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ΠΛΗΡΟΦΟΡΙΕΣ

Εξεταζόμενος	-	**Ημ. Συλλογής Δείγμ.**	-
ΑΜΚΑ	-	**Παραπέμπων**	-
Ημερ. Γέννησης	-	**Barcode**	26xxxxxxGR
Τύπος Δείγμ. #1	ΙΣΤΟΣ ΕΓΚΛΕΙΣΜΕΝΟΣ ΣΕ ΜΠΛΟΚ ΠΑΡΑΦΙΝΗΣ	**Ημερ. Παρ. Δειγμ.**	-
Τύπος Δείγμ. #2	-	**Ημερ. Αποτελ.**	-
Κωδικός Δείγμ. #1	-	**Τύπος όγκου**	ΚΑΡΚΙΝΟΣ ΠΝΕΥΜΟΝΑ

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Αποτελέσματα και ερμηνεία*

Βιοδείκτης	Αποτέλεσμα	Θεραπείες με ισχυρή κλινική σημασία		Θεραπείες με πιθανή κλινική σημασία	Θεραπείες με πιθανή αντίσταση
		Εγκεκριμένες/ βάσει οδηγιών θεραπείες για την ένδειξη (Level A)	Θεραπείες σε ισχυρές μελέτες (Level B)	Εκτός ένδειξης θεραπείες (Level C)	
EGFR	Exon 19 p.E746_A750del VAF: 30.5%	Afatinib Amivantamab+Chemotherapy Amivantamab+Lazertinib Dacomitinib Datopotamab Deruxtecan Erlotinib Gefitinib Osimertinib Osimertinib+Chemotherapy Erlotinib+Ramucirumab	Patritumab Deruxtecan	-	-
TP53	Exon 8 p.P278A VAF: 22.5%	-	-	-	-
Ανοσοϊστοχημικοί Βιοδείκτες					
Έκφραση PD-L1 (Πίνακας S2)	TPS <1	-	-	-	-
Έκφραση ERBB2 (IHC) (Πίνακας S1)	Αρνητικό (Score 0)	-	-	-	-
c-MET expression (IHC)	Negative (<50%) (0)	-	-	-	-

Στο πλαίσιο της Επικουρικής/Νεοεπικουρικής θεραπείας για μη μεταστατικό μη μικροκυτταρικό καρκίνο του πνεύμονα (στάδια I-III) λάβετε υπόψη τους ακόλουθους βιοδείκτες για πιθανή θεραπεία: EGFR, ALK και PD-L1. Για όλα τα άλλα ευρήματα, δεν υπάρχουν επί του παρόντος εγκεκριμένες θεραπείες ή καθιερωμένες κατευθυντήριες γραμμές για ασθενείς με νόσο πρώιμου σταδίου. Ωστόσο, αυτά τα ευρήματα ενδέχεται να αποκτήσουν κλινική σημασία σε περίπτωση υποτροπής ή εξέλιξης της νόσου σε μεταστατική.

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*Σημείωση: Το επίπεδο σημαντικότητας των παραλλαγών (Level of Evidence, LoE) (π.χ. A, B, C κλπ) βασίζονται στις οδηγίες για την αναφορά γενετικών παραλλαγών στον καρκίνο που δόθηκαν με κοινή συναίνεση των AMP, ACMG, ASCO και CAP. Για λεπτομερή περιγραφή των οδηγιών αυτών, ανατρέξτε στην Εικόνα 1.

^ Η ανάλυση συγκεκριμένων βιοδεικτών του παρόντος πολυγονιδιακού πάνελ πραγματοποιείται στο πλαίσιο διαπίστευσης κατά ΕΛΟΤ EN ISO 15189:2022 (βλ. ενότητα «Methodology»). Η διαπίστευση κατά ΕΛΟΤ EN ISO 15189:2022 αφορά αποκλειστικά τον αναλυτικό προσδιορισμό των εν λόγω βιοδεικτών. Οι ερμηνείες που σχετίζονται με την πρόβλεψη ανταπόκρισης σε θεραπεία δεν περιλαμβάνονται στο πεδίο διαπίστευσης.

