Review Article

The treatment of patients with non-small cell lung cancer carrying uncommon *EGFR* mutations, *HER2* mutations, or brain metastases: a systematic review of pre-clinical and clinical findings for dacomitinib

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Background: Accumulating evidence has shown that dacomitinib has potential activities for patients with non-small cell lung cancer (NSCLC) harboring uncommon epidermal growth factor receptor (*EGFR*) mutations, human epidermal growth factor receptor 2 (*HER2*) mutations, or central nervous system (CNS) metastases.

Methods: This study aimed to give a systematic review on its potential applications in the above settings by searching MEDLINE/PubMed, Embase, Cochrane Library, American Society of Clinical Oncology.org, European Society for Medical Oncology.org, and ClinicalTrials.gov.

Results: The literature search yielded 649 publications in total. According to our findings, dacomitinib exhibited promising efficacy in patients with major uncommon *EGFR* mutations (including G719X, S768I, and L861Q). Both *EGFR* exon 20 insertional mutation (Ex20ins) and *HER2* Ex20ins demonstrated significant internal heterogeneity in response to dacomitinib, among which specific subtypes (including *EGFR* D770delinsGY, A763_Y764insFQEA, and *HER2* M774delinsWLV) were highly sensitive. Other uncommon *EGFR* mutations including 18del and L747P have also been shown responsive to dacomitinib. Interestingly, limited studies suggested dacomitinib application on certain first or third generation tyrosine kinase inhibitors (TKIs)' resistant secondary mutations. Last but not least, both pre-clinical and clinical data indicated that dacomitinib has an encouraging intracranial tumor control ability, regardless of uncommon mutations.

Conclusions: Dacomitinib demonstrated good disease control on patients with NSCLC harboring major uncommon *EGFR* mutations and specific *EGFR* or *HER2* mutation subtypes, and selective clinical application of dacomitinib is considerable in this setting, especially for those with intracranial metastases.

Keywords: Dacomitinib; lung cancer; uncommon mutations; brain metastases

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Introduction

Lung cancer remains one of the most common cancers with the second-highest morbidity and highest mortality worldwide (1), among which non-small cell lung cancer (NSCLC) accounts for nearly 80%. The development of tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor (*EGFR*) and other driver genes has greatly changed the landscape of advanced NSCLC treatment (2). Second-generation (2G) *EGFR*-TKIs play a distinctive role among EGFR inhibitors due to their broad inhibitory activity of human epidermal growth factor receptor (HER) family members including HER1 (also called EGFR), HER2, and HER4 (3-5). In the pooled analysis of Lux-Lung serial studies, afatinib demonstrated superior efficacy for major uncommon mutations, and it has been recommended as preferred choice for patients with NSCLC harboring major uncommon mutations by the national comprehensive cancer network guidelines (5,6). As another 2G TKI, dacomitinib also demonstrated promising efficacy on this subset of patients in pre-clinical studies and limited real-world studies (4,6,7). In addition, many studies have also shown the potential efficacy of dacomitinib for patients with *HER2* mutations and brain metastases (4,8-11).

Dacomitinib is another broad-spectrum, irreversible, highly selective *EGFR*-TKI (12). The ARCHER 1050 study demonstrated the excellent efficacy of dacomitinib over gefitinib in the first-line treatment of patients with NSCLC harboring classic *EGFR* mutations (namely 19del and L858R) (13). However, patients with brain metastases were excluded from this experiment due to the poor penetration ability of the control group (gefitinib) into the blood-brain barrier and the lack of data on the inhibitory activity of dacomitinib on brain metastases (12). Moreover, patients with uncommon mutations were also excluded from this study. Hence, data on the efficacy of dacomitinib for patients with uncommon mutations or central nervous system (CNS) metastases are limited (4,11,14), which makes clinicians uncertain about using dacomitinib in these scenarios.

This systematic review intends to give a comprehensive summary on potential applications of dacomitinib for patients with NSCLC carrying uncommon mutations (including *EGFR* and *HER2*) or CNS metastases, hoping to be helpful for clinicians' decision-making. We present this article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-95/rc).

Highlight box

Key findings

- The efficacy of dacomitinib against different uncommon *EGFR* and *HER2* mutation subtypes is highly heterogeneous, and the highly selective clinical application of dacomitinib is necessary for this setting.
- Dacomitinib has demonstrated good intracranial tumor control and should be considered clinically.

What is known and what is new?

- Dacomitinib has been approved for first-line treatment for *EGFR*-mutated non-small cell lung cancer (NSCLC); however, evidence of dacomitinib for uncommon *EGFR/HER2* mutations and brain metastases in NSCLC is currently limited.
- This study aimed to give a comprehensive review of its potential applications by compiling available publications.

What is the implication, and what should change now?

- Dacomitinib exhibited promising efficacy in patients with major uncommon *EGFR* mutations (including G719X, S768I, and L861Q).
- Dacomitinib showed an encouraging intracranial tumor control ability, regardless of uncommon mutations.

Methods

Definition of study population and outcome

The study population was defined as advanced NSCLC patients with uncommon *EGFR* mutations, *HER2* mutations, or CNS metastases. Uncommon *EGFR* mutations were defined as those mutations other than 19del and L858R in the EGFR domain as previously described in literature (2). CNS metastases referred to both parenchymal metastases and leptomeningeal metastases. The percentage of objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) for each of the currently available publications.

Data sources and search strategy

A systematic literature review was performed on 1 August 2022 according to the PRISMA criteria of 2009. We reviewed MEDLINE/PubMed, Embase, Cochrane Library, the American Society of Clinical Oncology (ASCO) Meeting Library, the European Society of Medical Oncology (ESMO) Library, and ClinicalTrials.gov for citation or ongoing trials without time limitation. We also searched the Google Scholar (https://scholar.google.com)

