

# Top 20 *EGFR*+ NSCLC Clinical and Translational Science Papers That Shaped the 20 Years Since the Discovery of Activating *EGFR* Mutations in NSCLC. An Editor-in-Chief Expert Panel Consensus Survey.

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**Abstract:** The year 2024 is the 20<sup>th</sup> anniversary of the discovery of activating epidermal growth factor receptor (*EGFR*) mutations in non-small cell lung cancer (NSCLC). Since then, tremendous advances have been made in the treatment of NSCLC based on this discovery. Some of these studies have led to seismic changes in the concept of oncology research and spurred treatment advances beyond NSCLC, leading to a current true era of precision oncology for all solid tumors. We now routinely molecularly profile all tumor types and even plasma samples of patients with NSCLC for multiple actionable driver mutations, independent of patient clinical characteristics nor is profiling limited to the advanced incurable stage. We are increasingly monitoring treatment responses and detecting resistance to targeted therapy by using plasma genotyping. Furthermore, we are now profiling early-stage NSCLC for appropriate adjuvant targeted treatment leading to an eventual potential “cure” in early-stage *EGFR*+ NSCLC which have societal implication on implementing lung cancer screening in never-smokers as most *EGFR*+ NSCLC patients are never-smokers. All these advances were unfathomable in 2004 when the five papers that described “discoveries” of activating *EGFR* mutations (*del19*, L858R, exon 20 insertions, and “uncommon” mutations) were published. To commemorate this 20<sup>th</sup> anniversary, we assembled a global panel of thoracic medical oncology experts to select the top 20 papers (publications or congress presentation) from the 20 years since this seminal discovery with December 31, 2023 as the cutoff date for inclusion of papers to be voted on. Papers ranked 21 to 30 were considered “honorable mention” and also annotated. Our objective is that these 30 papers with their annotations about their impact and even all the ranked papers will serve as “syllabus” for the education of future thoracic oncology trainees. Finally, we mentioned

potential practice-changing clinical trials to be reported. One of them, LAURA was published online on June 2, 2024 was not included in the list of papers to be voted on but will surely be highly ranked if this consensus survey is performed again on the 25<sup>th</sup> anniversary of the discovery *EGFR* mutations (i.e. top 25 papers on the 25 years since the discovery of activating *EGFR* mutations).

**Keywords:** *EGFR* mutations, expert panel, top 20 papers, 20th anniversary, NSCLC

## The Papers That Inaugurated the *EGFR* Era in NSCLC

In 2004, five papers described the identification of activating epidermal growth factor receptor (*EGFR*) mutations in non-small cell lung cancer.<sup>1–5</sup> The first two papers described exon 19 deletions and L858R mutations with some unique patient characteristics, such as predominance in never-smokers, females, and adenocarcinoma.<sup>1,2</sup> The third study included more patients and indicated that the proportion of patients with del19 to L858R was approximately 2:1.<sup>3</sup> The fourth and fifth papers further described the identification of exon 20 insertions after sequencing more NSCLC samples from Japan and Taiwan, respectively.<sup>4,5</sup> Little did we know these discoveries would lead to tremendous advances not only in the treatment of NSCLC but also for all solid tumors and push the paradigm of oncology treatment from a histological classification to a molecular classification. To commemorate the 20<sup>th</sup> anniversary of the discovery of *EGFR* mutations. We surveyed an expert panel to vote for the 20 most impactful *EGFR*+ NSCLC papers that have influenced the past and future direction of precision oncology in lung cancer and solid tumors since this seminal discovery.

## Objectives

1. Highlight important papers that shaped the history on the advancement in the treatment and understanding of the biology of *EGFR*+ NSCLC for the education of future thoracic oncologists.
2. Notable papers not ranked among the top 20 will also be described to provide further historical context.

## Methods

### Panel Members

The editor-in-chief sent invitations to panel members via e-mail with follow-up in-person discussions during international congresses and meetings to assemble a list of “candidate” manuscripts and invitations to vote and rank the most impactful 20 papers during the past 20 years. Consideration of panel membership is given to balancing the sex, practice locations, and length of practice of the panel members. A total of 21 members ranked the list of candidate papers individually and independently. The final panel consisted of 11 female members, nine practicing currently and primarily in Asia, five from Europe with Professor Garassino now practicing in the US, and seven from the US with Professor Lopes having previously practiced in Asia (Singapore) and South America (Brazil).

### Compilation of the List of “Candidate” Papers

The editor-in-chief compiled the first list of papers to be ranked. The initial list was circulated among the panel members individually via e-mail who provided independent recommendations for additional papers to be included. All recommended papers were included in the list of candidate papers. There was no limit to the number of candidate papers and congress presentations that are not yet published that could be included. All papers that received a vote were ranked. One of the objectives of the process is to generate a broad list of papers that future trainee in thoracic medical oncology should be familiar with not just the top 20–30 papers. Importantly, individual manuscript and not individual trial (eg, AURA3 which has at least 5 secondary publications) are considered. Thus, each panel member has to decide importances of PFS versus OS if both are positive from the same trial. A list of 87 publications or presentations was assembled for members to vote on (Table 1).

### Criteria for Individual Papers and Presentations to Be Included

1. Impact the treatment development and paradigm of medical oncology.
2. Impact the current treatment of *EGFR*+ NSCLC in both early- and advanced-stage disease.

**Table 1** Voting Results of the 87 Manuscripts Selected for Inclusion

#	Rank	Publications/Presentation (First author, Journal/Congress, Year)	PubMed ID	Anonymized Panel Members 1 to 21																					Total votes	Total Scores
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
1	1	IPASS (Mok, NEJM 2009)	19692680	1	1	1	1	1	20	2	1	1	1	1	1	1	1	5	1	1	3	1	1	21	394	
2	2	PAPILLON PFS benefit (Zhou, NEJM 2023)	37870976	8	10	7	6	7	5	16	5	16	6	13	8	15	7	14	7	13	10	9	3	20	235	
3	3	FLAURA OS benefit (Ramalingam, NEJM 2020)	31751012	7	2	2	5	4	4	4	3	2	2	4	3	4	4	2	4	8	8	8		19	318	
4	4	ADAURA OS benefit (Tsuboi, NEJM 2023)	37272535	2	4	3	2	3	1	1	2	4	3	5	4	3	5	4	2		4	16	19	19	295	
5	5	FLAURA-2 PFS benefit (Blanchard, NEJM 2023)	37937763	4	7	5	3	18	2	3	4	8	4	9	10	12	8	8	10	7	1		5	19	271	
6	6	MARIPOSA PFS benefit (Cho, NEJM 2024)	Reference# 33	5	8	4	4	15	3	18		9	5	10	6	13	9	5	10	11	9	6		18	228	
7	7	First report of acquired EGFR T790M mutation (Kobayashi, NEJM 2005)	15728811	19	5	16	12	5	12	12	9	5	11	2	12	2		14	9	4	19	10		18	198	
8	8	Small cell transformation as resistance to 1G EGFR TKI (Sequist, STM 2011)	21430269	10	11	11	15	9	14		10	17	14	6	13	20	6	19	13	5	12	11		18	162	
9	9	Afatinib for uncommon EGFR mutations (Yang, TLO 2015)	26051236	15		13		12	13	13	8	14	8	18		19	16	17	19	18	11	20	9	18	112	
10	10	AURA3 PFS benefit (Mok, NEJM 2017)	27959700	9	6	8	13		9	5	6	7	7	3	5	6	3	2	12		19	10		17	227	
11	11	MARIPOSA-2 PFS benefit (Passaro, Ann Oncol 2023)	37879444	6	9	6	7		6	17		10		11	7	14	10	6	9	12	17	7	8	17	197	
12	12	Classification of EGFR PACC mutations (Rochibaux, Nature 2021)	34526717	12		14	17		10	14	7	11	13	14	14	11		16	19	6	2	18	9	17	150	
13	13	EGFR mutations and air pollution (Hill ... Swinton, Nature 2023)	37020004	3	14		9	11	8	20		20		12	11	5	2	17	3		5		4	15	171	
14	14	Structural-functional characterization of EGFR ex20ins mutations (Yasuda, STM 2013)	24353160	18		12	18	16		11			12	15		9	20	11	18	8	5	18		14	106	
15	15	Anti-PD-1 monotherapy in PD-L1+ EGFR+ NSCLC (Lisberg, JTO 2018)	29874546	14		17	19	17		7	19	12	16			15		15	17	20	14			13	71	
16	16	Gene fusions as resistance to EGFR TKIs (Kobayashi, Nat Comm 2022)	36153311	13		15	14		11	6				8				20	7		13			9	82	

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Table I (Continued).

#	Rank	Publications/Presentation (First author, Journal/Congress, Year)	PubMed ID	Anonymized Panel Members 1 to 21																					Total votes	Total Scores
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
17	17	First report of acquired <i>EGFR</i> C797S mutation (Thress, Nat Med 2015)	25939061			10		6			15	18	17			8						11	15	9	69	
18	18	Discovery of germline intronic <i>BIM</i> deletion polymorphism negatively modulates EGFR TKI response (Ng, Nat Med 2012)	22426421	11					18	15				7		17	19			6		12		8	61	
19	19	CAURAL (Osimertinib + durvalumab vs Osimertinib) ILD from TKI + IO (Yang, JTO 2019)	30763730	20		18	20		19	8				19	15							15		8	34	
20	20	FLAURA PFS benefit (Soria, NEJM 2018)	29151359					2				3	9				3	1		2		7		7	120	
21	21	ADAURA DFS benefit (Wu, NEJM 2020)	32955177								12	6	10					4	3		3		15		7	94
22	22	FLAURA CNS efficacy (Reungwetwattana, JCO 2018)	30153097		3			10			11									16	14		6	7	7	80
23	23	FLAURA and AURA3 3-week ctDNA dynamics (Gray, CCR 2023)	37379430	17			16	8	15	10						11						17		7	53	
24	24	AURA phase I (multi-cohort expansion, pre-date FDA Optimus project) (Jänne, NEJM 2015)	25923549										18					12	10		13		4	18	6	51
25	25	FLAURA subgroup analysis: Osimertinib response by PD-L1 expression (Brown, JTO 2020)	31605792	16				13		9				16						20		16		6	36	
26	26	HERTHENA-Lung01 (Yu, JCO 2023)	37689979			19	11					19					17	7						5	31	
27	27	BR.21 OS benefit (Shepherd, NEJM 2005)	16014882		16						17			20		7							20	5	25	
28	28	First report of <i>EGFR</i> exon 20 insertion mutations (Kosaka, CR 2004)	15604253					19	16										11	16			17	5	22	
29	29	Keynote-789 no PFS benefit (Yang, ASCO 2023)	Reference# 75					20					19			14	18		15					5	19	
30	30	Osimertinib toxicity post IO (Schoenfeld, Ann Oncol 2019)	30847464								13		15						16					2	4	38
31	31	IMPRESS negative PFS benefit (Soria, TLO 2015)	26159065		12											18			10				10	4	34	

