Biological agents in resistant tumors to first generation agents in NSCLC

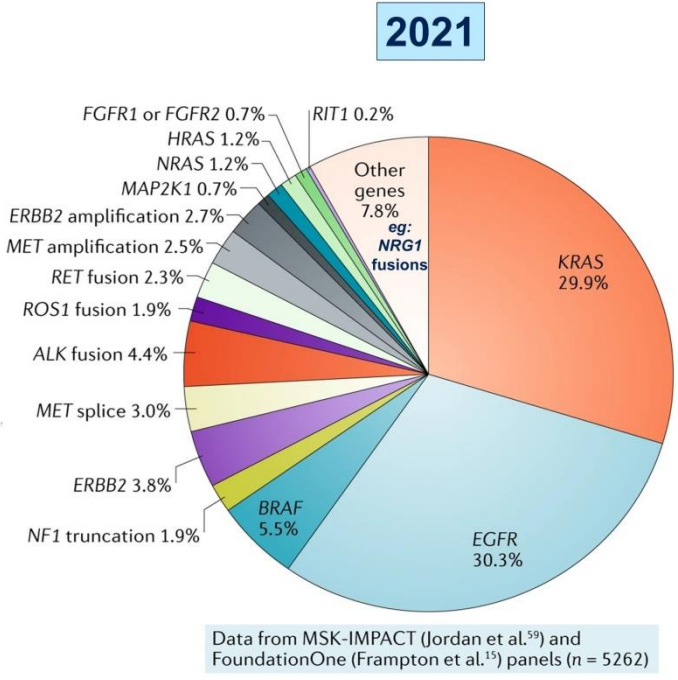
Guy Berchem MD, PhD

Centre Hospitalier de Luxembourg

Luxembourg Institute of Health

Oncogene addiction in NSCLC (ADC)

1st line situation +/- 70%
are oncogene addicted

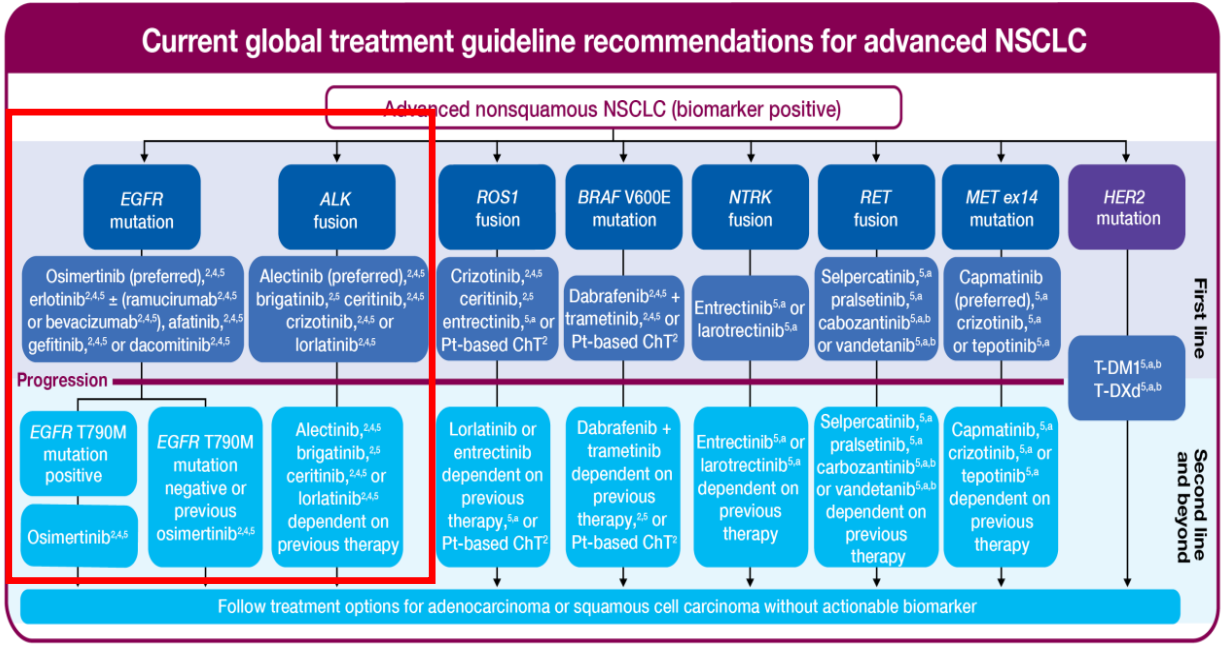


Skoulidis, F., Heymach, J.V. Nat Rev Cancer 19, 495–509 (2019).

Biological agents in resistant tumors to first generation agents in NSCLC

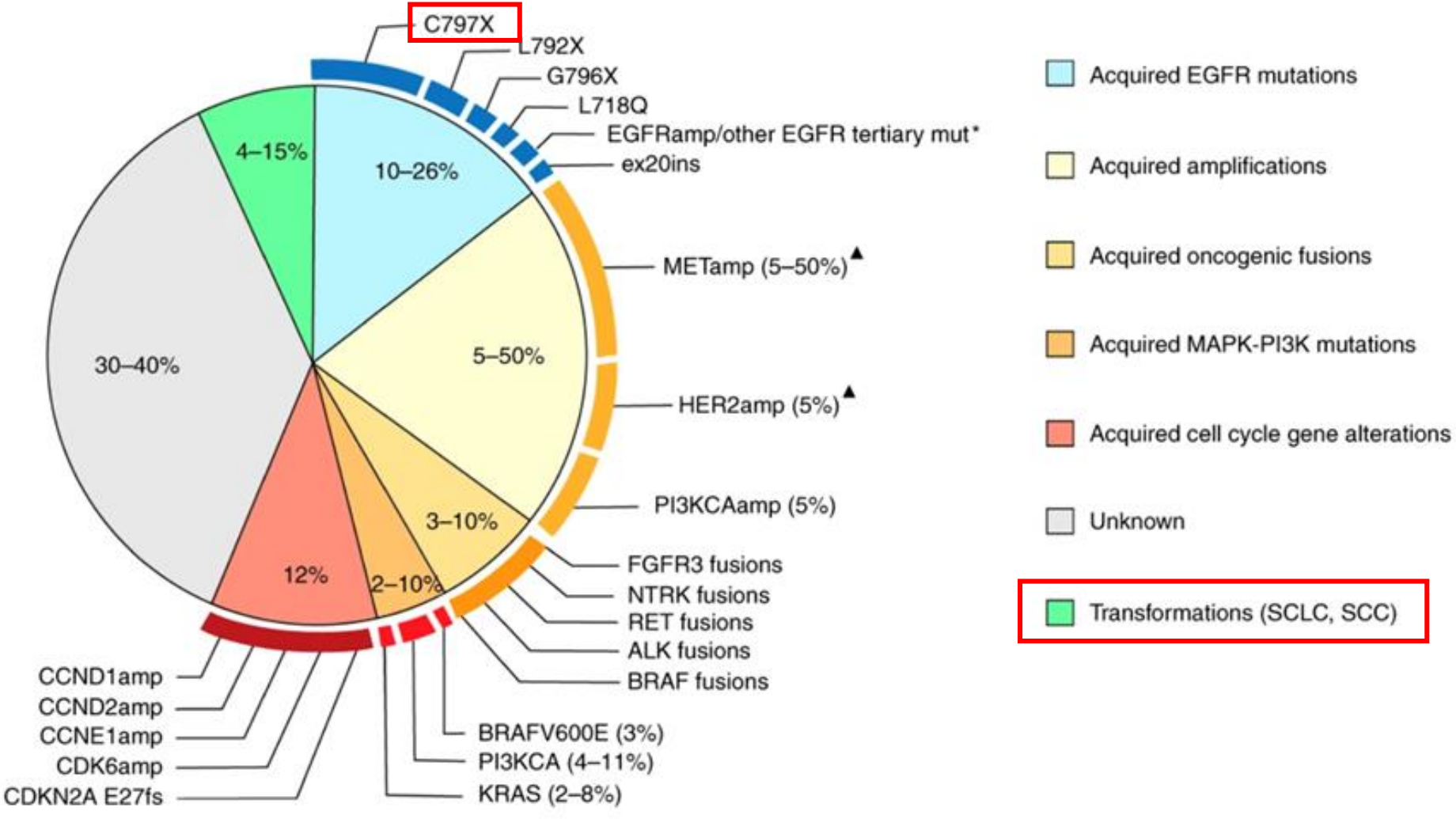
In general, how to procede…

- Classical TKI based treatment of oncogen addicted NSCLC
- What to do in case of (ineviteable) progression
  - Rebiopsy + NGS
  - Treatment of oligometastatic progressing disease
  - Addition of second agent
  - Chemotherapy
  - New drug (study or compassionate use)



Kim SY, Halmos B. *Lung Cancer Manag.* 2020;9(3):LMT36.
Planchard D, et al. *Ann Oncol.* 2018;29(suppl 4):iv192-iv237.

EGFR
What are the resistance mechanisms to osimertinib?



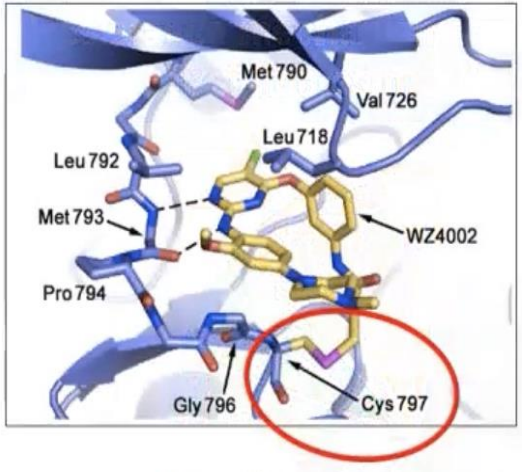
What other possibilities with availeable drugs in C797 mutated patients?

- Osimertinib + 1st gen EGFR TKI (gefitinib) [1]
  - A rapid decrease of the C797 subclone was noted but of short duration…
- Osimertinib + brigatinib + bevacizumab [2]
  - A partial remission was observed duration?
- Cetuximab + brigatinib [3, 4]
  - Invitro and animals…
  - 1 PR out of 10 patients, but 5 SD

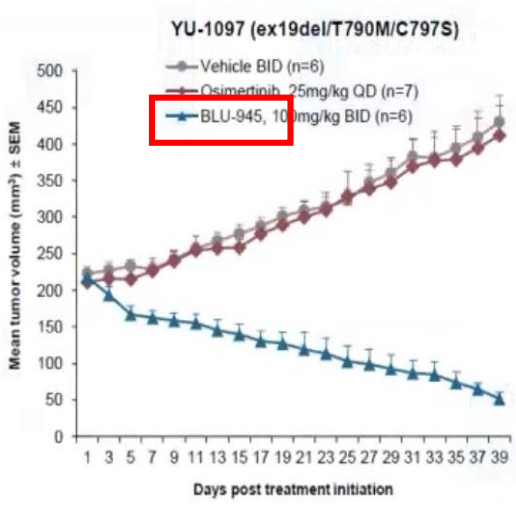
- => situation is not brilliant…

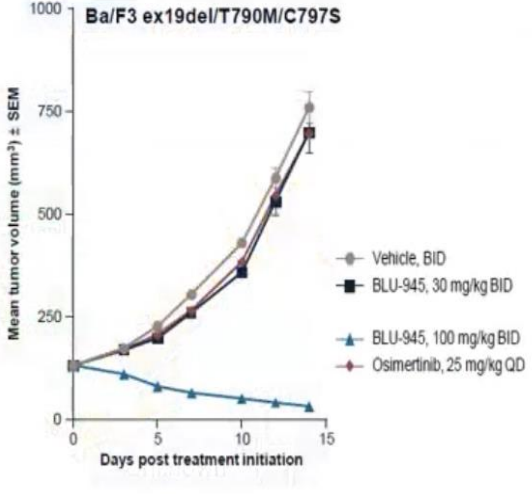
1. Arulananda S, Do H, Musafer A, Mitchell P, Dobrovic A, John T. Combination Osimertinib and Gefitinib in C797S and T790M EGFR-Mutated Non-Small Cell Lung Cancer. J Thorac Oncol. 2017 Nov;12(11):1728-1732. doi: 10.1016/j.jtho.2017.08.006.
2. Zhao J, Zou M, Lv J, Han Y, Wang G, Wang G. Effective treatment of pulmonary adenocarcinoma harboring triple EGFR mutations of L858R, T790M, and cis-C797S by osimertinib, bevacizumab, and brigatinib combination therapy: a case report. Onco Targets Ther. 2018 Sep 6;11:5545-5550. doi: 10.2147/OTT.S170358.
3. Uchibori, K., Inase, N., Araki, M. et al. Brigatinib combined with anti-EGFR antibody overcomes osimertinib resistance in EGFR-mutated non-small-cell lung cancer. Nat Commun 8, 14768 (2017). https://doi.org/10.1038/ncomms14768
4. Wang Y, Yang N, Zhang Y, Li Li, Han R, Zhu M, Feng M, Chen H, Lizaso A, Qin T, Liu X, He Y. Effective Treatment of Lung Adenocarcinoma Harboring EGFR-Activating Mutation, T790M, and cis-C797S Triple Mutations by Brigatinib and Cetuximab Combination Therapy. J Thorac Oncol. 2020 Aug;15(8):1369-1375. doi: 10.1016/j.jtho.2020.04.014.

