Durvalumab plus chemotherapy in patients with advanced EGFR mutation-positive NSCLC whose disease progressed on first-line Osimertinib: an ORCHARD study interim analysis

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Background

- Osimertinib is an irreversible, oral EGFR-tyrosine kinase inhibitor (TKI) that potently and selectively inhibits EGFR TKI-sensitising mutations and EGFR T790M resistance mutations, with efficacy in EGFRm NSCLC, including central nervous system metastases.

- Osimertinib is the preferred 1L treatment in patients with advanced EGFRm NSCLC; however, tumours treated with Osimertinib may eventually develop treatment resistance.

Background

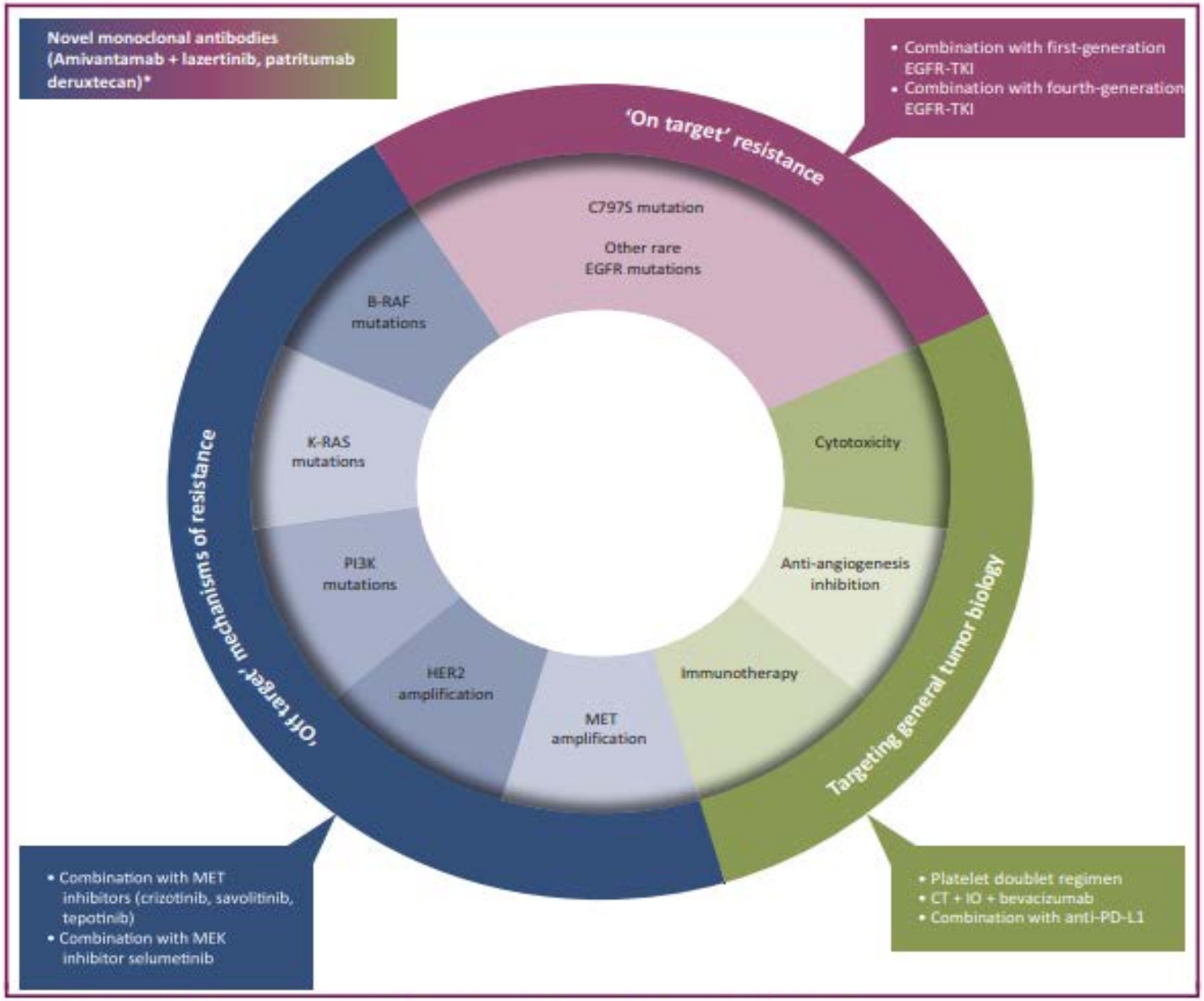


Figure 1. Mechanisms of resistance to osimetinib and potential strategies of treatments to overcome resistance.
CT, chemotherapy; IO, immunotherapy.
*Activity demonstrated across resistance mechanisms.

Table 1. Ongoing clinical trials on acquired resistance to osimertinib in EGFR-mutated NSCLC

Phase	Clinical trial number	Drug(s) class	NSCLC trial Population	Line of treatment	Treatment arm(s)	Primary endpoint	Status
III	NCT03515837 (KEYNOTE 789)	Combination of PD-1 inhibitor with CT	EGFR mutated	2-3	Experimental: Pembrolizumab + pemetrexed + chemo Active comparator: Placebo + pemetrexed + chemo	- PFS, OS	Recruiting
II	NCT03778229 (SAVANNAH)	MET inhibitors	EGFR mutated with MET amplification/high expression	$2 \leq n \leq 4$	Osimertinib + savolitinib	- ORR	Recruiting
II	NCT03944772 (ORCHARD)	MET inhibitors, first-generation anti-EGFR-TKI, anti-EGFR mAbs, combination of CT plus anti-PD-L1 mAbs	EGFR mutated	2	Osimertinib + savolitinib Osimertinib + gefitinib Osimertinib + necitumumab Durvalumab + carboplatin + pemetrexed	- ORR	Recruiting
