancer*. 2016;98:59-61. 11. Planchard D et al. *Ann Oncol*. 2015;26:2073-2078. 12. Kim TM et al. *J Thorac Oncol*. 2015;10:1736-1744. 13. Ou SHI et al. *Lung Cancer*. 2017;111:61-64. 14. Ham JS et al. *J Thorac Oncol*. 2016;11:e1-e4.

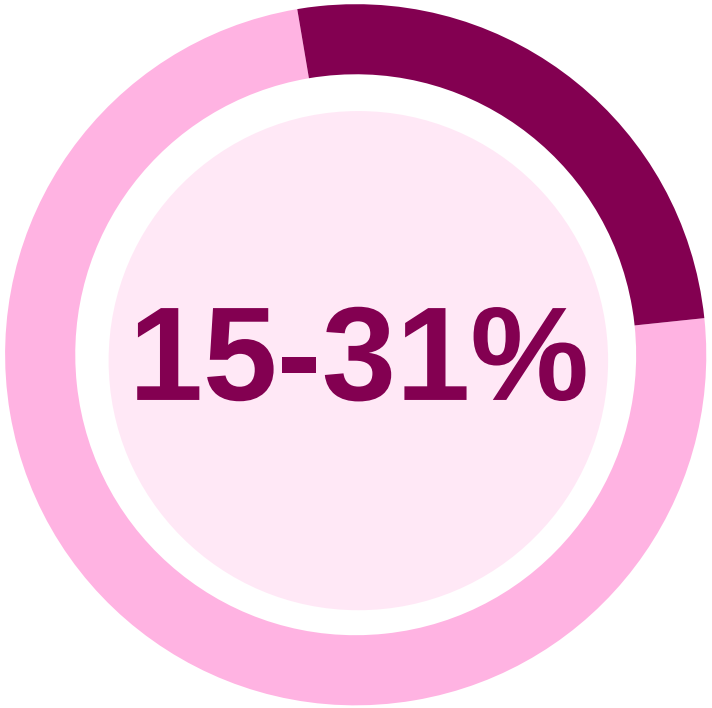
Incidence of *MET*-Driven Resistance Appears to be Higher Following Osimertinib

MET-driven resistance following EGFR-TKI therapy

First and Second-generation EGFR-TKIs[1-4]



Osimertinib[1,5-6]

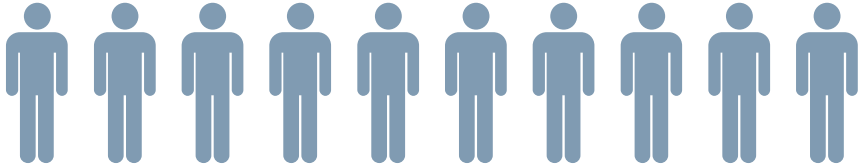


EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor; *MET* = MET proto-oncogene receptor tyrosine kinase.

1. Ramalingam SS et al. *Ann Oncol.* 2018;29:viii740. Abs LBA50. 2. Yu HA et al. *Clin Cancer Res.* 2013;19:2240-2247. 3. Sequist LV et al. *Sci Transl Med*. 2011;3:75ra26.
4. Engelman JA et al. *Science.* 2007;316:1039-1043. 5. Piotrowska Z et al. *Cancer Discov.* 2018;8:1529-1539. 6. Wang Y et al. *Lung Cancer.* 2018;118:105-110.

MET-Driven Resistance Following Osimertinib Treatment

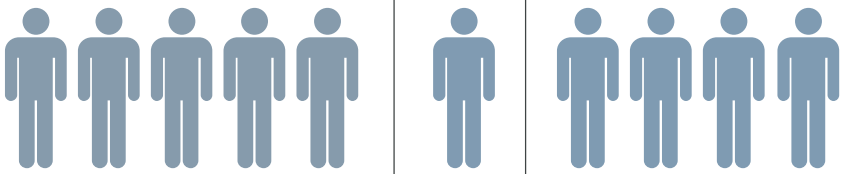
*EGFR*m NSCLC



Progression on First/Second-generation TKI

EGFR T790M is the most common resistance mechanism following First/Second-generation TKIs[1–3]