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Κωδικός Εγγράφου: Δ21_Lung_FFPE

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SAMPLE INFORMATION

Name	-	**Date Sp. Extracted**	-
ID/Medical ID	-	**Req. Physician**	-
Date of Birth	-	**Report No**	26xxxxxxGR
Material #1	PARAFFIN EMBEDDED TISSUE-BLOCK	**Date Received**	-
Material #2	-	**Date of Report**	-
Sample #1 ID	-	**Tumor type**	Lung Cancer

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1. Clinically Significant Biomarkers*

Biomarker	Result	Therapies with strong clinical significance		Therapies with potential significance	Therapies with potential resistance
		Approved/ Standard of care therapies (Level A)	Therapies in well powered studies (Level B)	Off label/ Investigational therapies (Level C)	
EGFR	Exon 19 p.E746_A750del VAF: 30.5%	Afatinib Amivantamab+Chemotherapy Amivantamab+Lazertinib Dacomitinib Datopotamab Deruxtecan Erlotinib Gefitinib Osimertinib Osimertinib+Chemotherapy Erlotinib+Ramucirumab	Patritumab Deruxtecan	-	-
TP53	Exon 8 p.P278A VAF: 22.5%	-	-	-	-
Immunohistochemistry Biomarkers					
PD-L1 expression (Table S2)	TPS <1	-	-	-	-
HER2 expression (IHC) (Table S1)	Negative (Score 0)	-	-	-	-
c-MET expression (IHC)	Negative (<50%) (0)	-	-	-	-

In the Adjuvant/Neoadjuvant setting for non-metastatic NSCLC (stages I-III): consider the following biomarkers for possible treatment: EGFR, ALK and PD-L1. For all other findings, there are currently no approved therapies or established guidelines for patients with early-stage disease. However, these findings may become clinically relevant in the event of disease relapse or progression to metastatic disease.

*Note: Variants' Level of Evidence (LoE) (e.g. A, B, C etc) are based on the Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. For a detailed description of the recommendation please refer to Fig. 1

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^ The analysis of selected biomarkers included in the present multigene panel is performed within the scope of accreditation according to ELOT EN ISO 15189:2022 (see «Methodology» section). Accreditation according to ELOT EN ISO 15189:2022 applies exclusively to the analytical determination of the selected biomarkers. Interpretations related to the prediction of therapeutic response are not included in the scope of accreditation.

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2. Methodology

NGS analysis

DNA is extracted from the sample under investigation using the Qiamp DNA FFPE Kit (Qiagen). RNA was extracted using the RNeasy FFPE Kit (Qiagen). A total of 83 unique genes is analyzed, including the entire coding sequences of 77 genes and 19 RNA fusions, using the Pan Cancer Panel NGS Assay (Genes2Me). This is a CE-IVD hybrid capture–based assay, in which target genomic regions are enriched through probe hybridization technology. The assay enables the detection of single nucleotide variants (SNVs), insertions/deletions (indels), copy number variations (CNVs), and RNA fusions (Table 1).

Sequencing is performed on the DNBSEQ-T7 next-generation sequencing platform (MGI). Raw sequencing data are processed and analyzed using the CliSeq Interpreter, a companion software for automated, cloud-based analysis. In addition, the SeqPilot software (Version 4.4, Build 505; JSI Medical Systems) is used for independent variant calling and result confirmation.

Alteration- and tumor type-specific therapeutic implications are classified using the OncoKB™ Levels of Evidence system, which assigns clinical actionability to individual mutational events. For additional details about the OncoKB™ curation process, please refer to the version-controlled OncoKB™ Curation Standard Operating Procedure.