II	NCT03940703 (INSIGHT-2)	MET inhibitor	EGFR mutated with MET amplification	≥1	Tepotinib and osimertinib	- Safety - ORR	Recruiting
I/II	NCT03784599 (TRAEMOS)	Anti-HER2-conjugated antibody	EGFR-mutated NSCLC and HER2 amplification or high expression	≥2	Trastuzumab–emtansine and osimertinib	- Safety - ORR	Recruiting
Ib	NCT04001777	Bcl-2 family protein inhibitor	EGFR-mutated third-generation TKI resistant or treatment naive	Any lines	APG-1252 plus osimertinib	- MTD - RP2D	Recruiting
I	NCT03891615	PARP inhibitor	EGFR mutated	≥2	Osimertinib + niraparib	- MTD	Recruiting
Phase I	NCT03516214 (EATON)	Third-generation anti-EGFR-TKI, MEK inhibitor	EGFR mutated, including TKI naive	Any lines	Nazartinib and trametinib	- MTD - RP2D	Recruiting
Phase II	NCT02759835	—	EGFR mut oligoprogressive disease (no more than five sites of progressive disease)	≥1	Osimertinib followed by LAT followed by osimertinib LAT followed by osimertinib	- PFS2	Active, not recruiting
II	NCT04136535 (ALTER-L031)	Multitarget TKI	EGFR mutated	≥1	Pemetrexed and carboplatin with or without anlotinib	- PFS	Active not yet recruiting
II	NCT03532698	NSAID	EGFR mutated	2	Osimertinib + aspirin	- ORR	Not yet recruiting
II	NCT04316351	Anti-PD-1 mAb, multitarget TKI	EGFR mutated with T790M	≥3	Toripalimab + pemetrexed + anlotinib	- ORR	Not yet recruiting

AE, adverse events; CT, chemotherapy; EGFR, epidermal growth factor receptor; LAT, locally ablative therapy; mAb, monoclonal antibody; MDT, maximum tolerated dose; NSAID, nonsteroidal anti-inflammatory drug; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; RP2D, recommended phase II dose; RR, response rate; TTP, time to progression.