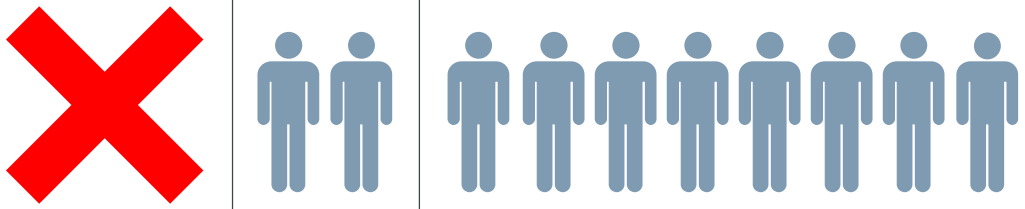
Resistance mechanisms[1–3]



T790M | *MET* | Other

Progression on osimertinib

Osimertinib blocks T790M[4,5] and therefore development of T790M-driven resistance

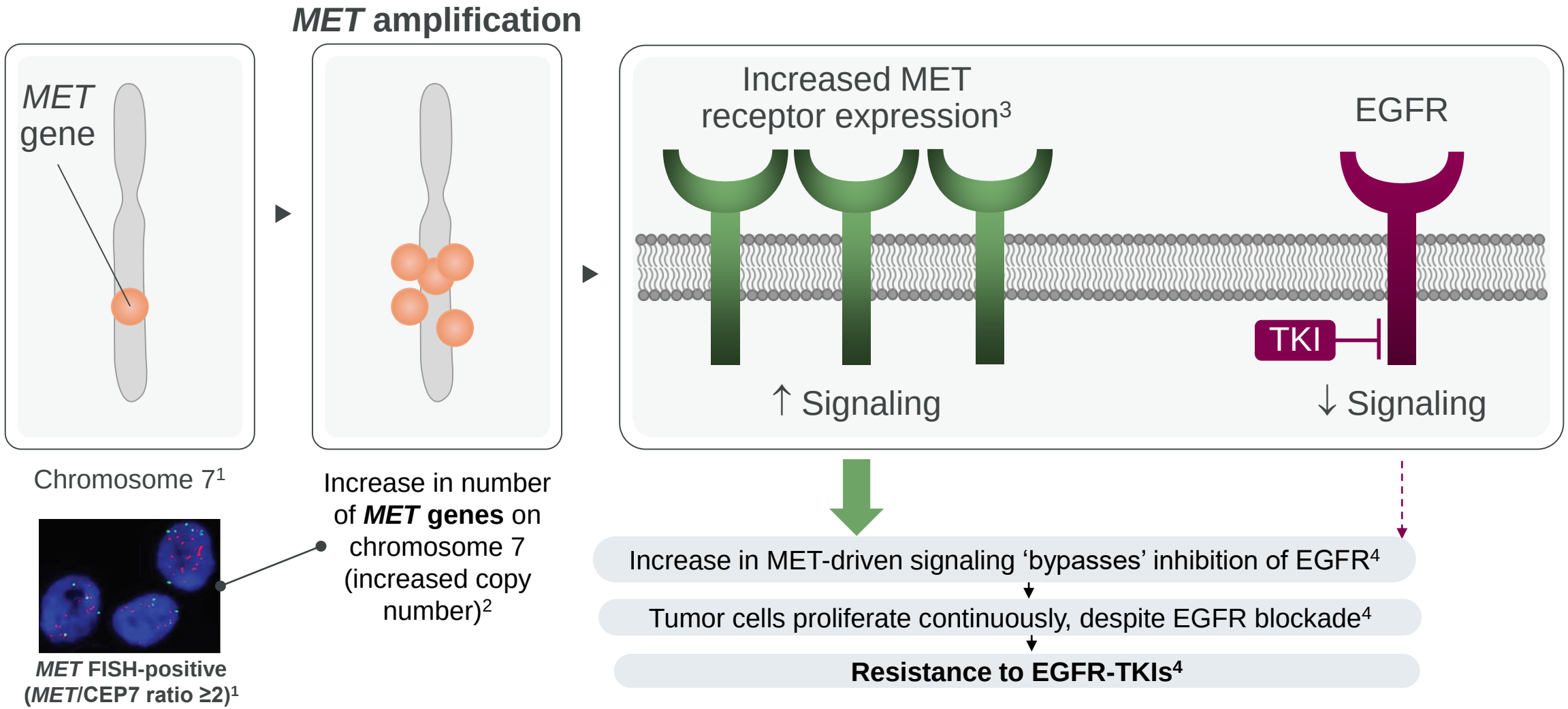


T790M | *MET* | Other

*EGFR*m = epidermal growth factor receptor mutation-positive; *MET* = MET proto-oncogene receptor tyrosine kinase; NSCLC = non-small cell lung cancer; TKI = tyrosine kinase inhibitor.

