IASLC 2022 World Conference on Lung Cancer

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EGFR-mutated Non-Small Cell Lung Cancer: Update from WCLC22 -Vienna

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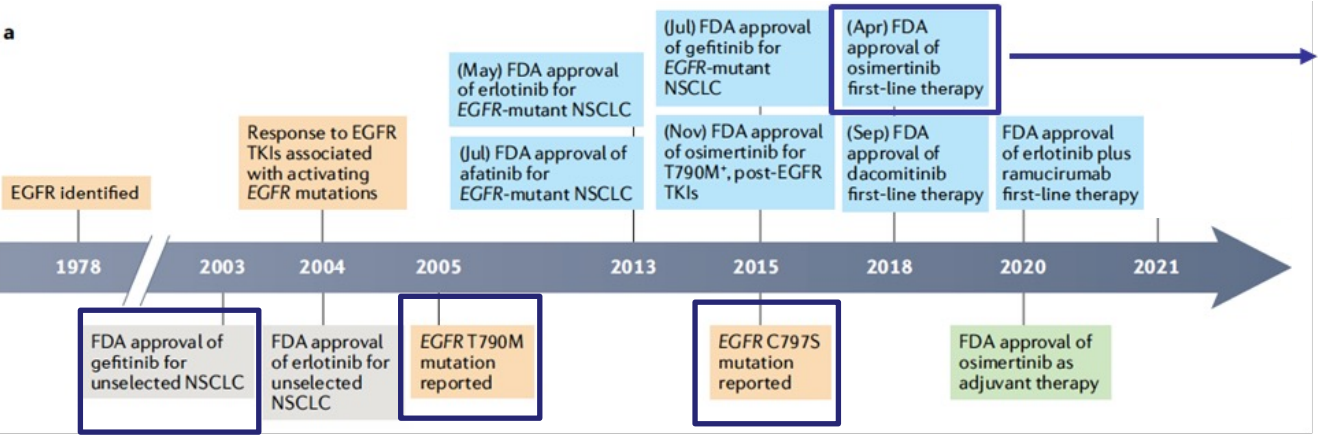
Presented by D. Gandara: BEST of WCLC 2022 Nov 12, 2022

Company	Relationship(s)
Genentech	Research Grant (Institutional)
Amgen	Research Grant (Institutional)
Astra Zeneca	Consultant (Institutional)
IO Biotech	Consultant (Institutional)
Guardant Health	Consultant (Institutional)
Oncocyte	Consultant (Institutional)
Roche Genentech	Advisory Board
Merck	Advisory Board
Novartis	Advisory Board
Boehringer Ingelheim	Advisory Board
Amgen	Advisory Board

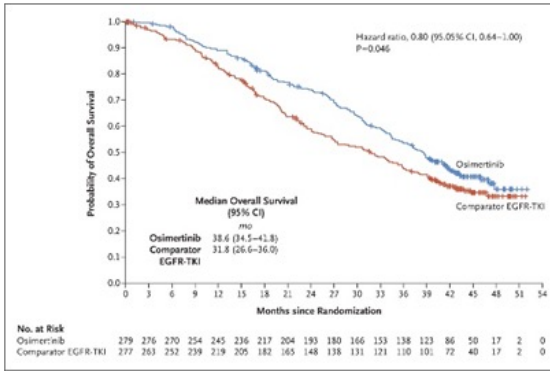
EGFR-mutated NSCLC -Advanced Stage Disease: Mechanisms of EGFR TKI Resistance (to Osimertinib) and How to Overcome them

- Real World Analysis of Mechanisms of Resistance to Osimertinib by plasma ctDNA
- Amivantamab Combinations in Refractory EGFR-mutated NSCLC
- Amivantamab + Osimertinib in Refractory EGFR-mutated NSCLC
- Osimertinib + Savolitinib in Refractory EGFRm MET-amplified NSCLC
- HER3-Directed ADC Patritumab Deruxtecan (HER3-DXd) in EGFR-Mutated NSCLC
- BBT-176: a 4th generation EGFR TKI targeting C797S in refractory EGFR-Mutated NSCLC

History of EGFR and Inhibitor Development



Osimertinib = OS in 1st line



1st Line Therapy for EGFR-mutated NSCLC Worldwide 2022

1st Gen TKIs	2nd Gen TKIs	3rd Gen TKI	Combinations
Gefitinib	Afatinib	Osimertinib	Gefitinib + Chemo
Erlotinib	Dacomitinib		Erlotinib + Bev/Ramu

Cooper AS, et al, Nat Rev Clin Oncol 2022; Ramalingam S et al, N Eng J Med 2020

Progressive Disease (PD) after 1st line TKI Therapy in Oncogene-driven Advanced NSCLC (e.g. EGFR or ALK)

Progressive Disease after 1st line TKI

Empiric Approach:
Choice of next line of therapy empirically:
-Next TKI
-Chemotherapy
-Immunotherapy

Precision Medicine Approach:
Choice of next line of therapy based on repeat biopsy or plasma ctDNA

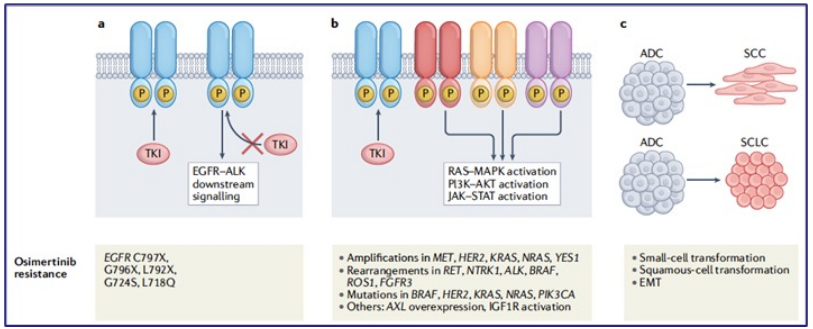
On-Target MOR
(Resistance Mutations)

