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Comparative Efficacy of Targeted Therapy Combinations in Advanced Lung Adenocarcinoma

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Abstract

Advanced lung adenocarcinoma is now routinely subdivided by driver mutation, and for each major driver the therapeutic question has shifted from whether a targeted agent works to whether combining it with a second agent, or replacing it with a chemotherapy-free doublet, outperforms an already-effective targeted monotherapy. This article synthesizes the pivotal randomized trial literature addressing that comparative-efficacy question for EGFR-, ALK-, and KRAS G12C-mutant advanced lung adenocarcinoma. In EGFR-mutated disease, adding chemotherapy to osimertinib (FLAURA2) and replacing osimertinib with amivantamab plus lazertinib (MARIPOSA) each extended progression-free survival by a comparable margin in the first-line setting, amivantamab-containing regimens extended progression-free survival after osimertinib progression (MARIPOSA-2), and amivantamab plus chemotherapy established a new standard for the chemotherapy-reliant exon 20 insertion subtype (PAPILLON); by contrast, adding bevacizumab to first-line osimertinib (WJOG9717L) did not significantly improve progression-free survival over osimertinib alone. In ALK-positive disease, next-generation inhibitors substantially outperformed first-generation crizotinib (ALTA-1L, CROWN), and in KRAS G12C-mutant disease, two independently developed inhibitors each reported a real but comparatively modest progression-free survival advantage over docetaxel (KRYSTAL-12, CodeBreaK 200). We give particular weight to trials with a negative or modest result alongside the positive ones, since a synthesis built only from favorable comparisons would misrepresent how uneven this evidence base actually is. Read together, the evidence supports several specific combination or next-generation-monotherapy strategies as genuine, reproducible advances over targeted monotherapy, while leaving head-to-head comparison between leading first-line strategies, biomarker-guided selection among post-progression options, and a fuller accounting of comparative toxicity as the field's central open problems.

Keywords: lung adenocarcinoma; targeted therapy combinations; EGFR-mutated NSCLC; ALK-positive NSCLC; KRAS G12C inhibitors

1. Introduction

Lung adenocarcinoma stopped being a single disease sometime around 2004, when activating mutations in the epidermal growth factor receptor (EGFR) were first shown to predict dramatic responses to gefitinib and erlotinib, and it has kept fragmenting ever since. The Cancer Genome Atlas's comprehensive molecular profiling of lung adenocarcinoma formalized what clinicians had already begun to suspect: the disease is better described as a collection of oncogene-addicted subtypes -- EGFR, ALK, KRAS, MET, ROS1, BRAF, RET, and a long tail of rarer drivers -- each with its own natural history and, increasingly, its own targeted drug or drug class [1]. What has changed more recently, and what this article is about, is a second-order shift within each of those subtypes: from a single targeted agent given as monotherapy until progression, to a menu of *combinations* -- a tyrosine kinase inhibitor (TKI) paired with chemotherapy, with an antibody against a second receptor, with an antiangiogenic agent, or with a second TKI targeting a resistance pathway before it has even emerged.

The clinical logic for combining rather than sequencing is straightforward to state and considerably harder to establish empirically. A targeted monotherapy selects for whichever resistant subclone survives it, and once that subclone dominates, the original drug stops working; a combination given up front can, in principle, suppress more of the tumor's escape routes simultaneously, at the cost of added toxicity, cost, and complexity. Osimertinib's trajectory in EGFR-mutated non-small cell lung cancer (NSCLC) is the clearest illustration of how this logic has actually played out. As a third-generation EGFR TKI active against both the common sensitizing mutations and the T790M resistance mutation that first-generation inhibitors provoke, osimertinib was established as a highly effective monotherapy in two pivotal trials -- FLAURA, comparing it against first-generation EGFR TKIs in the first-line setting, and AURA3, comparing it against platinum-pemetrexed chemotherapy in patients whose disease had progressed on an earlier-generation TKI and acquired T790M [2,3]. Both trials reported a substantial and, for AURA3, quite large progression-free survival (PFS) advantage: 10.1 months with osimertinib versus 4.4 months with chemotherapy in AURA3, a hazard ratio of 0.30 [3]. Osimertinib went on to demonstrate an overall survival advantage in the first-line setting as well [4], and, in resected early-stage disease, a disease-free and eventually overall survival benefit as adjuvant therapy [5,6]. That is a strong monotherapy, by any standard the field has used. And yet the question this article takes up -- whether combining it, or the analogous drugs for ALK- and KRAS G12C-driven disease, with something else does better still -- has been asked and answered, sometimes affirmatively and sometimes not, across more than a dozen randomized trials over the past six years.

