Antiangiogenesis May Not Be a Universal Booster of EGFR Tyrosine Kinase Inhibitors

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Since the concept of antiangiogenesis was introduced in oncology, various types of systemic anticancer treatment, from cytotoxic chemotherapy, molecular targeted therapy, to immunotherapy, had been attempted to be combined with antiangiogenic agents. At around 2010, cytotoxic chemotherapy and EGFR tyrosine kinase inhibitors (TKIs) were two pillars of systemic treatments for NSCLC, and the combination of antiangiogenic agents and EGFR TKIs was thus naturally to be explored.

Preclinically, there were several supportive evidences for synergism of antiangiogenesis and EGFR tyrosine kinase inhibition. The two pathways are intertwined, gefitinib decreased vascular endothelial growth factor (VEGF) expression through inhibition of HIF-1α,[1] and VEGF increased in erlotinib-resistant models.[2] The synergism of dual VEGF and EGFR inhibition was also shown in xenograft models. Bevacizumab plus erlotinib combination was found to have better tumor growth inhibition than erlotinib or gefitinib treatment in models with acquired resistance to erlotinib or gefitinib.[2] Combination of erlotinib and DC101, a mouse VEGF receptor (VEGFR)-2 antibody, was also found to have superior efficacy than either erlotinib or DC101 alone.[3] In addition, afatinib, a second-generation irreversible EGFR TKI, when combined with bevacizumab, had higher efficacy in *EGFR* T790M mutation containing xenograft models than monotherapy.[4]

In clinical testing, despite the preclinical works often focused on EGFR TKI-resistant settings, randomized trials mainly compared an EGFR TKI to its combination with either anti–VEGF or anti–VEGFR-2 antibody for patients who are naive to the EGFR TKI. In a randomized phase 2 study JO25567 in Japan, the superiority of bevacizumab plus erlotinib than erlotinib in terms of progression-free survival (PFS = 16.4 mo versus 9.8 mo, hazard ratio [HR] = 0.52, $p = 0.0005$) was shown for the first time, with similar overall survival (OS = 47.0 mo versus 47.4 mo, HR = 0.81, $p = 0.3267$) and objective response rate (ORR, 69% versus 64%, $p = 0.4951$) between the two arms.[5,6] Despite a similar but smaller randomized phase 2 study in the United States revealed nonsignificant improvement of PFS and even numerically worse OS in the combination group,[7] subsequently three phase 3 studies conducted in Japan, People's Republic of China, and Italy, respectively, confirmed the PFS benefit of bevacizumab plus erlotinib over erlotinib with HR at 0.55 to 0.66.[8–11] Consistently, OS and ORR were not significantly different except ORR in the BEVERLY study (bevacizumab plus erlotinib versus erlotinib, 70% versus 50%).[11] Rather than bevacizumab plus erlotinib combination, ramucirumab plus erlotinib versus erlotinib was tested in RELAY study and a PFS benefit of similar effect size was found (19.4 mo versus 12.4 mo, HR = 0.59, $p < 0.0001$). Ramucirumab plus erlotinib combination had been the only U.S. Food and Drug Administration–approved antiangiogenesis plus EGFR TKI combination up to now.

On the basis of prior success, as osimertinib emerged as the game changer of *EGFR*-mutant NSCLC, the addition of antiangiogenic agent to osimertinib became an attractive idea. Phase 1 studies of bevacizumab plus osimertinib combination in the first-line setting and ramucirumab plus osimertinib combination for patients with *EGFR* T790M mutation did not reveal unexpected toxicities beyond common toxicities of anti–VEGF antibody, anti-VEGFR antibody, or osimertinib, but the ORR (bevacizumab plus osimertinib in first-line: 80%, ramucirumab plus osimertinib for *EGFR* T790M: 76%) and

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Disclosure: Dr. Lin reports receiving personal fees from AbbVie, Bayer, BeiGene, Blueprint Medicines, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Merck KGaA, Novartis, PharmaEngine, and Roche outside of the submitted work. Dr. Wu reports receiving personal fees from Astellas outside of the submitted work.

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2022.06.012

Table 1. Ongoing and Future Studies of Osimertinib Plus Antiangiogenic Agent Combinations

Study Focus		Trials
Phase 3 study of bevacizumab plus osimertinib vs. osimertinib		NCT04181060
Different partner of antiangiogenic agent, randomized phase 2 study Ramucirumab plus osimertinib vs. osimertinib		NCT03909334
CNS metastases bevacizumab plus osimertinib vs. osimertinib	Brain	NCT02971501, NCT05104281
	Leptomeningeal	NCT04988607
Molecularly defined population bevacizumab plus osimertinib vs. osimertinib	Osimertinib-sensitive *EGFR* L858R mutation	NCT04988607
	Osimertinib-insensitive *EGFR* exon 20 insertions	NCT04974879
Ever-smokers	Clinical smoking history	To be explored
	Associated molecular feature: *p53* coalteration, smoking mutation signature	
Bevacizumab or ramucirumab plus osimertinib combination in osimertinib-resistant setting		To be explored

CNS, central nervous system.