Off-Target MOR
(Bypass Mechanisms Or Histologic Transformation)

On-Target: EGFR resistance mt

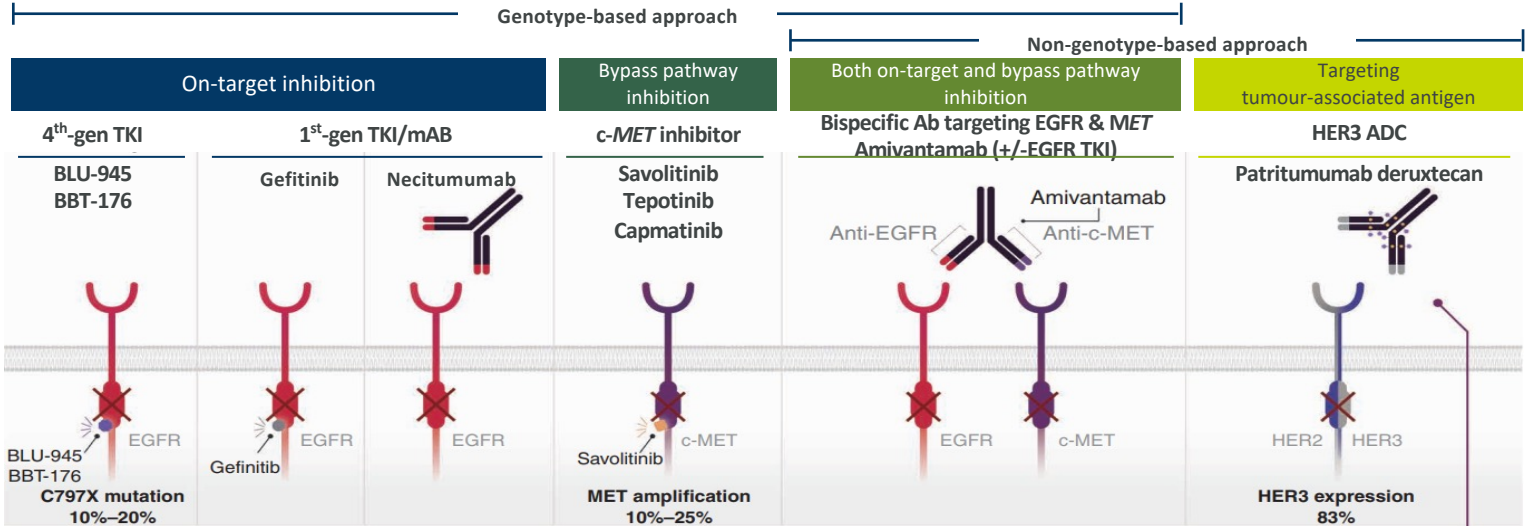
Off-Target: Diverse Bypass MOR

Histologic transformation



Cooper AS, et al, Nat Rev Clin Oncol 2022

Investigational Treatment Strategies under study for EGFR-mutated NSCLC with progressive disease after 1st-line Osimertinib (excludes histologic transformation as MOR)



Lim SM, et al. Cancer Discov 2022;12:16–9

Selected Clinical Trials under investigation for EGFR-mutated NSCLC with PD following 1st line Osimertinib therapy

Study	Phase	Regimen (targeted agents)	Target
SYMPHONY[1]	1/2	BLU-945	EGFR C797S
BBT-176[2]	1/2	BBT-176	EGFR C797S
ORCHARD[3]	2	Osimertinib + savolitinib, gefitinib, necitumumab, alectinib, selpercatinib, etc.	Based on each target
SAVANNAH[4]	2	Osimertinib + savolitinib	*MET* overexpression and/or amplification
SAFFRON[5]	3	Osimertinib + savolitinib vs platinum-based doublet	*MET* overexpression and/or amplification
INSIGHT 2[6]	2	Tepotinib + osimertinib vs tepotinib	*MET* amplification
MARIPOSA 2[7]	3	Amivantamab + lazertinib + platinum-based doublet vs. platinum-based doublet	All comers
NCT04676477[8]	1	Patritumab deruxtecan + osimertinib vs platinum-based doublets	All comers
COMPEL[9]	3	Osimertinib + pemetrexed cisplatin or carboplatin vs. pemetrexed cisplatin or carboplatin	All comers

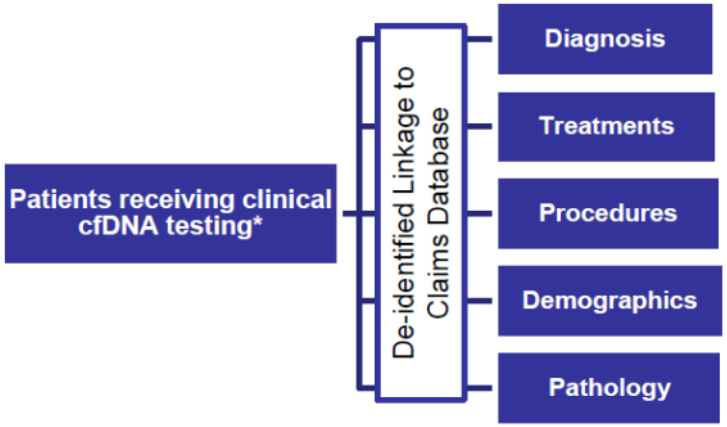
Study	Phase	Regimen (chemotherapy + IO ± antiangiogenic)	Target
CheckMate 722[10]	3	Nivolumab + platinum-based doublet vs. nivolumab + ipilimumab vs platinum-based doublet	All comers
KEYNOTE-789[11]	3	Pembrolizumab + pemetrexed-platinum vs. pemetrexed-platinum	All comers
ATTLAS[12]	3	Atezolizumab + bevacizumab + carboplatin/paclitaxel vs. pemetrexed/platinum	All comers*
ORIENT[13]	3	Sintilimab + IBI305 + pemetrexed-cisplatin vs. sintilimab + placebo + pemetrexed-cisplatin vs pemetrexed-cisplatin	All comers
NCT03924050[14]	3	Toripalimab + pemetrexed-platinum vs. pemetrexed-platinum	All comers