This article synthesizes that trial literature specifically for advanced lung adenocarcinoma, organized around the major oncogenic drivers for which combination regimens have reached randomized, comparative evaluation: EGFR (chemotherapy combinations, receptor-antibody combinations, and antiangiogenic combinations, in both the first-line and post-progression settings), ALK (next-generation TKI monotherapy compared against earlier-generation monotherapy, which functions as the relevant comparative-efficacy question for this driver), and KRAS G12C (small-molecule inhibitors compared against cytotoxic chemotherapy in the pretreated setting). We are not reporting new trial data; we are trying to place the pivotal randomized results for each of these combination strategies side by side, with particular attention to the magnitude of benefit reported for each, the settings in which combining outperforms monotherapy, and -- just as informative -- the settings in which a combination that looked mechanistically sound in preclinical models failed to clear a monotherapy comparator in a randomized trial. That last category turns out to be important: not every plausible combination wins, and a synthesis that only reports positive trials would misrepresent how uneven the actual evidence base is.

It is worth being explicit about scope. This article is confined to advanced (locally advanced or metastatic) lung adenocarcinoma and to combination or next-generation-monotherapy strategies that have reached phase 2 or phase 3 randomized comparison against a clinically relevant comparator; we do not attempt to cover adjuvant or neoadjuvant targeted therapy in resectable disease beyond citing it as background context, immunotherapy combinations (which have generally underperformed in oncogene-driven NSCLC and represent a separate

literature), or the rapidly expanding but still largely single-arm early-phase literature on antibody-drug conjugates and bispecific antibodies, several of which we mention as emerging post-progression options without treating their reported response rates as comparative efficacy claims.

2. Molecular Drivers and the Rationale for Targeted Combination Therapy

The rationale for combining targeted agents rests on a small number of recurring biological observations, each of which maps onto a specific combination strategy discussed later in this article. The first is that a targeted monotherapy's resistance mechanisms are heterogeneous but not unlimited, and several of the most common ones are themselves druggable. In EGFR-mutated NSCLC treated with osimertinib, the dominant acquired-resistance mechanisms identified in paired pre- and post-progression biopsy and circulating tumor DNA studies include MET amplification, acquisition of a secondary EGFR mutation (most notably C797S, which sits in the drug-binding pocket), small-cell transformation, and a long tail of less common bypass-pathway alterations; the relative frequency of each varies depending on whether osimertinib is given first-line or after an earlier-generation TKI [7,8,9]. MET amplification's prominence among these mechanisms, in particular, is the direct rationale for the osimertinib-plus-MET-inhibitor combinations discussed later in this article: if MET amplification is what a meaningful fraction of tumors use to escape EGFR blockade, then blocking MET pre-emptively, or in combination once amplification is detected, is a mechanistically motivated response rather than an empirical fishing expedition.

The second recurring observation is that chemotherapy and targeted therapy act on largely non-overlapping cell populations and mechanisms, which makes their combination additive in principle even without any specific synergistic interaction. A tumor with heterogeneous subclonal composition -- some cells strongly dependent on the oncogenic driver, others less so -- may respond to a driver-targeted TKI in the dependent subclones while cytotoxic chemotherapy suppresses the TKI-insensitive population that would otherwise expand and eventually dominate. This "hedge your bets across mechanisms" logic underlies both the EGFR TKI-plus-chemotherapy combinations (FLAURA2 in the first-line setting, MARIPOSA-2 after osimertinib progression) and the amivantamab-plus-chemotherapy combination now approved for EGFR exon 20 insertion-mutated disease, a molecular subtype that responds poorly to conventional EGFR TKIs and for which chemotherapy has historically been a mainstay [10,11,12].