1. Ramalingam SS et al. *Ann Oncol.* 2018;29:viii740. Abs LBA50. 2. Yu HA et al. *Clin Cancer Res.* 2013;19:2240-47. 3. Sequist LV et al. *Sci Transl Med.* 2011;3:75ra26. 4. Tan CS et al. *Mol Cancer.* 2018;17:1-14. 5. Westover D et al. *Ann Oncol.* 2018;29:i10-i19.

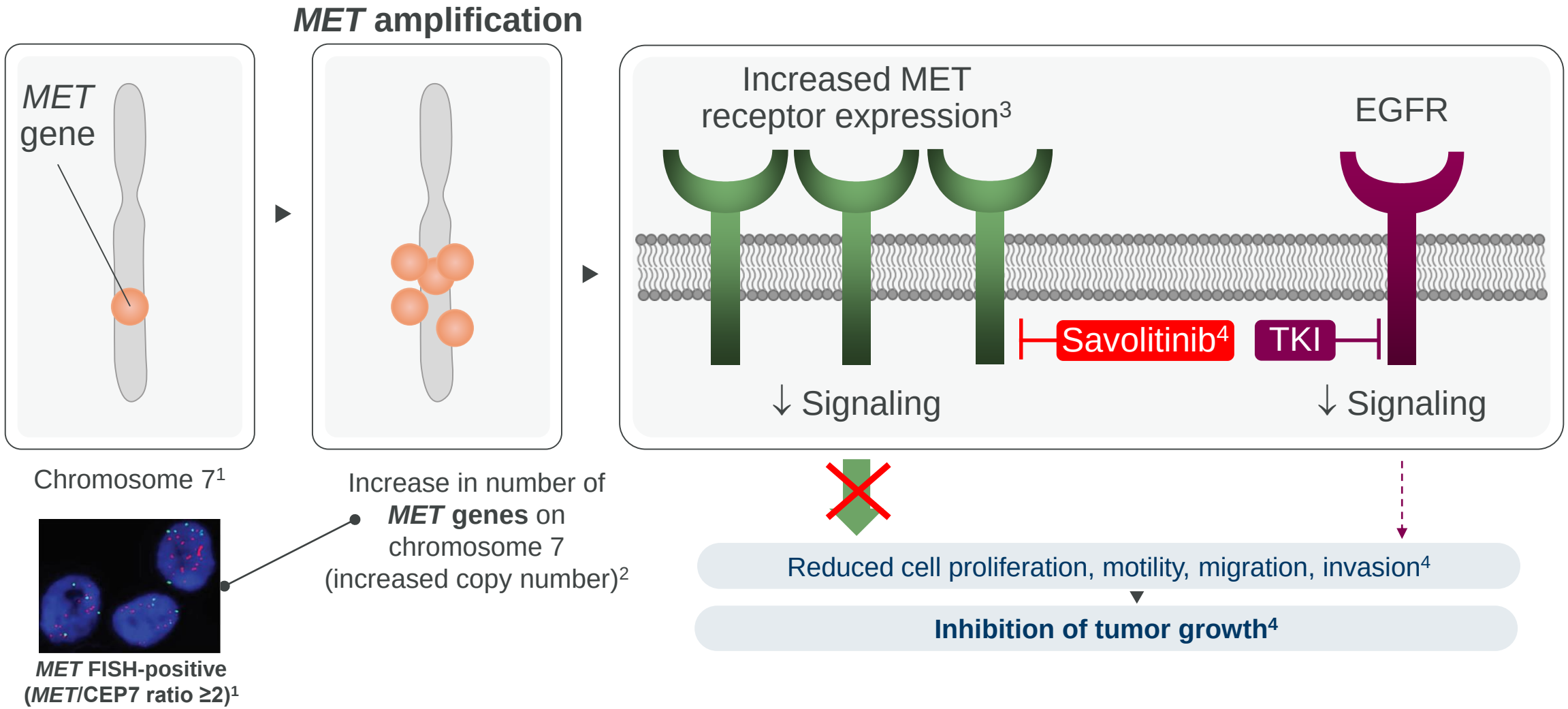
MET Amplification Leads to Increased Expression of MET Receptor Protein and Therefore Resistance to EGFR-TKIs



