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Dose escalation of osimertinib for intracranial progression in EGFR mutated non-small-cell lung cancer with brain metastases

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Abstract

Background. Osimertinib is a selective irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) with increased penetration across the blood–brain barrier compared with previous EGFR-TKIs, and thus, a 52% reduction in the risk of intracranial disease progression is seen when it is used as a first line of therapy compared with gefitinib and erlotinib. It is also efficient as second-line therapy for patients who developed the T790M resistance mutation following treatment with previous generation TKIs. Here, we report 11 patients who were treated by an increasing dose of osimertinib from 80 mg to 160 mg QD orally following intracranial progression in either first- or second-line setting.

Methods. This is a subcohort analysis from a larger nonrandomized, phase 2, open-label trial, evaluating the efficacy of osimertinib dose escalation from 80 mg to 160 mg in EGFR-mutated advanced non-small-cell lung cancer (NSCLC) patients with intracranial progression in either first- (arm A) or second-line setting (arm B for T790M+ and C for T790M–).

Results. Eleven patients, 5 in arm A, 4 in arm B, and 2 in arm C were reported in this study. The mPFS of osimertinib before dose escalation was 11.4 ± 8.9 (6.6–30.7) months for arm A, 8.7 ± 1.8 (6.3–11.2) for arm B, and 14.5 ± 7.8 (6.7–22.3) for arm C. Intracranial response rate to dose escalation was 54% (6 of 11) with 2 of 11 having intracranial stability. Median iPFS was 4.3 ± 7.4 (0.7–25.5) months; 3.8 ± 6.4 (1.8–18.9), 5.6 ± 9.7 (0.7–25.5), and 7.0 ± 2.7 (4.3–9.6) for arms A/B/C, respectively. Dose escalation was well tolerated with diarrhea and paronychia as the main dose-limiting symptoms.

Conclusions. Osimertinib 160 mg is feasible and may offer a therapeutic alternative for patients with isolated intracranial progression on osimertinib standard (80 mg) dose. Further studies on CNS osimertinib pharmacokinetics are needed to test this hypothesis.

Key Points

- Osimertinib dose escalation for intracranial (IC) progression, had a median iPFS of 8.1 ± 8.7 months.
- Dose escalation for IC and asymptomatic extracranial (EC) progression had iPFS of 3.1 ± 2.3 months.

Importance of the Study

Osimertinib has had a significant impact on treatment strategy in EGFR (+) NSCLC patients with brain metastases. It has a preferred CSF peak compared with first- and second-generation TKIs, and yet its CNS concentration in CSF remains substantially lower (14.4 nM) than its concentration in plasma (555.3 nM). Upon intracranial progression on standard osimertinib dose, patients have few therapeutic options and will mostly require surgical or radiotherapeutic strategies in order to achieve disease stability. Our experience with 11 patients reveals the possibility of continuing osimertinib treatment upon isolated intracranial progression with a dose escalation. This treatment method allows overcoming of pharmacokinetic resistance mechanisms and delivery of an effective intracranial drug concentration in addition to an 8.1 ± 8.7-month increase in median iPFS in patients with an advanced disease and few treatment options. Our data stand in concordance with previous case reports from Tsang et al. and Cordova et al.

The incidence of brain metastasis in EGFR+ non-small-cell lung cancer (NSCLC) is relatively high compared with EGFR wild-type NSCLC (70% vs 38%).[1] Therefore, brain imaging has become the standard of care for this subtype of patients, regardless of the clinical presentation, with a preference for brain MRI methodology.[2] The existence of brain metastases has a significant impact on treatment strategy. Single lesions might be controlled by stereotactic brain radiation; however, because EGFR-TKIs are brain-penetrating agents, brain radiation may be considered unnecessary.

Osimertinib, a third-generation EGFR-TKI, has excellent brain penetration compared with previous EGFR-TKIs. The FLAURA study[3] indicated a 52% reduction in the risk of intracranial disease progression compared with gefitinib and erlotinib in the first-line setting[4] and in the second line of therapy for patients who developed the T790M resistance mutation.[5] The BLOOM[6] and AURA[7] trials also showed similar efficacy in brain lesions as well as in leptomeningeal disease.