Genes Analyzed

77 Gene Alterations									
ABL1	AKT1	ALK	APC	ARAF	ATM	BRAF*	BRCA2*	CCNE1*	CDH1
CDKN2A*	CSF1R	CTNNB1	DDR2	DICER1	EGFR*	EIF1AX	ERBB2*	ERBB3	ERBB4
EZH2	FBXW7	FGFR1*	FGFR2*	FGFR3	FLT3	FOXL2	GNA11	GNAQ	GNAS
HGF	HNF1A	HRAS	IDH1	IDH2	JAK2	JAK3	KDR	KEAP1	KIT
KRAS	LAG3	MAP2K1	MDM2	MET*	MLH1*	MPL	MTAP*	MYC	NOTCH1
NPM1	NRAS	NTRK1	NTRK2	NTRK3	PDGFRA	PIK3CA	PIK3R1	POLD1	POLE
PTEN*	PTPN11	RAC1	RAF1	RB1	RET	ROS1	SMAD4	SMARCA4*	SMARCB1
SMO	SPOP	STK11	SRC	TERT	TP53	VHL			
19 Fusion Genes									
ALK	BRAF	EGFR	ERG	FGFR1	FGFR2	FGFR3	MET	NRG1	NTRK1
NTRK2	NTRK3	PBX1	PPARG	PRKACA	RAF1	RET	ROS1	TFE3	

*CNV (amplification/deletion) analysis is included for these genes

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Biomarkers within the scope of accreditation (ISO15189:2022)

-*AKT1, EGFR, ERBB2, KRAS, NRAS, METex14 skipping HRAS, IDH1, IDH2, KIT, PIK3CA, PDGFRA* (SNV/indel detection by NGS)
-*ALK, ROS1, RET, FGFR1,2,3, NTRK1,2,3*, *METex14 skipping* (Fusion detection by NGS)
-PDL1 SP263 & SP142 (IHC)
-*ALK* (FISH)
-*HER2* (IHC, FISH, DISH)

Sensitivity: Positive reference standards are tested with the assay, all corresponding mutation sites can be accurately detected, and the positive percent agreement (PPA) for all variants (SNVs, Indels, fusions and CNVs) assessed was 100%.
Specificity: Negative reference standards are tested with the assay, and the negative percent agreement (NPA) of SNVs, Indels, fusions and CNVs was 100%.
Limit of Detection (LoD): The limit of detection (LoD) of this assay is listed in the table below. The LoD is based on as low as 50 ng of gDNA input for library preparation. The assay can also be used to test microsatellite instability (MSI) with a tumor cell content as low as 10%.

The performance characteristics of the assay are summarized in the following table:

Feature	Performance
Precision (%)	>96
Reproducibility (%)	97
On-Target Ratio (%)	85–95
Analytical Sensitivity (%)	96
Analytical Specificity (%)	100
Repeatability (%)	96
Limit of Detection (LoD, VAF)	≥ 1%

Disclaimer

1. This test is mainly used to assist clinical decision-making, and the result does not represent clinical decision.
2. The test should be interpreted by combining the actual patient context. The medication information provided only on the basis of genetic test results, and the actual medication should follow the physician's instructions.
3. The clinical trials only present partial relevant clinical recruitment trials. For more comprehensive and updated information, please refer to the website: https://clinicaltrials.gov/.
4. As evidence on variants and drugs evolves, previous classifications may later be modified. The interpretation of a variant is based on current available evidence.
5. Sequence variants were reported using Human Genome Variation Society (HGVS) nomenclature. Classification and interpretation of variants follow guidelines of American College of Medical Genetics and Genomics (ACMG), Association of Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP).

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6. Database and references used: Reference genome (GRCh37), annotation using A Locus Reference Genomic (LRG), database referencing 1000G (phaseIII-ucsc), EXAC (0.3.1), dbSNP (147), PolyPhen2/SIFT (ensdb v73), PhyloP (2013-12-06), Clinvar (2018-8) and Cosmic(V80).

Limitations

1. Limited tissue detection may not represent the whole DNA variations of lesions because of tumor heterogeneity.
2. Scientific data show that not all patients carry genomic variations that are associated with targeted drug, therefore not all subjects can be matched with targeted therapies or clear resistance mechanism.
3. Genetic variation beyond the detection range of this test or some non-gene mutation related factors such as drug interactions may affect the clinical effects of drugs.
4. The detection could not distinguish between somatic mutations and germline mutations effectively without control sample analysis.
5. Every molecular test has an internal 0.5-1% chance of failure. This is due to rare molecular events and factors related to the preparation and analysis of the samples.