CEP7 = centromeric region of human chromosome 7; *EGFR* = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; FISH = fluorescence in situ hybridization; *MET* = MET proto-oncogene receptor tyrosine kinase.

1. Casadevall D et al. *Oncotarget*. 2015;6:16215-16226. 2. Kawakami H et al. *Cancers (Basel)*. 2015;6:1540-1552. 3. Organ SL et al. *Ther Adv Med Oncol.* 2011;3:S7-S19.
4. Morgillo F et al. *ESMO Open*. 2016;1:e000060.

Savolitinib is a Selective Inhibitor of MET Activity, and May Overcome *MET* Amplification as a Mechanism of Resistance

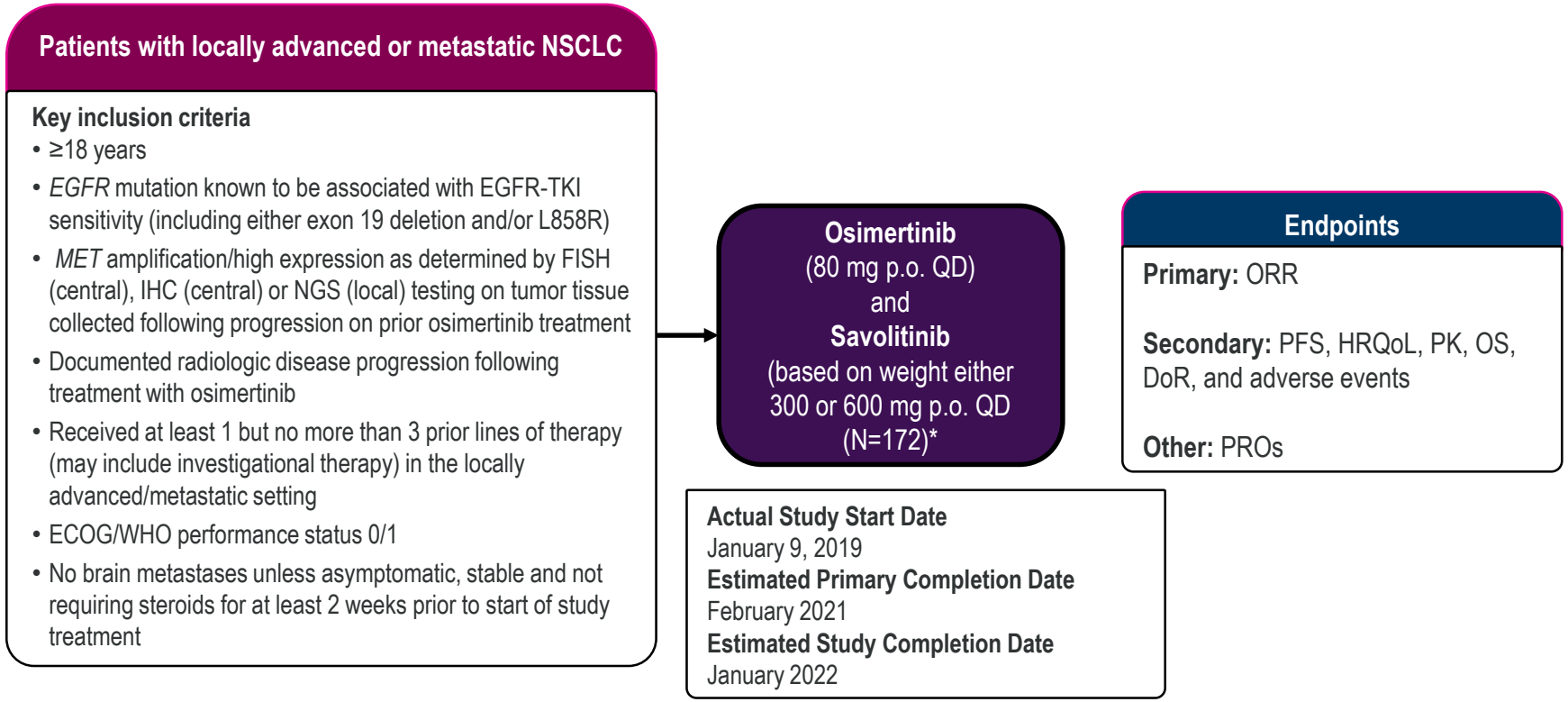


- *CEP7* = centromeric region of human chromosome 7; EGFR = epidermal growth factor receptor; FISH = fluorescence