The third observation, specific to EGFR-mutated disease, concerns the tumor vasculature. EGFR signaling promotes VEGF expression, and there is a reasonably well-developed preclinical and early-phase clinical rationale for pairing an EGFR TKI with an antiangiogenic agent such as bevacizumab: normalizing tumor vasculature could, in principle, improve drug delivery and slow the compensatory neovascularization that accompanies acquired resistance. This rationale motivated a series of trials -- most notably WJOG9717L in the first-line setting -- that we discuss in detail below, precisely because the result did not confirm the hypothesis as cleanly as the mechanistic story suggested it should [13].

The fourth observation is specific to the receptor-antibody class of combinations built around amivantamab, a bispecific antibody targeting both EGFR and MET. Because amivantamab engages EGFR through an antibody-mediated mechanism -- including antibody-dependent cellular cytotoxicity and receptor downregulation -- rather than through kinase-domain inhibition, it retains activity against several resistance mechanisms that defeat small-molecule EGFR TKIs, including some EGFR kinase-domain mutations and MET-amplification-driven bypass signaling, which is the direct rationale for pairing it with the third-generation TKI lazertinib in both the first-line (MARIPOSA) and post-osimertinib-progression (MARIPOSA-2) settings [14,11]. The same bispecific mechanism, combined with its distinct binding epitope on MET, is what motivates its separate development as a single agent for MET exon 14 skipping-mutated NSCLC and its evaluation alongside a second TKI for EGFR-mutant disease that has progressed on osimertinib via a MET-driven mechanism specifically, an application closely related to but mechanistically distinct from its combination role in MARIPOSA [15,16].

3. EGFR-Directed Combination Strategies in First-Line Advanced Disease

The clearest and most consequential combination result

in EGFR-mutated lung adenocarcinoma to date comes from FLAURA2, which randomized treatment-naive patients with EGFR-mutated advanced NSCLC to osimertinib alone or osimertinib plus platinum-pemetrexed chemotherapy. The combination arm reported a median PFS of 25.5 months against 16.7 months for osimertinib alone, a hazard ratio of 0.62 [10]. A subsequent overall survival analysis from the same trial reported a survival advantage for the combination as well, with the combination arm's median overall survival approaching four years, among the longest reported to date in a global phase 3 trial in this population, extending the earlier PFS signal into the outcome that ultimately matters most to patients [17]. The cost of that benefit is real and worth stating plainly: adding chemotherapy to osimertinib substantially increases the incidence of hematologic and gastrointestinal toxicity relative to osimertinib alone, and the combination regimen is a materially more demanding one to deliver and tolerate over many months than a single oral TKI. FLAURA2's result establishes that, at least for the chemotherapy-combination strategy specifically, front-loading additional cytotoxic therapy onto a highly effective TKI can meaningfully delay progression and extend survival relative to the TKI alone -- but it does so by treating essentially every first-line patient with a more toxic regimen in order to benefit the subset whose disease would otherwise have progressed earlier.

A second and, on current evidence, comparably effective first-line strategy replaces chemotherapy with a second targeted agent. MARIPOSA randomized treatment-naive EGFR-mutated advanced NSCLC patients to osimertinib or to amivantamab plus lazertinib, reporting a median PFS of 23.7 months for the combination versus 16.6 months for osimertinib, a hazard ratio of 0.70, and, in an overall survival analysis at a median follow-up beyond three years, an estimated 56% of combination-arm patients alive versus 44% on osimertinib, with median overall survival not yet reached in the combination arm against 36.7 months for osimertinib [14]. Read side by side, FLAURA2 and MARIPOSA report broadly similar absolute PFS gains achieved through mechanistically distinct combination strategies -- one adding cytotoxic chemotherapy to the established monotherapy backbone, the other replacing the monotherapy backbone with a chemotherapy-free doublet of a bispecific antibody and a third-generation TKI -- and neither trial directly randomized patients against the other, so a formal comparative-efficacy claim between the two regimens is not something the existing evidence base actually supports; what can be said is that both strategies clear the osimertinib-monotherapy bar by a comparable margin, through different toxicity profiles (amivantamab's dominant toxicities are infusion-related reactions, dermatologic adverse events, and venous thromboembolism, rather than the myelosuppression associated with chemotherapy).