*Includes patients with an EGFR mutation or ALK translocation EGFR, epidermal growth factor receptor; EGFRm, EGFR mutation positive; FISH, fluorescence in situ hybridisation; IO, immuno-oncology; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

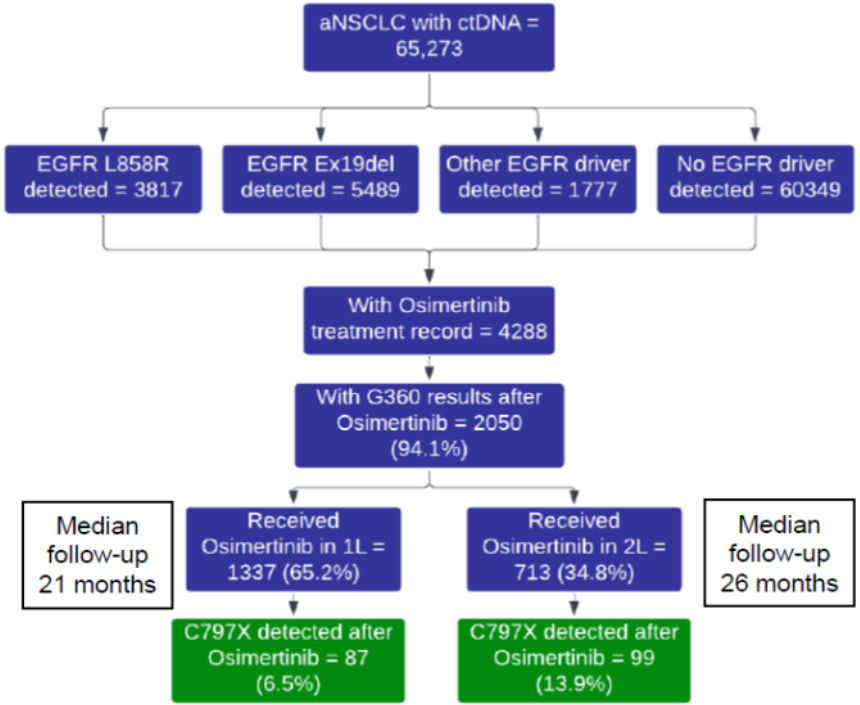
1. NCT04862780. Available at: https://clinicaltrials.gov/ct2/show/NCT04862780 (Accessed July 2022); 2. NCT04820023. Available at: https://clinicaltrials.gov/ct2/show/NCT04820023 (Accessed July 2022); 3. NCT03944772. Available at: https://clinicaltrials.gov/ct2/show/NCT03944772 (Accessed July 2022); 4. NCT03778229. Available at: https://clinicaltrials.gov/ct2/show/NCT03778229 (Accessed July 2022); 5. NCT05261399. Available at: https://clinicaltrials.gov/ct2/show/NCT05261399 (Accessed July 2022); 6. NCT03940703. Available at: https://clinicaltrials.gov/ct2/show/NCT03940703 (Accessed July 2022); 7. NCT04988295. Available at: https://clinicaltrials.gov/ct2/show/NCT04988295 (Accessed July 2022); 8. NCT04676477. Available at: https://clinicaltrials.gov/ct2/show/NCT04676477 (Accessed July 2022); 9. NCT04765059. Available at: https://clinicaltrials.gov/ct2/show/NCT04765059 (Accessed July 2022); 10. NCT02864251. Available at: https://clinicaltrials.gov/ct2/show/NCT02864251 (Accessed July 2022); 11. NCT03515837. Available at: https://clinicaltrials.gov/ct2/show/NCT03515837 (Accessed July 2022); 12. NCT03991403. Available at: https://clinicaltrials.gov/ct2/show/NCT03991403 (Accessed July 2022); 13. NCT03802240. Available at: https://clinicaltrials.gov/ct2/show/NCT03802240 (Accessed July 2022); 14. NCT03924050. Available at: https://clinicaltrials.gov/ct2/show/NCT03924050 (Accessed July 2022)

Real World Analysis of Mechanisms of Resistance to Osimertinib by plasma ctDNA:
Timing of Resistance relates to the Mechanism of Resistance