PFS (bevacizumab plus osimertinib in first-line: 19 mo, ramucirumab plus osimertinib for *EGFR* T790M: 11 mo) were also not remarkable if numerically compared with historical data of osimertinib monotherapy.[12,13] Two randomized phase 2 trials, WJOG8715L and BOOSTER, both revealed that there was no PFS benefit of bevacizumab plus osimertinib over osimertinib in second-line *EGFR* T790M mutation population.[14,15]

In this issue of the *Journal of Thoracic Oncology*, Kenmotsu et al.[16] present the first randomized study comparing bevacizumab plus osimertinib with osimertinib in the first-line setting—WJOG9717L. The primary end point, PFS, was 22.1 months in bevacizumab plus osimertinib versus 20.2 months in osimertinib arm, and there was no statistically significant difference (HR = 0.862, $p = 0.213$). In addition, grade 3 to 4 toxicities were numerically higher in the combination arm (56% versus 48%).

Despite there is still ongoing phase 3 study (NCT04181060) to be expected to put on the final puzzle on the issue of whether bevacizumab could add on additional efficacy to osimertinib, repeated failures of bevacizumab plus osimertinib combination in different settings raised the questions about the reasons behind these failures. One possible explanation, like that was proposed in the discussion of WJOG9717L, was short exposure of bevacizumab (median 33.4 wk) owing to toxicities. Because the PFS of first-line osimertinib treatment was often more than 18 months, the much shorter duration of bevacizumab was unlikely to have positive impact. However, this may not explain the whole story, as in second-line setting, where the duration of bevacizumab exposure was closer to PFS of osimertinib, the combination also did not derive additional benefit.

Have a closer look, we may find out that there is no strong evidence to support the synergistic or additive effect of antiangiogenesis agents to osimertinib. As in the summary of preclinical evidence,[1–4] most of the synergism demonstrations were based on erlotinib, gefitinib, or afatinib, but not on osimertinib. Another argument is that antiangiogenesis agents may endow osimertinib with better delivery, as what they did in other combinations. Nevertheless, there is no evidence that inadequate penetration is the major resistant mechanism for front-line or second-line osimertinib in the nonselective patient population, and osimertinib itself is an effective treatment for tumors in sanctuary sites, even for leptomeningeal disease.[17] In addition, there was no evidence that antiangiogenesis agents may help osimertinib to conquer the known resistant mechanisms. In previous studies,[18,19] common single-agent osimertinib-resistant mechanisms were described, for example, *EGFR* C797S, *MET* amplification, histologic transformation, and bypass pathways. In phase 1 studies of bevacizumab plus osimertinib and ramucirumab plus osimertinib combinations, *EGFR* C797S, *EGFR* L718Q, *EGFR* amplification, *MET* amplification, squamous cell transformation, and pleomorphic transformation were noted as resistant mechanism.[12,13] This indirect comparison indicated that antiangiogenesis agents did not help conquer single-agent osimertinib-resistant mechanisms, although delayed occurrence or decreased proportion of common osimertinib-resistant mechanism could not be totally ruled out.

To gain further insight and guide future studies, additional translational research and deeper mining of existing studies are necessary. The synergism of antiangiogenesis agents and osimertinib in osimertinib-sensitive or osimertinib-resistant settings may be investigated in

models like what had been done for first- and second-generation EGFR TKIs. To evaluate the relapse pattern and resistant mechanisms in studies of bevacizumab or ramucirumab plus erlotinib combination versus erlotinib may provide hints on what is the exact role of antiangiogenesis agents in the synergism. Furthermore, subgroup analysis, especially findings consistent in different studies, may help us to generate testable hypothesis in next trials. For example, ever-smokers have a more favorable HR of PFS than never-smokers in all three randomized studies of bevacizumab plus osimertinib versus osimertinib, potential study for this specific population may be designed, and the underlying molecular characteristics (co-occurring gene alterations, programmed death-ligand 1 expression, tumor mutation burden, or mutation signatures) of this benefit may be worth exploring.

Although antiangiogenesis may not be a booster for osimertinib according to current evidence, there are potential rooms for the combination in unique niches. Because there is potential improvement of central nervous system drug delivery by vascular normalization effect of antiangiogenesis agents,[20] several trials are pursuing osimertinib plus bevacizumab combination in patients with brain (NCT02971501, NCT05104281) or leptomeningeal (NCT04148898) metastases. Besides the anti–VEGF partner bevacizumab, anti–VEGFR2 ramucirumab plus osimertinib versus osimertinib is also being tested in randomized study (NCT03909334). Moreover, specific molecular subgroups are being explored, including osimertinib-sensitive mutation, such as *EGFR* L858R mutation (NCT04988607, when the result is available, it will be informative to compare the result with WJOG 9717L, as *EGFR* L858R mutation was the unfavorable subgroup for the combination arm in WJOG 9717L), and traditionally osimertinib-insensitive mutations, such as *EGFR* exon 20 insertions (NCT04974879). Finally, there are also uncharted areas waiting for reasonable studies: ever-smokers, or an associated molecularly defined group (e.g., *p53* coalteration or smoking mutation signature), on the basis of consistent subgroup analysis mentioned previously; and osimertinib-resistant setting, on the grounds that the preclinical evidence of synergism of antiangiogenesis to EGFR TKIs was actually mainly in TKI-resistant setting, but the antiangiogenic agent plus EGFR TKI combinations in TKI-resistant population had not been thoroughly evaluated in clinical trials (Table 1).

CRediT Authorship Contribution Statement

Tsung-Che Wu, Chia-Chi Lin: Conceptualization, Writing - review.

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