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Title
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Permalink
https://escholarship.org/uc/item/996006zb

Journal
Clinical Cancer Research, 27(4)

ISSN
1078-0432

Author
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Publication Date
2021-02-15

DOI
10.1158/1078-0432.ccr-20-4026

Peer reviewed

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Clin Cancer Res. Author manuscript; available in PMC 2021 August 15.

Published in final edited form as:

Clin Cancer Res. 2021 February 15; 27(4): 905–907. doi:10.1158/1078-0432.CCR-20-4026.

Osimertinib Plus Ramucirumab: The Best of Both Worlds?

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Summary:

Both osimertinib and the combination of erlotinib plus ramuciumab are approved for initial therapy of advanced *epidermal growth factor receptor* (*EGFR*) mutation positive non-small cell lung cancer (NSCLC). Osimertinib is also approved in previously treated T790M mutation positive patients. The accompanying manuscript reports on a study combining osimertinib with ramucirumab.

In this issue of CLINICAL CANCER RESEARCH, Yu and colleagues (1) evaluate the combination of osimertinib, a third generation EGFR inhibitor, and ramucirumab, an antibody directed against vascular endothelial growth factor receptor 2 (VEGFR-2), in T790M mutation positive NSCLC. EGFR inhibitors were first approved for NSCLC over 15 years ago. Tremendous efficacy was observed among a subset of patients. The benefit was subsequently demonstrated to be essentially restricted to patients whose tumors harbored mutations in the *EGFR* gene (2). Unfortunately, resistance to EGFR inhibition essentially always occurs, and the profound benefit seen with immune checkpoint inhibition in NSCLC has generally eluded *EGFR* mutation positive patients (3). As a result, five-year survival rates remain poor.

In the past decade, research has focused on improving outcomes among *EGFR* mutation positive NSCLC patients. Yet, until recently, most patients with metastatic disease received first generation EGFR inhibitor monotherapy, either gefitinib or erlotinib, as initial therapy. The most common mechanism of resistance was the appearance of a second mutation in *EGFR*, the T790M mutation. This mutation substitutes a bulky methionine for threonine, impeding the efficacy of gefitinib or erlotinib. While second generation EGFR inhibitors afatinib and dacomitinib demonstrated limited efficacy in a salvage setting, patients with this second mutation can be effectively treated with osimertinib, leading to its approval in this setting. The efficacy of osimertinib in patients with T790M mutations whose initial therapy was not erlotinib or gefitinib monotherapy is not particularly well described.

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Disclosures:

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In the last several years, multiple studies have shown alternate approaches associated with greater progression free survival (PFS) than first generation EGFR inhibitor monotherapy as initial therapy. These newer approaches fall into four categories: 1) second generation EGFR inhibitors (afatinib and dacomitinib), 2) third generation EGFR inhibitors (osimertinib), 3) erlotinib plus anti-angiogenic agents (bevacizumab and ramucirumab) and 4) gefitinib plus chemotherapy (carboplatin and pemetrexed) (4). These approaches are available in United States based on approval by the Food and Drug Administration or recognition from the National Comprehensive Cancer Network. Practitioners are left to choose among these options based on assessment of the relative efficacy, toxicity and potential treatment options at the time of disease progression (Figure 1).

Of course, there are limitations in comparing efficacy and toxicity of approaches in cross-trial comparisons. Interpretation of survival data among trials is difficult based on differences in study size, duration of follow up and availability of subsequent therapy at the time of disease progression. Also, while there is general agreement regarding the favorable tolerability of osimertinib, assessing tolerability of combinations is complicated by the disparate degree to which the same grade of different event types affect the patient experience (e.g. grade 3 hypertension, neutropenic fever, rash, or thrombocytopenia).

A wealth of preclinical data supports the particular relevance of anti-angiogenic approaches in *EGFR* mutation positive patients. *In vitro* and *in vivo* experiments demonstrate enhanced inhibition of tumor growth as well as evidence of cross talk between the EGFR and VEGFR pathways. Yet, as the historic standard of care has been erlotinib, clinical combinations have combined anti-angiogenic therapy with erlotinib.