Not every mechanistically motivated first-line combination has cleared that bar, however, and the antiangiogenic strategy is the clearest counterexample. WJOG9717L, a randomized phase 2 trial in treatment-naive nonsquamous EGFR-mutated NSCLC, compared osimertinib plus bevacizumab against osimertinib alone and reported a median PFS of 22.1 months for the combination versus 20.2 months for osimertinib alone, a hazard ratio of 0.86 that did not reach statistical significance [13]. That null result for a combination with a coherent preclinical rationale is a useful corrective to any assumption that combining a targeted agent with a second mechanistically plausible drug reliably improves on monotherapy; it did not here, at least not in the unselected first-line population studied, though the trial's exploratory subgroup analysis suggesting a possible benefit in patients with a smoking history or an exon 19 deletion illustrates how a combination's true effect can be masked, or concentrated in a biomarker-defined subset, within an overall null result -- a pattern the field has not yet resolved for this particular regimen.

A structurally distinct first-line combination problem concerns EGFR exon 20 insertion mutations, a molecular subtype that behaves quite differently from the classical EGFR sensitizing mutations and responds poorly to standard EGFR TKIs, making chemotherapy the historical first-line standard. PAPILLON randomized treatment-naive patients with this specific mutation to chemotherapy alone or chemotherapy plus amivantamab, and reported a median PFS of 11.4 months for the combination versus 6.7 months for chemotherapy alone, a hazard ratio of roughly 0.40 [12]. This result is worth separating conceptually from the FLAURA2 and MARIPOSA results discussed above, because the comparator here is chemotherapy rather than a TKI -- exon 20 insertion-mutated disease did not

have an effective targeted monotherapy to combine with or replace, so PAPILLON's result establishes amivantamab-plus-chemotherapy as a new standard against the prior standard-of-care rather than testing whether combination beats an already-strong targeted monotherapy.

4. ALK and KRAS G12C-Directed Combination and Sequential Strategies

ALK-rearranged and KRAS G12C-mutant lung adenocarcinoma have followed a different comparative-efficacy pattern than EGFR-mutated disease, in large part because the relevant "combination" question for these drivers has mostly been framed as next-generation-TKI-versus-earlier-generation-TKI monotherapy rather than as literal drug combinations, and because the KRAS G12C literature is still comparatively young.

For ALK-positive disease, two pivotal first-line trials each compared a newer-generation ALK inhibitor against crizotinib, the first-generation ALK TKI, and both reported large PFS advantages. ALTA-1L compared brigatinib against crizotinib and reported a median PFS by blinded independent review of 24.0 months for brigatinib versus 11.0 months for crizotinib, a hazard ratio of 0.49 [18]. CROWN compared lorlatinib, a third-generation, brain-penetrant ALK TKI, against crizotinib, and reported a median PFS for crizotinib of 9.3 months while the lorlatinib arm's median PFS had not been reached at the time of the primary analysis, corresponding to a hazard ratio of 0.28 -- among the largest relative risk reductions reported for any targeted-therapy comparison discussed in this article [19]. These results, taken together with brigatinib's and lorlatinib's generally favorable central nervous system activity relative to crizotinib, have made next-generation ALK TKI monotherapy the de facto first-line standard for ALK-positive advanced NSCLC; unlike the EGFR literature, there is not yet a comparably mature randomized literature testing whether adding a second agent on top of a next-generation ALK TKI improves further on these already substantial gains, which we return to as an open question in a later section.