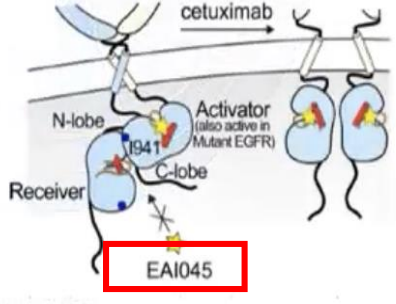
Progressing Towards a Fourth-Generation of *EGFR* Inhibitors?[1–3]



Ser 797 abrogates covalent binding of third-generation EGFR-TKI on Cys 797





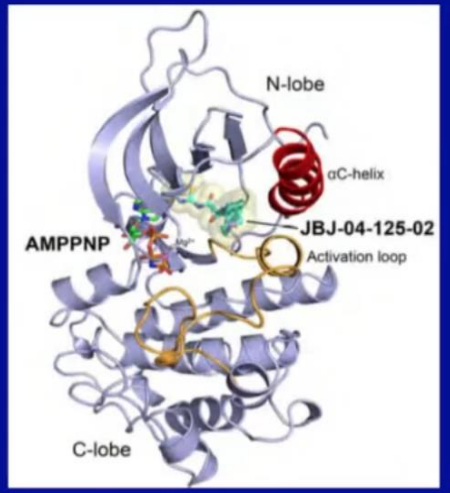


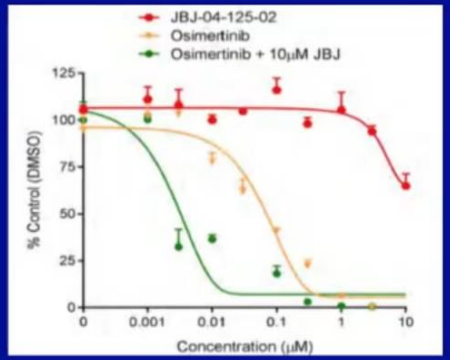
BID, twice daily; *EGFR*, epidermal growth factor receptor; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; QD, once daily; SEM, standard error of the mean; WT, wild type

1. Zhou W, et al. Nature 2009;462:1070–4; 2. Schalm S, et al. Presented at: European Society for Medical Oncology Asia Congress 2020; 20–22 November 2020; 3. Jia Y, et al. Nature 2016;534:129–32

JBJ-040125-02

- Able to inhibit cell proliferation and EGFR L858R/T790M/C797S signaling *in vitro* and *in vivo*
- Osimertinib may enhance the binding of JBJ-040-125-02
- Combination of Osimertinib and JBJ-040-125-02 may potentially increase inhibition of cell growth and increase apotosis.
- Relatively low bioavailability





To and Janne et al Cancer Discovery ePub May 15 2019

Jia et al Nature Letter 2016

What are the resistance mechanisms to osimertinib?

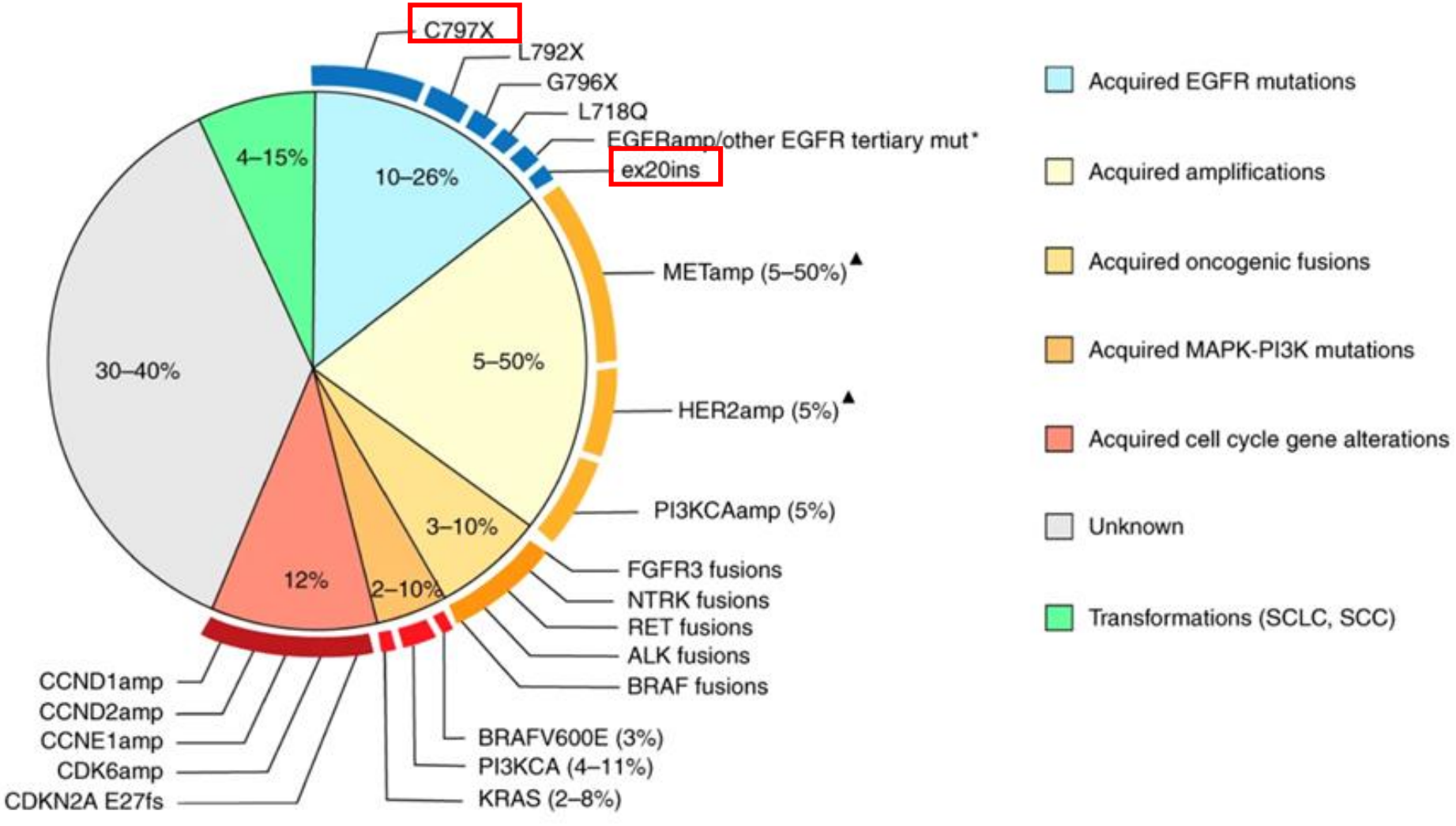
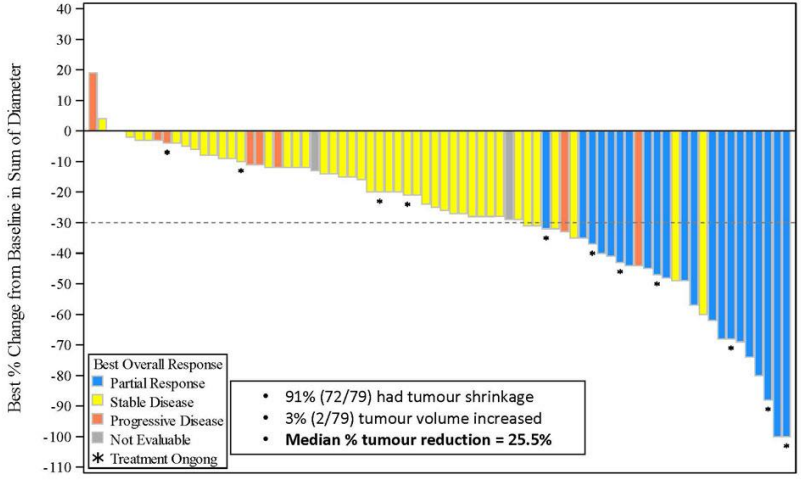


Table 3. Summary of prognostic impact of Exon20 insertions compared to other genotypes.

	Range Median OS (months)	Range Median PFS (months)	Range ORR (%)
TKIs			
Exon 20ins	4.8–19	1.4–3.0	0–20%
	6 studies	8 studies	7 studies
	177 patients (range 11–67)	183 patients (range 11–67)	194 patients (range 11–67)
Classic *EGFR*m (del 19 or L858R)	19.6–27.7	8.5–15.2	27.4–84%
	3 studies	3 studies	5 studies
	501 patients (range 37–278)	501 patients (range 37–278)	1193 patients (range 37–692)
T790M	13.5–27.7	1.0–2.9	0–25%
	3 studies	3 studies	4 studies
	67 patients (range 14–30)	67 patients (range 14–30)	114 patients (range 14–47)
Wild-type	10.4–21	2	16.50%
	2 studies	1 study	1 study
	990 patients (range 20–88)	1261 patients (range 15–39)	1261 patients (range 20–102)

Poziotinib

- Poziotinib (HMB781-36B) is an orally available, irreversible covalent TKI.
- Multi-cohort phase II ZENITH20
- Of the 79 patients participating in ZENITH20, twelve patients remained on treatment with median follow up of 9.2 months.
- FDA grants fast track status for poziotinib in March 2021
- ORR 27%
- PFS 5.5 mo
- OS 15 mo



1. Remon J, Hendriks LEL, Cardona AF, Besse B. EGFR exon 20 insertions in advanced non-small cell lung cancer: A new history begins. Cancer Treat Rev. 2020 Nov;90:102105. doi: 10.1016/j.ctrv.2020.102105.
2. 36MO – Sacher A, Le X, Cornelissen R, et al. Safety, tolerability and preliminary efficacy of poziotinib with twice daily strategy in EGFR/HER2 Exon 20 mutant non-small cell lung cancer. ESMO Targeted Anticancer Therapies (TAT) Virtual Congress (1-2 March 2021)

Mobocertinib (TAK-788)

- Irreversible covalent TKI, excellent preclinical activity in this situation [1, 2]
- Phase 1 study, 73 patients interesting responses in ex 20 ins [3]
- Phase 2 study, 70 previously treated NSCLC patients harboring EGFR ex20ins mutations [3]
- ORR and DCR were 44% and 86% respectively for the 160 mg dose