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3. Quality Control Results

Quality Control Index	Result	Criterion
Average effective sequencing depth[1]	**588**	≥ 500
Tumor cell content[2]	20%	≥20%
Overall Assessment[3]	PASS	

Note :

1. Average effective sequencing depth: Average sequencing depth on target without duplicated reads.
2. An overall tumor cell content percentage of ≥ 20% is recommended for the efficient detection of somatic alterations in the sample analyzed.
3. Overall Assessment: The quality control overall assessment results are divided into two levels: "PASS" and "RISK". When the overall quality assessment result is "RISK", 94-96% of coverage was achieved in the genes analysed, hence there is a small range where clinical actionable variations could be undetected.

ERBB2 (HER2) expression by IHC

ERBB2 staining is performed in a VENTANA BenchMark Series automated staining instrument using the ERBB2 clone 4B5, on formalin-fixed, paraffin-embedded (FFPE) tissue. The IHC test gives a score of 0 to 3+ that measures the amount of HER2 receptor protein on the surface of cancer cells. Scoring interpretation is as follows:

HER2 IHC positive (score 3+)
HER2 IHC equivocal (score 2+)
HER2 IHC negative (score 0 or 1+)
Scoring is based on the ASCO-CAP HER2 testing guidelines (PMID: 27841667, 37303228).
For mCRC the HERACLES criteria are also used (PMID: 26449765).

c-MET expression by IHC

The immunohistochemical investigation of c-Met protein overexpression is a recommended CE-IVD test, performed on formalin-fixed, paraffin-embedded (FFPE) tissue using the monoclonal antibody VENTANA MET, clone SP44, on the automated Ventana BenchMark Ultra platform.

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According to the LUMINOSITY study data, c-Met protein overexpression in non-squamous (NSQ), EGFR-wild type, non-small cell lung carcinomas (NSCLC) is defined as the presence of strong membranous and/or cytoplasmic staining (3+) in > 25% of tumor cells. c-Met expression is further categorized as follows:
- High expression: 3+ staining in ≥ 50% of tumor cells - Intermediate expression: 3+ staining in ≥ 25% and < 50% of tumor cells
In clinical practice, high c-Met expression serves as a predictive marker of response to targeted therapy against c-Met, using the antibody-drug conjugate Telisotuzumab vedotin (Teliso-V).

PD-L1 expression by IHC

PD-L1 protein expression is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. This assay is indicated as an aid in identifying NSCLC patients for treatment with immunotherapeutic agents.
VENTANA SP263 by IHC (CE IVD) is a qualitative immunohistochemical assay using Monoclonal Mouse Anti-PD-L1, Clone SP263, intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) tissue, using VENTANA BenchMark Series automated staining instrument. The specimen submitted for testing should contain at least 100 viable tumor cells to be considered adequate for evaluation.

FISH ALK

FISH analysis was carried out for the detection of rearrangements involving the ALK gene, using the ZytoLight FISH Tissue Implementation Kit (ZytoLight). Microtome sections (3μm) of the sample were hybridized with the ZytoLight SPEC ALK Dual Color Break Apart Probe using Thermobrite (Abbott Molecular) and evaluated microscopically. Signals from 50 nuclei from at least 5 different areas of the sections were microscopically analyzed. Imaging analysis was carried out using the ISIS FISH Imaging System, Metasystems.

