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The Butterfly Flies - Practice Changing Results of PAPILLON, First Line Chemotherapy and Amivantamab for the Treatment of NSCLC Patients with EGFR Exon 20 Insertions

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Abstract: Epidermal growth factor receptor (EGFR) exon 20 insertions are a rare subtype of EGFR mutations that do not respond to EGFR tyrosine kinase inhibitors developed for sensitizing mutations. In 2021, two drugs, amivantamab and mobocertinib each received FDA accelerated approval for second line use after platinum based therapy. These drugs were then brought to first line setting clinical trials; PAPILLON and EXCLAIM2. PAPILLON, which compared amivantamab plus chemotherapy to chemotherapy was positive, whereas EXCLAIM2, which compared mobocertinib to chemotherapy was negative. The PAPILLON regimen received subsequent FDA approval. In this commentary, we review the details of PAPILLON and also discuss why the rival trial, EXCLAIM2, may have failed.

Keywords: epidermal growth factor receptor, EGFR, first line therapy, targeted therapy, bispecific antibody, mobocertinib

Introduction

Completed in 2010, the phase 3 trial “First Line IRESSA™ Versus Carboplatin/Paclitaxel in Asia” (IRESSA Pan-Asia Study; IPASS) transformed the landscape of the treatment of not only lung cancer, but of oncology in general. IPASS showed that we can no longer depend only on clinical characteristics to select patients’ treatment regimens, but that molecular testing is imperative in selecting the best treatment regimen for targeted therapies for select gene mutations. Gefitinib showed to be an important therapy for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in patients who have never smoked or were light ex-smokers. It showed a benefit in progression free survival (PFS) in EGFR mutation positive tumors, demonstrating that EGFR mutation status was a strong predictive biomarker for the effect of gefitinib over carboplatin plus paclitaxel.¹ EGFR exon 20 insertions are the third most common EGFR mutations (following EGFR exon 19 deletion and 21 mutations), making up approximately 9.2% of EGFR mutations.²

Historically, compared to EGFR exon 19 deletion and 21 mutations, EGFR exon 20 insertions have proven to be difficult to treat. Amivantamab (a bispecific monoclonal antibody) and mobocertinib (a tyrosine kinase inhibitor) were the first two drugs targeting EGFR exon 20 insertions that were approved in the second line setting. In 2020, these two drugs were granted breakthrough therapy designation by the FDA, and amivantamab was the first EGFR 20 insertion targeted therapy to be granted accelerated FDA approval on May 21, 2021, followed by mobocertinib (TAK-788) being granted accelerated FDA approval on September 15, 2021.^{3,4} Two pivotal phase 3 trials have emerged, in order to assess these drugs in the first line in patients with NSCLC.

The first study, “A Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared With Carboplatin-Pemetrexed, in Participants With Advanced or Metastatic Non-Small Cell Lung Cancer Characterized by

Epidermal Growth Factor Receptor (EGFR) Exon 20 Insertions (PAPILLON)⁵, is an open label, phase 3 randomized controlled trial to compare the efficacy of amivantamab plus chemotherapy vs chemotherapy alone in participants with advanced or metastatic NSCLC with EGFR exon 20ins mutations which was recently presented at ESMO 2023 with a simultaneous publication in the *New England Journal of Medicine*. We here review the details of PAPILLON and also discuss why the rival trial, EXCLAIM2, may have failed.

Results from the PAPILLON Study

On July 17, 2023, Janssen announced that PAPILLON met its primary endpoint of PFS, which was statistically significant and clinically significant.⁵ At ESMO 2023, the results of this study were shared. A total of 308 patients were randomized in this study, with 153 randomized to the amivantamab and chemotherapy arm (151 ultimately receiving this) and 155 randomized to and receiving chemotherapy alone. The two arms were well-matched in a number of variables, including median age, sex, race, region of enrollment, body weight, ECOG performance status, history of smoking, time from initial diagnosis, time from metastatic diagnosis, histology type, and history of brain metastasis.