32	32	ISEL negative OS benefit (Thatcher, Lancet 2005)	16257339		15						16			9					17	4	27
33	33	Patritumab in resistant EGFR mutations (Jänne, Cancer Dis 2022)	34548309										17	16		17	14			4	20
34	34	EURTAC (Rosell, TLO 2012)	22285168											10		6			2	3	45
35	35	ARCHER1050 OS benefit (Mok, JCO 2018)	29864379		13		15											14		3	22
36	36	IMpower150 retro OS benefit in EGFR+ NSCLC (Reck, TLRM 2019)	30922878						18	13					12					3	20
37	37	LASER301 PFS benefit (Cho, JCO 2023)	37379502		18			7												2	17
38	38	LUX-Lung 3 PFS benefit (Sequist, JCO 2013)	23816960						14										12	2	16
39	39	Tata Memorial Hospital chemo + gefitinib OS benefit (Voronha, JCO)	31411950						19						8					2	15
40	40	FLAURA-2 CNS efficacy (Jänne, JCO 2023)	38042525		19		8													2	15
41	41	NEJ009 1 <sup>st</sup> OS benefit (Hosomi, JCO 2020)	31682542			20									9					2	13
42	42	ORIENT-31 quad regimen PFS benefit first report (Lu, TLO 2022)	35908558				14		20											2	8
43	43	EXCLAIM mobocertinib ORR benefit (Zhou, JAMA Oncol 2021)	34647988												15				19	2	8
44	44	Chrysalis-I: amivantamab in EGFR exon 20 insertion with mutation site dependent response (Park, JCO 2021)	34339292							15	20									2	7
45	45	Chrysalis cohort H-amivantamab + lazertinib (Cho, Nat Med 2023)	37710001					17							18					2	7
46	46	NEJ002 PFS benefit (Maemondo, NEJM 2010)	20573926											2						1	19
47	47	AURA3 ctDNA analysis (Papadimitrakopoulou, Cancer 2020)	31769875																5	1	16
48	48	TAILOR (erlotinib vs docetaxel) (Garassino, TLO, 2013)	23883922																6	1	15
49	49	RELAY gefitinib + ramucirumab (Nagakawa, JCO 2019)	31591063			9														1	12

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Table I (Continued).

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				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
50	50	TALENT (Gatzemeier, JCO 2007)	17442998				10																	1	11	
51	51	IFUM-part of gefitinib "reapproved package" in US (Douillard, BJC 2014)	24263064																					11	1	10
52	52	Pozotinib impact of location of EGFRex20ins mutations (Elamin; Cancer Cell 2022)	35820397																					12	1	9
53	53	EXCLAIM-2 (Pasi, ESMO Asia 2023)	Ref#24																					13	1	8
54	53	Checkmate-722(Mok, ESMO Asia 2022)	Reference# 74													13									1	8
55	53	LUX-Lung 6 (Wu, TLO 2014)	24,439929																				13	1	8	
56	53	Rociletinib phase I (Sequist, NEJM 2015)	25923550														13								1	8
57	54	NEJ009 2 <sup>nd</sup> OS "lost" (Miyachi, JCO 2022)	35960896																					16	1	5
58	55	FASTACT-2 ctDNA (Mok, CCR 2015)	25829397		17																				1	4
59	56	IMpower151 (Zhou, WCLC 2023) (NCT04194203)	Reference #64														20								1	1
60		EGFR exon 19 insertions (He, CCR 2012)	22190593																							
61		"Jackman criteria" for EGFR TKI progression (Jackman, JCO 2010)	9949011																							
62		First-SIGNAL PFS benefit (Han, JCO 2012)	22370314																							
63		WJTOG3405 PFS benefit (Mitsudomi, TLO 2010)	20022809																							
64		ENSURE PFS benefit (1G EGFR TKI approval in China) (Wu, Ann Oncol 2015)	26105600																							
65		EVIDENCE PFS benefit (Icotinib 1L approval in China) (He, TLRM 2021)	34280355																							

66	ADJUVANT translational (RB mutation poor prognostic) (Liu, Nat Comm 2021)	34750392																		
67	IPASS pos-hoc BICR-PFS benefit got gefitinib "re-approved" in US (Wu, Lung Cancer 2017)	28212993																		
68	ASPIRATION (Park, JAMA Oncol 2016)	26720423																		
69	AURA3 T790M subclonal analysis (Vaclova, Nat Comm 2021)	33741979																		
70	TIGER-3 (Yang, JTO-CRR 2020)	34589984																		
71	AURA leptomeningeal efficacy (Ahn, JTO 2020)	31887431																		
72	ISTANA (gefitinib vs docetaxel) (Lee, CCR 2010)	20145166																		
73	ATLAS PFS benefit (Ahn, JCO 2023)	37861993																		
74	ACHILLES/TORG1834 PFS benefit (Miura, ESMO 2023)	Reference# 53																		
75	INTEREST negative PFS benefit (gefitinib vs. docetaxel) (Kim, Lancet 2008)	19027483																		
76	DELTA (erlotinib vs. docetaxel) (Kawaguchi, JCO 2014)	24841974																		
77	V15-32 (gefitinib vs. docetaxel) (Maruyama, JCO 2008)	18779611																		
78	INTACT-1 negative OS benefit (Giaccone, JCO 2004)	14990632																		
79	INTACT-2 negative OS benefit (Herbst, JCO 2004)	14990633																		
80	TRIBUTE negative OS benefit (Herbst, JCO 2005)	16043829																		

(Continued)

Table I (Continued).

#	Rank	Publications/Presentation (First author, Journal/Congress, Year)	PubMed ID	Anonymized Panel Members 1 to 21																					Total votes	Total Scores	
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21			
81		ORIENT-31 2 <sup>nd</sup> PFS update (Lu, TLRM 2023)	37156249																								
82		FASTACT-2 PFS benefit (Wu, TLO 2013)	23782814																								
83		AENEAS PFS benefit aumolertinib phase 3 leading to China approval (Lu, JCO 2022)	35580297																								
84		FURLONG PFS benefit furmonertinib phase 3 leading to China approval (Shi, TLO 2022)	35662408																								
85		Befotertinib versus icotinib phase 3 PFS benefit leading to China approval (Lu, TLRM 2023)	37244266																								
86		AURA3 negative OS benefit (Papadimitrakopoulou, Ann Oncol 2020)	32861806																								
87		ADAURA PFS update (Herbst, JCO 2023)	36720083																								

**Abbreviations:** Ann Oncol, Annals of Oncology; BJC, British Journal of Cancer; Cancer Disv, Cancer Discovery; CR, Cancer Research; CCR, Clinical Cancer Research; ESMO, European Society of Medical Oncology ; JAMA Oncol, JAMA Oncology; JCO, Journal of Clinical Oncology; JTO, Journal of Thoracic Oncology; JTO-CRR, JTO Clinical Research & Reports; Nat Comm, Nature Communications; Nat Med, Nature Medicine; NEJM, New England Journal of Medicine; STM, Science Translational Medicine; TLO, The Lancet Oncology; TLRM, The Lancet Respiratory Medicine; WCCLC, World Conference of Lung Cancer.



3. Impact the development of basic and translational science of *EGFR*+ NSCLC.
4. Trial results that led to a drug approved in major countries are considered even if the approved drug is no longer part of standard of care.
5. Recommendations from panel members.
6. Not limited to canonical *EGFR* mutations (del19 or L858R).

## Exclusion

1. The original *EGFR* mutations discovery papers were excluded as we are selecting the papers after the seminal discovery. The 5 papers were cited in the introduction section.
2. No meta-analysis.
3. No review.
4. No consensus treatment guidelines.
5. Article chosen based on individual paper not individual trial as one trial can and usually generate multiple secondary publications.

## Ranking Method

Each panel member was contacted individually by the editor-in-chief for the list of 87 papers to rank. Each panel member returned the ranking individually and independent of other panel members. Papers were ranked by the total number of votes received and ranked from 1 to 20 with the highest total votes ranked first. Additionally, each top rank receives 20 points and decreases by one point with each decreasing rank. The total number of points per paper/presentation is an arithmetic sum calculated based on the number of aggregate points of each vote. If two or more papers received the same number of votes, the higher the aggregate points, the higher is the paper/presentation ranked. If two papers received the same number of votes and aggregate points, then the paper that has the highest rank vote is higher. If two more papers received the same number of votes, same aggregate points and same ranks then they are tied.

## Results

The anonymized voting results by the 21 panel members ranked by total number of votes, and aggregate points are presented [Table 1](#). Altogether, 59 manuscripts received at least one vote. Two papers received identical number of votes (2) and aggregate scores (15), and one was ranked higher (#39), because it received an 8<sup>th</sup> rank as the highest ranked vote rather than a 9<sup>th</sup> ranked vote as the highest rank vote for the other manuscript (#40). Four papers received one 13<sup>th</sup> rank vote, we did not further provide tiebreaker, and all 4 were ranked 53<sup>rd</sup>.