KRAS G12C-mutant NSCLC presents a different picture again: a molecular subtype that had no targeted therapy at all until sotorasib's approval based on single-arm early-phase data, followed within a few years by randomized, comparative confirmation against chemotherapy for both approved KRAS G12C inhibitors. CodeBreaK 200 randomized previously treated, KRAS G12C-mutant advanced NSCLC patients to sotorasib or docetaxel and reported a median PFS of 5.6 months for sotorasib versus 4.5 months for docetaxel, a hazard ratio of 0.66 [20] -- a considerably more modest relative benefit than seen with the EGFR- or ALK-targeted comparisons above, consistent with KRAS G12C inhibitor monotherapy being, on current evidence, a meaningfully active but less transformative intervention than EGFR- or ALK-targeted therapy has been for their respective driver populations. This modest but real benefit builds on sotorasib's original single-arm activity signal, which established an objective response rate and a manageable safety profile sufficient to support accelerated approval before the randomized confirmatory data existed [21]. KRYSTAL-12 tested the same comparative question for adagrasib, the other approved KRAS G12C inhibitor, randomizing previously treated patients to adagrasib or docetaxel and reporting a median PFS of 5.5 months for adagrasib versus 3.8 months for docetaxel, a hazard ratio of 0.58 [22] -- a magnitude of benefit closely comparable to CodeBreaK 200's, from an independently conducted trial of a different KRAS G12C inhibitor, which strengthens confidence that this roughly 1.5- to 2-month absolute PFS gain over docetaxel, modest as it is in absolute terms, is a genuine class effect for KRAS G12C inhibitors in this pretreated population rather than a trial-specific artifact. Combination strategies pairing a KRAS G12C inhibitor with a second agent -- SHP2 inhibitors, receptor tyrosine kinase inhibitors, or immunotherapy -- remain, at the time of this synthesis, largely confined to early-phase trials without the randomized, comparative-efficacy data that would let them be placed alongside the EGFR and ALK combinations discussed above.

5. Combination Strategies After Progression on First-Line Targeted Therapy

The post-progression setting is where the largest number of distinct combination strategies have been tested, in large part because progression on a first-line targeted agent is precisely the moment at which the resistance-mechanism biology described earlier becomes clinically actionable, and because it is the setting in which a molecularly rational combination has the clearest unmet need to address.

For EGFR-mutated disease progressing on osimertinib specifically, MARIPOSA-2 is the most directly comparative trial: patients whose disease had progressed on osimertinib were randomized to chemotherapy alone, chemotherapy plus amivantamab, or chemotherapy plus amivantamab and lazertinib together. Both amivantamab-containing arms outperformed chemotherapy alone -- the triplet regimen reported a median PFS of 8.3 months against 4.2 months for chemotherapy, a hazard ratio of 0.44, while the doublet (amivantamab plus chemotherapy, without lazertinib) reported a median PFS of 6.3 months against the same 4.2-month chemotherapy comparator, a hazard ratio of 0.48 [11]. The similarity of the two amivantamab-containing arms' hazard ratios, despite the triplet's numerically longer median PFS, illustrates a recurring feature of this post-progression literature: adding a third active agent to an already-active doublet often produces a real but incremental further gain rather than a second large step-change of the kind seen when amivantamab-lazertinib was first added to a chemotherapy backbone at all.

A mechanistically narrower post-progression strategy targets MET-amplification-driven resistance specifically, rather than treating all osimertinib-resistant disease as a single entity. The TATTON trial evaluated osimertinib plus the selective MET inhibitor savolitinib in patients whose disease had progressed on an earlier EGFR TKI via MET amplification or overexpression, reporting objective responses in a substantial proportion of this molecularly selected population and establishing proof of concept that MET-directed combination can restore disease control specifically in tumors that have escaped EGFR blockade through this one, biomarker-identifiable mechanism, rather than across the resistant population as a whole [23]. This biomarker-restricted design is a meaningfully different evidentiary standard than the all-comers randomized trials discussed elsewhere in this article, and it reflects the field's growing recognition that "post-osimertinib progression" is not a single clinical entity but a collection of distinct resistance mechanisms, each of which may call for a different rescue combination rather than a single default next-line regimen.

Beyond amivantamab- and MET-targeted combinations, the post-progression setting has also produced a genuinely new drug class: antibody-drug conjugates directed against targets expressed broadly across EGFR-mutated tumors rather than against the resistance mechanism specifically. Patritumab deruxtecan, an antibody-drug conjugate targeting HER3, was evaluated in the HERTHENA-Lung01 trial in patients previously treated with an EGFR TKI and platinum-based chemotherapy, reporting a confirmed objective response rate of 29.8% and a median PFS of 5.5 months in this heavily pretreated population [24]. We note this result as a genuine and independently confirmed efficacy signal in a difficult-to-treat population, while flagging that HERTHENA-Lung01 was a single-arm phase 2 trial rather than a randomized comparison against an active control, so its reported numbers describe activity rather than comparative efficacy against a specific alternative in the way the randomized trials discussed elsewhere in this article do; the subsequent confirmatory phase 3 program for this specific agent did not lead to regulatory approval, underscoring how a promising single-arm activity signal in this setting does not always translate into a confirmed comparative advantage.