When multiple approaches prove superior to an older standard of care, oncologists naturally attempt to combine aspects of these newer therapies to further improve outcomes. Studies attempting this have begun for initial treatment of patients with metastatic *EGFR* mutation positive NSCLC. The FLAURA2 study compares osimertinib monotherapy to the combination of a platinum chemotherapeutic, pemetrexed and osimertinib (NCT04035486). In this issue of CLINICAL CANCER RESEARCH, Yu and colleagues evaluate the combination of osimertinib and the anti-angiogenic agent ramucirumab in 25 previously treated patients with an acquired T790M mutation (1).

As osimertinib is associated with superior efficacy and a favorable toxicity profile compared to erlotinib, there has been tremendous enthusiasm about combining osimertinib with anti-angiogenic therapy. The combination has potential to combat the most common mechanism of resistance for all frontline treatment options except osimertinib while incorporating the potential added efficacy of an anti-angiogenic. However, the evaluated study population in the manuscript by Yu and colleagues, patients who received neither osimertinib nor an anti-angiogenic therapy as part of their initial therapy for advanced disease, has become increasingly uncommon. Therefore, the true value of this study lies in applying it to alternate clinical situations.

Relevance of the data from the study by Yu and colleagues is limited among patients who initially receive single agent osimertinib. In addition to the different molecular situation

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(osimertinib does not generate selective pressure for the secondary T790M mutation), these patients have already received the regimen's major driver of benefit, osimertinib. The relevance in patients who received erlotinib plus an anti-angiogenic agent is similarly unclear, as the benefit of switching out the EGFR inhibitor as opposed to initiating osimertinib monotherapy is questionable. This regimen could hypothetically be of benefit in patients who received a second generation EGFR inhibitor or carboplatin and pemetrexed plus gefitinib, but this would be an unverified extrapolation. Of course, the greatest potential impact of this data would be combining an anti-angiogenic agent with osimertinib as initial therapy.

With respect to efficacy, the objective response rate of 76% and the PFS of 11.0 months reported by Yu and colleagues are numerically greater than the phase III study of osimertinib vs chemotherapy, 71% and 8.5 months respectively (5), but not markedly better. While a 25 patients study cannot definitively demonstrate superiority over an historical control, this study did not provide strong evidence of increased efficacy. With respect to toxicity, the data reported by Yu and colleagues appears substantially worse than single agent osimertinib. Grade 3 treatment emergent adverse events (AEs) were seen in 64% as opposed to 23% with osimertinib alone (5). Both manuscripts present grade 3 or greater treatment related AEs (TRAEs) restricted to TRAEs seen in at least 10% of patients. Again, numerically these TRAEs were clearly higher for the addition of ramucirumab to osimertinib, 28% as opposed to 6%. Yet, all but one treatment related grade 3 adverse event was either hypertension or thrombocytopenia, events that can generally be treated or monitored respectively. In addition, one patient died of congestive heart failure felt to be related to treatment. Two other cardiac deaths were considered unrelated, including one case of pulmonary edema, which can be plausibly related to hypertension.

So, in summary, there has been tremendous progress in the last several years in the management of *EGFR* mutation positive NSCLC. The frontline approaches that have dominated the treatment landscape for the first 15 years of targeted therapy for this group have been largely supplanted by regimens that increase PFS, but five-year survival remains poor. The manuscript by Yu and colleagues give us information about the potential for improvement in efficacy with a generally tolerable safety profile of osimertinib plus ramucirumab, but the results are far from convincing. Whether this approach is truly offering us the best of two different treatment approaches as opposed to substantially increased toxicity for similar efficacy is unclear and will require larger studies to clarify.