Pulsatile administrations (eg, once every 3–4 days) of high-dose gefitinib, erlotinib, or icotinib for CNS metastases in EGFR-positive NSCLC patients who progressed on daily standard dose have also been reported.[8,9] Beneficial responses in some patients were observed in *EML4-ALK* (+) NSCLC under the treatment of crizotinib 500 mg once daily (QD) versus 250 mg twice daily (BID).[10]

Different approaches are commonly used to treat intracranial progression, such as stereotactic radiosurgery (SRS)[11] or surgery.[12] Whole brain radiation therapy (WBRT)[11] may also be considered, where no other alternatives exist. In this study, we assessed the intracranial response of dose escalation of osimertinib from 80 mg QD to 160 mg QD following intracranial progression in either the first or second line of treatment.

Methods

Here, we present the data of intracranial response to osimertinib dose escalation conducted as a part of a bigger study NCT02736513, aiming to test the effect of osimertinib in EGFR-mutated patients with brain metastasis. Dose escalation from 80 mg to 160 mg QD was allowed upon intracranial progression with or without asymptomatic extracranial progression. This is a nonrandomized subcohort analysis from a larger phase 2, open-label trial performed by Clalit Health Services - Israel from May 2016. Patient accrual is currently ongoing; data cutoff for this case series was March 25, 2020.

Patients were enrolled in 3 arms, TKI naive patients were assigned to arm A, while patients who progressed under EGFR-TKI were assigned to arm B/C upon the existence/lack of EGFR T790M mutation accordingly. Molecular pathology analysis was performed either by next-generation sequencing or RT-PCR using Clinical Laboratory Improvement Amendments of 1988 (CLIA) validated assays. All patients received osimertinib 80 mg orally once daily for at least 3 months and presented intracranial response before they were enrolled into the dose-escalation phase.

Primary endpoint for this phase was intracranial response to dose escalation of osimertinib. Further objectives were extracranial disease control and safety.

General Patient's Eligibility

Patients aged 18 years or older were eligible if they had histologically or cytologically proven, metastatic NSCLC disease (stage IV), at least 1 asymptomatic brain metastasis, which was untreated or previously treated with radiotherapy more than 6 months before screening and measurable as defined by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria, documented evidence of EGFR-TKI sensitizing mutation/s with or without positive Thr790Met, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, minimum life expectancy of 12 weeks, and an adequate hematological, liver, and renal function.

Key exclusion criteria included previous treatment with osimertinib; recent WBRT; evidence or past medical history of interstitial lung disease or radiation pneumonitis, which required steroid treatment; evidence of severe or uncontrolled systemic disease (including uncontrolled hypertension, uncontrolled diabetes, or active bleeding diathesis) or active infection (including hepatitis B, hepatitis C, and

HIV); and evidence or past medical history of cardiomyopathy and factors that increased the risk of calculated QT interval prolongation or risk of arrhythmic events.

This study was approved by the Institutional Review Board committee at Rabin Medical Center (0785-15 RMC) and Soroka University Medical Center (0299-17 SOR) in accordance with the declaration of Helsinki. All patients have written informed consent, and the study was performed under the good clinical practice (GCP) standard. This is an investigator-initiated study, sponsored by AstraZeneca. The corresponding author had final responsibility for the decision to submit the publication.

Patient's Eligibility for Dose Escalation

In case of objective CNS progression, occurring without extracranial symptomatic progression, osimertinib dose was escalated to 160 mg once daily. Preliminary criteria were at least 3 months of previous intracranial response to osimertinib standard 80 mg daily. For patients with further intracranial disease progression after dose escalation, brain radiotherapy (SRS or WBRT) was allowed, while treatment with osimertinib was interrupted and reinitiated at a dose of 160 mg 1 day after radiotherapy ended upon investigator decision. Treatment was continued until symptomatic extracranial progression, further intracranial progression following brain radiotherapy, unacceptable toxicity, withdrawal from study, termination of study, or death. In case of selected adverse events, dose interruption was allowed.