- Phase 3 ongoing
- Received FDA approval in this indication in September 2021

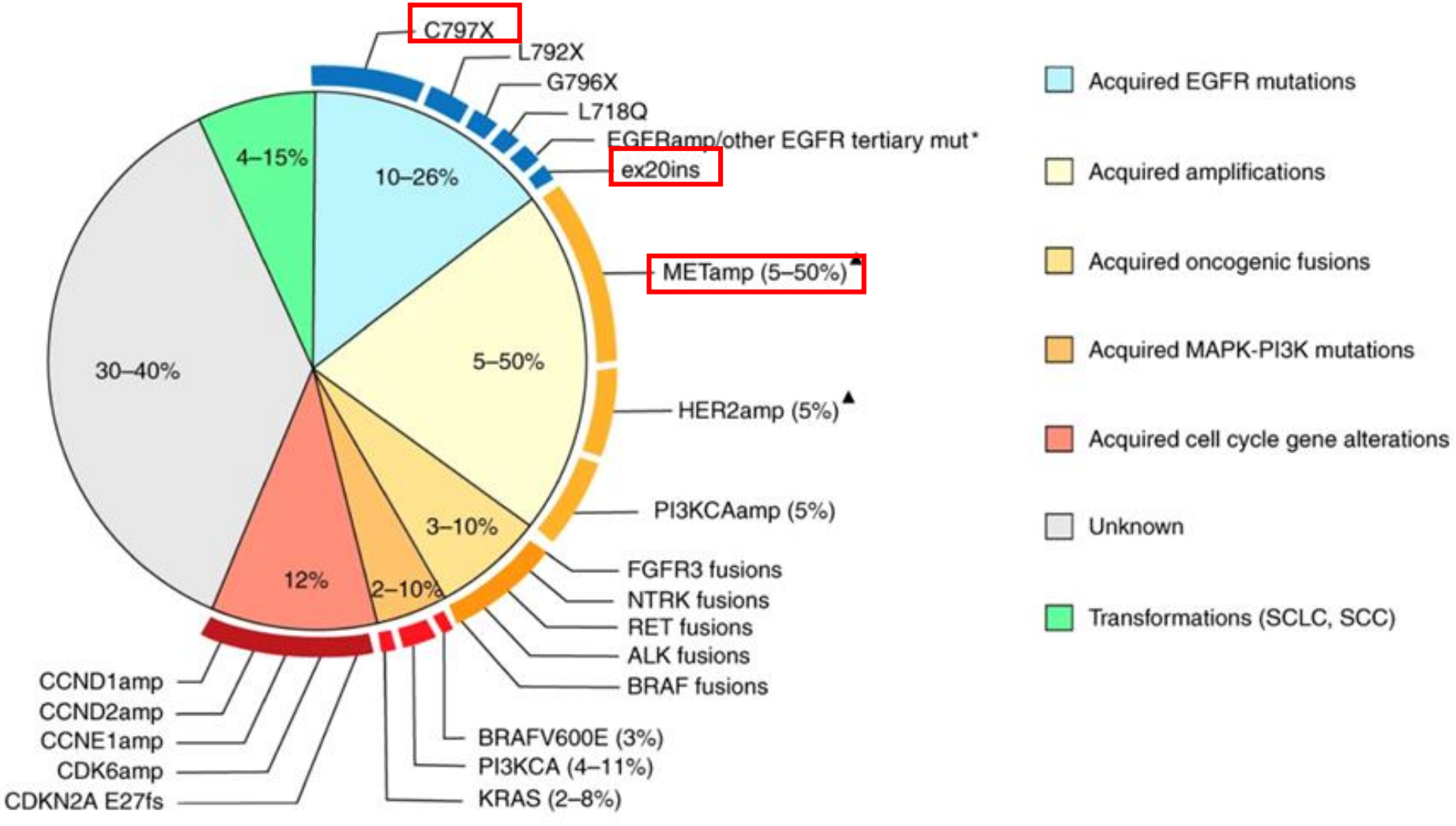
1. Mobocertinib (TAK-788): A Targeted Inhibitor of EGFR Exon 20 Insertion Mutants in Non–Small Cell Lung Cancer. F Gonzalvez, V M. Rivera et al. July 2021 Vol 11, Issue 7, DOI: 10.1158/2159-8290.CD-20-1683
2. Zhang SS, Zhu VW. Spotlight on Mobocertinib (TAK-788) in NSCLC with EGFR Exon 20 Insertion Mutations. Lung Cancer (Auckl). 2021 Jul 12;12:61-65. doi: 10.2147/LCTT.S307321.
3. Activity and Safety of Mobocertinib (TAK-788) in Previously Treated Non-Small Cell Lung Cancer with EGFR Exon 20 Insertion Mutations from a Phase I/II Trial. Riely GJ, Jänne PA Cancer Discov. 2021 Jul; 11(7):1688-1699.

Amivantamab

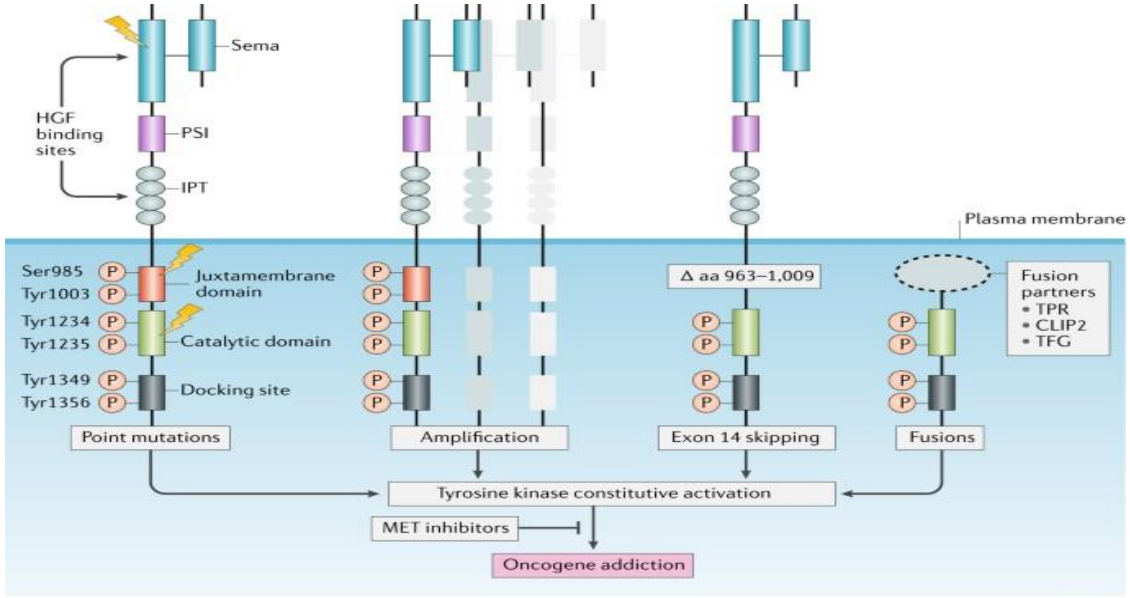
- Amivantamab (JNJ-61186372), a bispecific antibody targeting EGFR-MET, has shown preclinical activity in TKI-sensitive *EGFR*-mutated NSCLC models and in an ongoing first-in-human study in patients with advanced NSCLC [1].
- 50 pts with exon20ins mutations
- 14 responders, median duration of response was 10 months (1–16), with ongoing responses in 9 pts
- Recieves FDA approval in this indication in May 2021

1. Keunchil Park, Amivantamab (JNJ-61186372), an anti-EGFR-MET bispecific antibody, in patients with EGFR exon 20 insertion (exon20ins)-mutated non-small cell lung cancer (NSCLC). DOI: 10.1200/JCO.2020.38.15_suppl.9512 *Journal of Clinical Oncology* 38, no. 15_suppl (May 20, 2020) 9512-9512.

What are the resistance mechanisms to osimertinib?



c-MET alterations



1. **MET exon14 alteration 3~4%**
   - It prevents the MET receptor from being degraded, resulting in increased MET activity
   - Recognized as oncogenic-driver mutation and targeted therapy (Capmatinib and Tepotinib) have been already established as standard therapy.

2. **De novo MET amplification, 1~5%**
   - No standard therapy for MET+ NSCLC, although it was demonstrated as potential oncogenic driver gene alteration.

3. **TKI-resistant EGFR mt NSCLC, 7~15%**
   - MET-i +/- EGFR-TKI treatment strategy is under evaluation both for TKI resistance and naïve EGFR mt NSCLC. (e.g, amivantamab+TKI, Tepotinib+TKI, and Savolitinib+TKI)

Comoglio, P.M., Trusolino, L. & Boccaccio, C. *Nat Rev Cancer* 18, 341–358 (2018).
Camidge DR, et.al, JTO. 2021 Jun;16(6):1017-1029, Drilon A, et.al, JTO 2017;12: 15-26, Alessandro Leonetti, Br J Cancer. 2019 Oct;121(9):725-737.

New MET inhibitors

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Capmatinib in *MET* Exon 14–Mutated or *MET*-Amplified Non–Small-Cell Lung Cancer

J. Wolf, T. Seto, J.-Y. Han, N. Reguart, E.B. Garon, H.J.M. Groen, D.S.W. Tan, T. Hida, M. de Jonge, S.V. Orlov, E.F. Smit, P.-J. Souquet, J. Vansteenkiste, M. Hochmair, E. Felip, M. Nishio, M. Thomas, K. Ohashi, R. Toyozawa, T.R. Overbeck, F. de Marinis, T.-M. Kim, E. Laack, A. Robeva, S. Le Mouhaer, M. Waldron-Lynch, B. Sankaran, O.A. Balbin, X. Cui, M. Giovannini, M. Akimov, and R.S. Heist, for the GEOMETRY mono-1 Investigators*

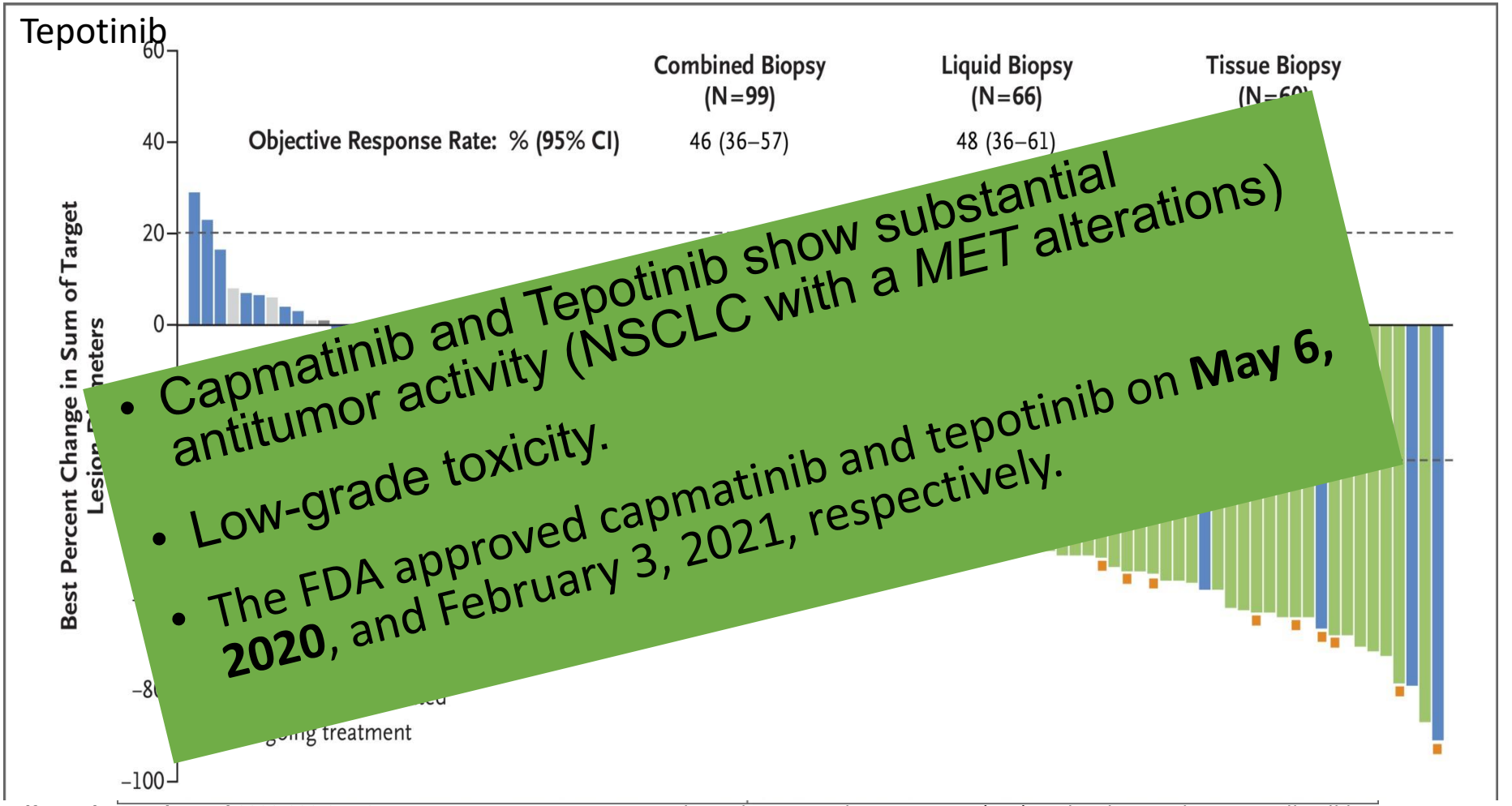
ORIGINAL ARTICLE

Tepotinib in Non–Small-Cell Lung Cancer with *MET* Exon 14 Skipping Mutations

P.K. Paik, E. Felip, R. Veillon, H. Sakai, A.B. Cortot, M.C. Garassino, J. Mazieres, S. Viteri, H. Senellart, J. Van Meerbeeck, J. Raskin, N. Reinmuth, P. Conte, D. Kowalski, B.C. Cho, J.D. Patel, L. Horn, F. Griesinger, J.-Y. Han, Y.-C. Kim, G.-C. Chang, C.-L. Tsai, J.C.-H. Yang, Y.-M. Chen, E.F. Smit, A.J. van der Wekken, T. Kato, D. Juraeva, C. Stroh, R. Bruns, J. Straub, A. Johne, J. Scheele, J.V. Heymach, and X. Le