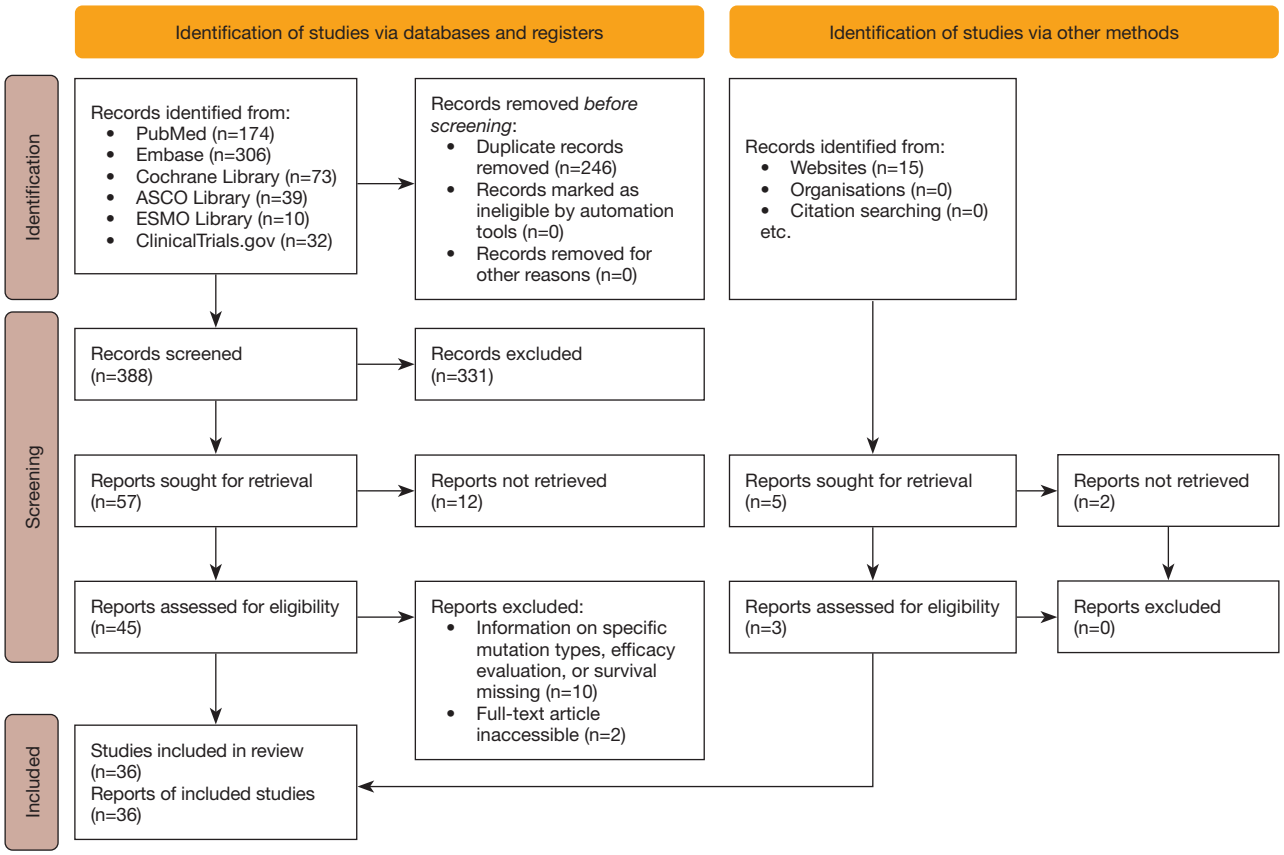

Figure 1 Flow chart of the study. ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology.

for additional reports. The terms used for the search were (lung cancer*[Title/Abstract]) AND (dacomitinib[Title/Abstract]) in PubMed, ('lung cancer*':ab,ti AND dacomitinib:ab,ti) in Embase, (lung cancer*):ti,ab,kw AND (dacomitinib):ti,ab,kw in Cochrane library and (dacomitinib, lung cancer) in ASCO and ESMO. The terms used for the search were ("lung cancer" as condition/disease) and ("dacomitinib" as other terms) in ClinicalTrials.gov. After removing duplicates, titles and abstracts were independently screened by two researchers (Yang LL and Luo XZ).

Selection criteria

The search criteria were limited to cell-line, animal, or human studies published in English language. Besides, to be included in this review, a publication had to fulfill the following inclusion criteria: studies performed in advanced NSCLC patients, or proper cell lines or animals, harboring uncommon *EGFR* mutations, *HER2* mutations or CNS metastases, treated with dacomitinib monotherapy. We included studies and abstracts without time limitations.

Results

The literature search yielded 649 publications in total. After excluding duplicates and applying the selection criteria, 36 studies were included in this systematic review (*Figure 1*). Overall, the eligible reports included 7 prospective trials, 9 retrospective studies, 4 conference abstracts, and 16 preclinical studies (*Tables 1-3*). The main uncommon mutation sites involved in this systematic review were shown in the molecular simulation graph (*Figures 2,3*).

Uncommon EGFR mutations

The most common mutations on the *EGFR* gene in NSCLC, including 19Del (49–72%) and L858R (28–43%), are called "common mutations", while other mutations (10–20%) on *EGFR* are called "uncommon mutations" or "rare mutations", with significantly heterogenic responses