Results

This study analyzes the response of 11 patients that underwent osimertinib dose-escalation protocol for intracranial progression. Five in arm A, 4 in arm B, and 2 in arm C. Table 1 summarizes the patients' characteristics. The median age was 61.0 ± 11.6 years (range 31–74), 6 males and 5 females, EGFR exon 19 del mutation presented in 7 (64%) patients, 3 (27%) had EGFR L858R and 1 had other EGFR activating mutations. The median duration of treatment on osimertinib 80 mg before dose escalation was 11.4 ± 8.9 (6.6–30.7) months for arm A, 8.7 ± 1.8 (6.3–11.2) months for arm B, and 14.5 ± 7.8 (6.7–22.3) months for arm C.

Response to Dose Escalation

In total, 6 of 11 patients (54%) had intracranial response, 2 of 11 had intracranial stability, and 3 had disease progression. The overall median intracranial progression-free survival (iPFS) on osimertinib 160 mg was 4.3 ± 7.4 (range 0.7–25.5) months; 3.8 ± 6.4 (range 1.8–18.9) months in arm A, 5.6 ± 9.7 (range 0.7–25.5) months in arm B, and 7.0 ± 2.7 (range 4.3–9.6) months in arm C.

Among arm A (N = 5), 1 patient (#A3) had intracranial partial response and was treated for 11 months; 2 patients had stable intracranial disease (#A4 for 4 months and #A5 for 6 months), and 2 patients (#A1 and #A2) had systemic disease progression and stopped treatment after 2 and 3 months accordingly. In arm B (N = 4), 3 patients (#B1–B3)

Table 1. Patients' Characteristics

Total Number of Patients	(N = 11)		
Gender (male/female)	6 (54.5%)/5 (45.5%)		
Median age	61.0 ± 11.6 years (range 31–74)		
EGFR ex 19 deletion	7 (64%)		
EGFR L858R	3 (27%)		
EGFR other	1 (1%)		
Status at Main Study Initiation	Arm A (naive)	Arm B (2ndT790M+)	Arm C (2ndT790M-)
Line of Therapy (naive/2ndT790M+/2ndT790M-)	5 (46%)	4 (36%)	2 (18%)
Number of Brain Mets, median and range	11 ± 5.8 (3–17)	17 ± 10.4 (5–31)	4.5 ± 0.5 (4–5)
Total diameter of brain mets, median and range (mm)	40 ± 39 (3–108)	41.5 ± 27.4 (31–99)	72.5 ± 51.1 (20.4–123.7)
Leptomeningeal spread	0 patients	1 patient	1 patient
Response to Osimertinib 80 mg			
Number of Brain Mets at best response, median and range	2 ± 1.6 (0–5)	3.5 ± 4.5 (2–13)	6.0 (±4.0, 2–10)
Total diameter of brain mets at best response, median and range (mm)	8 ± 13.6 (0–38)	17.5 ± 3.6 (14.8–30.8)	51.0 (±47, 4–99.3)
Osimertinib 80 mg duration of treatment, median and range (months)	11.2 ± 8.3 (7.1–30.4)	89.15 ± 1.7 (6.2–11.0)	14.3 ± 7.7 (6.6–22)
Leptomeningeal spread response	—	1 patient partial response	1 patient partial response
Status at dose escalation point			
Number of brain mets, median and range	9.0 ± 6.2 (2–17)	6.5 ± 13.3 (3–36)	3.5 ± 1.5 (2–5)
Total diameter, median and range (mm)	23.5 ± 12.8 (9.3–43)	16.4 ± 6.9 (13–30.8)	29.1 ± 25 (4–54.3)
Leptomeningeal spread	1 patient	1 patient	0 patients

had intracranial partial response with a median iPFS of 8.1 ± 9.6 months (range 3.1–25.5). Patient #B4 had clinical neurological progression and was excluded from the trail 2 weeks after dose escalation. In arm C, both patients had partial response with systemic stable disease with a median iPFS of 7 ± 2.7 months (4.3–9.6). No association was found between the intracranial disease load (number of metastases and total metastases' diameter) and the brain response.