Wolf J et al. N Engl J Med 2020;383:944-957
Paik PK et al. N Engl J Med 2020;383:931-943

Tumor Responses to Capmatinib and Tepotinib.



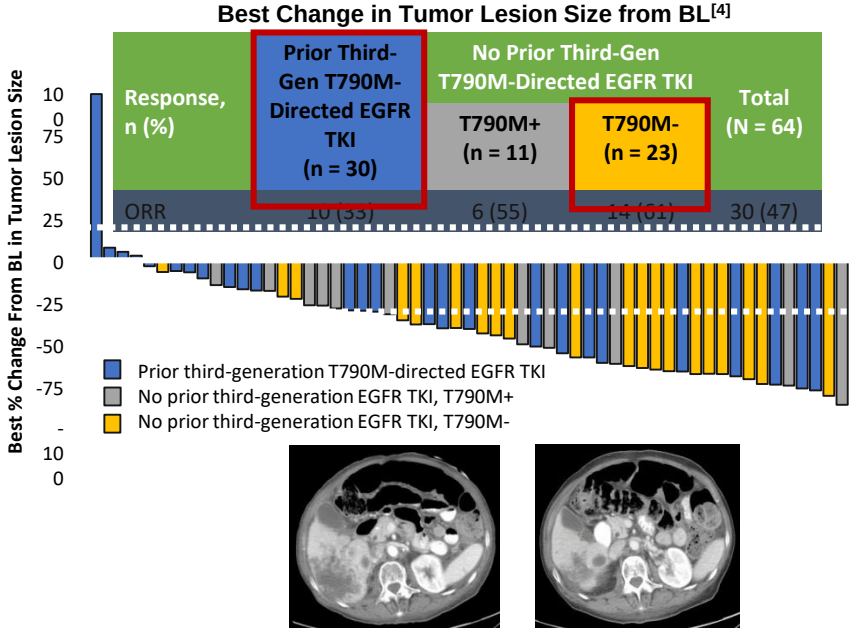
- Capmatinib and Tepotinib show substantial antitumor activity (NSCLC with a *MET* alterations)
- Low-grade toxicity.
- The FDA approved capmatinib and tepotinib on **May 6, 2020**, and February 3, 2021, respectively.

Wolf J et al. N Engl J Med 2020;383:944-957
Paik PK et al. N Engl J Med 2020;383:931-943

Xiuning, Paik et al, Tepotinib in patients (pts) with advanced non-small cell lung cancer (NSCLC) with MET amplification (METamp), JCO 2021 39:15_suppl, 9021-9021

MET amplification
Phase Ib TATTON: Osimertinib + Savolitinib

- 138 patients received osimertinib plus savolitinib 600 mg
- Objective partial responses were observed in 48%
- Responses were not related to cocommitant T790M status
- But serious adverse events an 2 deaths were observed



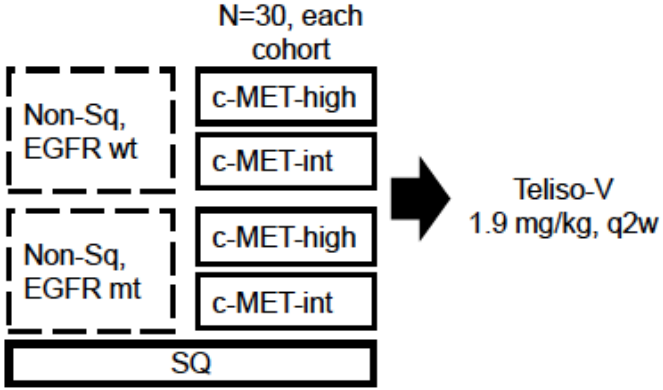
1. Drilon A, et al. J Thorac Oncol. 2017;12:15-26.
2. Piotrowska Z, et al. ASCO 2017. Abstract 9020.
3. Yang Z, et al. Int J Biol Sci. 2018;14:204-216.
4. Ahn MJ, et al. WCLC 2017. Abstract 8985.

Antibody Drug Conjugate in MET amp

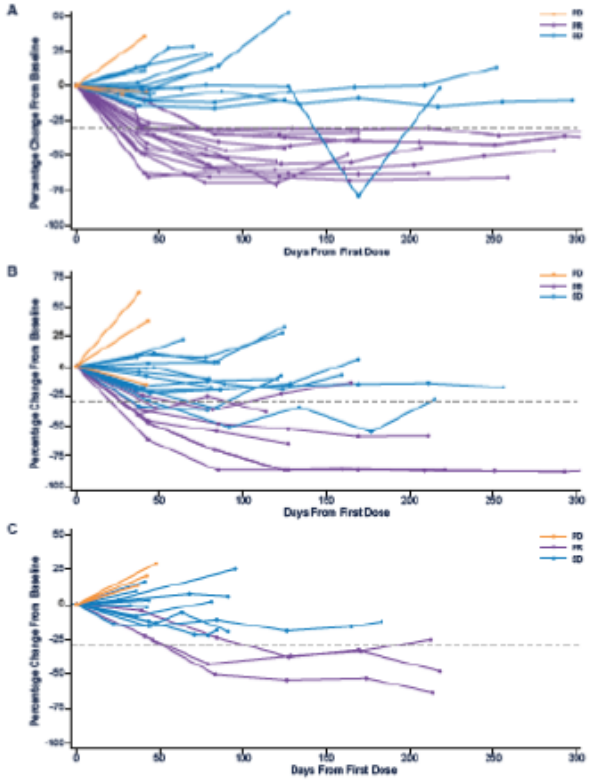
Telisotuzumab-Vedotin (Teliso-V)

c-MET targeted antibody (Telisotuzumab)
Payload: MMAE

Phase2 trial for pre-treated (≤ 2 lines)NSCLC was conducted.



c-Met intermediate: ≥25% to <50% at 3+
c-Met high: ≥50% at 3+ IHC



EGFR wt, non-Sq

	ORR	mDOR
All	35%	6.9 mo
High	54%	Not reported
Int	25%	Not reported

EGFR mt, non-Sq

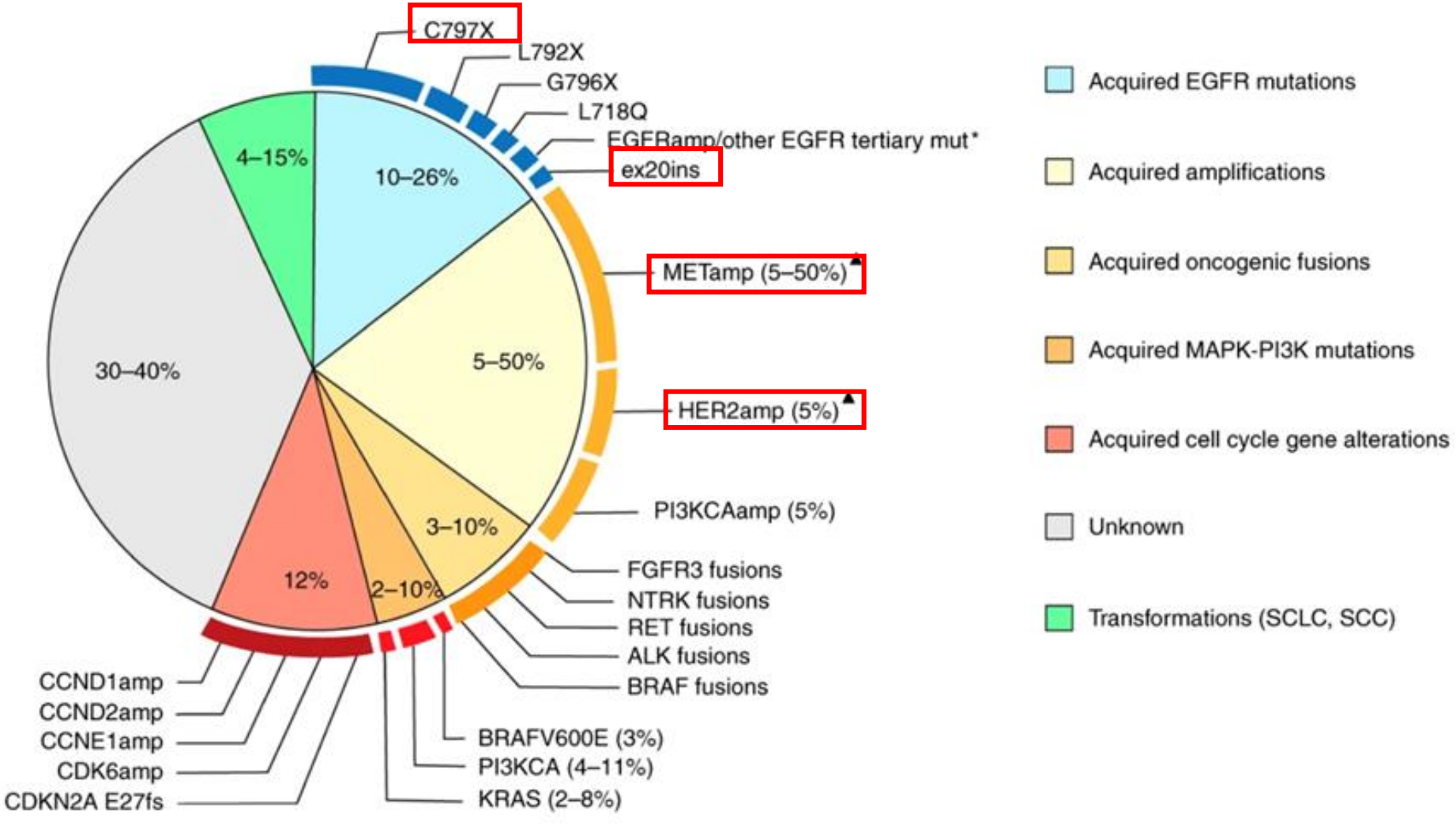
ORR	mDOR	
All	13%	NA
High	18%	Not reported
Int	0%	Not reported

Sq

ORR	mDOR
All	14%	4.0 mo

R.Camidge, et.al, AACR 2021

What are the resistance mechanisms to osimertinib?