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4. Important biomarkers findings

Gene	Finding (VAF)	Gene	Finding (VAF)
EGFR (exons 18,19,20,21)	**p.E746_A750del (30.5%)**	*ALK* rearrangement	Not Detected
*KRAS*_G12C	Not Detected	*ROS1* rearrangement	Not Detected
*BRAF*_V600E	Not Detected	*RET* rearrangement	Not Detected
MET ex14 skipping	Not Detected	*NRG1* rearrangement	Not Detected
ERBB2	Not Detected	*NTRK1/2/3* rearrangement	Not Detected

5. Immune Checkpoint inhibitors biomarkers

Biomarker/Variant	Result	Clinical Interpretation
Treatment effect - positive correlation		
POLE mutation (driver)	Not Detected	-
TP53 mutation	**Detected**	**May increase the benefit rate of PD-1/PD-L1 inhibitors**
KRAS mutation	Not Detected	-
Treatment effect - negative correlation		
PTEN inactivating mutation	Not Detected	-
JAK2 inactivating mutation	Not Detected	-
EGFR mutation (L858R/EX19del)	**Detected**	**May decrease the benefit rate of PD-1/PD-L1 inhibitors**
ALK rearrangement	Not Detected	-
STK11 inactivating mutation	Not Detected	-
KEAP1 inactivating mutation	Not Detected	-
MDM2 amplification	Not Detected	-

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6. Interpretations for targeted therapies

Genetic Variation:	*EGFR*: c.2236_2250del (p.E746_A750del)	VAF*: 30.5%	OncoKB

Treatment Information

Patients with in-frame deletions in exon 19 of EGFR or L858R in exon 21 are sensitive to EGFR targeted therapies (PMID: 29075127). They lead to increased receptor dimerization and increased kinase activity, when compared with the wild-type EGFR protein (PMID: 31562956). Thus, NSCLC patients carrying this type of mutations have shown responses to treatment with EGFR tyrosine kinase inhibitors (TKIs). Therefore the following treatment options have been approved for such patients:

- The Food and Drug Administration granted accelerated approval to datopotamab deruxtecan-dlnk for adults with locally advanced or metastatic epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) who have received prior EGFR-directed therapy and platinum-based chemotherapy. Efficacy was evaluated in a pooled subgroup of 114 patients with locally advanced or metastatic EGFR-mutated NSCLC who had received prior treatment with an EGFR-directed therapy and platinum-based chemotherapy and received datopotamab deruxtecan-dlnk at the recommended dose across two clinical trials: TROPION-Lung05 and TROPION-Lung01. TROPION-Lung05 (NCT04484142) was a multicenter, single-arm trial, while TROPION-Lung01 (NCT04656652) was a multicenter, open-label, randomized controlled trial.
- The Food and Drug Administration approved lazertinib in combination with amivantamab-vmjw for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test. Efficacy was evaluated in MARIPOSA (NCT04487080), a randomized, active-controlled, multicenter trial of 1074 patients with exon 19 deletion or exon 21 L858R substitution mutation-positive locally advanced or metastatic NSCLC and no prior systemic therapy for advanced disease. Lazertinib with amivantamab demonstrated a statistically significant improvement in PFS compared to osimertinib with a hazard ratio of 0.70. The median PFS was 23.7 months in the lazertinib with amivantamab arm and 16.6 months in the osimertinib arm (https://doi.org/10.1016/j.annonc.2024.05.541).
- The TKI Erlotinib is approved for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen. (PMID: 28017789, PMID: 22285168).
- The TKI Afatinib is approved for patients harboring EGFR mutations. The primary trial supporting approval was Study 1200.32 (LUX-3), a randomized, open-label, multicenter, multinational trial comparing the efficacy of afatinib to cisplatin/pemetrexed chemotherapy doublet for the first-line treatment of metastatic or unresectable, EGFR mutation-positive adenocarcinoma of the lung (PMID: 32559335, PMID: 28017789). The new label includes data on three additional EGFR mutations: L861Q, G719X and S768I.
- The third-generation EGFR TKI Osimertinib is approved for NSCLC patients with EGFR exon 19 deletions exon 21 L858R mutations as adjuvant therapy after tumor resection and first-line treatment of adult patients with metastatic NSCLC (PMID: 34301748, PMID: 32955177).