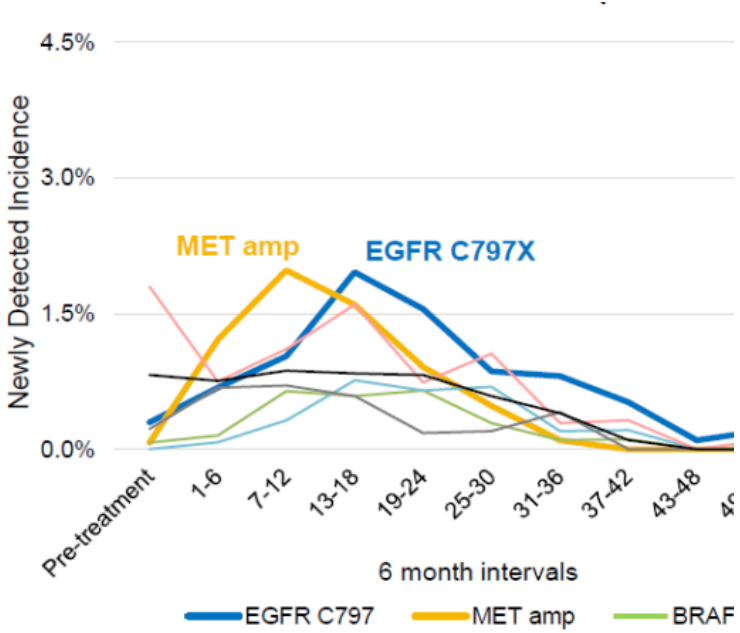
- INFORM is an aggregated commercial payer claims database with de-identified records of over 174,000 U.S.-based advanced cancer patients with clinical cfDNA* results.



*cfDNA testing done via either Guardant360 CDx or Guardant360



MET amplification is the most common acquired resistance mechanism during 1st year after Osimertinib given first line, followed by C797X during the 2nd year



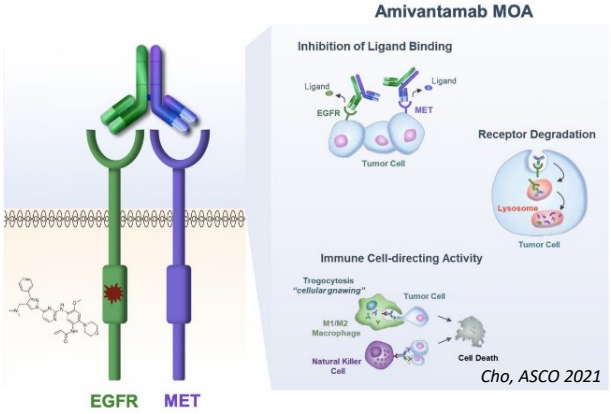
If there is PD within 1st year, likely to be MET-related

The longer the patient is on Osi, the more likely MOR is due to On-Target resistance mutation

Presented by S. Ramalingam WCLC 2022

Amivantamab-Lazertinib + Pem/Carboplatin in EGFR TKI-refractory EGFR-mutated NSCLC

Amivantamab (Bispecific MoAb)



Cho, ASCO 2021

Clinical Development of Amivantamab
- **Combo with TKI (lazertinib - 3G TKI)**
- **Combo with chemo**
- **Combo with TKI + chemo (LACP)**

CHRYSALIS-2 (NCT04077463) LACP Cohort: Amivantamab + Lazerinib + Pem/Carboplatin

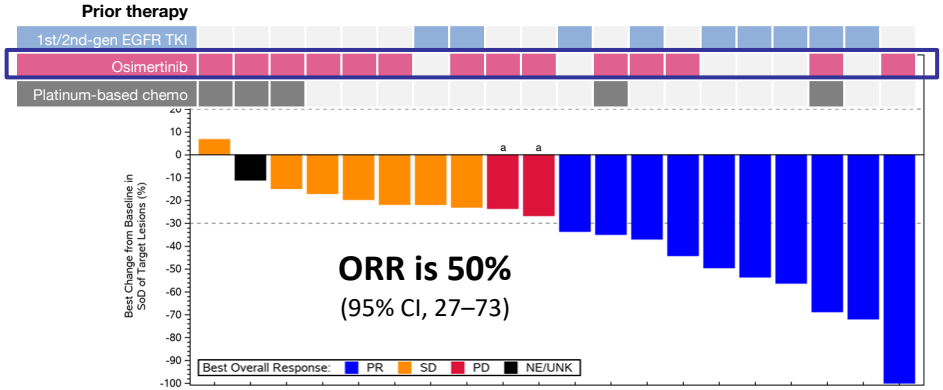
Eligibility
EGFR-mutated NSCLC post-TKI (max 3 prior lines)

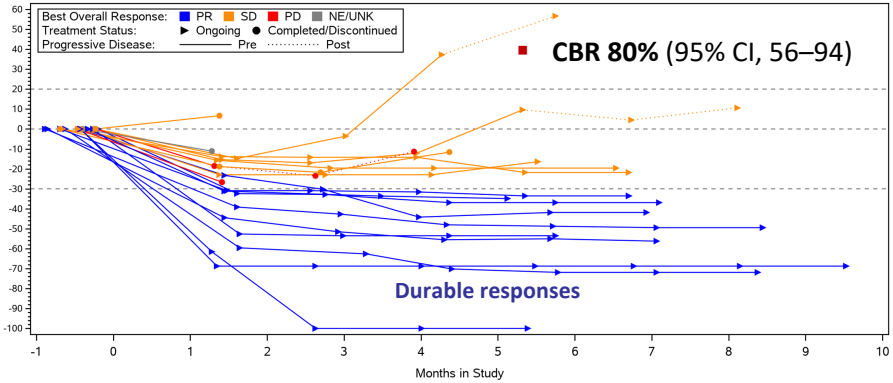
Dosing (21-day cycle)

Lazertinib	240 mg QD
Amivantamab	1400/1750[b] mg on C1 D1/D2, C1 D8, C1 D15, and C2 D1; then 1750/2100[b] mg C3 +Q3W
Chemotherapy	Pemetrexed (500 mg/m^2)
	Carboplatin (AUC5; stopped after 4 cycles)