in situ hybridization; *MET* = MET proto-oncogene receptor tyrosine kinase; TKI = tyrosine kinase inhibitor.

1. Casadevall D et al. *Oncotarget*. 2015;6:16215-16226. 2. Kawakami H et al. *Cancers (Basel)*. 2015;6:1540-1552. 3. Organ SL et al. *Ther Adv Med Oncol.* 2011;3:S7-S19. 4. Miranda O et al. *Cancers (Basel).* 2018;10:280.

SAVANNAH Study Design: Efficacy of Osimertinib in Combination With Savolitinib

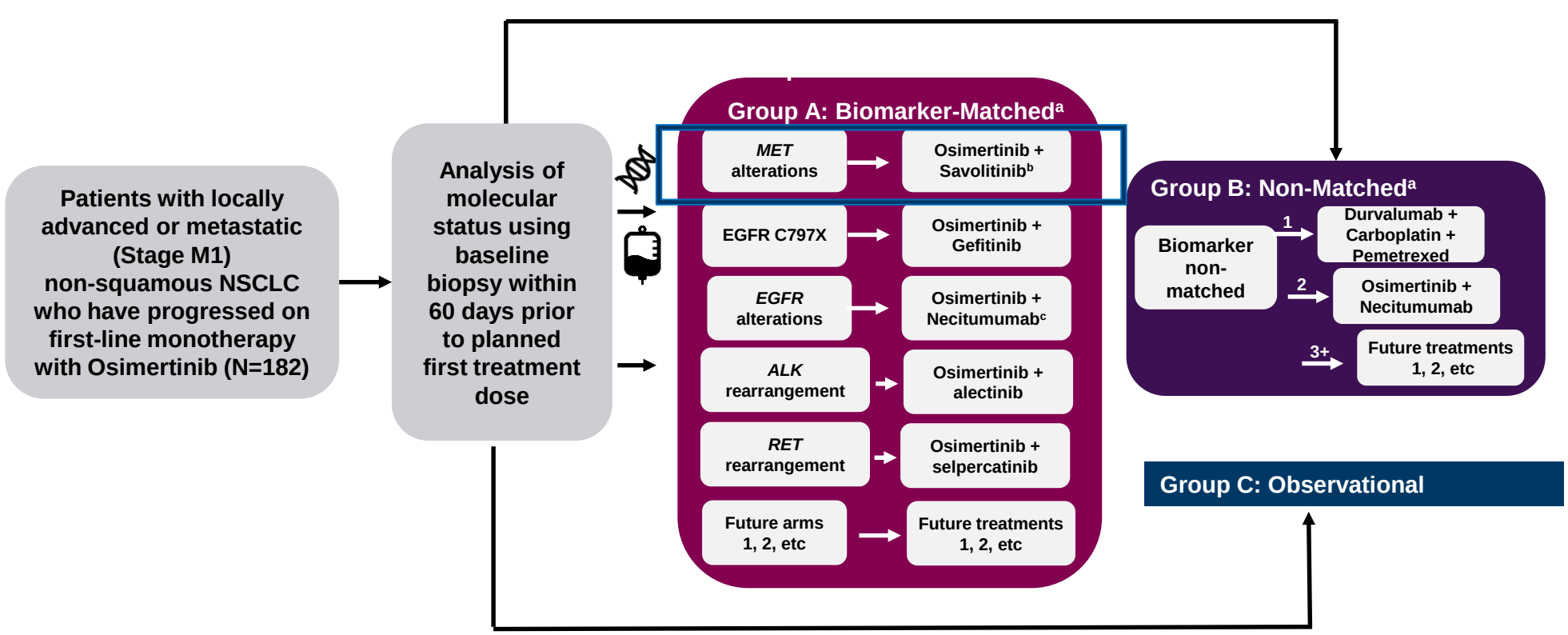
A Phase II, single arm study assessing the efficacy of osimertinib in combination with savolitinib in patients with *EGFR*m+ and *MET*+, locally advanced or metastatic non-small cell lung cancer who have progressed following treatment with osimertinib