Finally, amivantamab plus lazertinib has itself been tested directly in the specific population of patients whose disease progressed on osimertinib monotherapy, independent of the MARIPOSA-2 chemotherapy-backbone comparison described above; an early-phase trial in this osimertinib-relapsed population reported meaningful objective response and disease-control activity for the doublet without a chemotherapy backbone, providing an additional, chemotherapy-sparing option under investigation for at least some patients in this setting, alongside the chemotherapy-containing MARIPOSA-2 regimens [16]. Together with amivantamab's separate, single-agent role in MET exon 14 skipping-mutated NSCLC established in the CHRYSALIS study, this body of work illustrates how a single bispecific antibody has accumulated several distinct, evidence-supported roles across the EGFR-mutant and MET-altered treatment landscape depending on the specific molecular and clinical context in which it is deployed [15].

6. Comparative Efficacy Across Pivotal Trials

Table 1 places the pivotal randomized trials discussed in this article side by side, and Figure 1 plots the median PFS reported for the experimental (combination or next-generation-monotherapy) arm against its

comparator arm across the same set of trials. Three patterns are worth drawing out explicitly from this side-by-side view, beyond what any single trial result communicates in isolation.

Table 1: Pivotal randomized trials of targeted-therapy combinations and next-generation monotherapies in advanced lung adenocarcinoma, with reported median progression-free survival (PFS) and hazard ratios (HR) for the experimental arm versus comparator.

Trial	Regimen vs. Comparator (driver, line of therapy)	Median PFS, months (experimental vs. comparator)	Hazard Ratio (result)
FLAURA 2	Osimertinib+chemotherapy vs. osimertinib (EGFR-mutant, 1st line) [10]	25.5 vs. 16.7	0.62 (positive)
MARIPOSA	Amivantamab+lazertinib vs. osimertinib (EGFR-mutant, 1st line) [14]	23.7 vs. 16.6	0.70 (positive)
MARIPOSA-2	Amivantamab+chemo±lazertinib vs. chemo (EGFR-mutant, post-osimertinib) [11]	8.3 / 6.3 vs. 4.2	0.44 / 0.48 (positive)
PAPILLON	Amivantamab+chemotherapy vs. chemotherapy (EGFR exon20ins, 1st line) [12]	11.4 vs. 6.7	0.40 (positive)
ALTA-1L	Brigatinib vs. crizotinib (ALK-positive, 1st line) [18]	24.0 vs. 11.0	0.49 (positive)
CROWN	Lorlatinib vs. crizotinib (ALK-positive, 1st line) [19]	not reached vs. 9.3	0.28 (positive)
KRYSTAL-12	Adagrasib vs. docetaxel (KRAS G12C-mutant, pretreated) [22]	5.5 vs. 3.8	0.58 (positive)
CodeBreaK 200	Sotorasib vs. docetaxel (KRAS G12C-mutant, pretreated) [20]	5.6 vs. 4.5	0.66 (positive)
WJOG9717L	Osimertinib+bevacizumab vs. osimertinib (EGFR-mutant, 1st line) [13]	22.1 vs. 20.2	0.86 (not significant)

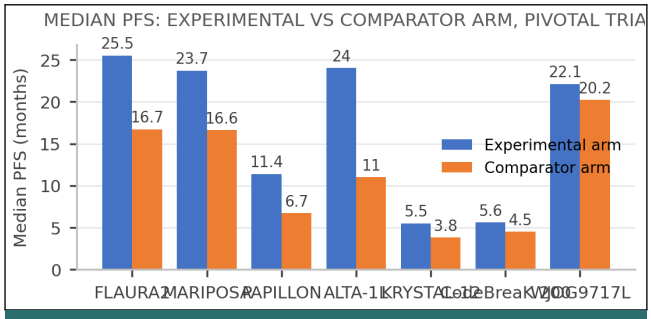

Figure 1: Median progression-free survival reported for the experimental (combination or next-generation-monotherapy) arm versus the comparator arm across seven pivotal randomized trials of targeted-therapy strategies in advanced lung adenocarcinoma. Lorlatinib's median PFS in CROWN had not been reached at the reported analysis and is omitted from this plot for that reason [10,14,12,18,22,20,13].