Demographics and Baseline Disease Characteristics, n (%)	Total (n=20)
Median age, years (range)	61 (38–83)
Male / female	9 (45) / 11 (55)
Race	
Asian	11 (55)
White	8 (40)
Black	1 (5)
Exon 19 del/L858R	13 (65) / 7 (35)
ECOG PS 0 /1	4 (20) / 16 (80)
Brain metastases at baseline[d]	10 (50)
Median no. of prior lines (range)	2 (1–3)
Prior therapy	
1st/2nd-generation EGFR TKI	9 (45)
Osimertinib	14 (70)
Platinum-based chemotherapy[e]	5 (25)

Amivantamab Combination in EGFR TKI-refractory NSCLC: LACP Cohort





Similar data in patients with brain metastases

Amivantamab + Osimertinib in EGFR-mutated NSCLC with PD after 1st line Osimertinib: Real World Data

Results

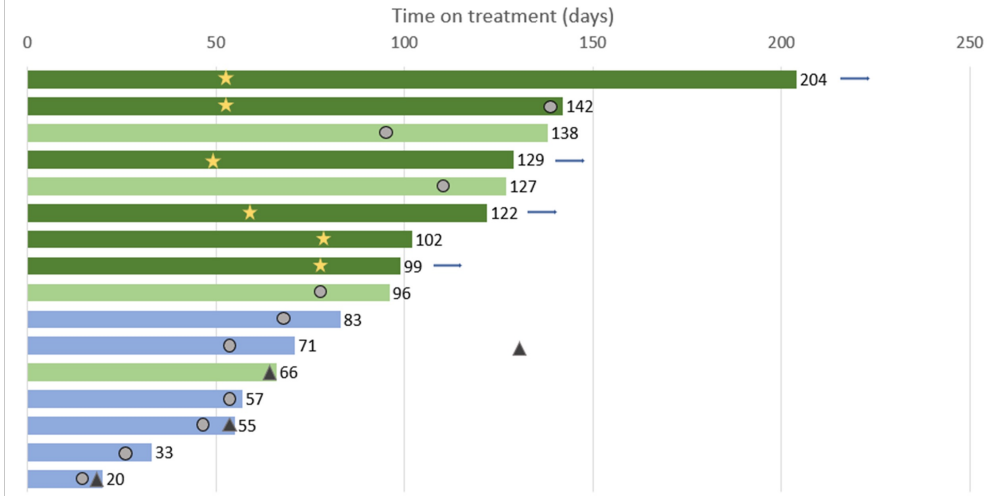
Table 1. Patient demographics, molecular characteristics and clinical outcome

Case	Sex	Age, years	EGFR Mutation at Amivantamab start	Prior line of treatment	Prior EGFR TKI	TKI received with Amivantamab	Time on treatment (Days)	Clinical benefit
1	F	58	Exon 19 Deletion (L747_P753delinsS); Exon 20 T790M	Gemictabine	Osimertinib	Osimertinib	204	PR; on-going
2	M	70	Exon 19 deletion (E746_A750del); Exon 20 T790M	Osimertinib	Osimertinib	Osimertinib	142	PR
3	F	53	Exon 20 duplication (V769_D770insE); Exon 20 T790M	Osimertinib	Osimertinib	N/A	138	SD
4	M	69	EGFR amplification; Exon 19 duplication (I740_K745dupIPVAIK)	Carboplatin/Paclitaxel/ Atezolizumab/ Bevacizumab (maintenance Atezo/Bev)	Poziotinib	N/A	129	PR; on-going
5	F	65	Exon 20 duplication (H773_V774dup); Exon 15 M600T	Poziotinib	Poziotinib	N/A	127	SD
6	F	69	Exon 21 L858R	Osimertinib	Osimertinib	Osimertinib	122	PR; on-going
7	F	73	Exon 20 complex (N771delinsHH)	Surgery	N/A	N/A	102	PR
8	F	52	Exon 18 G719S; Exon 20 R776H	Osimertinib	Osimertinib	Osimertinib	99	PR; on-going
9	F	55	Exon 20 duplication (S768_D770dup SVD)	Poziotinib	Poziotinib	N/A	96	SD
10	F	58	Exon 20 complex (N771delinsGF)	Poziotinib	Poziotinib	N/A	83	PD
11	F	65	EGFR amplification; Exon 18 G724S; Exon 19 deletion (L747_S752del)	Carboplatin/Pemetrexed/ Osimertinib	Osimertinib	Osimertinib	71	PD
12	F	40	Exon 19 deletion (E746_A750del); Exon 20 C797S	Osimertinib/ Selpercatinib	Osimertinib	Osimertinib	66	SD
13	M	31	Exon 19 Complex (L747_A755delinsSRD)	Osimertinib	Osimertinib	Osimertinib	57	PD
14	F	78	Exon 21 L858R	Docetaxel	Osimertinib	Osimertinib	55	PD
15	M	59	Exon 20 insertion (N771_P772insT); Exon 20 insertion (P772fs*126)	N/A	N/A	N/A	33	PD
16	M	80	EGFR Exon 20 Insertion (D770_D770delinsGY)	Cabozantinib/ Atezlizumab	Poziotinib	N/A	20	PD

