Poster # CO45

Clinical Efficacy and Safety of Targeted Therapies for HER2 Mutant Advanced or Metastatic Non-Small Cell Lung Cancer: A Systematic Literature Review

Federico Manevy, MSc[1], Pawana Sharma, MSc[2], Noman Paracha, MSc[1], Kostas Papadakis, MBA[1], Vadim Bernard-Gauthier, PhD[3], Ritu Gupta, MSc[4], Xuan Wang, MD, MSc[5]

[1]Bayer Consumer care AG, Basel, Switzerland, [2]ICON plc, London, United Kingdom, [3]Bayer Canadian Holdings Inc., Toronto, ON, Canada, [4]ICON plc, Delhi, India, [5]ICON plc, Stockholm, Sweden

BACKGROUND

- Lung cancer is the most frequently diagnosed cancer globally with almost 2.5 million new cases (12.4% of all cancers) diagnosed in 2022[1].
- Most lung cancers (80-85%) are grouped broadly as non-small cell lung cancer (NSCLC)[2]. Mutations in human epidermal growth factor receptor 2 (HER2) have been reported in approximately 2-4% of patients with NSCLC and are associated with poor patient outcomes[3].
- This **systematic literature review (SLR)** (PROSPERO registration number: CRD42024591639) summarizes the available literature evaluating the **clinical outcomes of treatments in HER2 mutant advanced or metastatic NSCLC.**

METHODS

- Embase, MEDLINE and MEDLINE In-process, E-pub Ahead of Print, the Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trial (CCRT) databases were searched on 5th September 2024 to identify **clinical trials with efficacy, safety and quality of life (QoL) data** reported in HER2 mutant advanced NSCLC.
- Clinical trial registries (from 2023) and conference abstracts from 2023-2024 (ASCO, ESMO, IASLC, and ELCC) were also searched.
- No limitation were set on timeframe and geography.

RESULTS

- A total of 41 clinical trials (58 publications) were included (Figure 1). 12 trials were conducted in East Asia (Figure 2).
- 35 trials were single arm, three were two or multi-arms, and three were multicohort of different doses for one treatment. No phase III trials were identified (Figure 3).
- 19 trials studied HER2 TKIs followed by nine trials on antibody-drug conjugate monotherapies (Figure 4).
- 19 trials provided data for HER2 mutation-positive patients as a subset of overall NSCLC cohorts.
- 20 focused on response rates as primary outcome; only two reported PFS as primary outcome and included HER2-mutated and/or HER2-amplified metastatic NSCLC.

Figure 2. **Included trials by region**

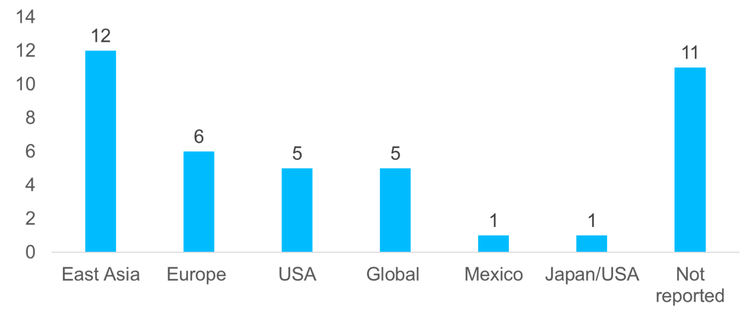
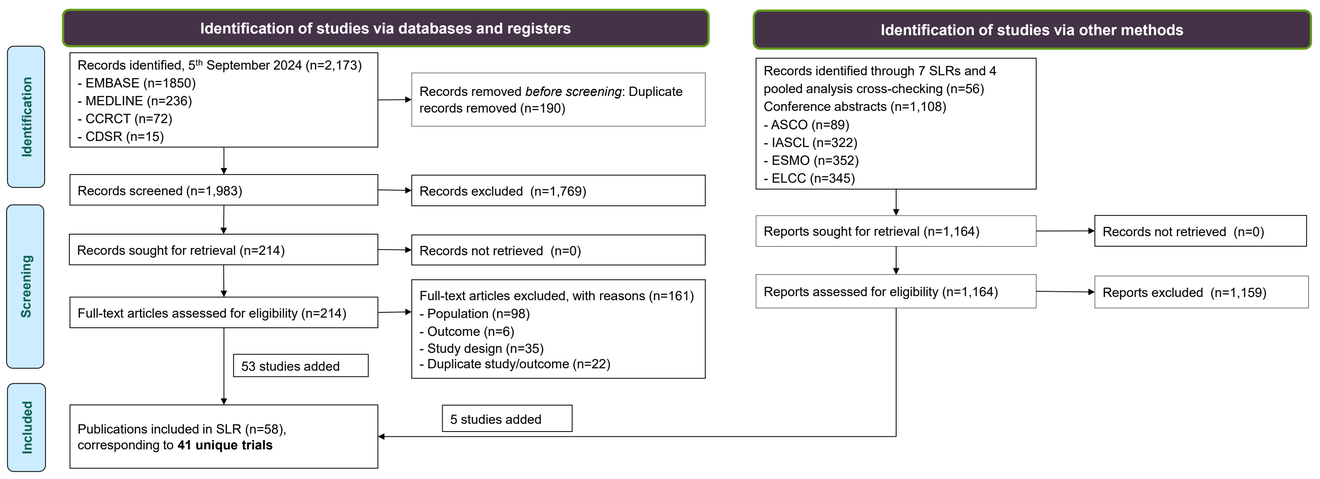