- *Estimated enrollment.
- DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; *EGFR* = epidermal growth factor receptor; *EGFR*m = epidermal growth factor receptor mutation-positive; FISH = fluorescence in situ hybridization; HRQoL = health related quality of life; IHC = immunohistochemistry; *MET* = mesenchymal-epithelial transition factor; NGS = next-generation sequencing; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; p.o. = orally; PRO = patient reported outcomes; QD = once daily; TKI = tyrosine kinase inhibitor; WHO = World Health Organization.
- Study NCT03778229. ClinicalTrials.gov website. Accessed February 19, 2019.

ORCHARD Study Design: Progression on First-Line Osimertinib[1,2]

A Phase II, multi-drug, biomarker-directed platform non-randomized study in patients with advanced NSCLC harboring *EGFR* sensitizing mutations whose disease has progressed on first-line treatment with osimertinib



Endpoints

Primary: ORR

Secondary: PFS, DoR, OS[d], PK, AEs

Exploratory:

- OS in patients not receiving treatment
- Correlation between MAF in baseline and/or serial plasma samples and response, genetic and biomarker profile analyses

- [a]Patient numbers may increase dependent on ORR at interim analysis. The modular study design also enables cohorts to be added as relevant resistance data emerge; [b]Following a protocol amendment, all newly enrolled patients with *MET* alterations will receive savolitinib 300 mg qd; [c]On days 1 and 8 of each 3-week cycle; [d]To include patients who fail screening with baseline NGS results.
- AE = adverse event; *ALK* = anaplastic lymphoma kinase; DoR = duration of response; *EGFR* = epidermal growth factor receptor; MAF = macrophage activating factor; *MET* = MET proto-oncogene receptor tyrosine kinase; NGS = next-generation sequencing; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PK= pharmacokinetics;
- PFS = progression-free survival; QD = once-daily; *RET* = rearranged during transfection.
- 1. Study NCT03944772. ClinicalTrials.gov website. 2. Cho BC et al. Poster presented at WCLC Annual Congress (Virtual); January 28-31, 2021; Singapore. Poster P76.27.

Transformation to small cell carcinoma

Concept of a reciprocal relationship between SCLC transformation and T790M mutation.

Suda et al. mentioned a reciprocal relationship between the SCLC transformation and the EGFR T790M mutation

- Several cases of both SCLC transformation and T790M mutation in patients with EGFR-mutant lung adenocarcinoma who failed EGFR TKI therapy have been reported.
- In these cases, SCLC transformation and T790M mutation were detected in different sites of tumor progression without coexisting

This case demonstrates the heterogeneity of acquired resistance during EGFR TKI treatment and highlights the importance of performing repeat tissue biopsy even when T790M mutation is detected in the plasma, especially when there is **rapid disease progression**.