Introduction

- **Phase II ORCHARD platform study aims to characterize resistance mechanisms and evaluate novel therapy combinations in patients with advanced EGFRm NSCLC that progressed on 1L Osimertinib**

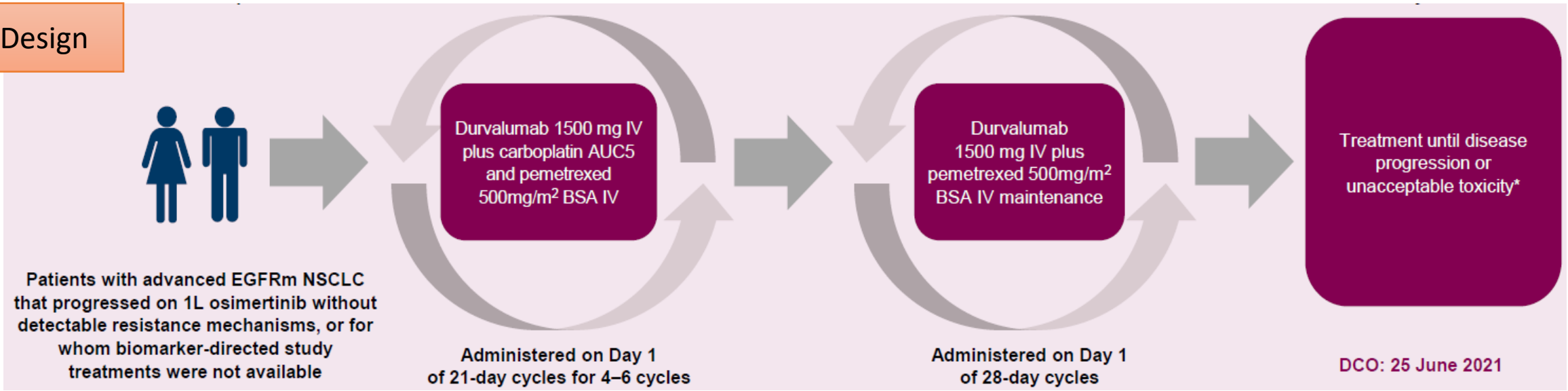
- **The anti-PD-1 antibody pembrolizumab was assessed previously in combination with platinum-doublet chemotherapy in 12 patients with EGFRm NSCLC that had progressed on Osimertinib. This combination did not improve outcomes compared with chemotherapy alone.**

- **Research is needed to confirm if ICIs in combination with other anticancer therapies can overcome the limited efficacy of ICIs alone**

Methods

- Biomarker-directed platform study in patients aged ≥18 years old (Japan, ≥20 years old) with locally advanced/metastatic EGFRm NSCLC that progressed on 1L Osimertinib 80 mg once daily (QD) monotherapy.
- Including asymptomatic brain metastases.

Study Design



- **Primary endpoint:** ORR confirmed by the investigator using RECIST v1.1
- **Secondary endpoints** PFS, DOR
- **Safety endpoints** included adverse events (AEs) assessed per Common terminology criteria for adverse events (CTCAE) v5
- •**Exploratory endpoints** included tumour mutational burden (TMB) and molecular aberrations on next-generation sequencing (NGS) of tumour samples, and their respective correlation with clinical response

Results

- Between 10 October 2019 and DCO (25 June 2021), 25 patients received ≥1 dose of study treatment in this treatment cohort.