The primary endpoint was PFS by blinded independent central review (BICR). The median PFS (95% CI) was 11.4 months (9.8–13.7) in the amivantamab-chemotherapy arm, versus 6.7 months (5.6–7.3) in the chemotherapy alone arm. Disease assessments were conducted via computed tomography (CT) or magnetic resonance imaging (MRI), within 28 days after randomization, and then at six week intervals for the first 18 months, and then every 12 weeks thereafter. Amivantamab plus chemotherapy reduced the risk of progression or death by 60%. The PFS benefit held true across predefined subgroup analyses as well, including age, sex, race, weight, ECOG performance status (PS), smoking status, and history of brain metastases. Median time to response was 6.7 weeks (range 5.1–72.5) in the amivantamab-chemotherapy group, and 11.4 weeks (range 5.1–60.2) in the chemotherapy only group. An objective response was reported in 73% (95% CI, 65–80) of patients in the amivantamab-chemotherapy group, and 47% in the chemotherapy alone group (95% CI, 39–56). Median duration of response was 9.7 months (8.2–13.5) in the amivantamab-chemotherapy group, and 4.4 months (4.1–5.6) in the chemotherapy only group. In regard to PFS after first subsequent therapy, the amivantamab-chemotherapy group reduced the risk of second progression or death by over 50%. Interim OS at 14.9 month follow up was not estimable (NE) in the amivantamab-chemotherapy group, and 24.4 months (22.1-NE) in the chemotherapy only group. Although the majority of patients in both arms had at least one adverse event (AE), serious AEs including AEs leading to death were comparable between arms, and treatment-related discontinuation of amivantamab was low at 7%. EGFR and MET-related AEs were increased with amivantamab-chemotherapy and were mostly grades 1–2. Chemotherapy-associated hematologic and gastrointestinal (GI) toxicities were comparable, except for neutropenia which was more common in the amivantamab-chemotherapy arm.⁶

And on March 1, 2024, based on the above results from the PAPILLON study, the FDA announced its approval of amivantamab and chemotherapy (carboplatin and pemetrexed) for the first line treatment of locally advanced or metastatic NSCLC with EGFR exon 20 insertions, bringing a prior second line agent up to first line with chemotherapy.⁷ On the same day, amivantamab was granted traditional approval for the treatment of locally advanced or metastatic NSCLC with EGFR exon 20 insertions who have progressed on or after platinum based chemotherapy.⁷

Takeda's Unfortunate Announcement

On the other hand, the second study, “TAK-788 as First-Line Treatment Versus Platinum-Based Chemotherapy for Non-Small Cell Lung Cancer (NSCLC) With EGFR Exon 20 Insertion Mutations” (EXCLAIM 2), had been ongoing but did not have a similar fate. Similar to PAPILLON, EXCLAIM 2 was a first line study, an open label, phase 3 randomized controlled trial to compare the efficacy of TAK-788 (mobocertinib) vs chemotherapy in participants with advanced or metastatic NSCLC with EGFR Exon 20ins mutations.⁸ On July 31, 2023, Takeda announced that EXCLAIM 2 failed in its trial, and that the study was stopped early.⁹ On October 2, 2023, Takeda announced that it will be voluntarily withdrawing mobocertinib in the United States for adult patients with EGFR exon 20 insertion mutation positive patients with locally advanced or metastatic NSCLC whose disease has progressed on or before platinum-based chemotherapy. This decision was made due to the primary endpoint in this phase 3 trial not being met, therefore, not fulfilling the

requirements needed by the FDA for accelerated approval. Per press release, Takeda intends to also initiate voluntary withdrawal of this drug globally.⁹

Comparison of Study Design

PAPILLON and EXCLAIM 2 were studies trying to improve upon the first line treatment landscape for patients with NSCLC harboring EGFR exon 20 insertion and the participant number was roughly similar in both studies, with N = 308 and N = 354 in PAPILLON and EXCLAIM 2, respectively. Both studies were open label and randomized patients 1:1. In both studies, cross-over was allowed for those on the control arm who had progressed.

Perhaps the most profound difference between these studies was between the treatments given in the study arms. The treatment arms differed in that chemotherapy with pemetrexed and carboplatin was included in both study arms in PAPILLON, while the experimental (TAK-788) arm in EXCLAIM 2 did not include chemotherapy. The control arm in EXCLAIM 2 was also different in that it included pemetrexed and carboplatin or cisplatin. The primary outcome measure of both studies was progression free survival (PFS). A side-by-side comparison of the trial design can be found in Table 1.