Shee Chai et al. Journal of Thoracic Oncology Vol. 12 No. 10

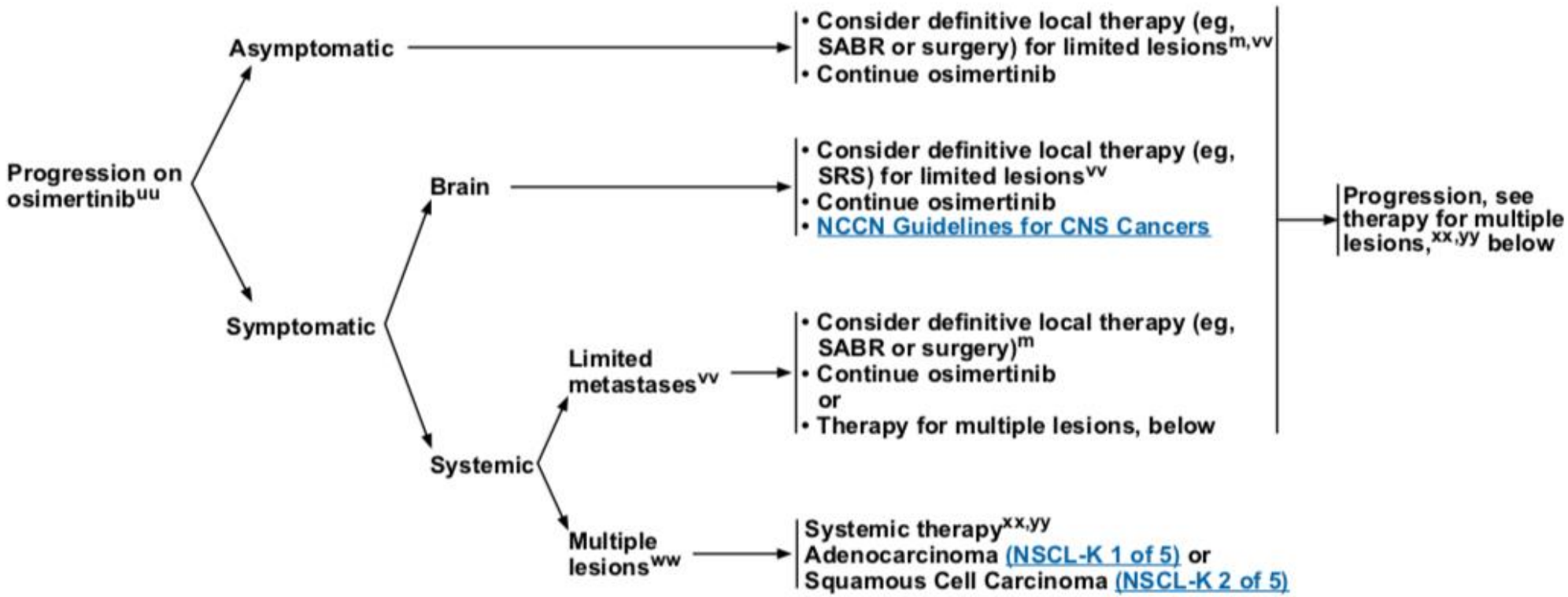
Hypothesis of SCLC conversion

There are two hypotheses for the pathogenesis of SCLC transformation after exposure to EGFR-TKIs in NSCLC patients with EGFR mutation

1. One hypothesis is that small populations with SCLC are present in the pre-treated tumor. As the adenocarcinoma component is successfully treated with EGFR-TKIs, the SCLC component finally becomes dominant and is detected by re-biopsy.
2. The other hypothesis is the histological transformation of EGFR-mutant adenocarcinoma to de novo SCLC during EGFRTKI treatment

N. Nishioka et al. *Respiratory Medicine Case Reports 25 (2018) 261–263*

***EGFR EXON 19* DELETION OR *L858R* MUTATIONS[mm]** **SUBSEQUENT THERAPY[pp]**



Take home message

- For those with progression, repeat liquid biopsy should be preferred and tissue biopsy when no mutation detected on liquid biopsy.

- Continue Osimertinib in patients with oligo-progressive disease.

- For patients who progress rapidly on second line therapy, repeat biopsy should be considered to look for SCLC transformation