Results

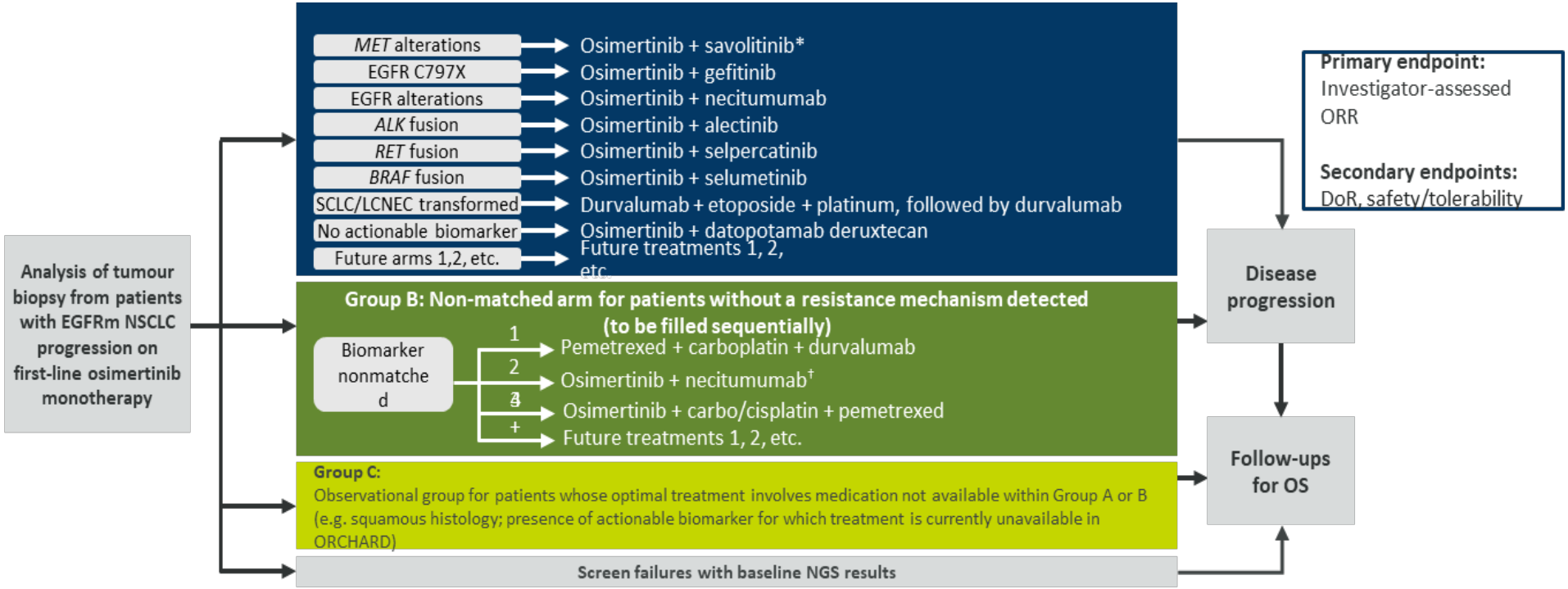
Response: 5/16 (31%)

Figure 1. clinical outcome for EGFR-mutant NSCLC receiving amivamtamab



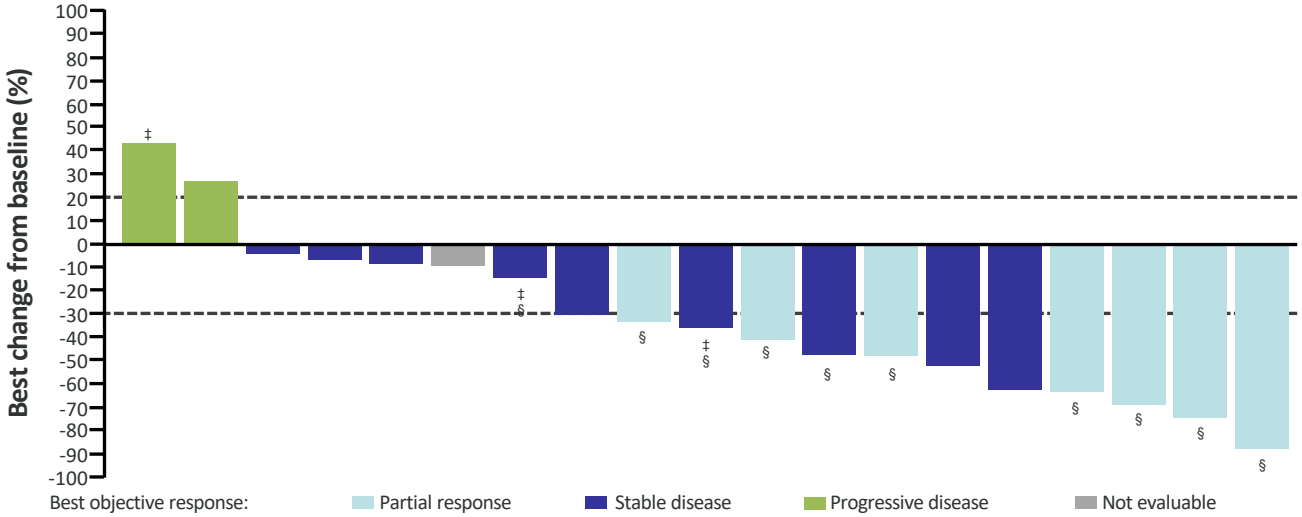
The ORCHARD study matches post-osimertinib therapy to presumptive mechanism of resistance[1,2]

Phase 2 study in patients with metastatic EGFRm NSCLC following progression with 1st-line osimertinib



ORCHARD: Osimertinib + Savolitinib in MET-amplified EGFR-mutated NSCLC after PD on 1st line Osimertinib*

ORCHARD defines *MET* alterations as the presence of ≥6 gene copies detected by NGS