First, the magnitude of benefit varies considerably by driver and by combination type, and that variation tracks reasonably well with the underlying biological rationale for each specific combination rather than following any single general rule about combining being better than monotherapy. The largest relative risk reductions in the table belong to the ALK next-generation-TKI comparisons (CROWN's hazard ratio of 0.28, ALTA-1L's of 0.49), which are not combinations at all but next-generation-monotherapy-versus-earlier-generation-monotherapy comparisons; the EGFR first-line combination trials (FLAURA2, MARIPOSA) report intermediate hazard ratios in the 0.6-0.7 range against an already-effective osimertinib comparator; the KRAS G12C monotherapy-versus-chemotherapy comparisons (KRYSTAL-12, CodeBreaK 200) report more modest hazard ratios around 0.6, consistent with a real but smaller absolute benefit against a weak (docetaxel) comparator in a driver population that has historically had no effective targeted option at all; and the one first-line EGFR antiangiogenic combination in the table, WJOG9717L, reports a hazard ratio close to 1 that did not reach statistical significance. Reading these results as a single "combination therapy works" narrative would flatten out exactly the variation that a clinician or a trial designer most needs to see.

Second, the choice of comparator matters enormously to how any single hazard ratio or PFS gain should be interpreted, and the table is deliberately constructed to make the comparator explicit for each row rather than reporting hazard ratios in isolation. A hazard ratio of 0.62 against an osimertinib comparator (FLAURA2) reflects a much larger absolute clinical accomplishment than numerically similar hazard ratios against docetaxel (KRYSTAL-12, CodeBreaK 200), because osimertinib monotherapy is itself already a highly effective treatment relative to chemotherapy, so improving on it by a comparable relative margin implies a larger improvement over the pre-osimertinib standard of care than the same relative margin achieved against a comparator, like docetaxel, that was never a strong benchmark to begin with.

Third, WJOG9717L's null result is worth keeping squarely in view alongside the positive results, not as an outlier to be explained away but as a data point that shapes how confidently this article's synthesis can generalize. Every other first-line EGFR combination or

replacement strategy shown in the table succeeded against its comparator by a clear margin; the one antiangiogenic-combination trial did not. That asymmetry is itself informative: it suggests that the specific mechanism being added to an EGFR TKI backbone matters more than the general principle of "adding something," and it is a caution against assuming that any mechanistically plausible second agent will reproduce the FLAURA2 or MARIPOSA result simply by virtue of also being combined with an EGFR TKI.

7. Open Challenges

Several gaps recur across the trials synthesized in this article, and naming them plainly is more useful than letting the positive headline results obscure them. First, essentially none of the pivotal combination trials discussed here were designed to answer the question a treating oncologist increasingly faces: given two or more evidence-supported first-line options for the same driver (for EGFR-mutated disease specifically, osimertinib alone, osimertinib plus chemotherapy per FLAURA2, or amivantamab plus lazertinib per MARIPOSA), which should a specific patient receive, and on what biomarker or clinical basis should that choice be made? FLAURA2 and MARIPOSA were each compared only against osimertinib monotherapy, not against each other, so cross-trial comparisons of their reported hazard ratios -- while a common feature of conference presentations and review articles, including implicitly in the table above -- carry all the usual caveats of comparing results across separate randomized populations, eras, and statistical designs rather than a single head-to-head trial, and a genuinely comparative trial between these two combination strategies does not yet exist.

Second, the resistance-mechanism literature that motivates several of the post-progression combinations discussed in this article (MET-directed combinations for MET-amplified resistance, amivantamab-based regimens more broadly) is more advanced for identifying which mechanisms occur than for establishing which specific rescue combination is optimal once a given mechanism is identified; TATTON's molecularly selected design is closer to the standard the field should be moving toward than the norm, and much of the broader post-progression literature is still evaluated in all-comers populations that lump together patients whose resistance arose through quite different biological routes [23,8,9].