Table 1. Baseline demographics and disease characteristics

Baseline demographics and disease characteristics	Durvalumab plus chemotherapy (N=25)
Age	
Median age, years (range)	61 (39–77)
≥18–<65 years / ≥65 years, n (%)	17 (68) / 8 (32)
Sex, n (%)	
Male / Female	6 (24) / 19 (76)
Race, n (%)	
Asian / White	19 (76) / 6 (24)
Smoking status, n (%)	
Current / Former / Never	1 (4) / 9 (36) / 15 (60)
WHO performance status, n (%)	
0 / 1	10 (40) / 15 (60)
Histology, n (%)	
Adenocarcinoma	25 (100)
No. of disease sites, n (%)	
1–2 / ≥3	5 (20) / 20 (80)
Mutations, n (%)	
Ex19del / L858R / T790M / other*	10 (40) / 9 (36) / 0 (0) / 4 (16)
CNS involvement at study entry, n (%)	
No / Yes	19 (76) / 6 (24)
Liver involvement at study entry, n (%)	
No / Yes	21 (84) / 4 (16)
Time to progression on first-line osimertinib therapy, n (%)	
<12 months†/ ≥12 months	8 (32) / 17 (68)

*L861Q (n=2), G719S (n=2); †>3months and <12 months

Patient Disposition & Relative dose intensity

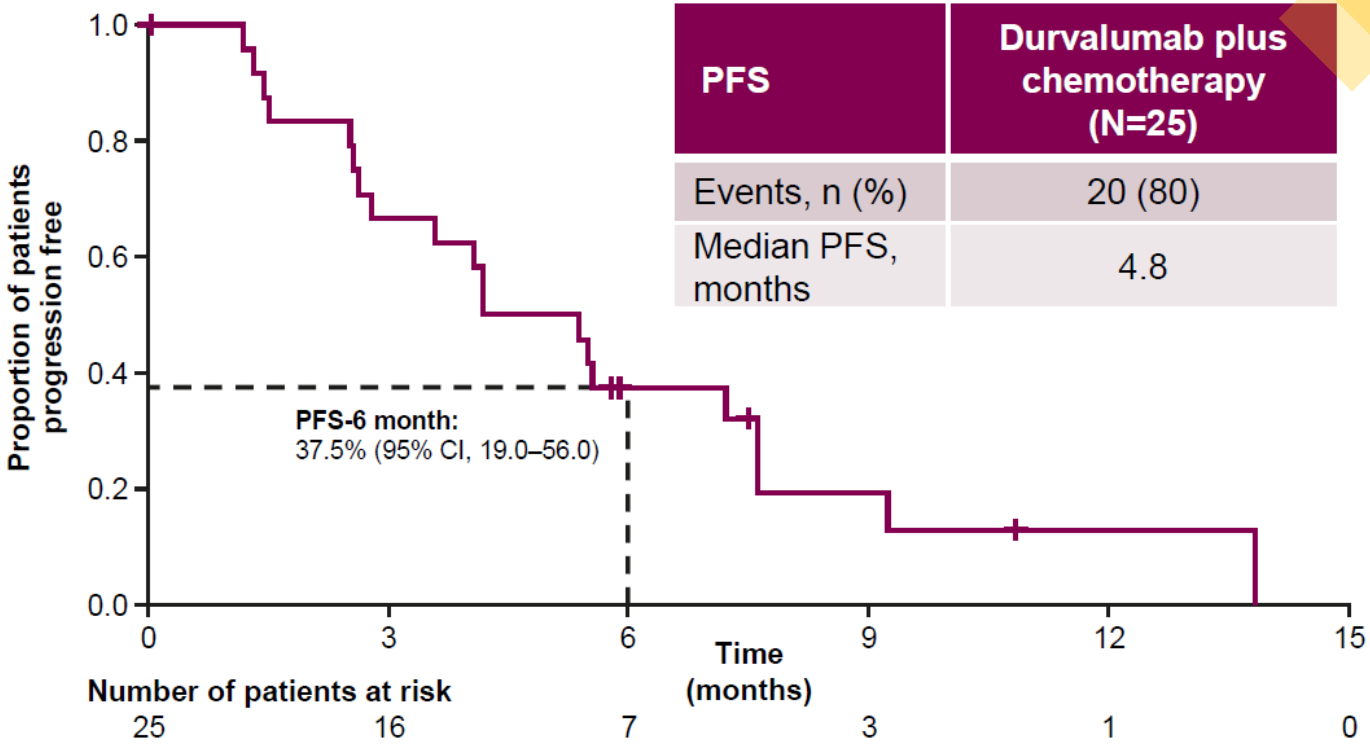
- At data cut off, all patients received ≥75% relative dose intensity for each study drug, and 22 patients (88%) had discontinued all treatments.