Interestingly, when analyzing the response of patients who received dose escalation due to isolated intracranial progression, 5 of 6 patients (#A3, #A4, #A5, #B1, #B4, and #C1) had a considerable intracranial response with a median iPFS of 8.1 ± 8.7 months. In this group, all but 1 patient maintained their previous extracranial responses through dose escalation. While dose escalation was administered due to both intracranial and asymptomatic extracranial progression (#A1, #A2, #B2, #B3, and #C2), the median iPFS was noticeably lower and consisted of 3.1 ± 2.3 months, with the best intracranial response observed being partial response in 3 of 5 (60%) and disease progression in 2 of 5 (40%). Extracranially, these patients had stable disease (2 of 5) or progression (3 of 5). Although most of the patients in this group did not benefit from dose escalation, we did observe 1 patient (#B2) who had a beneficial duration of treatment under dose escalation which lasted 8 months. In this period of time, the patient experienced intracranial partial response alongside extracranial disease progression (Figure 1). At the time of data cutoff (March 2020), all patients were excluded from the study, 5 patients due to systemic progression, 2 patients due to intracranial progression, and 4 patients died.

In order to understand the resistance mechanisms and the evolution of clonality, molecular profiling at the time of dose escalation was performed by liquid biopsy (Guardant360) in 5 patients (#A1, #A2, #A4, #A5, and #B2). However, no cfDNA was detected on top of the primary EGFR exon19 deletion in patient #A1. Molecular profiling upon progression on osimertinib 160 mg was performed in 4 patients (#A1, #A2, #A3, #A5, and #B2). Two had C797S mutation, 2 had cMET amplification, and 1 patient had NTRK I638V, ATM L1794R (Table 2).