Table 1 A summary of published clinical data on uncommon *EGFR* mutations

First author	Type	Year	Region	N	Gender	Age (year)	Histology	LOT	Mutation subtype	Method	Dosage	Best response	ORR	DCR	PFS (months)	OS (months)
Zhang (11)	R	2021	China	1	Female	62	AC	1	G719A	NGS	30 mg	PR	NA	NA	6.6	NA
				1	Female	64	AC	1	L861Q	NGS	30 mg	Non-CR/non-PD	NA	NA	10+	NA
Shen (15)	R	2021	China	1	Female	64	AC	4	L858R + L718Q	NGS	45 mg	PR	NA	NA	5	NA
Li (16)	R	2021	China	1	Female	38	AC	3	L858R + T790M + L792F + L792H	NGS	30 mg	PD	NA	NA	1	NA
				1	Male	58	AC	3	L858R + L792V + L718Q	NGS	30 mg	PD	NA	NA	1	NA
				1	Female	72	AC	3	L858R + L718Q	NGS	30 mg	PD	NA	NA	2	NA
				1	Male	81	AC	4	L858R + T790M + L792H	NGS	15 mg	PD	NA	NA	1	NA
				1	Male	45	AC	3	L858R + L718Q	NGS	30 mg	PD	NA	NA	1	NA
Chan (17)	CA	2021	Singapore	1	Female	73	AC	5	L858R + L718Q	NA	15 mg (occasionally 30 mg)	Non-CR/non-PD	NA	NA	5+	NA
Reckamp (18)	P	2014	USA	1	NA	NA	AC	1	G719C + S768I	ARMS	45 mg	PR	NA	NA	15.5	NA
Peng (14)	R	2021	China	1	Female	50	AC	1	G719A + I706T	NGS	45 mg	PR	NA	NA	1+	NA
Park (19)	P	2014	Korea	1	NA	NA	AC	2	G719X	NA	45 mg	PR	NA	NA	NA	NA
Morita (20)	R	2021	Japan	1	Female	71	AC	6	G719A	ARMS	45 mg→30 mg	PR	NA	NA	7.8	10.8
Li (4)	R	2022	China	11	NA	NA	AC	2–4	G719X, S768I, L861Q, L747P	NGS	NA	NA	54.5%	81.8%	10.3	1-year OS rate of 90.0%
				1	Male	46	AC	3	L858R + E709K	NGS	30 mg	PD	NA	NA	1.2	NA
				1	Male	65	AC	2	19del + G724S	NGS	30 mg	PR	NA	NA	9.4+	NA
Kris (21)	CA	2012	USA	7	NA	NA	NA	1	NA	NA	NA	NA	28.6%	71.4%	NA	NA
Han (22)	P	2021	China	30	NA	NA	NA	NA	NA	NGS	45 mg	NA	NA	NA	NA	NA
Choudhury (23)	P	2021	USA	1	NA	NA	AC	2	G719A	NGS	45 mg	PR	NA	NA	17+	NA
				2	NA	NA	AC	2	C797S + 19del, C797S + L858R	NGS	45 mg	SD	NA	NA	NA	NA
				1	NA	NA	AC	2	19del + G724S	NGS	45 mg	SD	NA	NA	5+	NA
Biswas (24)	CA	2021	India	2	NA	NA	NA	NA	G719X	NGS	NA	PR	NA	NA	NA	NA
				1	NA	NA	NA	NA	L861Q	NGS	NA	PR	NA	NA	NA	NA
Jänne (25)	P+	2011	USA	1	NA	NA	AC	NA	delD770insGY	ARMS	45 mg	PR	NA	NA	12.4	NA
				5	NA	NA	AC	NA	Ex20ins	ARMS	NA	NA	20%	60%	NA	NA
Jänne (9)	P	2014	USA	8	NA	NA	AC	NA	1 E709A + G719S, 1 G719S + R776H, 1 S768I + L858R, 3 T790M, 2 Ex20ins	ARMS	NA	NA	37.5%	75%	7.3	17.9
				1	NA	NA	AC	1	E709A + G719S	ARMS	NA	PR	NA	NA	NA	NA
				2	NA	NA	AC	1	Ex20ins	ARMS	NA	NA	0%	50%	NA	NA

EGFR, epidermal growth factor receptor; N, number; LOT, line of therapy; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; R, retrospective study; AC, adenocarcinoma; NGS, next generation sequencing; PR, partial response; NA, not applicable/not available; CR, complete response; PD, progressive disease; CA, conference abstract; P, prospective trials; ARMS, amplification refractory mutation system; SD, stable disease; Ex20ins, exon 20 insertional mutation.

Table 2 A summary of published clinical data on *HER2* alterations

First author	Type	Year	Region	N	Gender	Age (years)	Histology	LOT	Mutation subtype	Method	Dosage	Best response	ORR	DCR	PFS (months)	OS (months)
Reckamp (18)	P	2014	USA	1	NA	NA	AC	2	HER2 amplication + T790M + 19del	FISH	45 mg	PD	NA	NA	NA	NA
				1	NA	NA	AC	2	HER2 amplication + T790M + L858R	FISH	45 mg	SD	NA	NA	NA	NA
				1	NA	NA	Non-AC	2	HER2 amplication	FISH	45 mg	PR	NA	NA	2.8	NA
Kris (10)	P	2015	USA	26	15 were women	NA	AC	21 were pre-treated	HER2-mutant	NA	21 received 45 mg	NA	11.5%	92.3%	3	9
				1	NA	NA	AC	NA	M774delinsWLV	NA	NA	PR	NA	NA	3+	23+
				1	NA	NA	AC	NA	P780_Y781insGSP	NA	NA	PR	NA	NA	11	25+
				1	NA	NA	AC	NA	P780_Y782insGSP	NA	NA	PR	NA	NA	14	27
				1	Male	NA	AC	≥1	HER2 amplication [17]*	FISH	45 mg	SD	NA	NA	5	22
				1	Male	NA	AC	≥1	HER2 amplication [>2]*	FISH	45 mg	PD	NA	NA	1	15
				1	Male	NA	AC	≥1	HER2 amplication [2]*	FISH	45 mg	SD	NA	NA	5	7
				1	Male	NA	AC	≥1	HER2 amplication [2.4]*	FISH	45 mg	PD	NA	NA	1	5
Jänne (25)	P	2011	USA	2	NA	NA	AC	NA	HER2 amplication	NA	NA	SD	NA	NA	NA	NA
Kelly (26)	R	2010	USA	1	Male	50	LCNEC	3	HER2 amplication [6.1]*	FISH	45 mg	PR	NA	NA	6	NA

*, the ratio of HER2/CEP17. *HER2*, human epidermal growth factor receptor 2; N, number; LOT, line of therapy; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; P, prospective trials; NA, not applicable/not available; AC, adenocarcinoma; FISH, fluorescent in situ hybridization; PD, progressive disease; SD, stable disease; PR, partial response; R, retrospective study; LCNEC, large cell neuroendocrine carcinoma.

Table 3 A summary of published clinical data on CNS metastases

First author	Type	Year	Region	N	Gender	Age (years)	Histology	LOT	Mutation subtype	Method	Dosage	Best response for brain lesion(s)	iORR	iDCR	ORR	DCR	PFS (months)	OS (months)
Zhao (27)	R	2021	China	1	Male	47	AC	1	19del	NA	30 mg	CR	NA	NA	NA	NA	11	NA
				1	Male	55	AC	1	L858R	NA	30 mg	CR	NA	NA	NA	NA	8	NA
Zhang (11)	R	2021	China	32 (30 were evaluable, 8 evaluable for brain)	19 were female	Median: 57.5	31 were AC, 1 was ASC	All TKI-naïve	25 L858R, 5 19del, 1 L861Q, 1 G719A	13 by ARMS, 19 by NGS	Mostly (n=28) received 30 mg	NA	87.5% (85.2%†)	100%	66.70%	100%	NR	NA
				1	Female	62	AC	1	G719A	NGS	30 mg	PR	NA	NA	NA	NA	6.6	NA
				1	Female	64	AC	1	L861Q	NGS	30 mg	Non-CR/non-PD	NA	NA	NA	NA	10+	NA
Shen (15)	R	2021	China	1	Female	64	AC	4	L858R + L718Q	NGS	45 mg	PR	NA	NA	NA	NA	5	NA
Chan (17)	CA	2021	Singapore	1 patient with leptomeningeal metastases	Female	73	AC	5	L858R + L718Q	NA	15 mg (occasionally 30 mg)	SD§	NA	NA	NA	NA	5+	NA
Peng (14)	R	2021	China	14	7 were female	Median: 54	AC	1	5 L858R, 8 19del, 1 G719A + I706T	NGS	Mostly (n=9) received 30 mg	NA	85.70%	100%	92.90%	100%	NR	NA
				1 patient with leptomeningeal metastases	Female	41	AC	1	L858R	NGS	45 mg	SD§	NA	NA	NA	NA	4	NA
				1	Female	50	AC	1	G719A + I706T	NGS	45 mg	PR	NA	NA	NA	NA	1+	NA
Mizusaki (28)	R	2021	Japan	1 patient with leptomeningeal metastases	Male	72	AC	3	19del	NA	30 mg	CR	NA	NA	NA	NA	2.1+	NA
Li (4)	R	2022	China	23 (20 were evaluable)	14 were female	Median: 57.5	AC	2–5	5 19del, 14 L858R, 4 G719X	NGS	Mostly (n=12) received 30 mg	NA	NA‡	NA‡	15%	85%	6.5 (2.6–10.4)¶	NA
Biswas (24)	CA	2021	India	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	80%	NA	NA	NA