Table 1 Study Characteristics

	PAPILLON ⁹	EXCLAIM 2 ¹⁰
Participant number	308	354
General eligibility	Adult, 18 years or older	Adult, 18 years or older
CNS eligibility	Excluded if untreated brain metastases or untreated spinal cord compression	Excluded if current spinal cord compression or leptomeningeal disease
Study design	Randomized, parallel assignment, open label	Randomized, parallel assignment, open label
Primary endpoint	PFS by BICR	PFS by BICR
Study arms	A: Amivantamab + Chemotherapy (Pemetrexed and Carboplatin) B: Chemotherapy alone (Pemetrexed and Carboplatin)	A: TAK-788 (Mobocertinib) B: Chemotherapy (Pemetrexed and Carboplatin OR Pemetrexed and Cisplatin)
Stratification factors	ECOG PS (0 or 1), history of brain metastases (yes or no), and prior EGFR TKI (yes or no)	Baseline CNS metastases (yes vs no) and race (Asian vs non-Asian)
Inclusion criteria	<ul style="list-style-type: none"> • Histologically or cytologically confirmed, locally advanced or metastatic NSCLC with EGFR Exon 20ins activating mutation. • Measurable disease according to (RECIST) v1.1. • ECOG 0 or 1. • Participant must agree to genetic characterization of tumor status through the required pretreatment tumor biopsy (or submission of equivalent archival material), as well as baseline and periodic blood samples for analysis of tumor mutations in the bloodstream. • A female participant of childbearing potential must have a negative serum or urine test at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study. 	<ul style="list-style-type: none"> • Histologically or cytologically confirmed, locally advanced or metastatic NSCLC with documented primary EGFR Exon 20ins activating mutation. • Measurable disease according to RECIST v1.1. • ECOG 0 or 1. • Participant must agree to genetic characterization of tumor status through the required pretreatment tumor biopsy (or submission of equivalent archival material), as well as baseline and periodic blood samples for analysis of tumor mutations in the bloodstream. • A female participant of childbearing potential must have a negative serum or urine test at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study.
Exclusion criteria	<ul style="list-style-type: none"> • Evidence of synchronous NSCLC disease (as suggested by genetic characterization or radiographic appearance). • Untreated brain metastases (a participant with definitively, locally treated metastases who is clinically stable, asymptomatic, and off corticosteroid treatment for at least 2 weeks prior to randomization is eligible). • History of spinal cord compression that has not been treated definitively with surgery or radiation. • History of interstitial lung disease (ILD), including drug-induced ILD, or radiation pneumonitis. • Contraindication to the use of carboplatin or pemetrexed. • Participant has a history of hypersensitivity to, or cannot take, vitamin B12 or folic acid. 	<ul style="list-style-type: none"> • Evidence of synchronous NSCLC disease (as suggested by genetic characterization or radiographic appearance). • Presence of leptomeningeal disease. • History of spinal cord compression that has not been treated definitively with surgery or radiation. • History of uncontrolled hypertension. • History of interstitial lung disease (ILD), including drug-induced ILD, or radiation pneumonitis. • Contraindication to the use of carboplatin or pemetrexed. • Participant has a history of hypersensitivity to, or cannot take, vitamin B12 or folic acid.

(Continued)

Table 1 (Continued).

	PAPILLON⁹	EXCLAIM 2¹⁰
Dosing	<p>Amivantamab: 1400 milligram (mg) IV (1750 mg IV infusion if weight is ≥ 80 kilograms) once weekly up to Cycle 2 Day 1, then 1750 mg IV (2100 mg IV if weight is ≥ 80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3.</p> <p>Pemetrexed: 500 per meter square mg/m^2 IV infusion (with vitamin supplementation) on Day 1 of each 21-day cycle and then as maintenance monotherapy</p> <p>Carboplatin: AUC 5 IV infusion for up to 4 cycles on Day 1 of each 21-day cycle.</p>	<p>TAK-788: 160 milligram (mg) with or without food, capsules, orally, once daily</p> <p>Pemetrexed: 500 mg per meter square (mg/m^2) once on Day 1 of each 21-day cycle repeated every 3 weeks for 4 cycles, followed by maintenance monotherapy on Day 1 of a 21-day cycle thereafter.</p> <p>Cisplatin: 75 mg/m^2, IV infusion, once on Day 1 of 21-day cycle every 3 weeks for 4 cycles</p> <p>Carboplatin: AUC 5 IV infusion once on Day 1 of each 21-day cycle every 3 weeks for 4 cycles</p>
Primary Outcome Measure	Progression-free survival (PFS) according to RECIST v1.1 up to 18 months	Progression-free survival (PFS) according to RECIST v1.1 up to 40 months
Study start date	October 13, 2020	January 10, 2020
Planned primary completion date	September 30, 2023	February 10, 2026
Planned study completion date	January 31, 2025	June 12, 2026

While these two trials both include different drugs targeted at EGFR Exon 20ins, these studies are fundamentally different, which is important to note. PAPILLON was a study that used amivantamab as an add-on to chemotherapy, without testing the drug alone against chemotherapy. Conversely, EXCLAIM2 assessed TAK-788 against chemotherapy alone. Perhaps this may have contributed to the difference in outcomes, as PAPILLON was a positive study, while EXCLAIM2 was negative. EGFR exon 20 insertions, considered a more treatment resistant molecular subtype compared to traditional sensitizing EGFR mutations, perhaps needing the synergy of chemotherapy in addition to EGFR inhibition. Amivantamab is an EGFR and mesenchymal-epithelial transition factor bispecific antibody that has multiple mechanisms of action. These include ligand blocking, receptor degradation and immune cell-directing activity, such as antibody-dependent cellular toxicity.¹⁰ The immune cell engagement of amivantamab may pose a plausible explanation as to why it works in synergy with chemotherapy, although the exact mechanisms for this effect is not yet well-understood. Together, these mechanisms may bypass the ligand-site resistance against tyrosine kinase inhibitors in patients who have NSCLC with EGFR exon 20 insertions.