### Top 20 Most Influential Papers by Vote

#### No. 1. IPASS (Mok et al, NEJM 2009, PMID: 19692680) (21 Votes Out of 21 Voting Members, 394 Points)

Not surprisingly, the IPASS gathered the most number 1 votes and was the only paper that all panel members voted for, albeit with different ranks.<sup>6</sup> During the initial stage design of IPASS, knowledge about enriching for canonical *EGFR* mutations was purely based on clinical characteristics such as enriched among Asians, female, never-smokers, and patients with adenocarcinoma histology.<sup>7</sup> Clinical characteristic criteria were used to select patients for EGFR TKI treatment that was more beneficial from EGFR TKI when both gefitinib and erlotinib were initially approved, given the low overall response rate in unselected NSCLC patient populations leading to the initial approval.<sup>8–10</sup> The IPASS trial was designed to enrich for patient characteristics that would respond best to EGFR TKI and compared to gefitinib, one of the two first-generation (1G) EGFR TKI approved then to the standard of care carboplatin paclitaxel chemotherapy in a 1:1 randomization schedule with a non-inferiority statistical design. Tumor tissues were collected prospectively and analyzed for *EGFR* mutations retrospectively. The results of the IPASS indicated that even with very stringent clinical selection criteria, conducted in Asia, only enrolling adenocarcinoma histology and never-smoker/light former smokers; only approximately 50% of the samples tested positive for *EGFR* mutations. Those patients with tumors harboring *EGFR*

mutations benefited from EGFR TKI (median progression-free survival [PFS] = 9.6 months) versus chemotherapy (median PFS = 6.3 months) (hazard ratio [HR] = 0.48; 95% confidence interval [CI]: 0.36–0.64;  $P < 0.001$ ), while those patients without *EGFR* mutations had a relatively short median progression-free survival of 1.6 months from gefitinib versus 5.5 months from chemotherapy (HR = 2.85; 95%CI: 2.05–3.98;  $P < 0.001$ ). These results completely changed the mindset of oncologists in that identifying *EGFR* mutations molecularly was the optimal approach to use EGFR TKI. Otherwise, even using patient characteristics would only identify *EGFR* mutations half the time. This has led initially a few academic laboratories to offer a single *EGFR* gene mutation test using reverse transcription-polymerase chain reaction (RT-PCR) (as they owned the patent for detecting *EGFR* mutations) to now currently comprehensive molecular profiling with both DNA and RNA next-generation sequencing (NGS) are routinely offered by commercial laboratories. Fifty percent of patients who were primarily female, never-smokers with adenocarcinoma histology but did not harbor *EGFR* mutations puzzled thoracic oncologists for a few years until the discovery of anaplastic lymphoma kinase (ALK) and *ROS1* fusions in NSCLC,<sup>11,12</sup> followed by *RET* fusions.<sup>13–16</sup> Since then discovery of a few more actionable driver mutations in NSCLC patients (*HER2* exon 20 insertions, *BRAF* V600E, *MET* exon 14 splice site mutations, *KRAS* G12C), has led to molecular profiling being a necessary diagnostic step in the management of NSCLC.

A similar trial (First-SIGNAL) was conducted in Republic of Korea contemporaneously with IPASS and arrived at the same conclusion as IPASS.<sup>17</sup> Because there were fewer patients enrolled in the First-SIGNAL trial, the difference in the HR was not significant when analyzing the mutation status but importantly represented a supporting observation to IPASS.<sup>17</sup>

The IPASS also served as part of a registration trial for the “re-approval” of gefitinib in the US. Gefitinib was withdrawn officially on April 25, 2012 in the US (although access was severely limited since 2005) due to the failure of the ISEL trial to demonstrate improvement in overall survival (OS) when gefitinib was compared to placebo in the second line setting in unselected NSCLC.<sup>18</sup> A retrospective blinded independent central review (BICR) assessment of PFS in *EGFR*+ NSCLC patients enrolled into IPASS revealed a significant improvement in PFS among patients treated with gefitinib (N = 88) versus patients treated with chemotherapy (N = 98) (10.9 months versus 7.4 months respectively) (HR = 0.54; 95%CI: 0.38–0.79;  $P = 0.0012$ ).<sup>19</sup> Based on this BICR-assessed PFS in IPASS and the phase 4 single-arm IFUM study demonstrating gefitinib efficacy in European Caucasian *EGFR*+ NSCLC patients which is representative of the majority of US population (Caucasian),<sup>20</sup> gefitinib was “re-approved” as the first-line treatment for *EGFR*+ NSCLC in the US on July 13, 2015.<sup>21</sup>

## No. 2. PAPILLON PFS Benefit (Zhou et al, NEJM 2023, PMID: 37870976) (20 Votes Out of 21 Voting Members, 235 Points)

Although *EGFR* exon 20 insertion (*ex20ins*+) mutations were discovered in 2004 in the same year as canonical *EGFR* mutations,<sup>4,5</sup> only in 2021 did two drugs, amivantamab (bi-specific EGFR/MET antibody) and mobocertinib (EGFR TKI), receive US FDA accelerated approval based on ORR and duration of response (DOR) from two separate phase 2 studies, respectively.<sup>22,23</sup> However, the pivotal randomized phase 3 trial (EXCLAIM-2) comparing mobocertinib to platinum-based chemotherapy as first-line treatment for *EGFR**ex20ins*+ NSCLC patients showed that mobocertinib was not superior to platinum-based chemotherapy, with a numerically identical median PFS of 9.6 months (HR = 1.04; 95%CI: 0.77–1.39;  $P = 0.803$ ),<sup>24</sup> and mobocertinib was withdrawn globally.

The pivotal phase 3 trial (PAPILLON) for amivantamab in *EGFR* *ex20ins*+ NSCLC demonstrated that the addition of amivantamab to platinum-pemetrexed chemotherapy resulted in superior PFS compared to platinum-pemetrexed chemotherapy alone.<sup>25</sup> The median BICR-assessed PFS increased from 6.7 months in the chemotherapy arm (95%CI: 5.6–7.3) to 11.4 months (95%CI: 9.8–13.7) in the chemotherapy amivantamab combination arm (HR = 0.40; 95%CI: 0.30–0.53;  $P < 0.001$ ).<sup>25</sup> The success of PAPILLON represents the first landmark success in targeting *EGFR* *ex20ins*+ NSCLC since its discovery in 2004.

The failure of mobocertinib to prolong PFS over platinum-based chemotherapy represents a major disappointment, as the median PFS was similar at 9.3 months has not stopped the development of EGFR TKIs for *EGFR* *ex20ins*+ NSCLC. Another EGFR TKI, sunvozertinib, was developed in China and approved for *EGFR* *ex20ins*+ NSCLC in China

based on a single-arm study.<sup>26,27</sup> Other EGFR TKIs, such as furmonertinib<sup>28</sup> and zipalertinib (CLN-081/TAS6417)<sup>29</sup> have also been investigated for *EGFR ex20ins+* NSCLC. All currently developed EGFR TKIs are conducting first-line trials against platinum-pemetrexed chemotherapy, similar to the EXCLAIM-2 design. There is still considerable expectation that one of these trials will be positive and that *EGFR ex20ins+* NSCLC patients can be treated with an oral EGFR TKI rather than infusional chemotherapy and amivantamab. Hence, while PAPILLON received the second-highest number of votes indicating its significance as currently the only positive phase 3 trial in *EGFR exon20sin+* NSCLC, its aggregate point rank was only the fifth highest as many oncologists would prefer an oral pill and with many panel members' anticipation of eventual a positive trial with oral EGFR TKI versus chemotherapy.

### No. 3. FLAURA OS Benefit (Ramalingam et al, NEJM 2020, PMID: 31751012) (19 Votes Out of 21 Voting Members, 318 Points)

Both FLAURA OS<sup>30</sup> and FLAURA PFS<sup>31</sup> papers were voted into the top 20 list. The demonstration of an OS benefit from FLAURA despite crossover of 1G EGFR TKI to 3G EGFR TKI, essentially solidified the use of osimertinib (and other 3G EGFR TKIs) as first-line treatment for advanced *EGFR+* NSCLC. In the era of targeted therapies approved based on PFS, the achievement of OS is an important milestone. Hence, more panel members voted for FLAURA OS than FLAURA PFS results, as the OS convinced many health authorities to reimburse osimertinib. Furthermore, the achievement of OS benefit convinced many oncologists to continue osimertinib monotherapy rather than switching to FLAURA-2<sup>32</sup> or MARIPOSA<sup>33</sup> regimens that so far have only reported positive PFS data recently. Hence, while FLAURA OS has one fewer vote than PAPILLON, the overall aggregate point ranking was higher, as the panel members who voted for FLAURA OS ranked FLAURA OS's significance higher than PAPILLON PFS. Nonetheless, due to one fewer vote from the panel members for FLAURA OS, PAPILLON PFS was ranked higher in our ranking system.

### No. 4. ADAURA OS Benefit (Tsuboi et al, NEJM 2023, PMID: 37272535) (19 Votes Out of 21 Voting Members, 295 Points)

ADAURA compared 3 years of adjuvant osimertinib to placebo in patients with resected stage IB to IIIA *EGFR+* NSCLC. ADAURA first reported significantly improved PFS,<sup>34</sup> which led to the US FDA approval of 3 years of adjuvant osimertinib in early stage resected *EGFR+* NSCLC, regardless of whether adjuvant chemotherapy was given or not and for stage IB to IIIA resected disease.<sup>35</sup> Nonetheless, without OS benefit, the expense and side effects (even if minimum) of 3 years of osimertinib and the question of future further treatment at recurrence rather than adjuvant therapy remains a legitimate doubt of ADAURA when initially only PFS benefit data was achieved. The demonstration of OS benefit with 3 years of adjuvant osimertinib versus placebo (HR = 0.49; 95%CI: 0.34–0.70; P < 0.001) addressed the above concerns.<sup>36</sup> However, in a longer PFS follow-up, relapse occurred at a higher rate between 36 and 48 months than between 24 and 36 months in the osimertinib arm (osimertinib should have completed by 36 months), indicating that a longer duration of adjuvant osimertinib may be required to continue to suppress any residual *EGFR+* clones.<sup>37</sup> Currently, there is a single-arm study investigating the efficacy of 5-year adjuvant osimertinib in resected stage IB-III A *EGFR+* NSCLC (TARGET, NCT05526755).<sup>38</sup>

It is important to note that 71.4% of ADAURA patients were never-smokers,<sup>34</sup> and together with another top-20 paper, particulate matter (PM<sub>2.5</sub>) from air pollution can promote the growth of pre-existing *EGFR+* cells,<sup>39</sup> which raises an important question about the need for implementing low dose CT (LDCT) lung cancer screening in never-smokers, especially in Asian females.<sup>40</sup> Currently, we do not know how these early-stage *EGFR+* NSCLC patients were diagnosed and enrolled into ADAURA. Given that most lung cancers are diagnosed at an advanced stage based mostly on symptoms presentation, most patients in the ADAURA trial were likely diagnosed incidentally. With OS from ADAURA after 3 years of adjuvant osimertinib and with potential future data supporting a longer use of adjuvant osimertinib, a plan to implement LDCT lung cancer screening programs to screen Asian females should be considered in Asia and even globally, such as the Female Asian Nonsmokers Screening Study (FANSS) trial being conducted at New York University (NYU) (NCT05164757).