†, this rate was evaluated by modified RECIST (1.1). In the modified RECIST (1.1), up to five intracranial and up to five extracranial target lesions were included; intracranial target lesions of between 5 and 40 mm in diameter were allowed; ‡, as most patients with brain metastases in the later-line of therapy had received local therapy (e.g., radiotherapy), the assessment of iORR and iDCR was not performed; §, judged by RANO-LM criteria; ¶, median (range). CNS, central nervous system; N, number; LOT, line of therapy; iORR, intracranial objective response rate; iDCR, intracranial disease control rate; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; R, retrospective study; AC, adenocarcinoma; NA, not applicable/not available; CR, complete response; ASC, adenosquamous carcinoma; TKI, tyrosine kinase inhibitor; ARMS, amplification refractory mutation system; NGS, next generation sequencing; NR, not reached; PR, partial response; PD, progressive disease; CA, conference abstract; SD, stable disease; RECIST, Response Evaluation Criteria In Solid Tumors; RANO-LM, Response Assessment in Neuro-oncology, Leptomeningeal Metastasis.

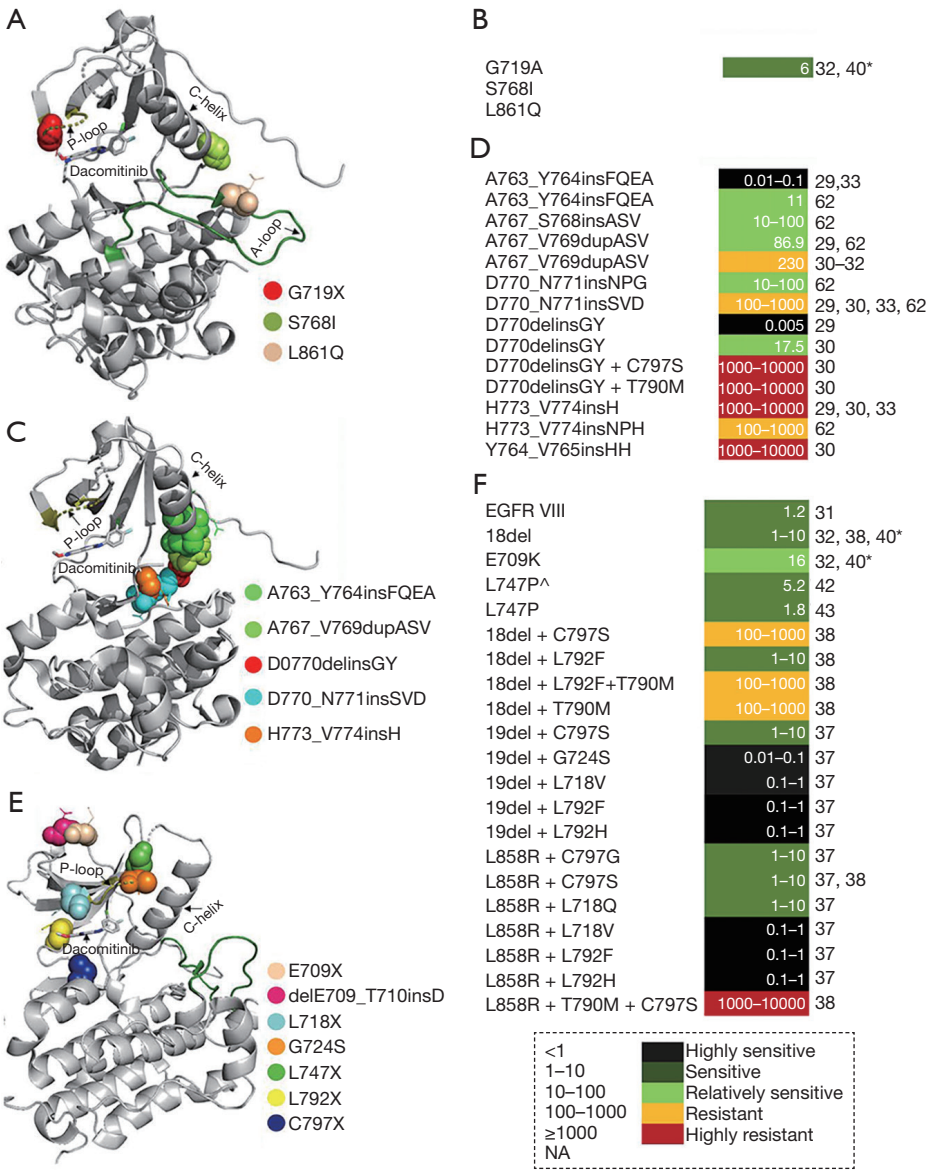

Figure 2 Molecular simulation graphs and assessment of dacomitinib activity in pre-clinical setting (Ba/F3 cells) for major uncommon *EGFR* mutations (A,B), *EGFR* 20 exon insertion mutations (C,D), and other uncommon *EGFR* mutations (E,F). Molecular simulation graphs were remodeled in EGFR (PDB: 4I23) protein structure by PyMOL software (version 2.3.4, Schrödinger, Inc., New York, USA). The graphs only show the approximate spatial location of the mutations and do not represent the specific mutation structure. The graphs were colored according to the scheme indicated in the graph and the corresponding drug sensitivity was classified as highly sensitive (<1 nM), sensitive (1–10 nM), relatively sensitive (10–100 nM), resistant (100–1,000 nM), highly resistant (≥1,000 nM), and NA based on current literature data. *, data were shown as IC_{90}; ^, cell model carrying L747P was A431. *EGFR*, epidermal growth factor receptor; NA, not available; PDB, Protein Data Bank; IC_{90}, 90% inhibiting concentration.

to *EGFR*-TKIs (2,29-32). According to the incidence and clinical significance, we mainly summarize *EGFR* mutations into the following three categories and a summary of the literature data is shown in *Table 1*.