Non selective **HER2** thyrosin kinase inhibitors

- Afatinib
- Dacomitinib
- Neratinib

Selective HER2 thyrosin kinase inhibitors

- Poziotinib
- Pyrlotinib
- Tarloxotinib
- Mobocertinib

Target mostly
HER 2 mutations

Monoclonal antibodies against HER2

- Trastuzumab

Antibody Drug Conjugates (ADCs)

- Trastuzumab emtansine (T-DM1)
- Trastuzumab-deruxtecan (T-Dxd)

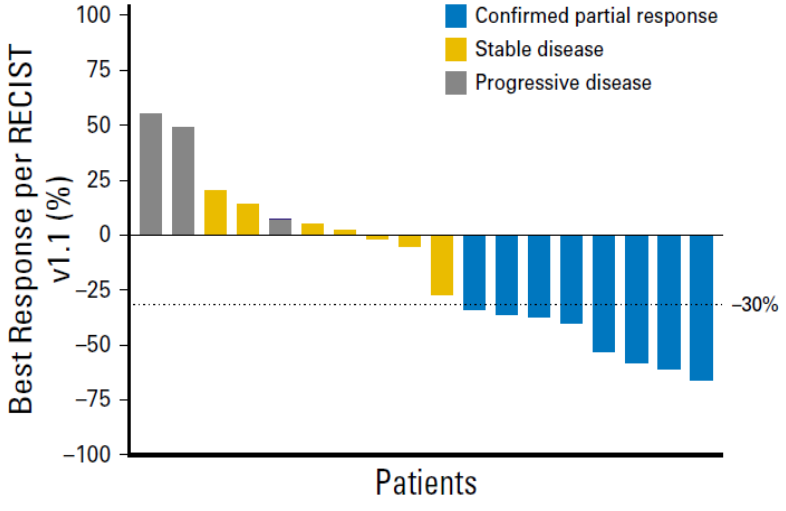
Trastuzumab

- Trastuzumab is a monoclonal antibody that binds to the extracellular domain of the HER2 receptor well known in breast cancer.
- In a retrospective study of 57 patients reported an ORR of 50% and a median PFS of 4.8 months in the chemotherapy and trastuzumab combination group.
- BUT in prospective studies, a lack of response trastuzumab + chemotherapy compared to chemotherapy alone has been consistently observed regardless of the HER2 ‘level’ of positivity as determined by IHC or FISH.
- The combination of trastuzumab with pertuzumab (HER2 dimerization blocker) has shown limited activity in the phase IIa MyPathway basket trial.

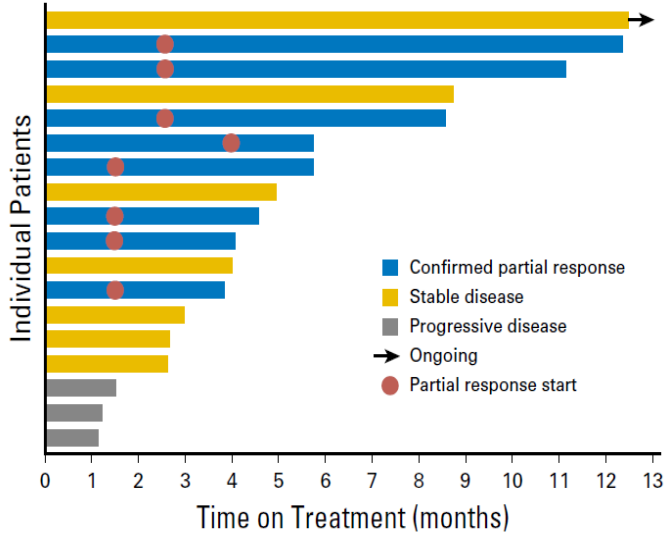
Mazières J, Barlesi F, Filleron T, et al. Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: results from the European EUHER2 cohort. Ann Oncol. 2016;27(2):281-286
Krug LM, Miller VA, Patel J, et al. Randomized phase II study of weekly docetaxel plus trastuzumab versus weekly paclitaxel plus trastuzumab in patients with previously untreated advanced nonsmall cell lung carcinoma. Cancer. 2005;104(10):2149-2155
Hainsworth JD, Meric-Bernstam F, Swanton C, et al. Targeted therapy for advanced solid tumors on the basis of molecular profiles: results from MyPathway, an open-label, phase IIa multiple basket study. J Clin Oncol. 2018;36(6):536-542.

Trastuzumab emtansine (T-DM1)

44% (95% CI: 22-69) achieved a partial response, meeting the primary endpoint



Median PFS was 5 months (95% CI: 3-9 months)



Three of four responders had HER2 amplification and two patients had a concomitant HER2 mutation.

TRAEs in >10% of patients were mainly grade 1 or 2 events and included elevated AST or ALT, thrombocytopenia, fatigue, infusion reaction, nausea, weight loss, maculopapular rash, anorexia, epistaxis, and anemia. There was only 1 patient with treatment-related grade 3 anemia.
No grade 4 or 5 AEs were reported. There were no dose reductions or discontinuations due to TRAEs.

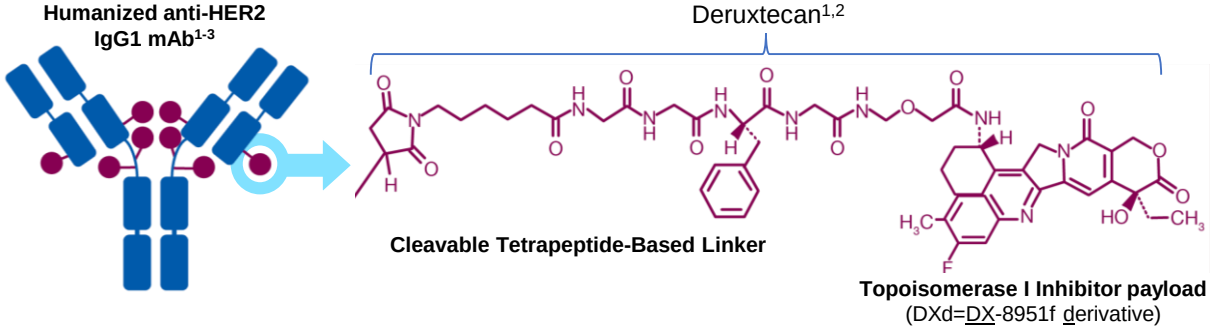
Li BT, et al. *J Clin Oncol*. 2018;36(24):2532-2537.

Trastuzumab-deruxtecan (T-Dxd)

T-DXd Was Designed With 7 Key Attributes

T-DXd is an ADC composed of 3 components[1,2]:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab, covalently linked to:
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker



Payload mechanism of action: topoisomerase I inhibitor [a,1,2]
High potency of payload [a,1,2]
High drug to antibody ratio ≈ 8 [a,1,2]
Payload with short systemic half-life [a,1,2]
Stable linker-payload [a,1,2]
Tumor-selective cleavable linker [a,1,2]
Bystander antitumor effect [a,1,4]

The payload DXd is highly membrane-permeable compared to that of T-DM1. The bystander effect is observed only in cells neighbouring HER2-positive cells, indicating low concern in terms of systemic toxicity.

[a]The clinical relevance of these features is under investigation.

1. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142. 4. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

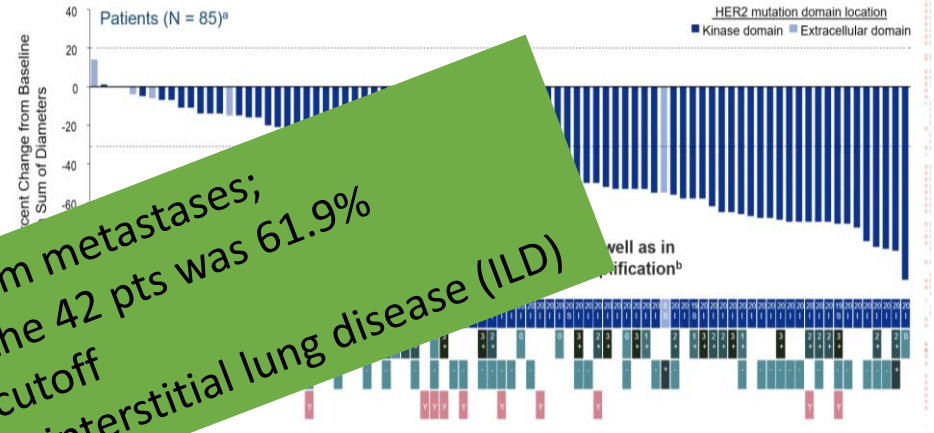
Trastuzumab Deruxtecan in Patients With HER2 Mut Destiny lung

2021 ESMO congress

Primary Data from DESTINY-Lung01: A Phase 2 Trial of Trastuzumab Deruxtecan (T-DXd) in Patients With *HER2*-Mutated (*HER2*m) Metastatic Non–Small Cell Lung Cancer (NSCLC)

Bob T. Li, MD, PhD, MPH[a], Egbert F. Smit, ... Nakagawa, Hibiki Udagawa, Julien M...

- 45.2% had central nervous system metastases;
- Confirmed ORR by ICR among the 42 pts was 61.9%
- DOR was not reached at data cutoff
- 5 cases (11.9%) of drug-related interstitial lung disease (ILD)



DESTINY-Lung...

Multicenter, interna...

Key eligibility criteria
- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline[a]
- ECOG PS of 0 or 1
- Locally reported *HER2* mutation (for Cohort 2)[b]

...expressing[c] or IHC 2+)
...DXd 5.4 mg/kg q3w
N = 41

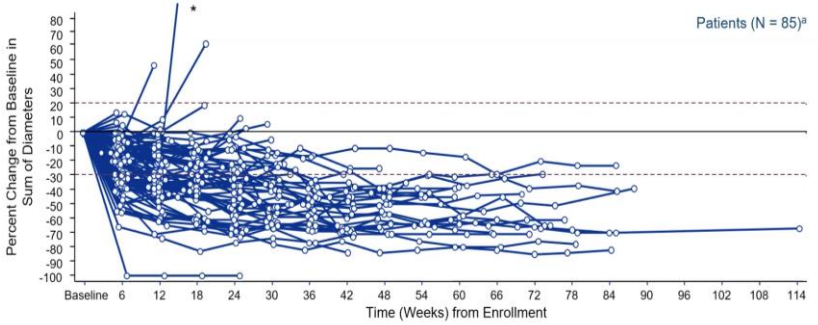
Cohort 2: *HER2*-mutated T-DXd 6.4 mg/kg q3w N = 42

Cohort 2 expansion: *HER2*-mutated T-DXd 6.4 mg/kg q3w N = 49

Primary end point
- Confirmed ORR by ICR[d]