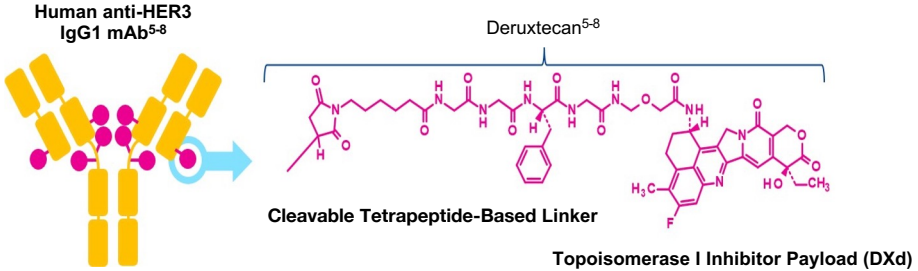


- ORR was 41% (7/17; confirmed PR)
- 7 (41%) had stable disease, including 3 patients with unconfirmed PR
- 1 (6%) had disease progression

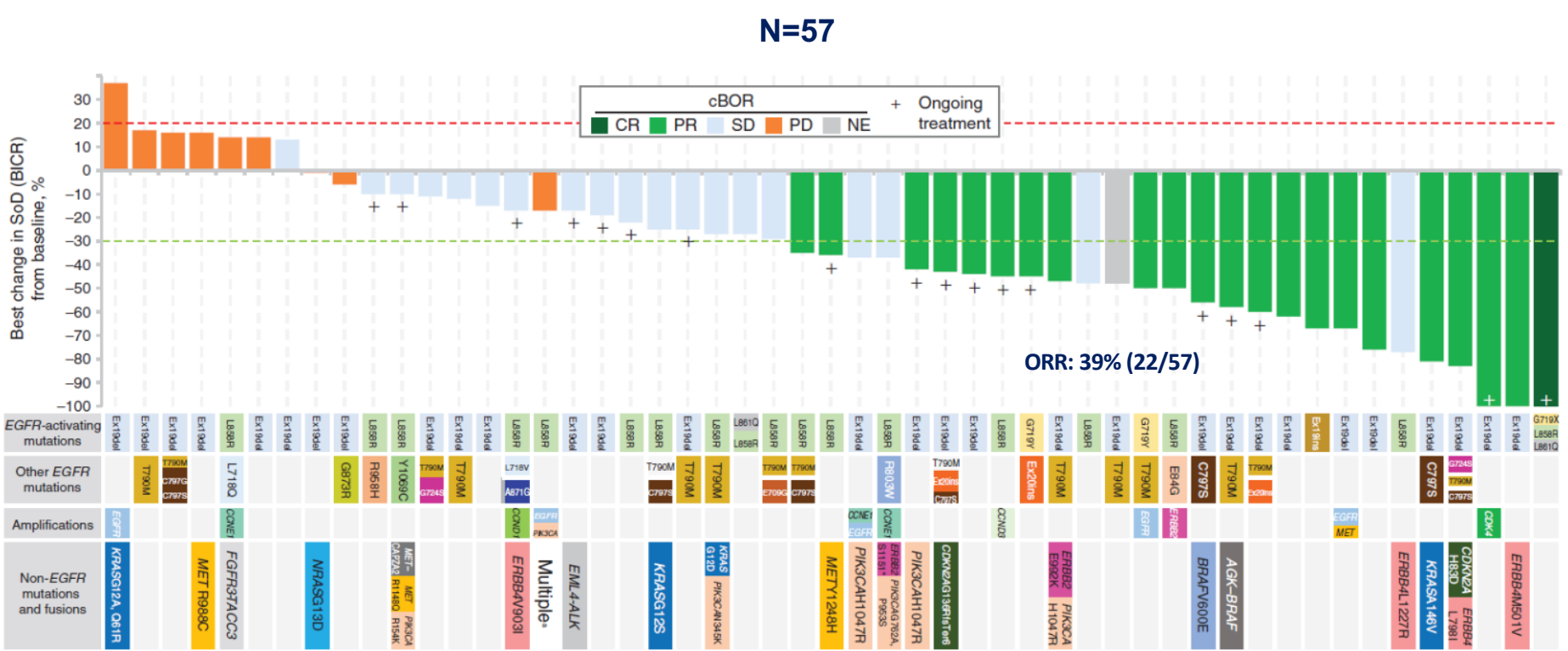
Ahn et al. ESMO 2021

Efficacy and Safety of a HER3-Directed Antibody Drug Conjugate Patritumab Deruxtecan (HER3-DXd; U3-1402) in *EGFR*-Mutated NSCLC

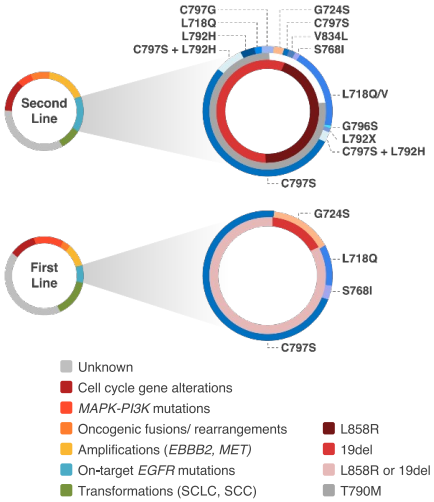
- **HER3 is expressed in most lung cancers**, including in >80% of *EGFR*-mutated NSCLC, and overexpression has been associated with worse clinical outcomes[1,3-4]
  - HER3 therefore represents a promising therapeutic target; however, no HER3 directed therapies are currently approved[3,4]
- **Patritumab deruxtecan (HER3-DXd**; U3-1402) is a novel, investigational HER3-directed ADC comprising a fully human anti-HER3 IgG1 mAb (patritumab) covalently linked to a topoisomerase I inhibitor payload, an exatecan derivative, via a tetrapeptide-based cleavable linker[5-8]