Third, toxicity and quality-of-life trade-offs are, in our reading, underweighted relative to PFS and OS hazard ratios in how this literature is typically summarized, including in the table above. FLAURA2's chemotherapy-added regimen and MARIPOSA-2's chemotherapy-containing arms carry materially more hematologic toxicity than TKI monotherapy; amivantamab-containing regimens carry a distinct toxicity profile dominated by infusion reactions, dermatologic adverse events, and venous thromboembolism risk that requires its own dedicated management pathway rather than being interchangeable, from a tolerability standpoint, with a chemotherapy-added regimen that reports a numerically similar hazard ratio. A synthesis organized purely around PFS and OS hazard ratios, as this article's comparative table necessarily is, risks implying that these regimens are more interchangeable than the patient experience of receiving them actually is.

Fourth, the ALK and KRAS G12C combination literature remains substantially less mature than the EGFR literature specifically with respect to genuine drug-drug combinations rather than next-generation-monotherapy comparisons or single-arm early-phase signals; whether adding a second agent to lorlatinib or brigatinib, or combining a KRAS G12C inhibitor with a second targeted agent, can reproduce the kind of incremental gain MARIPOSA-2 demonstrated for EGFR-mutant disease after osimertinib progression is, at the time of this synthesis, still an open empirical question rather than one the randomized evidence has answered either way.

Fifth, and more mundane but no less real: cross-trial comparison is hampered by inconsistent reporting of PFS by investigator assessment versus blinded independent central review, by different definitions of the analysis population (all-comers versus biomarker-selected), and by the simple fact that "docetaxel" and "osimertinib" are very different comparators to be improving upon, a point already raised above but worth repeating as a standing caution for any reader tempted to rank the trials in Table 1 by hazard ratio alone.

8. Conclusion

The randomized evidence synthesized in this article supports a specific and fairly disciplined claim: combining targeted agents, or replacing an effective

targeted monotherapy with a chemotherapy-free combination, has produced clear and clinically meaningful efficacy gains for several driver-specific strategies in advanced lung adenocarcinoma -- osimertinib plus chemotherapy and amivantamab plus lazertinib in first-line EGFR-mutated disease, amivantamab-containing regimens after osimertinib progression, amivantamab plus chemotherapy in EGFR exon 20 insertion-mutated disease, and next-generation ALK TKI monotherapy over earlier-generation ALK TKI monotherapy -- while other mechanistically plausible combinations, most notably osimertinib plus bevacizumab in the unselected first-line EGFR population, have not cleared their monotherapy comparator in randomized testing [10,14,11,12,18,19,13]. KRAS G12C-directed therapy, still the newest of the three drivers reviewed here, has established a real but comparatively modest advantage over chemotherapy for two independently developed inhibitors, a result that is consistent enough across sotorasib and adagrasib to be read as a genuine class effect rather than a trial-specific finding, even as it falls well short of the magnitude of benefit reported for EGFR- and ALK-targeted strategies [20,22].

What this body of evidence does not yet support is a confident, generalizable claim about which combination strategy is preferable for a given patient when more than one evidence-based option exists, because the pivotal trials were built to clear a monotherapy bar rather than to compare combination strategies against one another, and because toxicity and quality-of-life differences between regimens with numerically similar hazard ratios have received comparatively little head-to-head attention. Making further progress on comparative efficacy specifically, rather than simply adding new combinations to an already crowded landscape, will depend on trials designed explicitly to compare leading strategies against each other rather than each in isolation against a common monotherapy comparator, on biomarker-selected designs of the kind TATTON used for MET-amplified resistance rather than all-comers post-progression populations, and on an accounting of toxicity and patient-reported outcomes that carries as much weight in how these regimens are compared as the PFS and OS hazard ratios that have, to date, dominated the comparative-efficacy conversation in this disease.

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Ethical Approval

Not applicable. This article synthesizes previously published trial literature and did not involve new human participants, animal subjects, or the collection of primary data.

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