## No. 5. FLAURA-2 PFS Benefit (Jänne et al, NEJM 2023, PMID: 37937763) (19 Votes Out of 21 Voting Members, 271 Points)

FLAURA-2 was published in late 2023, immediately before the 20<sup>th</sup> anniversary of *EGFR* mutation discovery inclusion cutoff. Building upon FLAURA, FLAURA-2 compared the addition of platinum/pemetrexed chemotherapy to osimertinib versus osimertinib alone as first-line (1L) treatment for advanced *EGFR*+ (del19/L858R) NSCLC. The primary endpoint was investigator-assessed PFS. Stratification factors were Asian/Non-Asian, WHO performance status 0/1, and local/central *EGFR* mutation testing. Overall, the investigator-assessed median PFS increased from 16.7 months (95%CI: 14.1–21.3) in the osimertinib arm to 25.5 months (95%CI: 24.7 to not evaluable [NE]) in the osimertinib-chemo arm with an HR of 0.62 (95%CI: 0.49–0.79;  $P < 0.001$ ). Similarly, BICR-assessed PFS achieved the same HR of 0.62 (95%CI: 0.48–0.80,  $P < 0.001$ ) with 19.9 months (95%CI: 16.6–25.1) in the osimertinib compared to 29.4 months (95%CI: 25.1–NE) in the osimertinib + chemo arm. Importantly, patients with baseline brain metastasis the osimertinib + chemo arm achieved an HR of 0.47 over osimertinib alone with median PFS at 24.9 months from the combination arm when compared to 13.8 months from the osimertinib arm.<sup>32</sup>

Prior to the publication of the results, almost all thoracic oncologists expected the median PFS to be numerically longer in the osimertinib + chemotherapy arm than in the osimertinib alone arm. The unanswered question is the magnitude of the increase in the median PFS has to be over osimertinib monotherapy and the corresponding HR before oncologists are willing to consider, and patients are willing to receive concurrent chemotherapy and osimertinib that bring upon increase side effects, cost, time commitment by patients and their providers, healthcare resources, and health authorities to reimburse the combination regimen. Additionally, the recency of the PFS data and the lack of OS data currently further make adoption of the FLAURA-2 regimen a wait and see process in many regions of the world.<sup>41,42</sup>

## No. 6. MARIPOSA PFS Benefit (Cho et al, NEJM 2024, 18 Votes Out of 21 Voting Members, 228 Points)

MARIPOSA is another phase 3 trial that adopted a different treatment approach to build upon the success of FLAURA.<sup>33</sup> MARIPOSA compared lazertinib (a 3G *EGFR* TKI) with IV amivantamab to osimertinib monotherapy as first-line treatment for advanced *EGFR*+ NSCLC. The third arm was lazertinib monotherapy (as requested by the US FDA for a secondary comparison to osimertinib). The mechanism of action of amivantamab is postulated to be trogocytosis, which is different from chemotherapy, where optimal cytoreduction, especially against non-*EGFR*+ cancer cells, is given the tumor heterogeneity of *EGFR*+ NSCLC.<sup>43</sup> Patients were randomized 2:2:1 to the lazertinib + amivantamab, osimertinib, and lazertinib. The primary endpoint was the BICR-assessed PFS. Stratification factors were del19/L858R, brain metastasis (yes/no), and Asian/non-Asian. Lazertinib + amivantamab achieved a statistically significant improvement in median PFS compared to osimertinib or lazertinib monotherapy (23.7 months [19.1–27.7] versus 16.6 months [14.8–18.5]) with an HR of = 0.70 (95%CI: 0.58–0.85;  $P < 0.001$ ).<sup>44</sup> Notably, approximately 59% of the enrolled patients were Asians. Asian subgroup data were even better for the combination arm. The median PFS for the combination was 27.5 months (20.3–NE) versus 18.3 months (15.8–20.2) with an HR = 0.65 (95%CI: 0.50–0.83;  $P < 0.001$ ). A challenge to the wide adoption of lazertinib + amivantamab is the high incidence of grade 3 or higher adverse events; 37% of patients with venous thromboembolic events (VTE) (67%) were grade 2 requiring anti-coagulation. The rate of adverse events was similar among the Asian patients.<sup>44</sup>

As with FLAURA-2, we currently only have positive PFS benefit from MARIPOSA currently, and the need to include infusional medicine every 2 weeks in addition to oral pills may deter clinicians and patients. In addition, the numerical improvement in the median PFS was less than that in FLAURA-2. Nonetheless, these two studies re ranked next to each other on the list. Currently subcutaneous (SQ) form of delivery of amivantamab is being developed and may circumvent some of the adverse events of IV amivantamab such as infusion reaction and potentially lower the incidence rash while providing much better convenience to patients and clinicians and healthcare infra-structures.

### No. 7. First Report of Acquired *EGFR* T790M Mutation (Kobayashi et al, NEJM 2005, PMID: 15728811) (18 Votes Out of 21 Voting Members; 198 Points)

This historical paper was published in NEJM in 2005, approximately 9 months after the first report of the activating *EGFR* mutation was described as the first to describe the acquired *EGFR* T790M gatekeeper mutation from 1G *EGFR* TKI.<sup>45</sup> The *EGFR* T790M mutation is one of the most common on-target resistance mechanisms to 1G *EGFR* TKIs. The next 10 years or so since the discovery of the *EGFR* T790M mutation were dedicated to developing 2G and 3G *EGFR* TKIs to overcome this *EGFR* T790M mutation, culminating in the results of AURA3.<sup>46</sup> Given that 3G *EGFR* TKI monotherapy is the current standard of care for 1L treatment of advanced *EGFR*+ NSCLC, the incidence of *EGFR* T790M as an acquired on-target resistance will continue to dwindle and, in the next decade, may become a more historical footnote as it loses its clinical relevance.

### No. 8. Small Cell Transformation as Resistance to *EGFR* TKI (Sequist et al, Sci Transl Med 2011, PMID: 21430269) (18 Votes Out of 21 Voting Members; 162 Points)

This study is the first to describe small-cell transformation as a mechanism of resistance to *EGFR* TKI in *EGFR*+ NSCLC patients, in addition to other off-target resistance mechanisms.<sup>47</sup> Among the 37 patients analyzed, small cell transformation occurred in 5 (14%) patients, and 2 patients had epithelial–mesenchymal transition (EMT). Importantly, transformed small-cell histology is responsive to small-cell chemotherapy regimens. Linear plasticity was demonstrated, as the treated small-cell histology reverted to adenocarcinoma and was responsive to adenocarcinoma treatment. These findings were surprising at the time of publication. Subsequently, small-cell transformation has been found as resistance mechanisms to targeted therapy in other actionable driver mutations such as *ALK*+ NSCLC.<sup>48</sup> This study also reported *MET* amplification and *PIK3CA* as other off-target resistance mechanisms to *EGFR* TKI. *MET* amplification is a recurring off-target resistance mechanism in targeted therapy for NSCLC.<sup>49</sup> While the combination of *EGFR* TKI and *MET* TKI has been successfully used to treat acquired *MET* amplification,<sup>50</sup> very few published studies have demonstrated the combination of *EGFR* TKI and *PIK3CA* inhibitors with acquired *PIK3CA* mutations. As long as small cell transformation remains an recurring off-target resistance mechanism in TKI therapy in NSCLC, this translational paper will retain its importance with time.

### No. 9. Afatinib for *EGFR* “Uncommon” (G719X, S768I, L861Q) Mutations (Yang et al, Lancet Oncology 2015, PMID: 26051236) (18 Votes Out of 21 Voting Members; 112 Points)

This study was a retrospective analysis of three clinical trials (one single arm-LUX-Lung 2, two randomized trials of afatinib versus platinum-pemetrexed chemotherapy [LUX-Lung 3 and 6]) among the three “uncommon” *EGFR* mutations (G719X, S768I, and L861Q).<sup>51</sup> Among the 38 *EGFR*+ NSCLC patients with the three uncommon mutations (alone or in combination with other mutations), the BICR-assessed ORR was 71.1% (95%CI: 54.1–84.6), median PFS 10.7 months (95%CI: 5.6–14.7), and median overall survival was 19.4 months (95%CI: 16.4–26.9). Individuals carrying G719X, L861Q, and S768I mutations had ORRs of 78%, 56%, and 100%, respectively. The results were 13.8 months (95%CI: 6.8–NE), 8.2 months (95%CI: 4.5–16.6), and 14.7 months (95%CI: 2.6–NE), respectively, for the median PFS values. Based on the retrospective analysis data of 32 patients from this study, the BICR-assessed ORR was 66% (95% CI: 47–81), with a median DOR  $\geq$ 12 months of 52% and 33%  $\geq$ 18 months, respectively. On January 12, 2018, the US FDA approved afatinib for the treatment of these three uncommon *EGFR* mutations, with no limitations on prior therapy.<sup>52</sup> This is the first study to show these three “uncommon” *EGFR* mutations in NSCLC are actionable.

Notably, no randomized study was required by the US Food and FDA. At the European Society of Medical Oncology (ESMO) 2023 annual meeting a randomized trial (ACHILLES/TORG1834) conducted exclusively in Japan that compared afatinib 30 mg or 40 mg once daily to standard platinum/pemetrexed chemotherapy in NSCLC patients with “uncommon” *EGFR* mutations was presented.<sup>53</sup> ACHILLES randomized 68 patients who received afatinib and 34 who received chemotherapy. The median patient age was 71 years. The median PFS was 10.6 months for afatinib and 5.7 months for chemotherapy (HR = 0.422; P = 0.0007). The ORR was 61.4% for afatinib and 47.1% for chemotherapy. Importantly, the HR for the 40 mg starting dose of afatinib was 0.128 (95%CI: 0.050–0.327), while HR for the 30 mg



starting dose of afatinib was 0.704 (95%CI: 0.352–1.406). It is important to note that the median PFS of 10.6 months was essentially identical to the 10.7 months reported in a retrospective analysis. However, ACHILLES is at best a randomized phase 2 trial given the number of patients enrolled, but with four stratification factors, and is being conducted in a single country. Nonetheless, the efficacy of afatinib in treating “uncommon” *EGFR* mutations has remained one of the most important issues in the past 7 years until the presentation of ACHILLES/TORG1834.