Acknowledgments:

E. B. Garon is supported by the National Cancer Institute (CA208403).

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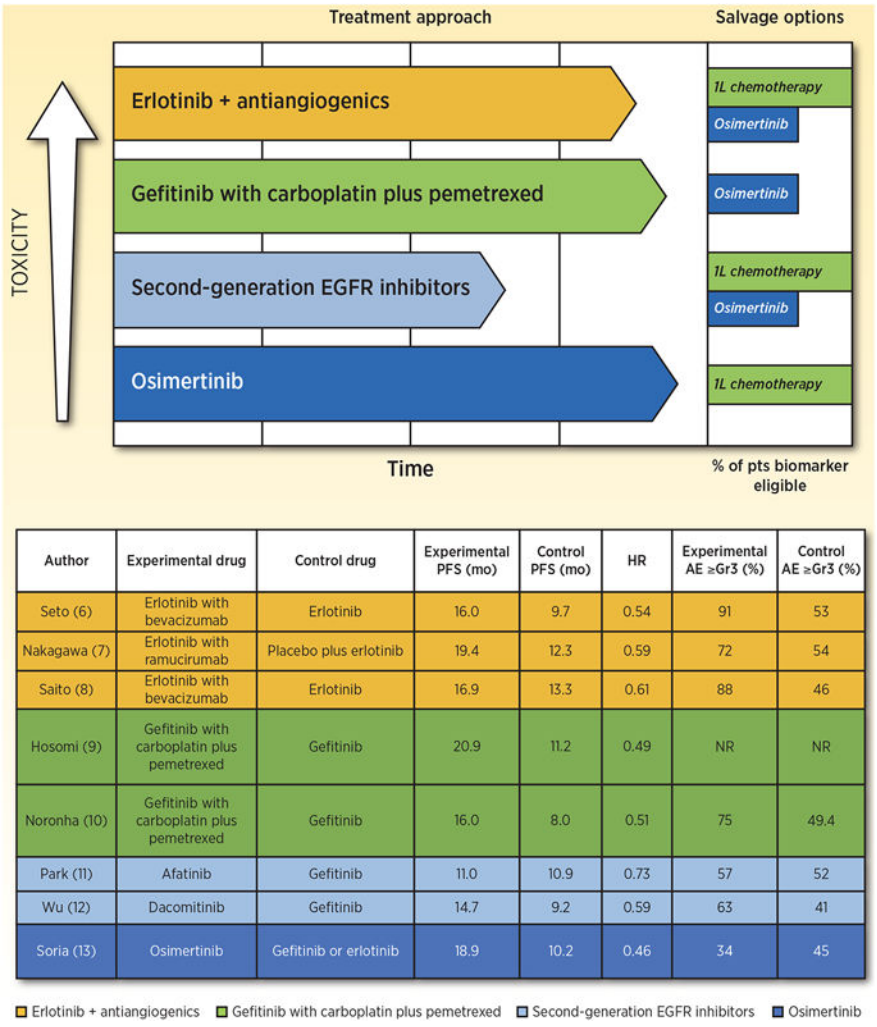

Author	Experimental drug	Control drug	Experimental PFS (mo)	Control PFS (mo)	HR	Experimental AE ≥Gr3 (%)	Control AE ≥Gr3 (%)
Seto (6)	Erlotinib with bevacizumab	Erlotinib	16.0	9.7	0.54	91	53
Nakagawa (7)	Erlotinib with ramucirumab	Placebo plus erlotinib	19.4	12.3	0.59	72	54
Saito (8)	Erlotinib with bevacizumab	Erlotinib	16.9	13.3	0.61	88	46
Hosomi (9)	Gefitinib with carboplatin plus pemetrexed	Gefitinib	20.9	11.2	0.49	NR	NR
Noronha (10)	Gefitinib with carboplatin plus pemetrexed	Gefitinib	16.0	8.0	0.51	75	49.4
Park (11)	Afatinib	Gefitinib	11.0	10.9	0.73	57	52
Wu (12)	Dacomitinib	Gefitinib	14.7	9.2	0.59	63	41
Soria (13)	Osimertinib	Gefitinib or erlotinib	18.9	10.2	0.46	34	45

Erlotinib + antiangiogenics Gefitinib with carboplatin plus pemetrexed Second-generation EGFR inhibitors Osimertinib

Figure 1.

Considerations for selecting initial therapy in *EGFR* mutation positive patients. 1L, first-line; AE, adverse event; NR, not reported.