- Median treatment duration was 5.3 months (range, 0.9–14.3) for durvalumab and pemetrexed, and 2.9 months (range, 0.7–5.1) for carboplatin

- The median follow-up period was 9.7 months (range, 1.3–18.5) in overall survival patients.

Progression-free survival

- Median PFS was 4.8 months (95% confidence interval [CI]: 2.6, 7.6); PFS rate at six months was 37.5% (95% CI: 19.0, 56.0; **Figure 2**)



PFS	Durvalumab plus chemotherapy (N=25)
Events, n (%)	20 (80)
Median PFS, months	4.8

Figure 2: Progression-free survival
PFS-6 month, PFS rate at six months

Response Rates

- All 25 patients had measurable disease at baseline.
- Confirmed ORR was 3/25 (12%; all confirmed partial responses); 17/25 (68%) patients had stable disease (≥six weeks) including six (24%) with unconfirmed partial responses.
- Four (16%) patients had disease progression and one (4%) was not evaluable (**Table 2**)

Table 2. ORR and best objective response

ORR	Durvalumab plus chemotherapy (N=25)
ORR, n (%; 80% CI)	3 (12; 4.5, 24.8)
Best objective response, n (%)	
Confirmed complete response	0
Confirmed partial response	3 (12)
Stable disease ≥6 weeks	17 (68)
Unconfirmed partial response	6 (24)
Stable disease	11 (44)
RECIST 1.1 disease progression	4 (16)
Death	0
Not evaluable	1 (4)
Incomplete post-baseline assessments	1 (4)

CI, confidence interval; ORR, objective response rate

Duration of response

- Median DoR in patients with a confirmed partial response (n=3) was 12.2 months
- Duration of treatment in all patients according to response type is presented in **Figure 3**
- There was no clear correlation between length of time on prior 1L Osimertinib and best response with durvalumab plus chemotherapy