### No. 10. AURA3 PFS Benefit (Mok et al, NEJM 2017, PMID: 27959700) (17 Votes Out of 21 Voting Members; 227 Points)

The AURA3 PFS improvement of osimertinib over platinum-based chemotherapy as second-line (2L) treatment of 1G *EGFR* TKI-refractory NSCLC patients that developed *EGFR* T790M+ represents the ultimate achievement of a decade quest to overcome the *EGFR* T790M mutation, given *EGFR* T790M mutation accounts for the dominant percentage of acquired resistance to 1G *EGFR* TKIs.<sup>46</sup> Despite the lack of OS benefit,<sup>54</sup> a convincing improvement in median PFS from 4.4 months with platinum/pemetrexed chemotherapy to 10.1 months with osimertinib with an HR of 0.30 (95%CI: 0.23-0.41; P < 0.001)<sup>46</sup> led health authorities in Asia to approve their home-grown 3G *EGFR* TKIs (lazertinib in the Republic of Korea, aumolertinib, furmonertinib, befotertinib, and rezivertinib in People’s Republic of China) based on their activity against *EGFR* T790M from large-scale phase 2 trials with benchmarking to the PFS from AURA.<sup>55–59</sup>

### No. 11. MARIPOSA-2 PFS Benefit (Passaro et al, Ann Oncol 2023, PMID: 37879444) (17 Votes Out of 21 Voting Members; 194 Points)

MARIPOSA-2 was the first randomized trial to compare treatment options after progression on 1L osimertinib treatment.<sup>60</sup> The patients were randomized 2:1:2 to receive platinum/pemetrexed (CP), amivantamab/platinum/pemetrexed (ACP), and lazertinib/amivantamab/platinum/pemetrexed (LACP). The primary endpoint was BICR-assessed median PFS and the comparison of LACP to CP primarily. With the addition of each agent, there was an incremental increase of approximate 2 months in the median PFS, with a BICR-assessed PFS of 8.3 months (95%CI: 6.8-9.1) for LACP. However, the challenge is that a very high incidence of grade 3 adverse events (92%) and high incidence of VTE led to modification of the treatment regimen with the addition of lazertinib/amivantamab after the completion of chemotherapy<sup>60</sup> and may deter or delay the adoption of the LACP regimen by many clinicians.<sup>61,62</sup> MARIPOSA-2 gave us the possibility of efficacious treatment post osimertinib (or by extension a 3G *EGFR* TKI), and how the regimens will be adopted depends on the future results of randomized trials using an antibody drug conjugate (eg, HER3-DXd from HERTHENA-Lung02 trial) or a different quad regimen (chemotherapy + immune checkpoint inhibitor + anti-angiogenic agent), such as ORIENT-31,<sup>63,64</sup> IMpower151,<sup>65</sup> and ATTLAS.<sup>66</sup> Given that IMpower150 is approved as a post-first- and second-generation *EGFR* TKI in Europe based on the OS benefit from a retrospective analysis,<sup>67</sup> it is important to compare the quad regimen of MARIPOSA-2 with the quad regimen of IMpower150, IMpower151, and ATTLAS.

### No. 12. EGFR PACC Structure-Based Classification of EGFR Mutations (Rochibaux et al, Nature 2021, PMID: 34526717) (17 Votes Out of 21 Voting Members; 150 Points)

The discovery of mutations in the *EGFR* kinase domain in NSCLC, known as “classical” mutations, has led to the development of *EGFR* TKIs and significantly improved patient survival. Although classical mutations account for approximately 70% of cases, the remaining 30% of “atypical” *EGFR* mutations have received less attention. Amivantamab (and previously mobocertinib) has received FDA approval for treatment of *EGFR* *ex20ins*+ NSCLC, marking a milestone in the subclassification of *EGFR* mutations. Other atypical *EGFR* mutations are heterogeneous outside the exon 20 insertions. This study used a structure/function-based approach to classify *EGFR* mutations into four major subgroups: classical, P-loop  $\alpha$ C-helix compressing (PACC), T790M-like and exon 20 insertions; Each group has different structural features and, therefore, is associated with sensitivity to different *EGFR* TKIs.<sup>68</sup> Many atypical mutations belonged to the PACC group, accounting for 13.7% of all the identified *EGFR* mutations. Interestingly, the common atypical mutations, G719X and S768I, belong to the PACC subgroup, whereas L861Q is a classical mutation.

Preclinical and retrospective clinical data indicate that PACC mutations are more sensitive to second-generation TKIs than to first- or third-generation TKIs; however, yet there is currently no TKI has been designed for the PACC population. This study established the classification and subgrouping of all EGFR kinase domain mutations, guiding both clinical practice and drug development over the next decade. The challenge is whether EGFR TKI development will be classified according to the PACC classification or the traditional FDA approval of “uncommon” mutations, including both PACC (G719X and S768I) and classical mutations (L861Q). Several editorials of Robichaux paper have been published to contextualize these findings.<sup>69,70</sup>

### No. 13. Air Pollution Particulate Matter (PM) Promotes *EGFR*+ NSCLC (PMID: 37020004) (Hill et al, Nature 2023, 15 Votes Out of 21 Voting Members; 171 Points)

This important translational publication demonstrated from several large country wide database that there is a positive correlation between particulate matter smaller than 2.5  $\mu\text{m}$  ( $\text{PM}_{2.5}$ ) and the incidence of lung cancer.<sup>39</sup> Importantly, only three years of exposure to high  $\text{PM}_{2.5}$  significantly increase the incidence of lung cancer.  $\text{PM}_{2.5}$  can promote the formation of *EGFR*+ lung cancer by expanding pre-existing *EGFR*+ cells rather than causing DNA damage. Most importantly, the authors demonstrated the presence of *EGFR* mutations in the normal lung tissue of patients without lung cancer. However, the most important question regarding the genesis of the initial *EGFR* mutations remains unknown. If  $\text{PM}_{2.5}$  can be shown to generate de novo *EGFR* mutations then the direct missing link between air pollution and *EGFR*+ NSCLC can be established.

### No. 14. Structural Function Relationship of *EGFR* Exon 20 Insertion (Yasuda et al, Sci Transl Med 2013, PMID: 24353160) (14 Votes Out of 21 Voting Members; 106 Points)

In 2013, this study examined how various *EGFR* exon 20 insertions affect the conformational changes of the kinase domain of the EGFR protein and shown with pre-clinical data that the first-generation EGFR TKI gefitinib and erlotinib were not able to inhibit most of them.<sup>71</sup> However, one specific *EGFR* exon 20 insertion (A763\_Y764insFQEA) responded well to the 1G EGFR TKI. Indeed, a recent summary of published case reports indicated that this specific mutation responded to 1G, 2G, and 3G EGFR TKIs.<sup>72</sup> This study aimed to develop alternative EGFR TKIs against *EGFR* exon 20 insertions and further improve the classification of all reported *EGFR* mutations, as published by Robichaux et al.<sup>68</sup> This paper provided the scientific basis that all *EGFR* exon20ins+ NSCLC may not be treated with the same TKI and that subdivision of *EGFR* exon20ins+ NSCLC in the alpha-helix, near-loop and far-loop subgroups may provide the optimal treatment strategy.

### No. 15. Anti-PD-1 Monotherapy in PD-L1+ *EGFR*+ NSCLC (Lisberg et al, J Thorac Oncol 2018, PMID: 29874546) (13 Votes Out of 21 Voting Members; 71 Points)

In this paper, Dr. Aaron Lisberg and the UCLA team conducted an investigator-initiated trial (IIT) investigating the activity of pembrolizumab in *EGFR*+ NSCLC with PD-L1 expression  $\geq 1\%$ .<sup>73</sup> The rationale is that monotherapy with pembrolizumab has demonstrated improved OS in both Keynote-024<sup>74</sup> and Keynote-042,<sup>75</sup> especially among PD-L1  $\geq 50\%$ . However, patients with both *EGFR*+ and *ALK*+ NSCLC has been excluded from all first-line immunotherapy trials for advanced NSCLC.

Despite the simplicity of the design of this hypothesis testing IIT, the results were illustrative. Among the seven patients with canonical *EGFR* mutations and PD-L1  $\geq 1\%$ , the ORR was 0%. Among the four patients with canonical activating *EGFR* mutation and PD-L1 expression level  $\geq 50\%$ , three were evaluable, and the ORR was 0%. Among the two patients with *EGFR* exon 20 insertion and PD-L1 expression level  $\geq 50\%$ , the ORR was 0%. Altogether, among the 8 evaluable patients with actionable *EGFR* mutations, the ORR of pembrolizumab was 0%. While this study is limited in patient number, this was the first study to demonstrate that immune checkpoint inhibitors alone have very limited efficacy, if any, in *EGFR*+ NSCLC, even if the PD-L1 expression is 50% or more. This observation was consistent with the lack of efficacy of immune checkpoint inhibitor chemotherapy combination trials in *EGFR*+ NSCLC in the Keynote-789<sup>76</sup> and Checkmate-722 trials.<sup>77</sup>

## No. 16. Gene Fusions as Variable Resistance Mechanisms to EGFR TKIs (Kobayashi et al, Nat Comm 2022, PMID: 36153311) (9 Votes Out of 21 Voting Members; 82 Points)

Although rare, actionable RTK fusions (*ALK*, *RET*, *ROSI*, *NTRK*, and *FGFR3*) have been reported to confer resistance to all three generations of EGFR TKIs.<sup>78</sup> Good clinical responses have been reported in combination with specific RTK and EGFR TKI.<sup>78</sup> Hence, this study by Kobayashi, Jänne, et al, although not novel, is the largest survey of genomic rearrangement or fusion as resistance to EGFR TKIs.<sup>79</sup> They confirmed that other rare fusions not commonly found in NSCLC, such as *ABLI*, *JAK2*, *FGFR2* and the intergenic fusion of *RET*, do not confer resistance to EGFR-TKIs. Indeed, some of these rearrangements, as detected by DNA hybrid capture, were not transcribed into RNA when sequenced by targeted RNA NGS. This study demonstrated the complexity of the coexisting genomic background of *EGFR*+ NSCLC and the need for comprehensive NGS (DNA + RNA) to detect both authentic on- and off-target resistance mechanisms to all generations of EGFR TKIs.

## No. 17. First Report of *EGFR* C797S Mutation (Thress et al, Nat Med 2015, PMID: 25939061) (9 Votes Out of 21 Voting Members; 69 Points)

Similar to the discovery of *EGFR* T790M acquired resistance mutation, the *EGFR* C797S mutation was an on-target resistance mutation to 3G covalent EGFR TKI and was first reported by Thress et al.<sup>80</sup> Covalent TKI requires the formation of a disulfide bond with their target protein usually through a cysteine amino acid residue. With the expansion of oncology knowledge, an acquired *EGFR* C797S mutation is expected to develop as part of an on-target resistance mechanism against covalent EGFR-TKIs. This is similar to the first-generation covalent BTK inhibitor for chronic lymphocytic leukemia (CLL) which *BTK* C481S was reported in 2014.<sup>81</sup> Given that the actual *EGFR* C797S mutation does not increase the activation potential of the founder *EGFR* mutation, 3G noncovalent reversible competitive EGFR TKIs must be developed. The current challenge is that the *EGFR* C797S mutation only accounts for approximately ~10–15% of the acquired resistance mechanism to osimertinib,<sup>82</sup> which limits the scope of drug development only specifically designed to target *EGFR* C797S if the pre-clinical potency of these investigational EGFR TKIs against canonical *EGFR* mutations (del19, L858R) are similar to osimertinib. This is because FLAURA-2,<sup>32</sup> MARIPOSA,<sup>33</sup> and MARIPOSA-2<sup>60</sup> results simultaneously move the standard of care for the first and second treatments of advanced *EGFR*+ NSCLC beyond just targeting *EGFR* C797S.