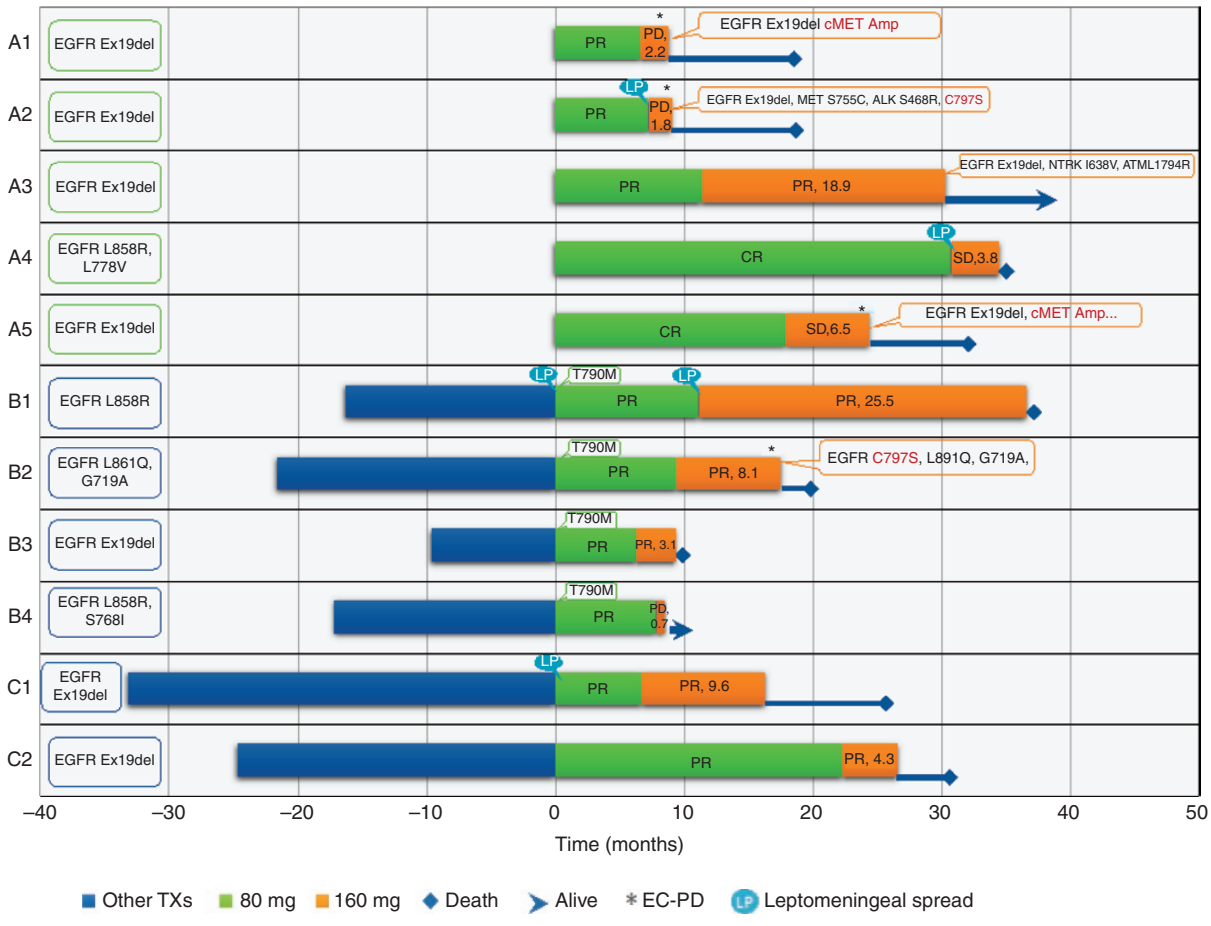

Figure 1. T1-weighted brain MRI scans with gadolinium enhancement in axial view. *Top images*: Patient #B3 demonstrating brain metastases evolution before and after osimertinib dose escalation; *blue arrows* show left thalamus metastasis with partial response. *Bottom images*: Patient #B1 demonstrating brain solid and leptomeningeal metastases; *orange arrows* show left thalamus cerebellum metastases with leptomeningeal features and partial response.

Table 2. Molecular Analysis at Study Initiation, at Time of Dose Escalation and at Study End

Pt. no. and Initials	Former Anti-EGFR Therapy	Primary EGFR Mutation	Mutation on Trial Entry	cfDNA at Dose Escalation	Mutation Upon Progression on 160 mg
Arm A					
A1, Y.F.	—	Exon 19 del	Exon 19 del	Exon 19 del	EGFR E746_A750del 4.8%, MET amp ++.
A2; D.K.	—	Exon 19 del	Exon 19 del	EGFR E746_A750del 11.7%, EGFR amp, TP53 Q331* 7.6%	Exon 19 del, MET S755C+ALK S468R, C797S
A3; B.S.	—	Exon 19 del	Exon 19 del	Not done	Exon 19 del., NTRK I638V, ATM L1794R
A4; H.D.	—	L858R, L778V	L858R, L778V	Undetectable	Not done
A5, Y.S.	—	Exon 19 del	Exon 19 del	Undetectable	EGFR exon 19 deletion (E746_A750del), MET amplification, SMARCB1 M1V, AXIN1 R533_H534insQVHH, CDKN2A/B loss, MTAP loss exons 2–8, TP53 R249S
Arm B					
B1; Y.R.	Erlotinib	L858R	T790M	Not done	Not done
B2; D.Z.	Gefitinib, afatinib	L861Q, G719A	T790M	Undetectable	C797S, L861Q, G719A,G796G
B3, M.G2.	Afatinib	Exon 19 del	T790M	Not done	Not done
B4, S.R.	Afatinib	L858R, S768I	T790M	Not done	Not done
Arm C					
C1; I.O.	Gefitinib	Exon 19 del	Negative T790M	Not done	Not done
C2; O.A.	Afatinib	Exon 19 del	Negative T790M	Not done	Not done

EGFR, epidermal growth factor receptor.

Table 3. Adverse Events Upon Osimertinib 160 mg

	Grades 1–2	Grade 3	Grades 4–5
Diarrhea	5/11 (45%)	0	0
Fatigue	3/11 (27%)	1/11 (9%)	0
Nail toxicity	2/11 (18%)	2/11 (18%)	0
Rash	3/11 (27%)	0	0
Dry skin	4/11 (36%)	0	0
Pruritus	3/11 (27%)	0	0
Headache	4/11 (36%)	0	0
Constipation	1/11 (9%)	0	0
Thrombocytopenia	2/11 (18%)	0	0
Decrease appetite	3/11 (27%)	0	0
Leukopenia	1/11 (9%)	0	0
Acne	1/11 (9%)	0	0

Safety

Adverse events for osimertinib 160 mg QD are summarized in Table 3. Grade 3 adverse events (fatigue and paronychia) were reported in patients #B1 and #B2. The most common adverse events were diarrhea grade 1–2 (45%) that increased from 36% at the 80 mg dose and paronychia (36%). Dose reduction was required in 4 patients (#A4, #B1, #A3, and #B2) to 160 mg for 5 days and 80 mg for the remaining 2 days. One patient, #A3, required further reduction to 160 mg for 2 days and 5 days of 80 mg. The adverse events that led to the dose reduction were paronychia in 3 patients and diarrhea in 2 patients.