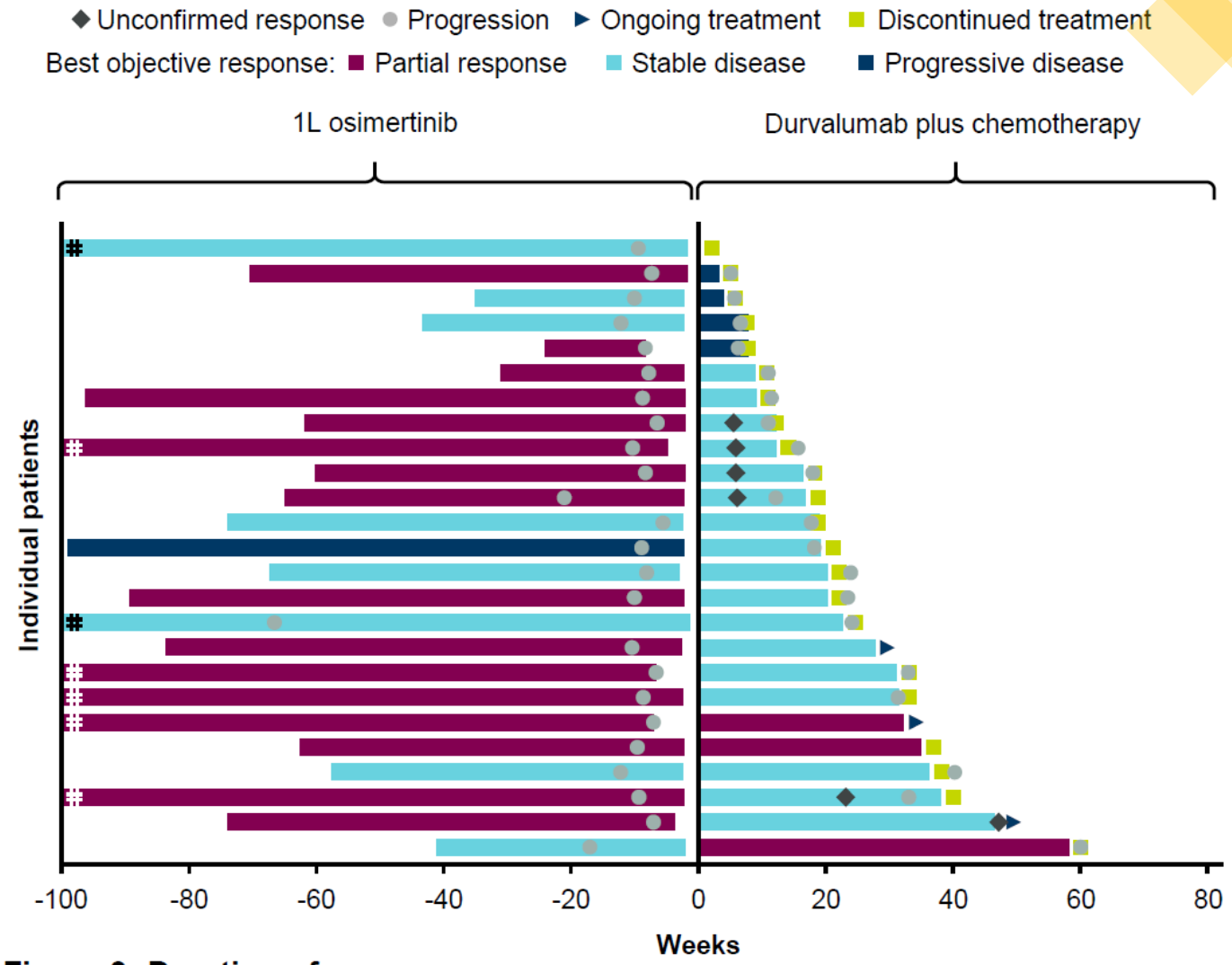


Figure 3: Duration of response

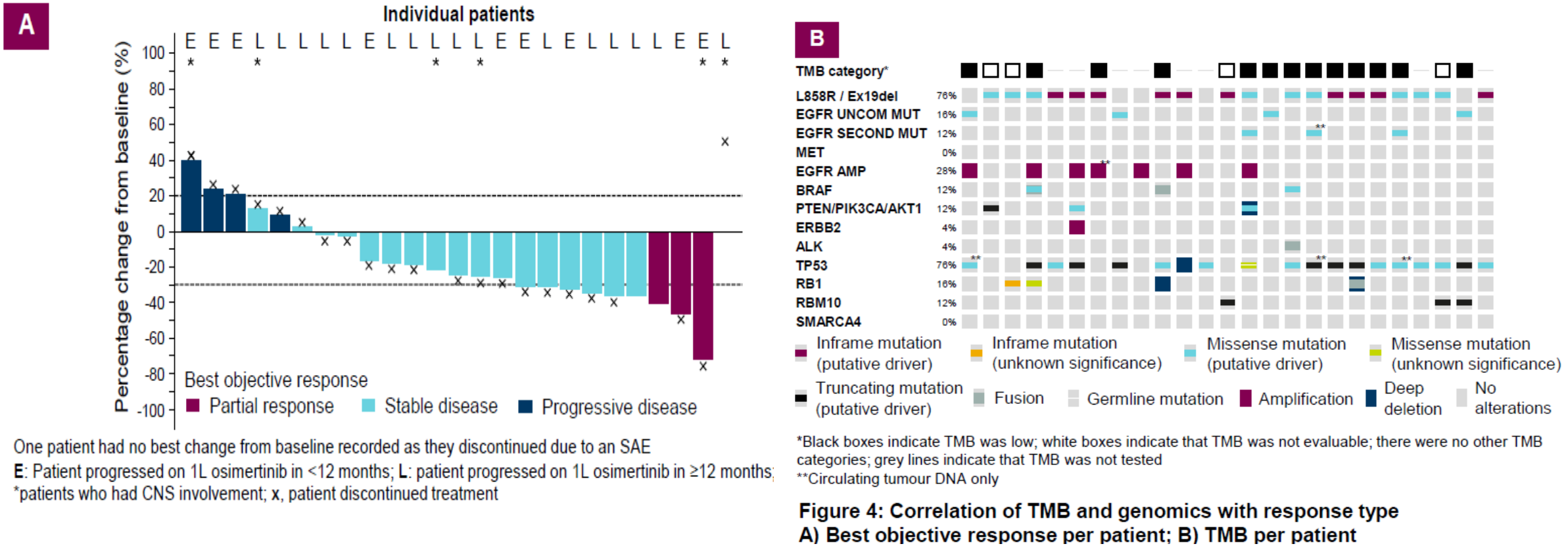
#, patient received 1L osimertinib for ≥100 weeks
1L, first line