## No. 18. Discovery of Germline *BIM* (Bcl-2-Like 11) Intronic Deletion Polymorphism as Resistance to EGFR TKI (Ng et al, Nat Med 2012, PMID: 22426421) (8 Votes Out of 21 Voting Members; 61 Points)

Ng et al, identified a ~ 1000 basepair germline intronic deletion polymorphism in exon 2 of *BIM*.<sup>83</sup> *BIM* is a pro-apoptotic protein, and the inhibition of signal transduction in the presence of TKIs leads to cell death. This deletion polymorphism is primarily found in approximately 10–15% of Asians but may also be found in similar incidence in Hispanic patients.<sup>84</sup> The presence of this deletion in exon 2 led to differential splicing and incorporation of exon 3, rather than exon 4, into the mature messenger RNA of *BIM*. The BH3 domain that induces apoptosis is located in exon 4. Hence, *BIM* deletion polymorphism results in the differential splicing and translation of mRNA into a protein with a TKI-resistant phenotype.<sup>83</sup> It was originally identified by investigating the mechanisms of imatinib-resistant CML. In this seminal paper, retrospective analysis of the absence or presence of *BIM* intronic deletion polymorphism demonstrated *BIM* deletion polymorphism resulted in shortened PFS in *EGFR*+ NSCLC patients treated with gefitinib<sup>83</sup> and eventually other EGFR TKIs.<sup>83,85</sup> Importantly, *BIM* polymorphism also confers resistance to crizotinib in both *ALK*+ and *ROSI*+ NSCLC patients.<sup>86,87</sup> Combination therapy with osimertinib and either anti-angiogenic agents or chemotherapy may increase treatment efficacy in *EGFR*+ NSCLC patients harboring the genomic *BIM* intronic deletion polymorphism.<sup>88,89</sup> However combination therapy is known to increase the efficacy of most *EGFR*+ NSCLC treatments regardless, so the most effective way to treat *BIM*+/*EGFR*+ NSCLC remain unknown. Retrospective analysis of



FLAURA-2 and MARIPOSA data is important for determining the optimal treatment for *EGFR*+ NSCLC patients with an underlying germline intronic *BIM* deletion polymorphism.

### No. 19. CAURAL *EGFR* TKI + IO Toxicity in *EGFR* T790M+ NSCLC (Yang et al, *J Thorac Oncol* 2019, PMID: 30763730) (8 Votes Out of 21 Voting Members; 34 Points Total)

In the early days of immunotherapy, there was a rush to combine immune checkpoint inhibitors (ICIs) with chemotherapy and TKIs. This trial was initiated during a phase 1 study of durvalumab, an anti-PD-L1 monoclonal antibody combined with osimertinib (TATTON).<sup>90</sup> Interstitial lung disease (ILD) occurred in 35% of patients enrolled in TATTON.<sup>90</sup> CAURAL was discontinued based on the TATTON data after 29 patients were enrolled (15 with osimertinib monotherapy and 14 with osimertinib plus durvalumab). The ORR was 80% (95% CI: 52–96) among osimertinib-alone patients versus 64% (95% CI: 35–87) in the combination group. Confirmed progression was noted in 27% (4/15) and 29% (4/14) of the patients in the osimertinib alone and combination treatment arms, respectively. The treatment was 23.9 months in the osimertinib-alone arm versus 17.1 months in the combination arm. ILD incidence was noted in 3% (1/14) of the patients in combination.<sup>91</sup> Hence with limited number of patients enrolled, the addition of ICI to osimertinib did not seem to improve PFS compared to osimertinib alone. Furthermore despite being terminated early, CAURAL together with TATTON and the Lisberg et al paper, all pointed to the lack of efficacy of ICI in *EGFR*+ NSCLC with or without the combination osimertinib and contributed to the current treatment paradigm that no ICI and *EGFR* TKI combination.

### No. 20. FLAURA PFS Benefit (Soria et al, *NEJM* 2018 PMID: 29151359) (7 Votes Out of 21 Voting Members; 120 Points)

FLAURA PFS is the first report indicating the advantage of 3G *EGFR* TKI over 1G *EGFR* TKI in terms of significantly improved efficacy and much lower toxicity, and led to the US FDA approval of osimertinib in the 1L treatment of advanced *EGFR*+ NSCLC. The BICR-assessed median PFS improved from 9.7 months to 17.7 months with an HR of 0.45 (95%CI: 0.36–0.57;  $P < 0.001$ ).<sup>31</sup> Given the high cost (higher price per tablet and longer duration of treatment) of osimertinib at its initial approval and that the majority of acquired resistance is of the *EGFR* T790M mutation, many oncologists still advocated the sequential use of 1G and 3G *EGFR* TKI at the time of FLAURA PFS presentation without OS benefit. With the eventual OS benefit of FLAURA, many 3G *EGFR* TKIs developed in Asia have been approved as 1L treatments based on PFS benefits, including aumolertinib (AENEAS),<sup>92</sup> furmonertinib (FURLONG),<sup>93</sup> lazertinib (LASER301),<sup>94</sup> and befotertinib.<sup>95</sup>

## The Ten “Honorable Mention” Papers (21-30)

### No. 21. ADAURA DFS Benefit (Wu et al, *NEJM* 2020, PMID: 32955177) (7 Votes Out of 21 Voting Members, 94 Points)

As described in the ADAURA OS paper, the first publication of ADAURA disease-free survival (DFS) was positive, which led to US FDA approval of 3 years of adjuvant osimertinib for patients with resected stage IB to IIIA *EGFR*+ NSCLC.<sup>34</sup> The FDA approval had no stage restrictions and no mandate for the use of adjuvant chemotherapy.<sup>35</sup> A minority of the panel members recognized the important of being the first report of positive results hence their ranking of ADAURA DFS was high while the majority only ranked ADAURA OS and preserved their votes for other papers.

### No. 22. FLAURA Central Nervous System Efficacy (CNS) Activity (Reungwetwattana et al, *JCO* 2018, PMID: 30153097) (7 Votes Out of 21 Voting Members, 80 Points)

The design of the FLAURA trial required a baseline CNS scan, and patients with baseline CNS metastasis underwent regular follow-up surveillance CNS scans to assess their response and progression. However, in patients without baseline CNS metastasis, regular CNS imaging was not required in the FLAURA trial. Overall 61 and 67 patients had baseline CNS metastasis in the osimertinib and 1G *EGFR* TKI arms, respectively. The BICR-assessed intracranial-ORR (IC-ORR) was

66% (osimertinib) and 43% (1G EGFR TKIs) in patients with CNS lesions (odds ratio = 2.5; 95%CI: 1.2-5.2; P = 0.011). CNS objective response rates for measurable lesions were 91% (osimertinib) and 68% (1G EGFR TKI) in patients with > one measurable CNS lesion (odds ratio = 4.6; 95%CI: 0.9-34.9; P = 0.066).<sup>96</sup> Subgroup analysis confirmed the CNS activity of osimertinib. The design of FLAURA-2 was similar to that of FLAURA, with no requirement for regular imaging in patients without baseline CNS metastases. FLAURA-2 demonstrated that the addition of chemotherapy to osimertinib increased the IC-ORR compared with osimertinib alone.<sup>32,97</sup> A similar CNS subgroup analysis of FLAURA-2 did not receive any vote, likely because of the FLAURA-2 CNS data was published very close to the initial FLAURA-2 publication. Plus based on the initial FLAURA-2 results,<sup>32</sup> there is wide acceptance that patients with CNS metastasis would benefit from combination osimertinib and chemotherapy thus limiting the significance of this stand alone CNS metastasis efficacy study of FLAURA-2 at this time.<sup>97</sup>

### No. 23. FLAURA and AURA3 3-Week ctDNA Clearance (Gray, CCR 2023, PMID: 37379430) (7 Votes Out of 21 Voting Members, 53 Points)

This is a pooled analysis of the clearance of *EGFR*+ circulating tumor (ct) DNA from both FLAURA and AURA3 using the Cobas test, which showed that early clearance of *EGFR*+ ctDNA is an early marker of longer PFS, regardless of the treatment arm.<sup>98</sup> Previously, ctDNA analysis from AURA3<sup>99</sup> and FLAURA<sup>100</sup> confirmed that ctDNA is correlated with tumor burden, and *EGFR*+ ctDNA-negative cohort at the start of treatment had a longer PFS. Further AURA3 analysis also indicated that the allele frequency of the *EGFR* T790M alleles is important as “subclonal” T790M (< 30% fractional ctDNA) is associated *PIK3CA* mutations and shorter survival.<sup>101</sup> We embrace the era of plasma genotyping for prognostication, disease monitoring, and determination of acquired resistance. Gray et al represent one of the best examples on the use of plasma genotyping. Cobas plasma genotyping, which is based on reverse transcriptase-polymerase chain reaction (RT-PCR), is less sensitive than NGS. NGS can reliably detect other genomic alterations such as *TP53* mutations, *PIK3CA* mutations, gene fusions, and even *BIM* deletion polymorphisms that can provide granular information on the co-genomic alterations on individual *EGFR*+ NSCLC. We anticipate that the next few years we will see the novel use of plasma genotyping, especially regarding the contribution of *TP53* mutations and devising strategy to overcome co-occurring *TP53* mutations in *EGFR*+ NSCLC.