Figure 1. **PRISMA flow diagram**



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Trials included in SLR

Table 1. **Summary of included trials characteristics**

Trial characteristics	Range or number
Number analysed*, range	2-245
Median follow-up, range	3-17 months
Females, range	33.3%-100%
Median age, range	56-67 years
Non-smoker	5.6%-100%
NSCLC histology	Adenocarcinoma (76%-100%)^; Squamous (0-7%)

*7 trials had <10 sample size; ^19 trials with 98-100% with adenocarcinoma and none with large cell carcinoma

Figure 3. **Trial design of included trials**

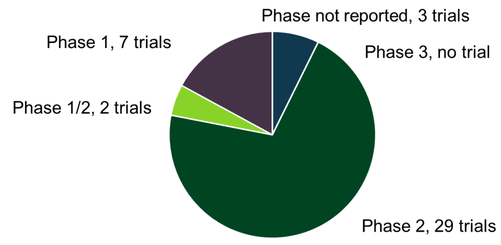
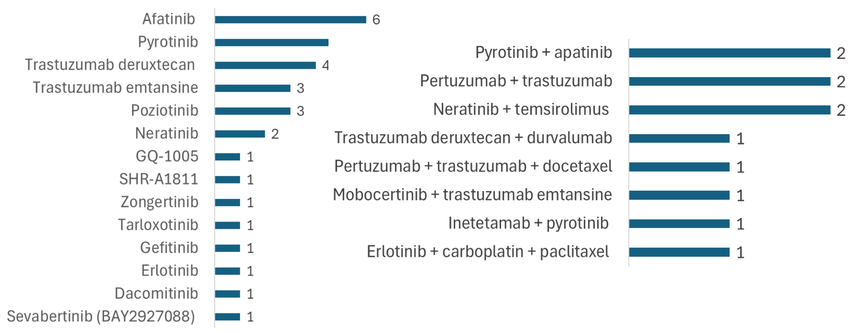


Figure 4. **Treatment of HER2-mutant NSCLC reported in the included trials**



EFFICACY RESULTS

- **≥2Ls (27 trials):** for the second line treatment and above, results varied widely (Figure 5 and 6). **PFS** ranged from 2.76 (95% CI: 1.87 - 4.6) to 15.4 months (95% CI: 8.3 - not estimable); **OS**, from 8.1 to 19 months; ORR, from 0% to 74% (six trials reported ORRs of less than 20%, 10 trials reported ORRs between 20% to 50%, and nine trials reported ORRs of more than 50%); and DCR, from 38% to 100% across the trials.
- **1L (4 trials):** evidence for treatment naïve patients was available for selective HER2 TKIs, including pyrotinib and poziotinib monotherapies where both have shown better results (Figure 5 and 6). ORR ranged from approximately 30% to 39%; and DCR ranged from 70% to up to 90%.
- **≥1Ls** (eight trials - patients received mix of no prior treatment or >1L treatment).
- Five trials did not specify lines of treatment.

Figure 6. **OS summary of the included trials**

Study name	Intervention	Median OS (months)
1L		
Liu 2023[4]	PYR	14.3
Song 2022[5]	PYR	12.5
≥1Ls		
Kris 2015[10]	DAC	9
Song 2022[5]	PYR	10.5
≥2Ls		
DESTINY-LUNG01[14]	T-DXd*	18.6
DESTINY-LUNG02[15]	T-DXd^	19
	T-DXd*	17.3
DRUP[8]	TRA+PER	10
Elamin 2022[9]	POZ	15
Fan 2020[18]	AFA	10.02
HUDSON platform study[20]	T-DXd+DUR	10.6
Iwama 2022[21]	T-DM1	8.1
LUX-LUNG 8[23]	AFA or ERL	Not reported; HR: 0.06 (0.01 to 0.57)
Mazieres 2022[12]	TRA+PER+DOC	17.6
NICHE[24]	AFA	14
Song 2022[5]	PYR	6.7
Tsurutani 2020[28]	T-DXd*	17.3
Wang 2019[29]	PYR	12.9
Zhou 2020[30]	PYR	14.4
Treatment line not reported		
PUMA-NER-4201[33]	NER	10
	NER+TEM	15.8
CALGB (Alliance) 30406[34]	ERL	17.5