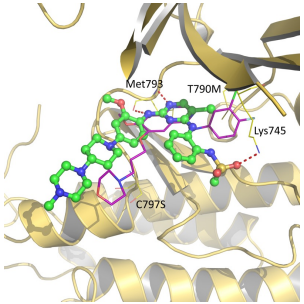
HER3-DXd 5.6 mg/kg Demonstrates Antitumor Activity in *EGFR*-Mutated NSCLC With Diverse TKI Resistance Mechanisms



- **BBT-176 is a novel 4th generation EGFR TKI with high potency against C797S-containing *EGFR* mutations**
- **C797S is the most common on-target *EGFR* mutation following progression, conferring resistance to Osimertinib[1]**



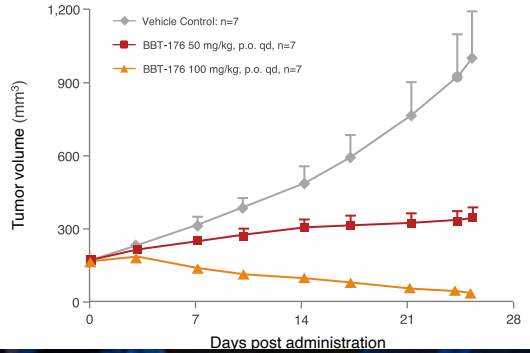
Docking model of BBT-176 with *EGFR* LTC



IC_{50} (nM) Values in Biochemical EGFR Tyrosine Kinases and Engineered Ba/F3 Cells

Compound		WT	D	L	DT	LT	DC	LC	DTC	LTC
BBT-176	Enzyme	21.2	3.1	4.1	1.6	2.4	4.4	5.4	1.8	163*
	Cell	645	67	164	147	114	76	244	148	276
Osimertinib	Enzyme	12.5	2.4	2.8	1.4	1.6	304.4	573.7	124.8	NA
	Cell	164	1	2	3	3	509	829	979	1,303

WT (wildtype), D (19del), L (L858R), T (T790M), C (C797S)
*Under different assay condition (1 mM ATP)



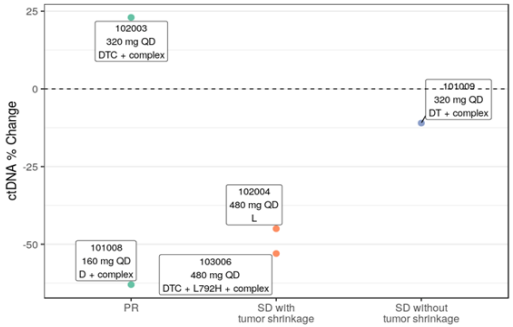
LD1-0025 PDX model for lung cancer harboring *EGFR* DTC

1. *Oncogene*;40:1-11 (2020)
2. *N Engl J Med*;376:629-640 (2017)

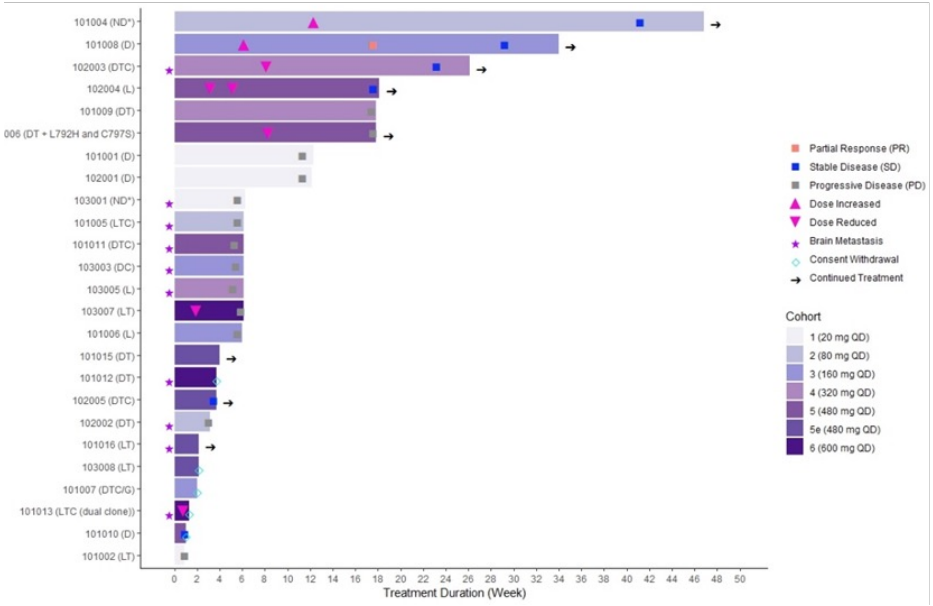
BBT-176: 4th generation EGFR TKI active against C797S-containing *EGFR* mutations

Baseline Characteristics of Enrolled Patients

CHARACTERISTIC	ALL PATIENTS (N=25)
Median age (range)	63 (38-79)
Female	17 (68%)
Asian	25 (100%)
ECOG PS (0, 1)	7 (28%), 18 (72%)
Number of prior systemic anticancer regimens	
1 (%)	2 (8%)
2 (%)	7 (28%)
≥3 (%)	16 (64%)
Prior EGFR TKI treatment	25 (100%)
Prior Gefitinib, Erlotinib, Afatinib or Dacomitinib	25 (100%)
Prior Osimertinib or Lazertinib	20 (80%)
Brain metastasis, stable (%)	10 (40%)
EGFR mutation detected by ctDNA (19del, L858R)	14 (56%), 9 (36%)*
containing C797S	8 (32%)



Duration of Treatment and Tumor Response, All Patients by Dose Level



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