### No. 24. AURA Phase I (Jänne et al, NEJM 2015, PMID: 25923549) (6 Votes Out of 21 Voting Members, 51 Points)

This phase I trial demonstrated the initial success of targeting the *EGFR* T790M mutation with osimertinib, and the design of this phase I trial is a model for future phase I trial designs.<sup>102,103</sup> The goal of the US FDA Optimus project is to optimize the dosing of oral TKIs with a minimum biologically active dose rather than the maximum tolerated dose (MTD).<sup>104</sup> Osimertinib was administered at 20, 40, 80, 160, and 240 mg once daily and activity was observed at the lowest dose of 20 mg once daily. Hence dose expansion was able to be dosed at 20 mg upwards to allow assessment for both efficacy and safety. Eventually the recommended phase 2 dose (RP2D) was determined to be 80 mg once daily. However, 160 mg dose was also effective and well tolerated allowing osimertinib to be dosed at 160 mg once daily to potentially overcome CNS progression. Furthermore, no dose-limiting toxicity was observed at a dose of 240 mg once daily dose.<sup>102,103</sup> The inclusion of multiple patient groups including *EGFR* TKI-naïve advanced *EGFR*+ NSCLC patients in this phase I trial at 80 mg and 160 mg allowed the quick estimate of the best biologically active doses versus adverse events and preliminary activity of osimertinib in untreated advanced stage *EGFR*+ NSCLC patients.<sup>103</sup> These data provided the data necessary to quickly implement the 1L FLAURA trial. This phase I trial design was ahead of its time and served as an excellent guide for implementing the US Optimus Project. Despite not reaching a dose-limiting toxicity (DLT) dose, the ability to achieve clinical activity at the lowest dose allows the sponsor and investigators to assess the efficacy-toxicities at each level and allows the recommended RP2D of 80 mg once daily while providing the efficacy data to allow dose escalation in case of disease progression with ample efficacy-safety at a higher dose.<sup>102</sup>

### No. 25. FLAURA Osimertinib Activity Independent of PD-L1 Expression (Brown et al, J Thorac Oncol 2020, PMID: 31605792) (6 Votes Out of 21 Voting Members; 36 Points)

This is one of the less well-known retrospective analyses of the FLAURA trial, in which the efficacy of osimertinib and 1G EGFR TKI (gefitinib and erlotinib) was investigated based on the level of PD-L1 expression. There was no difference in ORR and DOR among osimertinib-treated patients regardless of PD-L1 expression status (unknown, non-expressors, or expressors).<sup>105</sup> The same observation was made in gefitinib- and erlotinib-treated patients. The limitation of this study is that the PD-L1 level was only known in approximately 20% of the patients in each arm. While this is “reverse” of the design of the Lisberg’s paper,<sup>72</sup> the results provided half of the rationale that PD-L1 expression level does not modulate efficacy of EGFR TKIs.

### No. 26. HERTHENA-Lung01 Phase 2 (Yu et al, J Clin Oncol 2023, PMID: 37689979) (5 Votes Out of 21 Voting Members, 31 Points)

This is a phase 2 study reporting the efficacy of an antibody–drug conjugate (ADC), patritumab deruxtecan (HER3-DXd), in *EGFR*+ NSCLC who progressed on EGFR TKI and chemotherapy. Overall, 93% (209/225) of the patients had received 3G EGFR, and 32.1% had CNS metastasis. The median PFS achieved by 209 3G EGFR TKI-experienced patients at 5.6 mg/kg was 5.5 months (95%CI: 5.1–6.4). The incidence of interstitial lung disease (ILD) was 5.3% among the 225 patients. The incidence was higher among patients who had prior immunotherapy, regardless of the timing of immunotherapy: none (3.9%), early use of IO (7.9%), and IO as the last treatment regimen prior to HER3-DXd (7.7%).<sup>106</sup>

A pivotal phase 3 trial comparing HER3-DXd versus platinum-based chemotherapy post-3G EGFR-TKI is being conducted (HERTHENA-Lung02).<sup>107</sup> If the outcome is positive, it will allow full regular approval of HER3-DXd as a treatment option for *EGFR*+ NSCLC patients who had progressed on a 3G EGFR TKI.

### No. 27. BR.21 OS Benefit (Shepherd et al, NEJM 2005, PMID: 16014882) (5 Votes Out of 21 Voting Members, 25 Points)

BR.21 is a randomized trial that led to the initial full approval for erlotinib in the US States. BR21 demonstrated the OS benefit of erlotinib over placebo in platinum chemotherapy-refractory unselected NSCLC patients.<sup>108</sup> In contrast, a similarly designed trial ISEL that compared gefitinib to placebo failed to show a statistical improvement in OS<sup>18</sup> and led to severe limitations in the use of gefitinib in the US and eventual withdrawal in 2012. Both trials were conducted prior to the knowledge of activating *EGFR* mutations. Based on the EURTAC trial,<sup>109</sup> erlotinib has been approved as the first-line treatment for advanced *EGFR*+ NSCLC. Eventually, erlotinib (alone or in combination with ramucirumab) was only approved for *EGFR*+ NSCLC patients, and its broad indication as second-line treatment for unselected NSCLC patients based on BR.21 was rescinded by the FDA based on the mechanism of action and target for 1G EGFR TKI.

### No. 28. First Report of *EGFR* Exon 20 Insertions (Kosaka et al, Cancer Res 2004, PMID: 1560425) (5 Votes Out of 21 Voting Members, 22 Points)

In the Introduction, we describe five papers that reported the discovery of activating *EGFR* mutations in NSCLC in 2004. Kosaka et al<sup>4</sup> and Huang et al<sup>5</sup> also reported *EGFR* exon 20 insertion mutations with simultaneous publications. However, Kosaka’s paper was more explicit in describing the deletions/insertions in exon 20 in their abstract, and Kosaka’s paper included more patients in their report. Hence it is important to succinctly describe the results in the results section of the abstract.

### No. 29. Keynote-789 Negative PFS Benefit (Yang et al, ASCO 2022, 5 Votes Out of 21 Voting Members, 19 Points)

As one of the lists of 20, Lisberg’s ICI monotherapy paper showed the lack of efficacy of ICI in PD-L1 expressing *EGFR*+ NSCLC. Checkmate-722<sup>75</sup> and Keynote-789<sup>76</sup> are two similarly designed randomized phase 3 trials that confirmed that the addition of ICI to chemotherapy in the post-EGFR TKI setting did not improve PFS over

chemotherapy alone. Median PFS was 5.6 months (95%CI: 5.5–5.8) for chemotherapy + pembrolizumab versus 5.5 months (95%CI: 5.4–5.6) for chemotherapy alone, with an HR of 0.80 (95%CI: 0.65–0.97) and a P-value of 0.0122.<sup>76</sup> Checkmate-722 reported almost identical results with the median PFS of chemotherapy + nivolumab was 5.6 months versus 5.4 months for chemotherapy alone with an HR of 0.75 (95%CI: 0.56–1.00) with a P-value of 0.0528.<sup>75</sup> Given the similar design and results, panel members voted for Keynote-789 instead of Checkmate-722 demonstrating the much stronger foothold and influence of pembrolizumab over nivolumab in thoracic oncology.

### No. 30. Osimertinib Toxicity Post IO (Schoenfeld et al, Ann Oncol 2019, PMID: 30847464) (4 Votes Out of 21 Voting Members, 38 Points)

This is not a well-known publication given that there are many reports of severe immune-related adverse events (irAEs) from immune checkpoint inhibitors (ICI) in the literature. Among the 70 patients analyzed (ICI followed by osimertinib [N = 41] and osimertinib followed by ICI [N = 29]), irAEs occurred in 15% (6/41) of patients who received ICI followed by osimertinib (pneumonitis [N = 4], hepatitis [N = 1], colitis [N = 1]), but in 0% of patients who received osimertinib followed by ICI. The time interval between 0 and 3 months from the end of ICI and start of osimertinib was when five of the six reported irAEs occurred.<sup>110</sup> The implication of this paper is that it is important to wait for molecular profiling rather than just starting with ICI or ICI + chemotherapy combination since once ICI is given a washout period of up to 3 months may be needed before osimertinib can be safely used for treatment of *EGFR*+ NSCLC.

### General Observations

1. Regional preferences. Asian panel members have mostly voted for the discovery of *BIM* intronic deletion polymorphism that is found primarily in Asians.
2. Recency bias? Newest papers got more attention, although the ability to build on upon 20 years of treatment advances lead to significant PFS improvement results from FLAURA-2, MARIPOSA, and MARIPOSA-2 recently and PFS and OS benefit in ADAURA represent true and massive treatment advances in the last 2-3 years and not a true recency bias.
3. Progression-free survival/disease-free survival (DFS) vs overall survival. The OS benefit from FLAURA was ranked third highest, whereas the PFS benefit from FLAURA was 20<sup>th</sup> based on our current ranking system which put more emphasis on being selected than achieving the higher rank from the vote. The OS benefit from ADAURA was ranked fourth, but ADAURA DFS just missed the top 20 list (21<sup>st</sup> ranked, seven votes 94 points). Nonetheless, the PFS benefit from AURA3 was ranked 10<sup>th</sup> on the list despite the lack of OS benefit from AURA3. Hence, when a trial demonstrated both PFS/DFS and OS benefit, then OS “trumps” PFS/DFS. Also, our ranking system favors being chosen (voted by panel member) than how high the vote was ranked. FLAURA PFS has 7 votes out of 21 voting members, but an aggregate score of 120 which would have placed it among 14<sup>th</sup> if we rank by aggregate score. This indicated a minority of voting members placed high importance on PFS despite also the presence of OS benefits, while most voting members preserved their votes for other publications. Similarly, ADAURA DFS (rank #21) would have ranked #16 if total aggregate points were the criteria for ranking. ADAURA DFS has 7 votes but aggregates points of 94 indicating panel members who voted for ADAURA DFS stressed its importance, while the majority again reserved/preserved their votes for other publications. However, PFS benefit without OS benefit is still considered significant if the trials proved targeting the underlying biology of the tumor is correct.
4. Historical discoveries, such as the *EGFR* T790M and *EGFR* C797S mutations were both chosen to be among the 20 papers. However, it remains to be seen how Kobayashi et al’s paper on *EGFR* T790M discovery<sup>45</sup> will be ranked in the next decade with a decreasing incidence of *EGFR* T790M due to the use of 3G *EGFR* TKIs. Sequist et al’s study of small cell transformation and *MET* amplification as resistance mechanisms to 1G *EGFR* TKI<sup>47</sup> may have a chance to stand the test of time, as these discoveries are still relevant in our current daily practice with 3G *EGFR* TKIs and with other TKIs therapy in NSCLC.

5. Preliminary emerging treatment was chosen by a few panel members, but most panelists were waiting for pivotal phase 3 data. For example, both phase 1 (4 votes, 20 points)<sup>111</sup> and phase 2 trials of HER3-DXd (HERTHENA-Lung02) (5 votes, 31 points)<sup>106</sup> were ranked. However, the pivotal trial of HER3-DXd (HERTHENA-Lung01) is still ongoing,<sup>107</sup> and it remains to be determined whether the median PFS of 5.6 months reported by HERTHENA-Lung02<sup>106</sup> will achieve statistical significance over platinum-pemetrexed chemotherapy in a post-osimertinib setting and how it will be compared to the two regimens tested in MARIPOSA-2.
6. The role of immunotherapy in the treatment of *EGFR*+ NSCLC is limited, but many definitive studies have been conducted. ORIENT-31<sup>63,64</sup> and ATLAS<sup>67</sup> were single-country trials. Checkmate-722<sup>77</sup> and Keynote-789<sup>76</sup>, both negative trials, were still not published months after their presentations at congresses. However, none of these phase 3 trials were selected among the top 20 papers. On the other hand, Lisberg's proof principle paper on the negative role of immunotherapy in PD-L1 expressing *EGFR*+ NSCLC was selected as one of the top 20 papers.<sup>73</sup> Hence negative randomized phase 3 trials (Checkmate-722, Keynote-789) that proved a negative treatment effect while important could not compete with the many positive trials in the intervening 20 years. Nonetheless, these negative should still be taught to future thoracic oncology trainees.