Discussion

The intracranial efficacy of osimertinib has a significant impact on treatment strategy in EGFR (+) NSCLC patients with brain metastases.[13] In the naive setting, osimertinib has an excellent intracranial efficacy[3,4] and is the preferred first-line therapy recommended by the ESMO and the NCCN. Therefore, immediate osimertinib therapy and monitoring of the intracranial response is reasonable in most cases. Osimertinib is indicated in cases of intracranial progression under first- or second-generation EGFR-TKIs only when the T790M resistance mutation is present.[14–16] Currently, those who do not harbor the EGFR T790M clone, are not eligible for osimertinib as a second line of treatment and other strategies such as surgery, SRS, or WBRT are required to control their intracranial progression. This study focuses on intracranial progression under osimertinib either as a first or second line of treatment and presents an intracranial response rate of 54% with an intracranial control rate of 72% and a median intracranial PFS of 4.3 ± 7.4 (range 0.7–25.5) months.

Our limited experience with 11 patients showed that patients with isolated intracranial progression benefited from an additional median iPFS with osimertinib of 8.1 ± 8.7 months (range 0.7–25.5 months). Thus, it is suggested that dose escalation of osimertinib to 160 mg QD may be advised mainly for this group of patients.

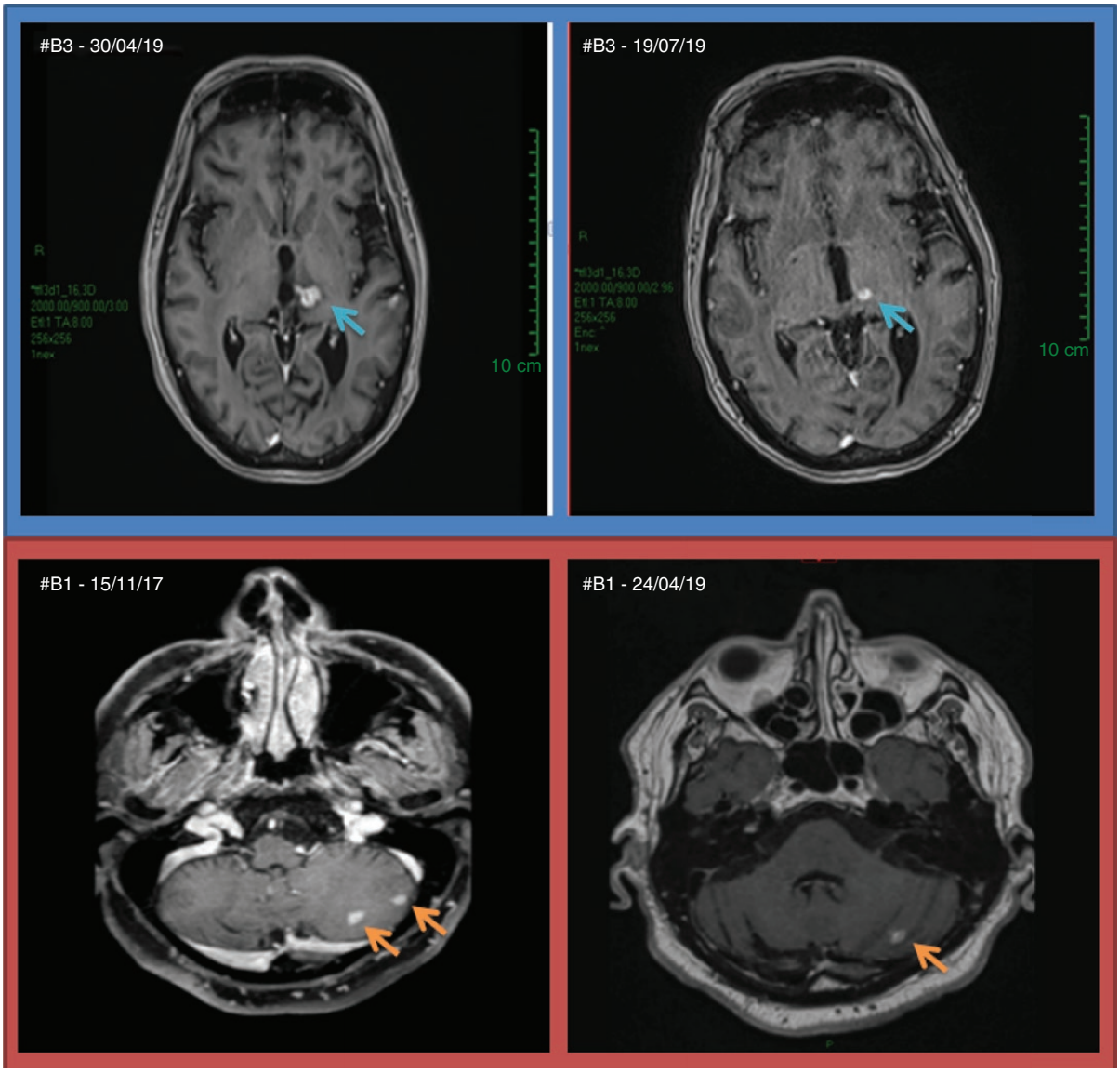

Figure 2. Intracranial best response, duration of treatment of osimertinib, and molecular profile.

In the group of patients with both intracranial and asymptomatic extracranial progression, partial intracranial response following dose escalation was seen in 3 of 5, albeit subsequent extracranial progression led to termination of treatment with a median iPFS of 3.1 ± 2.3 months (range 1.8–8.1 months).

This limited experience may suggest that dose escalation of osimertinib allows overcoming pharmacokinetic barriers, rather than overcoming mechanistic resistance to osimertinib.

The overall intracranial response rate to dose escalation was higher than the extracranial ORR (54% and 36%, respectively) with disease control rate (DCR) of 72% and 63%, respectively. An Intracranial response was not associated with intracranial disease burden, nor with previous duration of response to the standard dose of 80 mg QD. Remarkably, 3 of the patients had leptomeningeal spread which was very well controlled under 160 mg osimertinib (Figure 1).