Additional differences in the two studies were the stratification factors. While PAPILLON stratified patients for ECOG PS (0, 1), history of brain metastasis (yes, no) and prior EGFR TKI (yes, no), EXCLAIM-2 stratified patients based on baseline central nervous system (CNS) metastasis (yes, no) and race (Asian vs non-Asian). While the details of the patient characteristics from EXCLAIM 2 would need to be reviewed when it becomes available, it is possible that perhaps stratifying for ECOG PS was more important than race (Asian vs non-Asian). Patients with untreated brain metastases were additionally excluded from PAPILLON, while they may have been included in EXCLAIM 2, except for those with leptomeningeal disease. Amivantamab is a bi-specific monoclonal antibody with limited penetration to the CNS, and TAK-788 is thought to have poor CNS penetration due to its large molecular size.¹¹

What Went Wrong?

Reflecting on EXCLAIM-2, one must note that cisplatin, not only carboplatin was included in the chemotherapy regimen, which brings with it more severe toxicities that can lead to premature drug discontinuation. Even with this, out of 170 patients in the mobocertinib arm, 70 had dose interruptions and 45 had dose reductions, while in the chemotherapy arm, out of 163 patients, only six had dose interruptions and 20 had dose reductions. This speaks to the severity of intolerability of long term mobocertinib, and dose reduction appears to come with a decreased effect with this drug. This is further evidenced by the shortened time to deterioration in symptoms such as diarrhea (16.73 [10.21–27.41]) and appetite loss (1.90 [1.35–2.68]) in the mobocertinib arm when compared with chemotherapy. However, it is worth noting that although the PFS events (primary endpoint) and median PFS was similar between arms, the objective response rate (ORR) and duration of response (DOR) both favored mobocertinib,

with of ORR 75% (65–80) vs 47% (39–56) with chemo and DOR of 12.0 months (8.5–23.6) vs 8.4 (5.7–11.0) with chemo.¹² This speaks to the drug's activity although maintaining treatment at the active dose was challenging for many patients in the phase 3 setting given high rates of gastrointestinal toxicities. An additional potential pitfall of this study included the lack of central testing of EGFR ex20ins, which may be a contributing factor, as only local testing was conducted prior to randomization.

Concluding Thoughts

“Just living is not enough”, said the butterfly, “one must have sunshine, freedom, and a little flower”.

— Hans Christian Anderson, *The Complete Fairy Tales*

Moving forward, there is still more work needed to be done. The combination of chemotherapy and amivantamab is far from sunshine, freedom and flowers. As we intensify first line therapy, we must be cognizant of the increased inconveniences and toxicities that patients would need to deal with, for even a longer period of time as the PFS improves. Although the attempt failed, the oral therapy only regimen with mobocertinib had the potential to increase patient convenience and access to a profound extent, which was a benefit that it could have offered. Although clinical trials are ongoing to develop the subcutaneous version of amivantamab, as the PAVILLON regimen is combined with chemotherapy anyway, the benefit of the subcutaneous version is limited. Better strategies to manage toxicities is also something that would need immediate attention.

Furthermore, there are additional unmet needs, especially when it comes to patients with brain metastases. The incidence of developing brain metastases in patients with NSCLC and EGFR exon 20 insertions is not insignificant, and for example, in the Phase 1–2 study of mobocertinib, 35% of patients had brain metastases at baseline.¹³ New compounds such as CLN-081, a targeted oral therapy for patients with NSCLC and EGFR exon 20 insertion, which is currently recruiting patients in its phase 1 and 2 trial, as well as DZD9008, an oral EGFR inhibitor for patients with NSCLC and EGFR or HER2 mutations may offer new approaches to treating this patient population. These agents are being developed to improve on the safety profile as well as to provide oral therapy, a convenient option for patients.^{14–16} As the vast majority of the patients in this study were Asian and White, additional research will be needed in the future to investigate these drugs in minority populations such as in the Hispanic and Black populations. Lastly, long term follow-up, sequential therapy/PFS2 and ultimately overall survival will be important to assess in the coming months and years, as well as investigating the optimal sequence of therapies for patients with NSCLC and EGFR exon 20 insertions.

“We delight in the beauty of the butterfly, but rarely admit the changes it has gone through to achieve that beauty”. – Maya Angelou.

Disclosure

Dr Misako Nagasaka reports personal fees from AstraZeneca, Daiichi Sankyo, Novartis, EMD Serono, Pfizer, Lilly, Genentech, Regeneron, BMS, Caris Life Sciences, Takeda, Janssen, Blueprint Medicine, Mirati; non-financial support from AnHeart Therapeutics, outside the submitted work. The authors report no other conflicts of interest in this work.

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