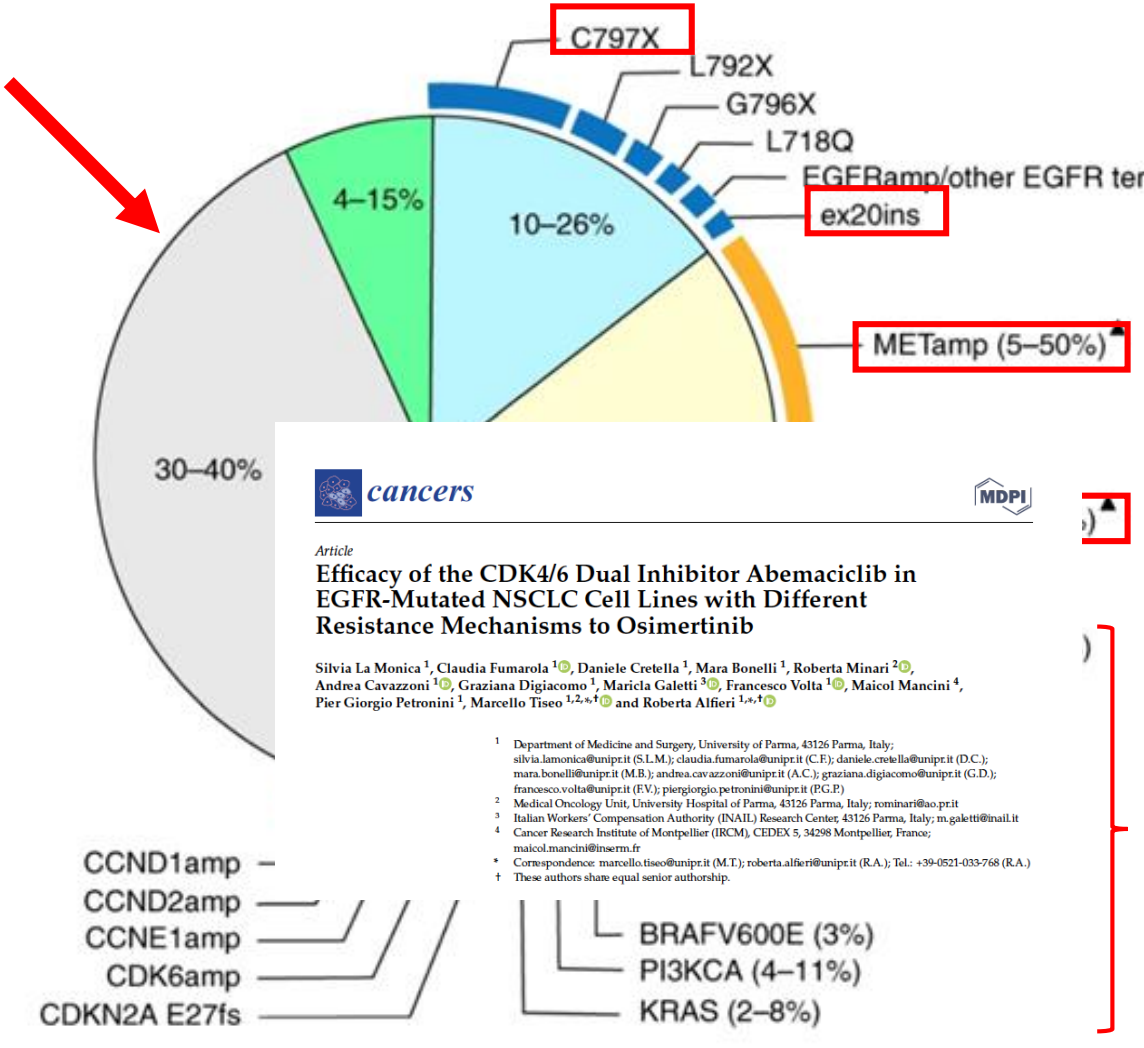
Secondary end points
- DOR
- PFS
- OS
- DCR
- Safety

Exploratory end point
- Biomarkers of response



Data cutoff: May 3, 2021
- 91 patients with *HER2*m NSCLC were enrolled and treated with T-DXd
- 15 patients (16.5%) remain on treatment to date
- 76 patients (83.5%) discontinued, primarily for progressive disease (37.4%) and adverse events (29.7%)

What are the resistance mechanisms to osimertinib?



cancers
MDPI
Article

Efficacy of the CDK4/6 Dual Inhibitor Abemaciclib in EGFR-Mutated NSCLC Cell Lines with Different Resistance Mechanisms to Osimertinib

Silvia La Monica [1], Claudia Fumarola [1], Daniele Cretella [1], Mara Bonelli [1], Roberta Minari [2], Andrea Cavazzoni [1], Graziana Digiacomo [1], Maricla Galetti [3], Francesco Volta [1], Maicol Mancini [4], Pier Giorgio Petronini [1], Marcello Tiseo [1,2,*,†] and Roberta Alfieri [1,*,†]

[1] Department of Medicine and Surgery, University of Parma, 43126 Parma, Italy; silvia.lamonica@unipr.it (S.L.M.); claudia.fumarola@unipr.it (C.F.); daniele.cretella@unipr.it (D.C.); mara.bonelli@unipr.it (M.B.); andrea.cavazzoni@unipr.it (A.C.); graziana.digiacomo@unipr.it (G.D.); francesco.volta@unipr.it (F.V.); piergiorgio.petronini@unipr.it (P.G.P.)
[2] Medical Oncology Unit, University Hospital of Parma, 43126 Parma, Italy; rominari@ao.pr.it
[3] Italian Workers' Compensation Authority (INAIL) Research Center, 43126 Parma, Italy; m.galetti@inail.it
[4] Cancer Research Institute of Montpellier (IRCM), CEDEX 5, 34298 Montpellier, France; maicol.mancini@inserm.fr
* Correspondence: marcello.tiseo@unipr.it (M.T.); roberta.alfieri@unipr.it (R.A.); Tel.: +39-0521-033-768 (R.A.)
† These authors share equal senior authorship.

- Acquired EGFR mutations
- Acquired amplifications
- Acquired oncogenic fusions
- Acquired MAPK-PI3K mutations
- Acquired cell cycle gene alterations
- Unknown
- Transformations (SCLC, SCC)

Amivantamab EGFR-MET bispecific AB + Lazertinib 3rd gen EGFR TKI

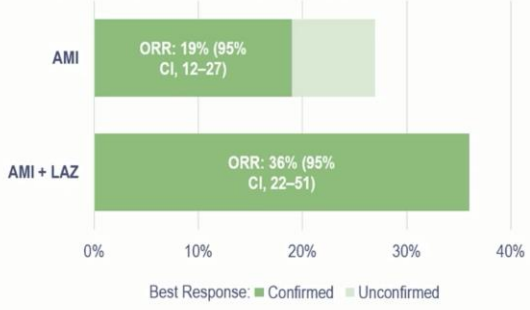
2021 ESMO congress

Amivantamab Monotherapy and in Combination with Lazertinib in Post-osimertinib EGFR-mutant NSCLC: Analysis from the CHRYSALIS Study

Natasha B. Leighl[1], Catherine A. Shu[2], Anna Minchom[3], Enriqueta Felip[4], Sophie Cousin[5], Byoung Chul Cho[6], Keunchil Park[7], Ji-Youn Han[8], Michael Boyer[9], Chee Khoon Lee[10],

Efficacy: AMI Monotherapy and AMI + LAZ

(descriptive cross-cohort analysis)

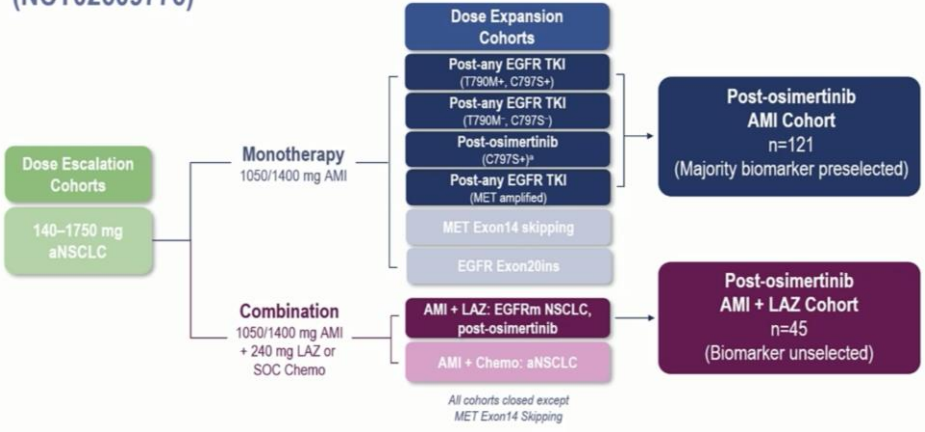


	AMI (n=121)	AMI + LAZ (n=45)
Best response[a]	27%	36%
Confirmed ORR* (95% CI)	**19%** (12–27)	**36%** (22–51)
CR	0	1 (2%)
PR	23 (19%)	15 (33%)
SD	53 (44%)	14 (31%)
PD	39 (32%)	11 (24%)
NE	6 (5%)	4 (9%)
mDOR (95% CI)	**5.9 mo** (4.2–12.6)	**9.6 mo** (5.3–NR)
CBR (95% CI)	48% (39–57)	64% (49–78)
mPFS (95% CI)	4.2 mo (3.2–5.3)	4.9 mo (3.7–9.5)
mF/U (range)	6.9 mo (0.7–38.6)	11.1 mo (1.0–15.0)

*ORR among patients with identified EGFR/MET-based osimertinib resistance was 18% for AMI and 47% for AMI + LAZ[1]

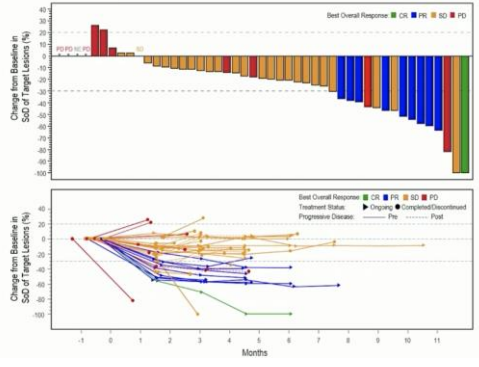
CHRYSALIS Study Design

(NCT02609776)



Addition of lazertinib to amivantamab was associated with numerically higher objective response rate and longer duration of response after progression on osimertinib

Heavily Pretreated: Antitumor Activity of Amivantamab + Lazertinib



Among 47 efficacy-evaluable[a] patients at a median follow-up of 4.5 mo (range, 0.3–9.7):

- ORR = 21% (95% CI, 11–36)
- CBR = 51% (95% CI, 36–66)
- Median time on treatment = 3.7 mo (range, 0.03–9.7)
- Responses observed early
  - mTTR = 1.5 mo (range, 1.3–4.2)
- 10/10 patients who responded are progression-free and remain on treatment
- 10/26 patients with stable disease remain on treatment (longest at 9.6+ mo)

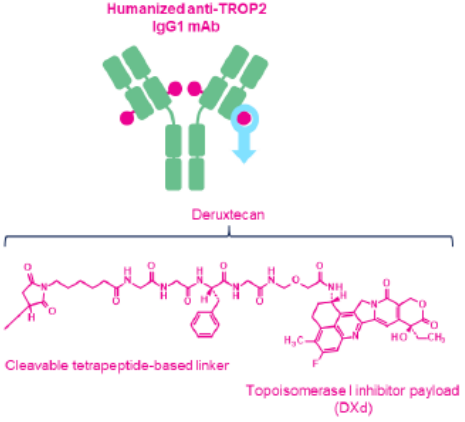
Datopotamab Deruxtecan in NSCLC with Actionable genomic alterations

2021 ESMO congress

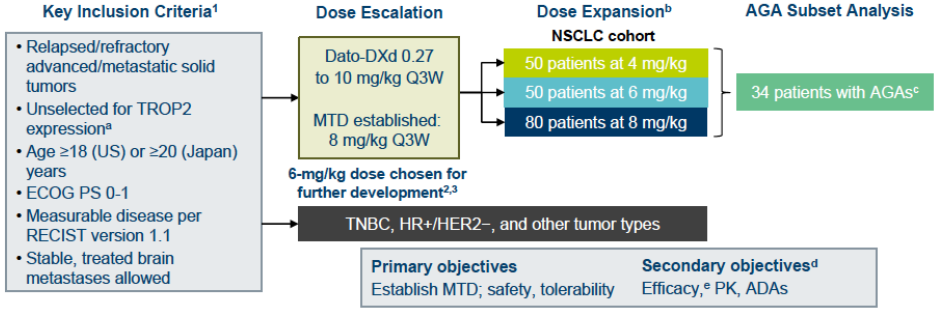
Efficacy of Datopotamab Deruxtecan (Dato-DXd) in Patients With Advanced/Metastatic Non-Small Cell Lung Cancer (NSCLC) and Actionable Genomic Alterations (AGAs): Preliminary Results From the Phase 1 TROPION-PanTumor01 Study

Edward B. Garon,[1] Melissa L. Johnson,[2] Aaron E. Lisberg,[1] Alexander Spira,[3] Noboru Yamamoto,[4] Rebecca S. Heist,[5] Jacob M. Sands,[6] Kiyotaka Yoh,[7]

- Trop-2 is a highly expressed antigen on NSCLCs.
- Here we study patients with pre-treated mut activators.