Safety and tolerability

- Most AEs were mild or moderate in severity.
- There were no interstitial lung disease events
- The most common Grade ≥3 AEs were Neutropenia (n=5, 20%) and Anemia (n=3, 12%)
- One (4%) patient reported an AE (nausea) resulting in discontinuation of carboplatin
- There were no deaths due to AEs

Exploratory endpoints

- TMB was uniformly low within this particular ORCHARD study cohort **(Figure 4)**
- NGS identified that TP53 (n=19, 76%) mutations, EGFR amplifications (n=7, 28%), and EGFR secondary mutations (n=3, 12%) were the most common aberrations
- There was no association between best response and EGFR sensitizing mutation type



One patient had no best change from baseline recorded as they discontinued due to an SAE

E: Patient progressed on 1L osimertinib in <12 months; **L**: patient progressed on 1L osimertinib in ≥12 months; *patients who had CNS involvement; **x**, patient discontinued treatment

*Black boxes indicate TMB was low; white boxes indicate that TMB was not evaluable; there were no other TMB categories; grey lines indicate that TMB was not tested

**Circulating tumour DNA only

Figure 4: Correlation of TMB and genomics with response type
A) Best objective response per patient; B) TMB per patient

AKT1, AKT serine/threonine kinase 1; ALK, anaplastic lymphoma kinase, serine/threonine kinase; AMP, amplification; CNS, central nervous system; EGFR, epidermal growth factor receptor; ERBB2, Erb-B2 receptor tyrosine kinase 2; MUT, mutation; PTEN, phosphatase and tensinhomolog; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RB1, retinoblastoma gene; RBM10, RNA binding motif protein 10; SAE, serious adverse event; sens, sensitive; SMARCA4, SWI/SNF related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4; uncom, uncommon; TP53, tumor protein P53; 1L, first-line

Conclusions

- According to study stop criteria (<10% chance that objective response rate [ORR] is ≥45%), recruitment was closed for this specific ORCHARD study arm
- Durvalumab plus chemotherapy was well tolerated with no new or unexpected safety signals
- Further biomarker analyses are ongoing to better understand the efficacy data concerning use of immune checkpoint inhibitors (ICIs) plus chemotherapy in this particular patient population
- The ORCHARD study continues to evaluate other novel therapy combinations in biomarker-matched and non-biomarker matched patients with advanced EGFRm NSCLC that progressed on 1L Osimertinib.

My take…

- This data was consistent with known fact that mEGFR NSCLC will be having very poor chance of benefit from IO therapy.
- If any clinical trial is available will be preferred option in this group of the patients.
- Chemotherapy – Platinum based doublet is the preferred choice.

- **THANK YOU**