## Future Impactful Trials

Given the recent rapid publication of positive data, especially in 2023 and since then, some pending trials will likely be highly impactful within the next 1–2 years and will eventually become part of the top 25 papers on the 25<sup>th</sup> anniversary of the discovery of actionable *EGFR* mutations.

## LAURA (NCT03521154)

After completion of the votes and submission of the expert panel consensus manuscript, there was a press release that LAURA trial where continuous use of osimertinib until disease progression achieved PFS benefit followed definitive chemoradiation and the results were presented and published during the annual meeting of the American Society of Clinical Oncology (ASCO).<sup>112</sup> LAURA was published online on June 2, 2024 while the Lynch NEJM paper was published online in April 2024.<sup>1,112</sup> Hence, LAURA is published strictly after the first 20 years of the discovery of actionable *EGFR* mutations. The panel members via e-mail decided not to revote partly of the inclusion cutoff date and the lack of detailed efficacy data until June 2024. The genesis of the LAURA trial is that the improvement in DFS<sup>113</sup> and OS<sup>114</sup> after 1 year of maintenance durvalumab treatment in unresectable unselected stage III NSCLC after chemoradiation has become the standard of care in the treatment of locally advanced unresectable NSCLC. However, the benefit of durvalumab did not extend to *EGFR*+ or *ALK*+ NSCLC by subgroup analysis,<sup>113,114</sup> although patients with these two actionable driver mutations were limited, the current US FDA indication did not rule out the use of maintenance durvalumab in locally advanced unresectable stage III *EGFR*+ or *ALK*+ NSCLC post chemoradiation. LAURA randomized patients in a 2:1 ratio to maintenance osimertinib or placebo until disease progression, unacceptable toxicity, or other discontinuation criteria are satisfied. The median PFS was 39.1 months (95%CI: 31.5-NE) with osimertinib and 5.6 months (95%CI: 3.7-7.4) with placebo; the overall HR was 0.16 (95%CI: 0.10-0.24;  $P < 0.001$ ).<sup>112</sup> LAURA also completed the data supporting the use *EGFR* TKI use at essentially all stages of *EGFR*+ NSCLC (except stage IA). Furthermore, the principle of LAURA is likely able to extend the practice concept of TKI maintenance in other never-smoker predominant actionable driver mutation positive NSCLC with an approved, CNS-penetrant, and highly tolerable mutation-specific TKI rather than immunotherapy maintenance. LAURA in the future will be ranked high as a top 25 paper in 25 years going forward. With 81% of the patients who progressed in the placebo group crossed over to receive osimertinib, we eagerly await if LAURA will achieve OS benefit as in the PACIFIC trial.

## HERTHENA-Lung02 (NCT05338970)

HERTHENA-Lung02 is a highly anticipated pivotal registration clinical trial in which (HER3-DXd) was compared to platinum-based chemotherapy as second-line treatment for advanced osimertinib-refractory *EGFR*+ NSCLC. If positive, HER3-DXd could be the first antibody–drug conjugate approved for *EGFR*+ NSCLC, adding a new treatment modality for *EGFR*+ NSCLC.



## ADAURA2 (NCT05120349)

For the very early stage of *EGFR*+ NSCLC, ADAURA2 (NCT05120349) is enrolling patients with stage IA2 (1.0–2.0 cm) and IA3 (2.0–3.0 cm) disease with either 3 years of adjuvant osimertinib or placebo in a 1:1 ratio. If this trial is positive, then the use of adjuvant osimertinib may be extended to very early stage (> 1 cm and < 3 cm) *EGFR*+ NSCLC. If ADAURA2 is positive for PFS in the future, the biological implication is that even a very low level of residual clones of *EGFR*+ tumor cells can lead to relapse in the future.

## NeoADAURA (NCT04351555)

In the current golden era of perioperative chemoimmunotherapy, the 3-arm NeoADAURA trial is designed to investigate the neoadjuvant use of osimertinib alone, chemotherapy alone, or a combination of both in resectable stage II–IIIA *EGFR* + NSCLC. Approximately 351 *EGFR*+ NSCLC patients will be randomized in a 1:1:1 ratio to receive osimertinib for 9 weeks or three cycles of platinum/pemetrexed + osimertinib or chemotherapy + placebo. The primary endpoint was the major pathological response ( $\leq 10\%$  residual cancer cells in the surgical specimen post-surgery), which will centrally assessed. This trial may teach us how significant is major pathological response in the neoadjuvant treatment of *EGFR*+ NSCLC versus the role of adjuvant osimertinib.

## FURVENT (NCT05607550)

The first positive phase 3 trial in *EGFR exon20ins*+ NSCLC propelled PAPILLON to be the second-rank study in the past 20 years in this expert panel consensus. However, as we all know, the regimens in PAPILLON are IV every 3 weeks. For *EGFR* + NSCLC, oncologists and patients alike prefer oral TKIs. However, the failure of mobocertinib in the EXCLAIM-2 trial to demonstrate superior PFS compared to chemotherapy<sup>24</sup> left the PAPILLON regimen (IV chemotherapy and IV amivantamab) combination every three weeks as the standard of care for *EGFR exon20ins*+ NSCLC in the foreseeable future. Furmonertinib, a third-generation *EGFR* TKI that has been approved in China for the first-line treatment of advanced canonical *EGFR* mutations (del19 and L858R) has demonstrated preliminary activity at a high dose (160 mg or 240 mg once daily) against *EGFR* exon 20 insertion mutations with an IRC-confirmed ORR of 78.6% (95%CI: 59.1–91.7) (22/28) among treatment-naïve patients receiving 240 mg once daily. For patients with platinum-refractory *EGFR exon20ins*+ NSCLC, the ORR was 38.6% (95%CI: 20.2–59.4) (10/28) with furmonertinib 160 mg once daily and ORR of 46.2% (95%CI: 26.6–66.6) (12/28) with furmonertinib 240 mg once daily.<sup>115</sup> FURVENT is an on-going 3-arm phase 3 trial comparing furmonertinib at 160 mg once daily, furmonertinib at 240 mg once daily to platinum-based chemotherapy among treatment-naïve *EGFR exon20ins*+ NSCLC patients.

## Sunvozertinib versus Carboplatin-Pemetrexed in *EGFR exon20ins*+ NSCLC (NCT05668988)

In August 2023, sunvozertinib was approved in China for the treatment of locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations whose disease has progressed on or after, or who are intolerable to, platinum-based chemotherapy.<sup>27</sup> This approval is based on a single-arm phase 2 study in China demonstrating among 97 patients evaluable for efficacy analysis, 59 (61%) patients achieved a confirmed ORR of 61% (95%CI: 50–71).<sup>26</sup> This global registration trial if positive will lead to approval of sunvozertinib monotherapy for the treatment of *EGFR exon20ins*+ NSCLC.

## TARGET (NCT05526755)

Another early adjuvant trial is TARGET (NCT05526755), a global phase 2 trial investigating the efficacy of 5 years of adjuvant osimertinib. The primary endpoint is DFS.<sup>38</sup> Given that there is an increased degradation of DFS between year three to year four than from year two to year three in ADAURA,<sup>37</sup> potentially indicating that 3 years of adjuvant osimertinib may not be optimal as we know TKIs are not curative but more suppressive of tumor persistence cells. Randomized trials are required if the DFS results from 5 years of adjuvant osimertinib are better than 3 year osimertinib results from ADAURA to compare 3 years versus 5 years of adjuvant osimertinib.

## Maturing OS Data from FLAURA-2, MARIPOSA, MARIPOSA-2, and LAURA

Additionally, these four current trials, FLAURA-2, MARIPOSA, MARIPOSA-2, and LAURA with initial positive PFS benefits, some of them may eventually reach OS benefit in the future and may leapfrog the PFS positive manuscripts in future consensus panel ranking.

### Limitations of This Consensus Panel Survey

While the expert panel members are practicing in Asia, Europe, and North America; and have practice experience in South America; and are balanced between sexes (11 females, 10 males), only one panel member is from People's Republic of China (deputy editor-in-chief, Fengying Wu). Given the immense contribution to the *EGFR*+ NSCLC especially in the recent years, some of the papers originated from PRC may have been under-represented. Furthermore, there are personal subjectivities and experiences and regional preferences likely due to drug approval and practice patterns especially drug availability and coverage that influenced each panel member's vote. Latin American and South America viewpoints are under-represented in the consensus survey. Given *EGFR*+ NSCLC is a common global disease and represents the success of precision oncology, 21 panel members still are not comprehensive representative of all global opinions. Nonetheless, we hope that this consensus survey will spur other countries, regions, and medical professional societies to conduct a similar survey which can serve as an education syllabus and foundation for future thoracic oncology trainees on the science and management of *EGFR*+ NSCLC.

### Conclusions

There have been tremendous advances for the treatment of *EGFR*+ NSCLC especially just in the past 1–2 years. One of the “future” trials, LAURA, is now positive for PFS benefit and will become the standard of care globally and will be included in future consensus surveys. If this project is repeated in 5 years at the 25<sup>th</sup> anniversary of the discovery of *EGFR*+ NSCLC, some of these top 20 papers will likely fall off the list even if the list are expanded to 25 papers. In this consensus survey, we aim to include as many noteworthy translational research papers as possible. We can envision with more and more pivotal trials involving combination therapy with chemotherapy, monoclonal antibodies, antibody drug conjugate and may be even with bispecific T-cell engagers (BiTE) and CAR-T cells in the future that all pivotal papers chosen will be clinical papers. However, the significance of many clinical trials will fade with time as standard of care changes with advances and that we do not neglect the contributions of translational papers in *EGFR*+ NSCLC that laid the foundation for these clinical trials. The editor-in-chief would like to see the *BIM* intronic deletion polymorphism could be successfully overcome as an intrinsic resistance mechanism to TKI therapy (not just in *EGFR*+ NSCLC, but also *ALK*+ NSCLC, *ROS1*+ NSCLC, and CML) in the near future.

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