Our data stand in concordance with previous reports. Both Tsang et al. and Cordova et al. have previously reported clinical benefit from an increased dose of osimertinib.[17,18] The BLOOM study showed that leptomeningeal disease was treated initially by osimertinib 160 mg daily.[5] Therefore, it is not clear whether 80 mg is enough for leptomeningeal disease or if it requires 160 mg initially. Myung-Ju et al. have reported that lazaretinib, a third-generation EGFR-TKI, had intracranial response to a range of dosing schedules in 18 patients; however, no association to dosing was reported.[19]

Osimertinib has a preferred CSF peak compared with first- and second-generation TKIs,[3] and yet its CNS

concentration in CSF remains substantially lower (14.4 nM) than its concentration in plasma (555.3 nM).[6,7] This might explain why some patients will require a higher daily dose of osimertinib either initially or in a later phase.

Liquid biopsies for ctDNA profiling on progression seem to direct future therapies as we saw in 5 of our patients (Table 3). Once there is mechanistic resistance, such as C797S point mutation or MET amplification, extracranial progression occurs and treatment should shortly be adjusted. Interestingly, although outside of the scope of this study, 3 patients in this study continued osimertinib on top of further systemic therapies and maintained their intracranial control (Figure 2). Further studies are required in order to understand the role of osimertinib, especially in allowing better brain control, beyond progression in addition to other systemic therapies.

Tolerability of osimertinib 160 mg was nearly similar to 80 mg, except an increase in diarrhea and paronychia as the most common adverse events (57% and 14%, respectively). Dose reduction was required in 4 patients. This stands in agreement with previous reports from the AURA study, which reported grade ≥3 possibly causally related (investigator assessed) adverse events in 16% of patients, and the most common were rash (grouped terms; 42%; grade ≥3, 1%) and diarrhea (39%; <1%).[5]

In conclusion, this study presents the benefit of dose escalation of osimertinib from 80 mg QD to 160 mg QD in cases, where isolated brain progression occurs under 80 mg. A more prominent response was observed when patients started osimertinib as second line versus first line; however, further investigation is needed. Osimertinib 160 mg QD is feasible in most patients.

Keywords

brain metastases | dose escalation | osimertinib | EGFR

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