Note: * 6.4 mg/kg Q3W; ^5.4 mg/kg Q3W

Figure 5. **PFS summary of the included trials**

Study name	Intervention	Median PFS (months)
1L		
Liu 2023[4]	PYR	7.3
Song 2022[5]	PYR	8.9
ZENITH20 (ZENITH20-4)[8]	POZ	5.6
≥1Ls		
De Grève 2015[7A*]	AFA	4
DRUP[8^]	TRA+PER	4
Elamin 2022[9^]	POZ	5.5
Kris 2015[10^]	DAC	3
Li 2018[11^]	T-DM1	5
Mazieres 2022[12^]	TRA+PER+DOC	6.8
Song 2022[6^]	PYR	5.6
ZENITH20[13^]	POZ	7.8
≥2Ls		
DESTINY-LUNG01[14]	T-DXd[$]	8.2
DESTINY-LUNG02[16]	T-DXd	10
DESTINY-LUNG02[16] (Chinese)	T-DXd	10.8
DESTINY-LUNG05[17**]	T-DXd	10.8
Fan 2020[18]	AFA	2.8
Gandhi 2014[19*]	NER+TEM	5
HUDSON platform study[20]	T-DXd+DUR	5.7
Iwama 2022[21]	T-DM1	2.8
Li 2024[22]	SHR-A1811[¥]	8.4
LUX-LUNG 8[23]	AFA or ERL	Not reported; HR: 0.06 (0.01, 0.59)
NICHE[24]	AFA	4
PATHER2[26]	PYR+APA	5.9
SOHO-01[28]	SEV (BAY 2927088)	7.1
Song 2022[6]	PYR	4
SUMMIT[27]	NER	5.5
Tsurutani 2020[28]	T-DXd[$]	11.3
Wang 2019[29]	PYR	6.4
Zhou 2020[30]	PYR	6.9
ZENITH20 (ZENITH20-2)[31]	POZ	5.5
≥3Ls		
Elamin 2022[9]	POZ	4
ZENITH20 (ZENITH20-2)[31]	POZ	6.2
≥4Ls		
ZENITH20 (ZENITH20-2)[31]	POZ	5.5
Treatment line not reported		
Kanemura 2024[32]	MOB+T-DM1	6.1
PUMA-NER-4201[33]	NER	3.0
	NER+TEM	4.1
CALGB (Alliance) 30406[34*]	ERL	4.2

Notes: ^some patients include first line treatment;
*sample size less than 10; [$]6.4 mg/kg Q3W dose;
[¥]4.8 mg/kg dose; **Data for investigator assessed - reports 'not estimable' for ICR assessed

SAFETY RESULTS

- 24 trials reported safety outcomes in **≥2Ls** and two trials in 1L. In **≥2Ls**, the overall mortality rates varied significantly, ranging from 0% to 53%; and the overall treatment discontinuation rates varied from 50% to 98.9%.
- Commonly reported AEs included rash, diarrhea, vomiting, fatigue, anemia and interstitial lung disease. In Liu et al. (2023), which included treatment-naïve patients treated with pyrotinib, an overall mortality rate of approximately 50% was reported.

QoL RESULTS

DESTINY-Lung02 (T-DXd) and ZENITH20-2 (poziotinib) reported QoL outcomes. Overall HRQoL was maintained, as measured by the EORTC QLQ-C30, in patients treated with T-DXd, while QLQ-C30 scores showed slight improvement from baseline in those treated with poziotinib.

CONCLUSIONS

The clinical evidence on T-DXd and novel HER2 TKIs has shown rapid and durable clinical response in HER2 mutant NSCLC, though efficacy varies considerably, and comparative data remained limited.

Disclosures

P Sharma, R Gupta, and X Wang are employees of ICON plc, a clinical research organization paid by Bayer, Inc., to conduct the study.

F Manevy, N Paracha, K Papadakis, V Bernard-Gauthier, are employed by Bayer Inc., and hold stock/stock options in the company.

Additional information

Full list of articles included in SLR available upon request.

For additional information, please contact Federico Manevy (federico.manevy.ext@bayer.com)

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