Major uncommon mutations

Li *et al.* presented the later-line efficacy of dacomitinib on patients with NSCLC harboring uncommon *EGFR* mutations in a relatively small scale, and the findings

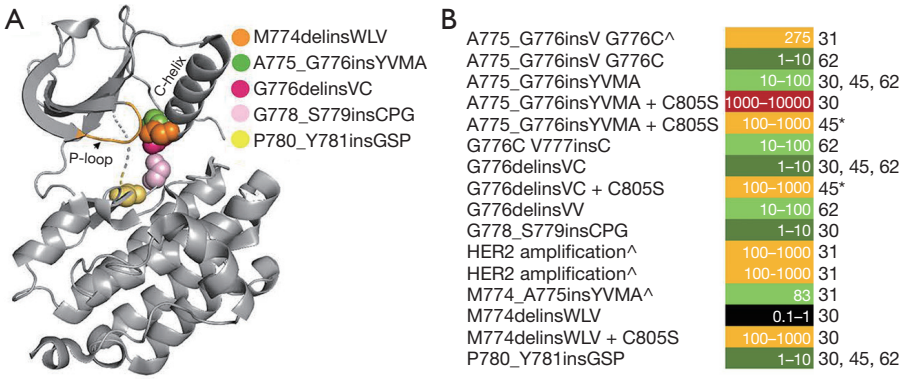

Figure 3 Molecular simulation graphs and assessment of dacomitinib activity in pre-clinical setting (Ba/F3 cells) for *HER2* alterations (A,B). Molecular simulation graphs were remodeled in HER2 (PDB: 3PP0) protein structure by PyMOL software (version 2.3.4, Schrödinger, Inc.). The graphs only show the approximate spatial location of the mutations and do not represent the specific mutation structure. The graphs were colored according to the scheme indicated in the graph and the corresponding drug sensitivity was classified as highly sensitive (<1 nM), sensitive (1–10 nM), relatively sensitive (10–100 nM), resistant (100–1,000 nM), highly resistant (≥1,000 nM), and NA based on current literature data. *, data were shown as IC_{90}; ^, cell models carrying *HER2* amplification, *HER2* amplification, and M774_A775insYVMA were Calu-3, H1819, and H827, respectively. *HER2*, human epidermal growth factor receptor 2; PDB, Protein Data Bank; NA, not available; IC_{90}, 90% inhibiting concentration.

confirmed ORRs of 57.1%, 0%, 33.3%, and median PFS (mPFS) of 10.3, 0.7, 6.5 months as to G719X (n=7), L861Q (n=2), and S768I (n=3) (*Figure 2A*), respectively (4). Other studies on patients carrying major uncommon mutations treated with dacomitinib were mostly case reports, of which G719X subtype was the most reported. We pooled 5 G719X-carrying cases with dacomitinib treatment responses and survival data in multi-line settings from the literature, and the results showed an ORR of 100% and an mPFS of 7.8 months (11,14,18,20,23). Consistent with clinical observations, the IC_{90} value of dacomitinib-treated Ba/F3 cell lines carrying the G719X mutation was only 6 nM, compared to that of 1.6 nM for classic mutation 19del (*Figure 2B*). Two cases carrying L861Q mutation treated with dacomitinib were reported in literature (11,24). Different from the two patients with primary drug resistance reported in Li *et al.*'s work (4), both the two patients had disease controlled, of which one patient achieved partial response (PR), and the other one with brain metastases had stable disease and achieved an PFS of more than 10 months.

Exon 20 insertion mutation (Ex20ins)

The Ex20ins is the second prevalent subtype (~16%) among uncommon *EGFR* mutations (2,33-37). In an open-label phase II clinical trial, two patients harboring Ex20ins (specific sites not known) were enrolled, with an ORR of 0% and a DCR of 50% (9). Results from a phase I clinical trial showed that one (carrying D770delinsGY) of the six patients with Ex20ins treated with dacomitinib achieved PR, and the overall ORR, DCR, and mPFS were 20%, 60%, and less than 3 months, respectively (25). Subsequent preclinical studies conducted by Kobayashi *et al.* (38) demonstrated that, though not sensitive to erlotinib and osimertinib, D770delinsGY and other insertions with a G770 equivalence were still responsive to 2G TKIs (especially for dacomitinib). Via establishing Ba/F3 pre-clinical models harboring Ex20ins, Kobayashi *et al.* revealed by the dose-response proliferation assays that D770delinsGY and A763_Y764insFQEA were two uniquely sensitive subtypes to dacomitinib [50% inhibitory concentration (IC_{50}) <0.1 nM], but other subtypes [including A767_V769dupASV (namely V769_D770insASV), D770_N771insSVD, and H773_V774insH] were not (38), which were consistent with other preclinical findings (39-42) (*Figure 2C,2D*).

Secondary uncommon *EGFR* mutations

Secondary uncommon *EGFR* mutations after 1G/3G TKIs resistance mainly included C797S/G, L718Q/V, and L792F/H (*Figure 2E*), which were found to be more enriched in the 3G TKI osimertinib-resistant setting (43). Chan (17) and Shen *et al.* (15) respectively reported a case of an elderly woman, both of which were detected with L718Q mutation after osimertinib resistance. And their conditions were

both controlled after receiving dacomitinib treatment (≥5 lines), among whom one of them achieved PR and both patients obtained the PFS of more than 5 months. An *in vitro* experiment conducted by Nishino *et al.* (44) also revealed that dacomitinib was effective against L718Q/V- or L792F/H-mutated (*in cis* with activating *EGFR* mutations and without T790M) Ba/F3 cells with IC_{50} values <1 nM. Consistently, an *in vitro* study by Kobayashi *et al.* (45) demonstrated that L792F-mutated afatinib-resistant Ba/F3 cells were highly sensitive to dacomitinib (IC_{50} <10 nM) (*Figure 2F*). However, there are also conflicting results. In Li *et al.*'s case series study, five patients with later-line osimertinib-resistant lung cancer were treated with dacomitinib (≥3 lines), whose resistance mutations at EGFR L792 (*in cis* with T790M) and/or L718 were detected by NGS; however, all patients progressed within 2 months. Dynamic molecular simulations showed that L792H (*in cis* with T790M) and L718Q mutations may interfere with the binding of dacomitinib to EGFR, leading to primary drug resistance (16). We believe that complicated tumor heterogeneity after multi-line therapies, different drug dosages, and patient status may all affect dacomitinib performance, leading to different treatment outcomes.