TROPION-PanTumor01 Study Design



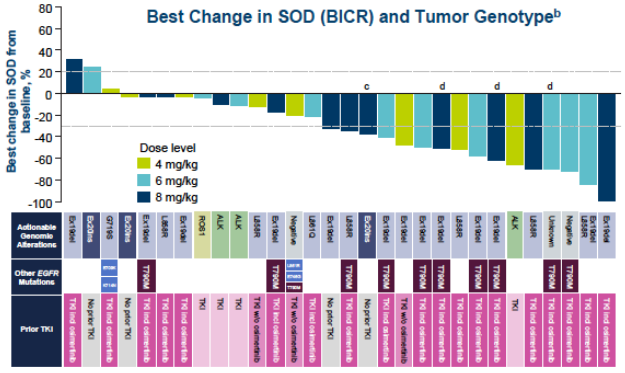
NSCLC With AGAs: Antitumor Activity

Best Overall Response (BICR)

Patients[a]	Dato-DXd n=34
ORR, n (%)	12 (35)
CR	0
PR	12 (35)
SD, n (%)	14 (41)
Non-CR/PD, n (%)	2 (6)
PD, n (%)	2 (6)
NE, n (%)	4 (12)
DOR, median (95% CI), mo	9.5 (3.3-NE)

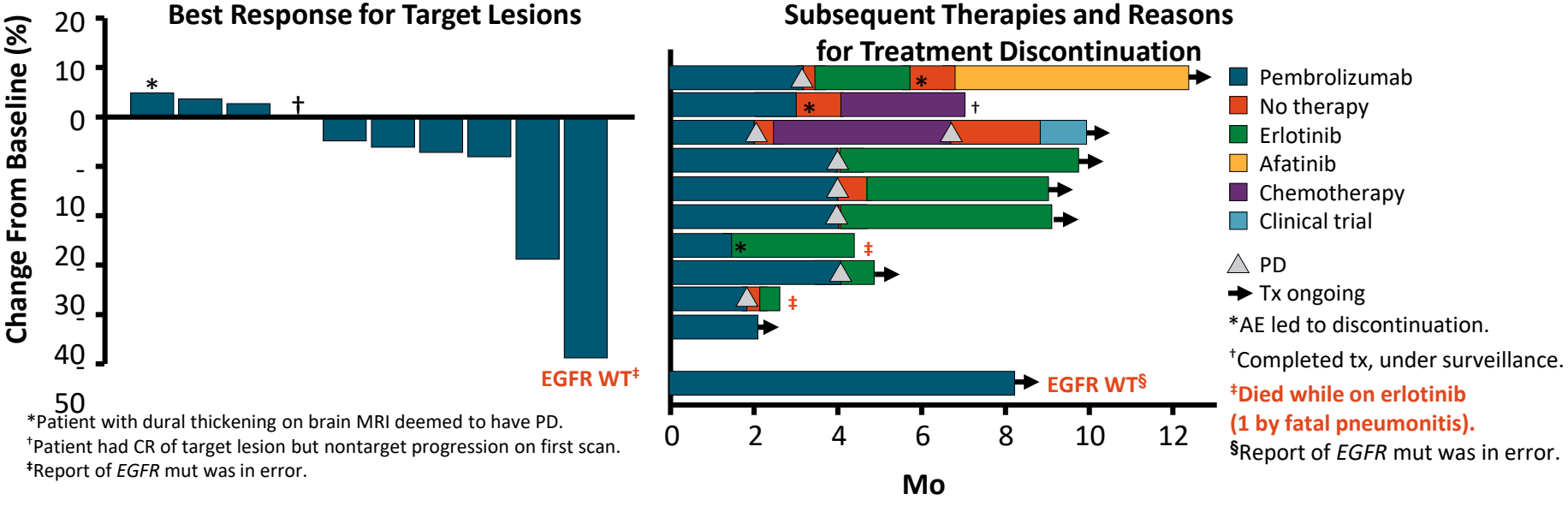
- Clinical activity was observed in *EGFR* (Ex19del, L858R) including after osimertinib and across other AGAs

Best Change in SOD (BICR) and Tumor Genotype[b]



Lack of Efficacy With Immune Checkpoint Inhibition in *EGFR* Mutation–Positive NSCLC

- Phase II study of pembrolizumab in patients with PD-L1–positive *EGFR*-mutated advanced NSCLC (planned N = 25); stopped for futility at 11 patients

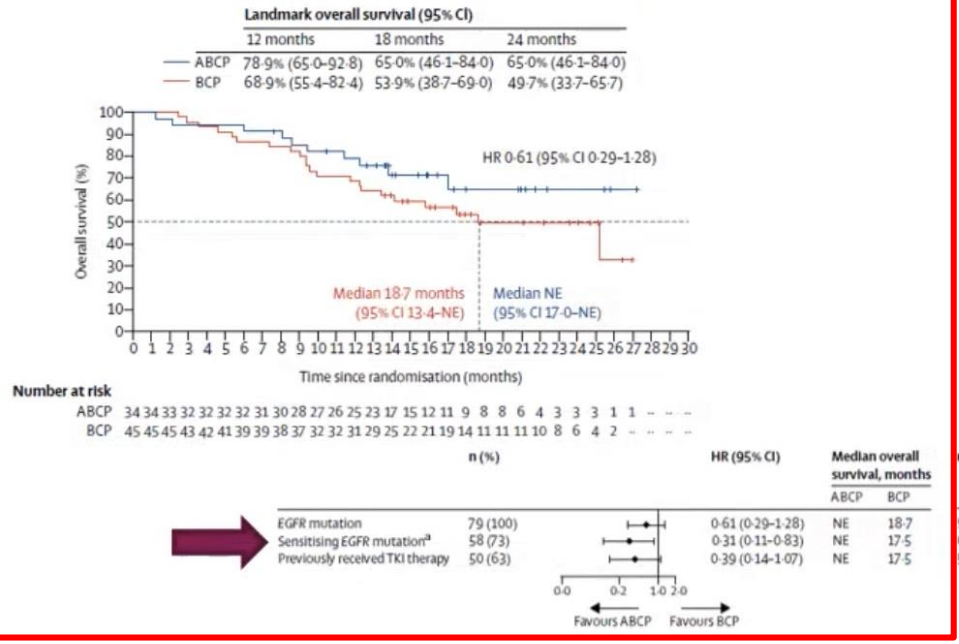


*Patient with dural thickening on brain MRI deemed to have PD.
†Patient had CR of target lesion but nontarget progression on first scan.
‡Report of *EGFR* mut was in error.

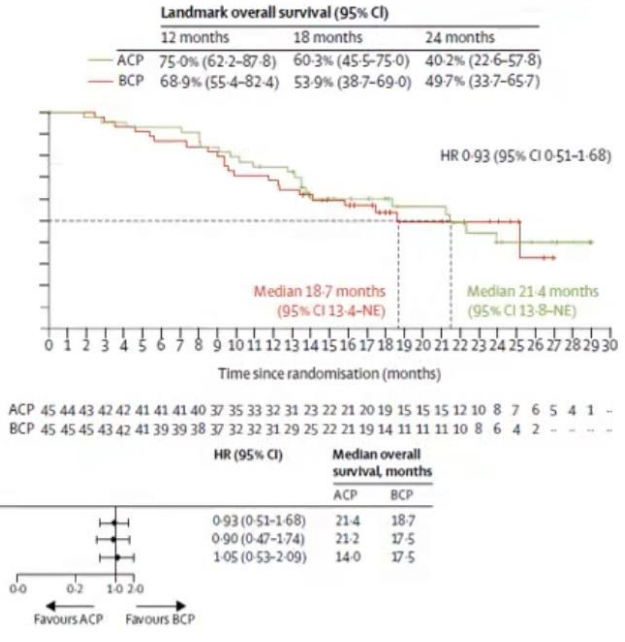
Lisberg. J Thorac Oncol. 2018;13:1138.

EGFR Mutations: Anti-PD-L1 in Combination With Chemotherapy and Antiangiogenic Therapy

Atezolizumab + bevacizumab + carboplatin + paclitaxel
Vs. bevacizumab + carboplatin + paclitaxel



Atezolizumab + carboplatin + paclitaxel
Vs. bevacizumab + carboplatin + paclitaxel

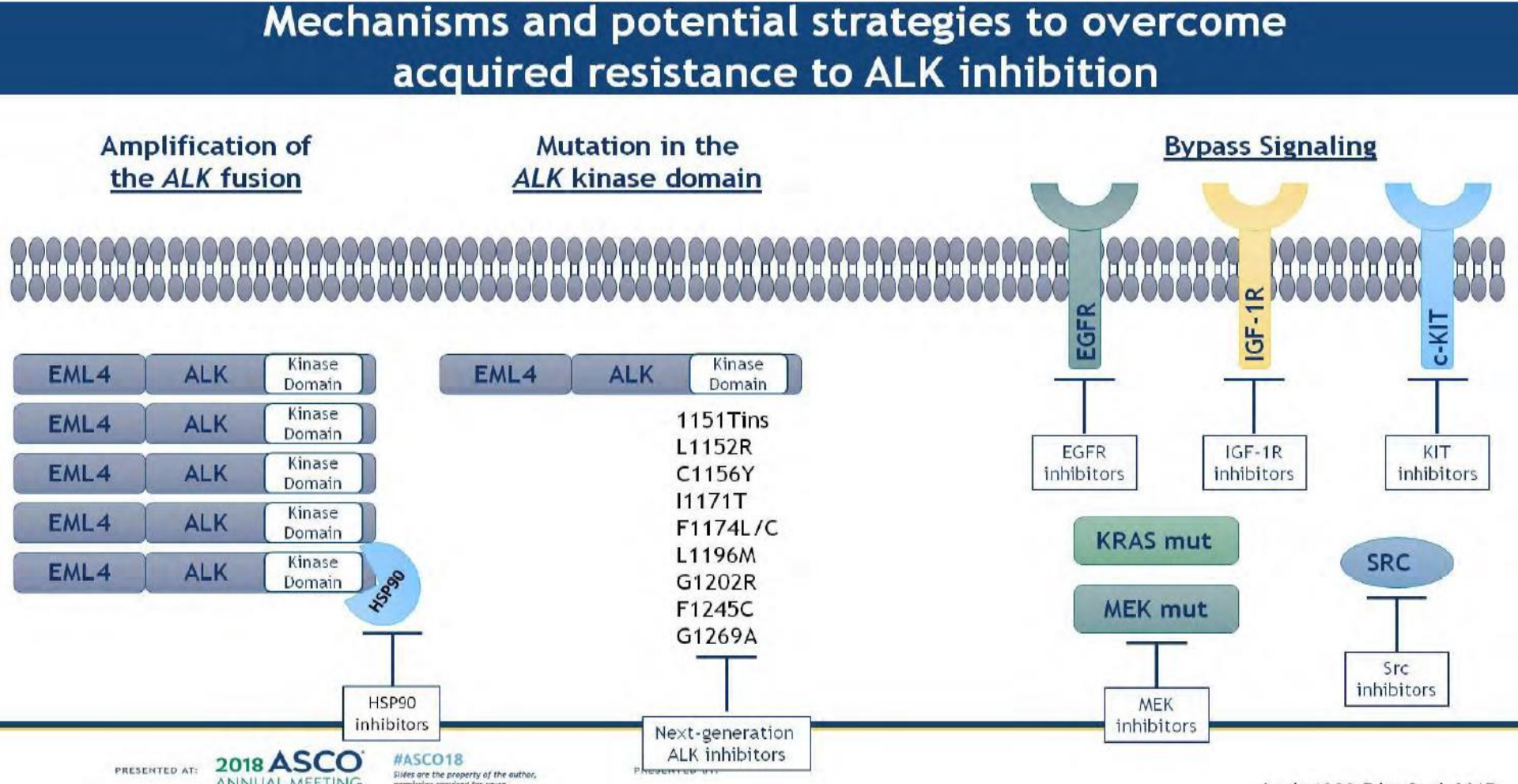


Data cut-off: 22 January 2018; [a]sensitising *EGFR* mutations are defined as exon 19 deletions or Leu858Arg mutations

ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; ACP, atezolizumab + carboplatin + paclitaxel; BCP, bevacizumab + carboplatin + paclitaxel; CI, confidence interval; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; PD-L1, programmed cell death ligand-1; NE, not estimable; TKI, tyrosine kinase inhibitor

1. Reck M, et al. Lancet Respir Med 2019;7:387–401

EML-Alk translocated patients



EML-Alk translocated patients

Next generation ALK and ROS1 Inhibitors : Better CNS penetration, more potent, active against resistance kinase domain mutations