Other uncommon EGFR mutations

Except for major uncommon mutations and Ex20ins, other uncommon mutations spread across all exons of EGFR, but mainly in exons 18–21. As the quite low incidence (~1%) and exceptionally broad and complex distribution, studies on these uncommon mutations are currently very limited (2). From a therapeutic point of view, this part of mutations can be divided into primary uncommon mutations [E709X, delE709_T710insD (also called 18del), L747P/S, etc.] and secondary uncommon mutations (C797S/G, L718Q/V, L792F/H, etc.) (*Figure 2E*).

The E709X mutation (~0.3%) generally occurs as part of a complex mutation (2). Preclinical studies by Kobayashi *et al.* (46) showed that this mutant site was most sensitive to afatinib (IC_{90}: 0.7 nM), followed by neratinib (IC_{90}: 6 nM) and dacomitinib (IC_{90}: 16 nM), whereas resistant to osimertinib and 1G TKIs (*Figure 2F*). In the afatinib uncommon mutations database (https://www.uncommonegfrmutations.com/) reported by Yang *et al.*, nine patients (all in complex form and four of them were treatment-naïve) with E709X were included, with an ORR of 33.3% and a DCR of 55.6% (47). Currently, clinical data on dacomitinib for E709X are scarce. Li *et al.* reported that a patient carrying E709K combined with L858R mutation developed primary drug resistance after third-line dacomitinib treatment, and the PFS lasted only 1.2 months (4). Another patient with E709A combined with G719S mutation reported by Jänne *et al.* received first-line dacomitinib and responded (9). Currently, clinical data on dacomitinib treatment for delE709_T710insD (namely 18del) are lacking. Preclinical data suggested that delE709_T710insD was potentially sensitive to dacomitinib (IC_{50}: 1–10 nM) (*Figure 2F*) (41). In addition, 16 patients with delE709_T710insD mutation (14 of them were treatment-naïve) were identified in the afatinib uncommon mutations database, and 13 of them responded, which is consistent with preclinical findings (41).

The L747P missense mutation, located in exon 19 of *EGFR*, is rarely observed (~0.59%) in NSCLC (48,49). Current studies revealed that this mutation presented primary resistance to 1G-TKIs with the PFS ranging from 0.5–2.9 months, and its sensitivity to 3G TKI osimertinib remains unclear. However, numerous studies have demonstrated better therapeutic responsiveness and efficacy of 2G TKI (afatinib) for this rare mutation, with a much longer PFS ranging from 12 to 24 months (48,49). In Li *et al.*'s study, two patients carrying L747P who were treated with later-line dacomitinib (≥3 lines) were enrolled. Both patients were in remission (PR) and continued to benefit, with the PFS of 6.6 and 9.1 months, respectively (4). In line with Li *et al.*'s clinical results, in the study by Yang *et al.* (48) and Yoshizawa *et al.* (49), A431 cells or Ba/F3 cells carrying L747P also demonstrated high sensitivity to dacomitinib, with IC_{50} values of 1.8 and 5.2 nM for dacomitinib (*Figure 2F*) relative to IC_{50} values of 45.3 and 147.3 nM for gefitinib, respectively. Besides, via instructing an L747P-mutant patient-derived xenograft mice model, Yang *et al.* showed that both dacomitinib and afatinib showed potent anti-tumor activities compared with osimertinib and poziotinib (48). Interestingly, compared with afatinib, dacomitinib also significantly reduced mice weight ($P<0.001$) and induced severe skin destruction (48). Nevertheless, the two patients carrying L747P in Li *et al.*'s work who received dacomitinib developed only grade 1–2 rash and grade 1 oral ulcer (4).

***HER2* mutations**

Different from the increase of gene copy number in breast cancer, variations of *HER2* (2–5%) in NSCLC mainly occur in the kinase region (most of them are *HER2* Ex20ins, accounting for ~56%) (50). The most common *HER2* Ex20ins include A775_G776insYVMA, G776delinsVC and P780_

Y781insGSP (*Figure 3A*), which make up ~94% of *HER2* Ex20ins according to previously published works (10,39).

The phase II clinical trial conducted by Kris *et al.* (10) disclosed that among 26 patients (17% of them were treat-naïve) carrying *HER2* mutations (25 Ex20ins and 1 missense mutation) treated with dacomitinib, their ORR, DCR, mPFS, and median OS (mOS) were 11.5%, 92.3%, 3 and 9 months, respectively. Specifically, among three patients who obtained PR, two patients with P780_Y781insGSP subtype had the longest PFS (11 and 14 months) and OS (25+ and 27 months), and one patient with M774delinsWLV had a PFS of 3+ months and an OS of 23+ months. Consistent with the data of Kris *et al.*, preclinical studies conducted by Koga *et al.* and Kosaka *et al.* suggested that Ba/f3 cells carrying P780_Y781insGSP or M774delinsWLV were highly sensitive to dacomitinib, with IC_{50} values of 1–10 and <1 nM (*Figure 3B*), respectively (39,51,52). In addition, despite the lack of clinical data, preclinical studies suggested that both G776delinsVC (39,51,52) and G778_S779insCPG (39) subtypes were sensitive to dacomitinib (IC_{50}: 1–10 nM), suggesting the potential of dacomitinib for patients carrying these mutations. According to preclinical data, as the most common *HER2* mutation, A775_G776insYVMA subtype was moderately sensitive to dacomitinib (IC_{50}: 10–100 nM); however, no PRs (ORR: 0%, DCR: 92.3%) were observed in 13 pre-treated patients carrying A775_G776insYVMA reported by Kris' *et al.* (10). More clinical data are needed to confirm the potential of dacomitinib for patients carrying this mutation (39,51,52).

For *HER2* amplification, in Kris *et al.*'s study, four patients with *HER2* amplification had an ORR of 0%, and a DCR of 75%, with the PFS ranging from 1–5 months and OS from 5–22 months (10). The *HER2*-amplified cell line constructed by Engelman *et al.* also suggested that this type of mutation was insensitive to dacomitinib (40). Interestingly, one patient with a higher degree of amplification (HER2/CEP17 ratio of 17) had a prolonged survival, indicating a correlation between the degree of *HER2* amplification and the efficacy of dacomitinib (10). In addition, a significant decrease in the *HER2* amplification level clinically may suggest a better therapeutic efficacy of dacomitinib, according to the two responded patients (both cases got PR) reported by Reckamp *et al.* (18) and Kelly *et al.* (26). A summary of the literature data is shown in *Table 2*.

CNS metastases

In Kim *et al.*'s studies, by utilizing cassette dosing in wild-type and Abcb1/Abcg2-deficient mice, osimertinib and dacomitinib were demonstrated to be consistently ranked with a comparatively high brain penetration, while erlotinib, gefitinib, and afatinib were categorized in the low brain penetration group (53). Pharmacokinetic studies revealed that dacomitinib concentrations in rat whole brain homogenates were similar to those in plasma (brain:plasma ratio of 1.2:1), and radiolabeling could be detected in most CNS tissues and cerebrospinal fluid of rats administered ^{14}C-dacomitinib for up to 48 hours (53). A preclinical study conducted by Zahonero *et al.* demonstrated that dacomitinib could effectively cross the BBB and inhibit EGFR signaling in *EGFR*-amplified glioblastomas (GBM) brain xenografts, leading to a drastic impairment in tumor growth (54). Consistently, Chen *et al.*'s work indicated that metabolite ratios were significantly decreased while the apoptotic index was significantly elevated in the dacomitinib-treated group compared with the C6 glioma control group (55).

In the post-hoc analysis of the ARCHER 1050 trial, according to the independent review committee, only 1 (0.4%) patient in dacomitinib group but 9 (4.0%) patients in gefitinib group developed new brain metastatic lesions (odds ratio: 0.11, P=0.034). Since patients with brain metastases were excluded from the ARCHER 1050 trial, current data on the efficacy of dacomitinib in patients with brain metastases are mainly derived from real-world studies and case reports (4,11,14,15,17,24,27,28,56) (*Table 3*). Peng *et al.*'s work demonstrated 14 *EGFR*-mutant NSCLC patients carrying brain metastasis who were treated with first-line dacomitinib, among which measurable responses of CNS metastases (92.3% with brain parenchymal metastasis) were observed in 85.7% of patients, and they obtained an ORR of 92.9% and a DCR of 100% (14). In another larger real-world study, Zhang *et al.* included a total of 32 TKI-naïve NSCLC patients with brain metastases, all of whom received dacomitinib monotherapy (11). Among 8 CNS evaluable patients, the intracranial ORR (iORR) was 87.5% and the intracranial DCR (iDCR) was 100%, which was consistent with Peng *et al.*'s findings (14). Furthermore, in 30 evaluable patients, the iORR was 66.7% and the iDCR was 100%, but intracranial PFS (iPFS) was not reached (11). Different from the above studies, Li *et al.* described the efficacy of later-line dacomitinib in patients with brain metastases (4). As most patients with brain metastases in the later line of therapy had received local therapy (e.g., radiotherapy), the assessment of iORR and iDCR was not performed. A comparative evaluation (49 evaluable patients included) revealed a lower ORR (16.7% *vs.* 32.3%,

P=0.233) but a significantly higher DCR (88.9% *vs.* 61.3%, P=0.039) of patients with brain metastases than those of patients without brain metastases, and they did not observe any significant differences as to mPFS (P=0.587) and mOS (P=0.647) between the two groups, reflecting the potent efficacy of dacomitinib in patients carrying brain metastases in later-line settings (4). On the other hand, 9 of 15 (60%) patients with symptomatic brain metastases had the relief of their symptoms, and only 3 patients (13.0% of all patients with brain metastases) re-progressed due to brain progression (4).

In particular, limited evidence showed that dacomitinib was effective not only for patients with brain metastases carrying common mutations but also for patients carrying uncommon mutations (11,14). In four brain-metastatic patients harboring G719X compound mutations, Li *et al.*'s study revealed an ORR of 25% and a DCR of 75% in the later-line settings (4). Chan (17) and Shen *et al.* (15) respectively reported a patient with CNS-metastatic NSCLC harboring L858R/L718Q compound mutations, and both patients got their intracranial lesions controlled, with the PFS of more than 5 months.

Discussion

Due to the exclusion of clinical trials and the scarcity of study population, evidence on dacomitinib for patients harboring uncommon mutations/CNS metastases is limited (3,57,58), though accumulating evidence have shown its potential in this setting (10,14,18,25,44). Herein, a comprehensive review of dacomitinib on its potential applications from both pre-clinical and clinical findings is presented, in hope of helping clinicians on decision-making, clinical trial design, and drug development.

Compared to common mutations, uncommon mutations are generally less sensitive to TKIs (59-64). Nevertheless, some uncommon mutations including G719X (~3%), S768I (~1%), and L861Q (~1%), also called "major uncommon mutations" are still sensitive to 1G EGFR-TKIs, with ORRs ranging from 41.6% to 53.8% and mPFS, 2.2 to 7.7 months (59,62-64). In the KCSG-LU15-09 trial conducted by Cho *et al.* (30), osimertinib achieved ORRs of 53%, 78%, 38% and mPFS of 8.2, 15.2, 12.3 months regarding G719X (n=19), L861Q (n=9), and S768I (n=8), respectively. Apart from osimertinib, evidence suggested that 2G TKI was also favorable for this subset of patients. A combined post-hoc analysis by Yang *et al.* demonstrated that for G719X (n=18), L861Q (n=16), and S768I (n=9), the ORRs were 77.8%, 56.3%, and 100%, and the mPFS were 13.8, 8.2, and 14.7 months, respectively (5). A previous study conducted by Yang *et al.* also showed that the median time-to-treatment failure (mTTF) was 14.7, 10.0, and 15.6 months in patients treated with first-line afatinib who had G719X, L861Q, and S768I mutations, respectively (47). However, there have been few studies on the efficacy and safety of dacomitinib for patients harboring major uncommon EGFR mutations (3,57,58).

Regarding the different therapeutic responses between 3G TKI osimertinib and 2G TKIs on major uncommon mutations, scholars have given some inspiration from the molecular structure perspective. Different from traditional classification according to exons, Robichaux *et al.* developed a new structure-based classification (65), and G719X and S768I subtypes are classified as the "P-loop C-helix compressing" type, where changes in the orientation of the P-loop can cause destabilization of osimertinib binding. However, 2G TKIs do not interact with the P-loop of EGFR and maintain interaction points in the hydrophobic cleft, thus keeping full effectiveness for G719X and S768I. The L861Q mutation, categorized as the "classical-like" type, is distal from the drug-binding pocket (BDP) and has low impact on the overall structure of EGFR, thus binding of osimertinib to the mutant EGFR was not blocked.