Cellular ALK Phosphorylation Mean IC50 (nM)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4-ALK V1	38.6	4.9	11.4	10.7	2.3
EML4-ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4-ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4-ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4-ALK I1171T	51.4	1.7	33.6*	6.1	11.5
EML4-ALK F1174C	115.0	38.0*	27.0	18.0	8.0
EML4-ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4-ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4-ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4-ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4-ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4-ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4-ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4-ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4-ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

IC50 ≤ 50 nM

IC50 > 50 <200 nM

IC50 ≥ 200 nM

Gainor et al. Cancer Discovery 2016

ALK G1202R Lorlatinib > Ropotrectinib

ROS1 G2032R Ropotrectinib > Lorlatinib

Table 1. Ropotrectinib Potently Inhibited WT and Mutant ALK/ROS1/TRK in Ba/F3 Cell Proliferation IC_{50} (nM

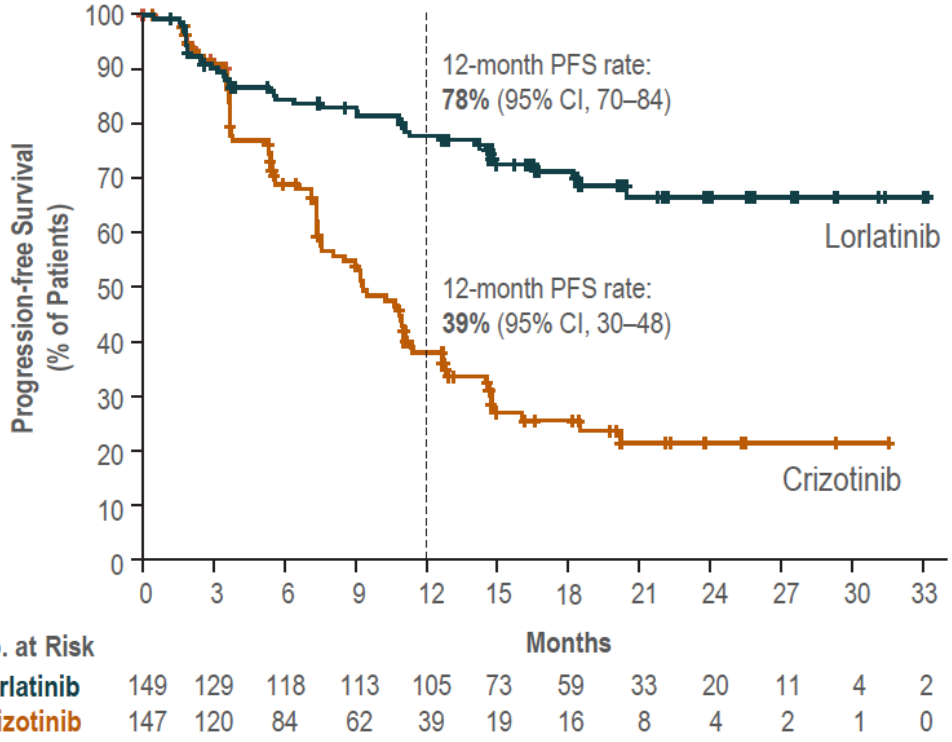
	EML4-ALK V1		CD74-ROS1			LMNA-TRKA		ETV6-TRKB		ETV6-TRKC		
Inhibitor	WT	G1202R	WT	G2032R	D2033N	WT	G595R	WT	G639R	WT	G623R	G623I
Ropotrectinib	27	63.6	<0.2	3.3	1.3	<0.2	0.4	<0.2	0.6	<0.2	3	1.4
Crizotinib	55.7	400	14.6	266.2	200.9							
Ceritinib	7.1	965	42.8	1813	169.2							
Alectinib	11.6	417										
Brigatinib	10.9	190.5	21	1172	128.4							
Lorlatinib	0.5	41.5	0.2	160.7	3.3							
Ensartinib			39.5	371.8	401.9							
Entrectinib			10.5	1813	169.2	0.5	705	<0.5	1384	0.6	1623	1351
Larotrectinib						4	1024	10.9	3000	10.2	3293	742.3

Drilon et al ASCO 2018

EML-Alk translocated patients

VIRTUAL 2020 ESMO congress

CROWN trial of Lorlatinib vs Crizotinib : Primary Endpoint PFS by BICR



	Lorlatinib (n=149)	Crizotinib (n=147)
Patients with event, n (%)	41 (28)	86 (59)
Median PFS, months (95% CI)	NE (NE–NE)	9.3 (7.6-11.1)
HR (95% CI) 1-sided P value*	**0.28** (0.19-0.41) <0.001	

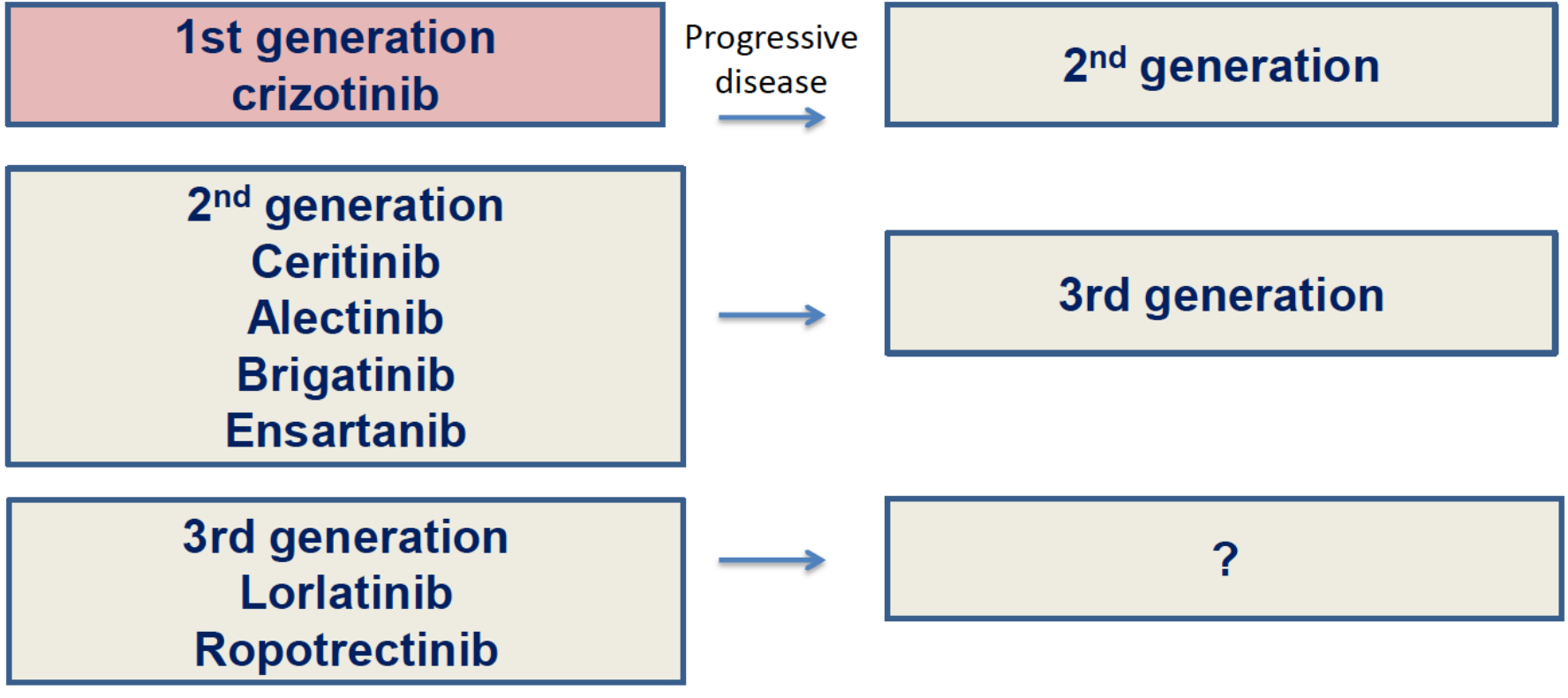
*By stratified log-rank test.

Solomon et al. ESMO 2020

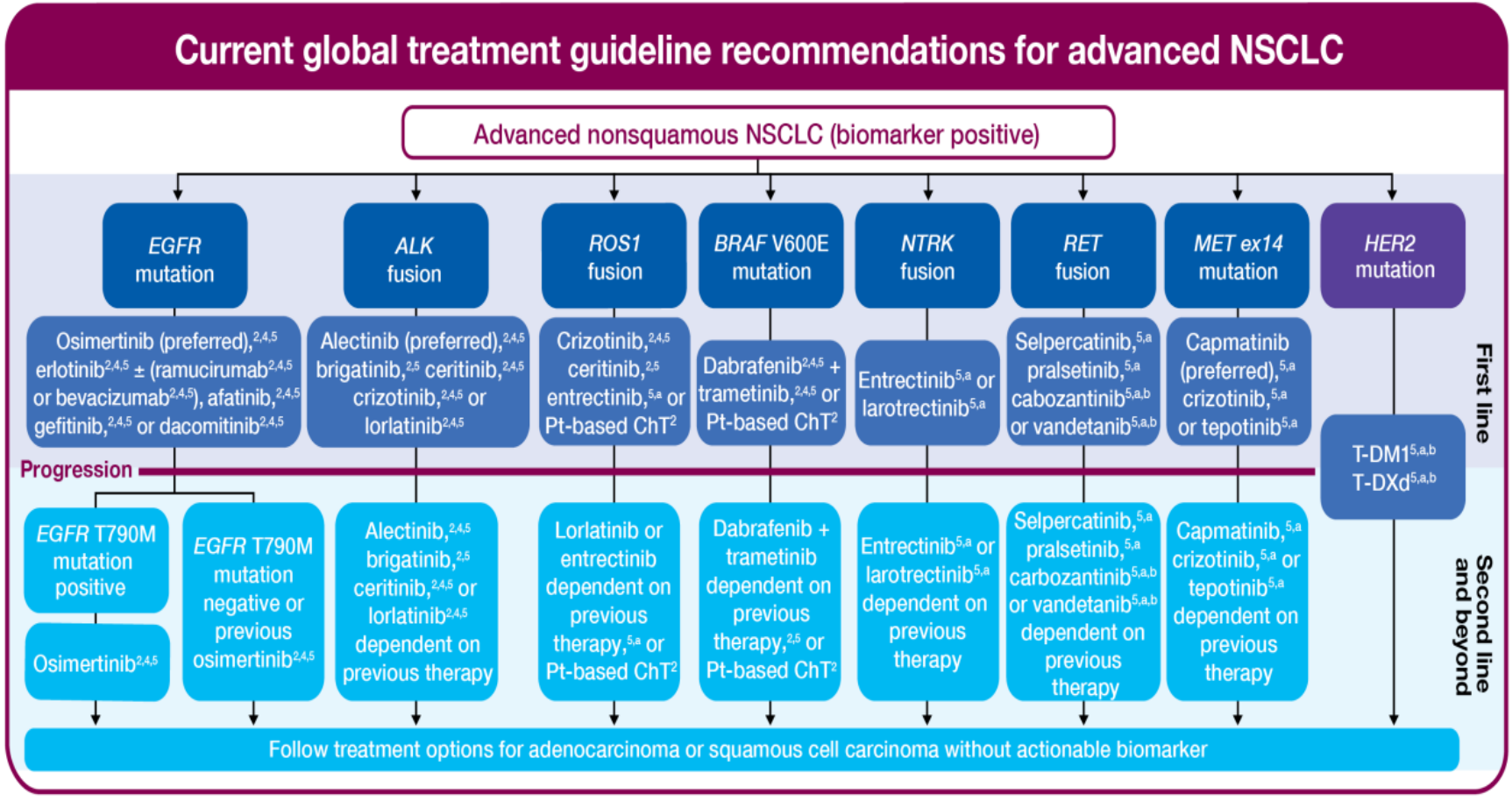
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival

EML-Alk translocated patients

Treatment algorithms for ALK+ NSCLC



Current Treatment Paradigm for Molecular Biomarker–Positive Advanced NSCLC



Thank you very much!