Interestingly, when the data in the literature were compared, it was found that 2G TKI dacomitinib and afatinib were less effective on L861Q than G719X and S768I (4,30,47), while osimertinib was the opposite (30). Robichaux *et al.* (65) revealed that G719X and S768I could change the orientation of the P-loop which may lead to the destabilization of osimertinib binding, but 2G TKIs do not interact with the P-loop of EGFR, thus keeping full effectiveness for G719X and S768I. This finding is reflective, suggesting that the concept of "major uncommon mutation" is a definition of incidence, and we should not simply treat it as a therapeutic whole. In this setting, the head-to-head data on dacomitinib versus afatinib or osimretinib in treatment of major uncommon mutations are very expecting. Interestingly, limited data suggest that dacomitinib also exhibits a potent brain-introducing effect in patients with uncommon mutations. Therefore, dacomitinib is worth looking forward to in patients with major uncommon mutations carrying brain metastases. It needs to note that some case reports have reported the clinical benefits of dacomitinib in patients with brain metastases who have non-common EGFR mutations; the usage of dacomitinib has been focused on posterior-line therapy (15,17). One study also suggests a

clinical benefit after first-line dacomitinib intervention in patients with brain metastatic lung cancer who have non-common mutations (14). Due to the scarcity of patients with uncommon EGFR mutations, further studies are needed to determine whether dacomitinib can provide clinical benefit to patients with uncommon EGFR mutations in the settings of first-line therapy.

Currently, data in the literature demonstrate the potential application of dacomitinib for patients with major uncommon mutations, but no convincing conclusions can be drawn. A single-arm, open-label, phase II trial (NCT04504071) designed to investigate the safety and efficacy of dacomitinib in advanced NSCLC patients with uncommon *EGFR* mutations is ongoing in China. Hopefully, this prospective phase II clinical study conducted by Han *et al.* may provide us with more definitive data (22,66).

Previous studies demonstrated very limited efficacy of 1G TKIs (including gefitinib, erlotinib, and icotinib) for patients with *EGFR* Ex20ins, with an ORR of 0–6.9%, an mPFS of 1.4–3.0 months, and an mOS of 4.8–26 months (33,36,59). The 2G TKI afatinib seems to be more favorable under comparison with 1G TKIs, with an observed ORR of 8.7–20%, an mPFS of ~2.7 months, and an mOS of ~9.2 months (18). *HER2* EX20ins significantly tilt the C-helix toward the BDP of HER2 protein, resulting in a significant spatial blockage at the entrance of the BDP, which in turn prevents most conventional TKIs from binding to this particular conformation-altered BDP and acting (10,39). Nevertheless, as pan-HER2 inhibitors, studies have shown that 2G TKIs have certain efficacy for this subset of patients. Data from a small retrospective study showed that the mPFS and mOS for patients harboring P780_Y781insGSP subtype treated with afatinib were 10.0 and 19.7 months, respectively (67), while those for patients harboring other subtypes were only 3.3 and 7.0 months, respectively. Liu *et al.* revealed that afatinib obtained an ORR of 19% and an mTTF of 2.9 months in treating *HER2*-mutant NSCLC, among which the A775_G776ins YVMA subtype achieved an ORR of 33% and an mTTF of 9.6 months (67).

According to our findings, pre-clinical and clinical data revealed that both *EGFR* and *HER2* Ex20ins exhibited significant internal heterogeneity in response to dacomitinib, among which *EGFR* D770delinsGY, *EGFR* A763_Y764insFQEA, and *HER2* M774delinsWLV were uniquely sensitive to dacomitinib, indicating the feasible clinical applications of dacomitinib on this subset of patients. Interestingly, for *HER2* amplification, despite pre-clinical and partial clinical evidence suggesting a less favourable efficacy (40), case reports revealed a correlation between high levels of *HER2* amplification and dacomitinib efficacy, and rapid declines in amplification levels may predict better treatment outcomes (10,16,26). In addition, due to controversial results and data paucity, the clinical efficacy of dacomitinib on A767_V769dupASV and D770_N771insNPG still needs to be further confirmed. However, realizing that more and more potent TKIs specifically targeting *EGFR* and/or *HER2* Ex20ins (such as amivantamab/mobocertinib/pyrotinib) are emerging, future research on dacomitinib should focus more on combination therapies and precision populations (58,68).

Some uncommon *EGFR* mutations including 18del and L747P have also been shown responsive to dacomitinib (41,48). In addition, pre-clinical studies suggested that dacomitinib also showed sensitivity to certain TKI-resistant (mainly osimertinib) secondary mutations (including L792X, L718X, and G724S). Given that osimertinib has been widely used, and there is currently no recommended standard treatment (mainly chemotherapy) for uncommon secondary mutations after drug resistance, the role of dacomitinib in the setting appears to be interesting, especially for the elderly and those who are not willing to receive intensive chemotherapy.

Concerning the side effects of dacomitinib, the common side effects of dacomitinib in NSCLC patients with common EGFR mutations include diarrhea, paronychia, dermatitis acneiform, stomatitis, decreased appetite, and so on in the clinical trial (13). Nevertheless, data on the side effect of dacomitinib for NSCLC patients harboring uncommon mutations is limited. A phase II trial demonstrated the common side of dacomitinib for NSCLC patients harboring uncommon mutations may include rash, diarrhea, oral mucositis, oral mucositis, paronychia, dry skin, and so on (69). Data suggest that patients with uncommon mutations have similar common side effects of gastrointestinal and skin disorders when treated with dacomitinib compared to common mutations. However, those have yet to be proven due to limited data.

Whether the efficacy of dacomitinib is affected by ethnic differences in NSCLC populations with uncommon EGFR mutations is a worthwhile consideration for clinical drug selection. Due to the scarcity of the study population, evidence of response rates on dacomitinib for diverse ethnicities is still limited. Further efforts should focus more on the efficacy differences in diverse populations.

A limitation of this paper is that the complexity of the

type of literature collected and the large heterogeneity between the data made it difficult to combine the data, so we did not conduct a meta-analysis.

With the increasingly widespread and ubiquitous application of NGS technology, more and more uncommon mutations have been discovered, which is further rapidly changing the landscape of precision therapy of NSCLC. The challenge, however, is a smaller and smaller target population that corresponds to an increasingly complex mutational spectrum. Consistent with Kris *et al.* (10), we believe that efforts to build open, searchable databases to share precise molecular signatures of tumors to connect hospitals, institutes, and pharmaceutical companies could go a long way toward confronting these complexities.

Conclusions

Accumulating data have demonstrated promising efficacy of dacomitinib in patients with major uncommon *EGFR* mutations. The efficacy of dacomitinib against different uncommon *EGFR* and *HER2* mutation subtypes is highly heterogeneous, among which some are clinically applicable. Finally, dacomitinib has demonstrated good intracranial tumor control and should be considered for specific individuals clinically.

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Footnote

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