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- The oral EGFR kinase inhibitor Dacomitinib is approved for the first-line treatment of patients with metastatic NSCLC and EGFR exon 19 deletion or exon 21 L858R substitution mutations, based on results from the ARCHER 1050 phase 3 clinical study, indicating the drug's potential as a significant treatment advance for this patient population (PMID: 28958502, PMID: 28958502).
- The kinase inhibitor Gefitinib is approved for the frontline treatment of patients with metastatic, EGFR-positive NSCLC with an exon 19 deletion or exon 21 (L858R) substitution. The FDA approval of Gefitinib is based on data from the Phase IV IFUM1 (IRESSA Follow-Up Measure) study, assessing Gefitinib as a first-line treatment for Caucasian patients with locally advanced or metastatic EGFR mutation-positive NSCLC. This was supported by results from the IPASS2 (IRESSA Pan-ASia Study) clinical trial (PMID: 24263064, PMID: 21670455).
- Finally, FDA approved ramucirumab in combination with erlotinib for first-line treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) mutations. Efficacy was evaluated in RELAY (NCT02411448), a multinational, randomized, double-blind, placebo-controlled, multicenter study, where ramucirumab plus erlotinib demonstrated superior progression-free survival compared with placebo plus erlotinib (PMID: 31591063, 33905962).
- Amivantamab, as a single agent, may also be beneficial. FDA has finally accepted and granted Priority Review for patritumab deruxtecan (HER3-DXd) for the treatment of adult patients with locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC) previously treated with two or more systemic therapies. Submission based on HERTHENA-Lung01 results showing patritumab deruxtecan demonstrated clinically meaningful and durable responses in patients with advanced EGFR-mutated non-small cell lung cancer previously treated with two or more systemic therapies.

Gene information

EGFR (Epidermal Growth Factor Receptor) is a transmembrane receptor that is activated by EGF family extracellular ligands (PMID: 24691965). EGFR is a member of the ErbB family of receptors, including the receptors ERBB2, ERBB3, and ERBB4. Binding of EGFR by its ligands, including EGF ligands and transforming growth factor alpha (TGFα), activates downstream signaling pathways including the canonical MAPK and PI3K/AKT/mTOR signaling cascades (PMID: 22239438). EGFR can homodimerize or heterodimerize with other ErbB family members to initiate signaling (PMID: 25621509). Activation of EGFR-mediated signaling ultimately results in cellular proliferation, migration, and differentiation (PMID: 18045542). While EGFR usually is expressed at low levels in normal adult tissues, hyperactivation of this receptor by somatic mutations and/or amplification of the EGFR gene is found in many cancer types such as lung, brain, colorectal and head and neck cancer (PMID: 10880430, 17318210). In lung cancer, activating mutations in EGFR result in a constitutively activated form of the receptor that is sensitive to EGFR tyrosine kinase inhibition (PMID: 15329413). Tyrosine kinase inhibitors targeting EGFR, including afatinib, erlotinib, and gefitinib, have been approved for first-line treatment of non-small cell lung cancer patients (PMID: 14977817, 24868098, 26039556, 25963089). Second-site resistance mutations in EGFR can occur in cancers previously treated with these inhibitors (PMID: 29068003). Osimertinib is a second-line tyrosine kinase inhibitor that has been FDA approved for relapsed patients with non-small cell lung cancer with the EGFR resistance mutations T790M, L858R, and exon 19 deletions (PMID: 27923840). Additionally, copy number amplification of the EGFR gene result in receptor overexpression in several cancer types, including brain and colorectal cancers, and these cancers may also be sensitive to EGFR inhibition (PMID: 11426640).

Variant Information

The EGFR exon 19 E746_A750del mutation occurs in the EGFR tyrosine kinase domain. In-frame deletions of EGFR exon 19 result in constitutive activation of EGFR tyrosine kinase activity and confer sensitivity to EGFR tyrosine kinase inhibitors (TKIs) including

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gefitinib, erlotinib and afatinib in lung adenocarcinoma (PMID: 15118073, 15118125, 15329413). In two clinical studies, two patients with non-small cell lung cancer (NSCLC) harboring the EGFR E746_T751delinsA mutation had non-progressive disease or a minor response upon treatment with gefitinib lasting 5-13.5 months (PMID: 15897572, 15710947). The EGFR E746_A750del alteration is known to be oncogenic.

Afatinib

DrugBank

Afatinib, a second-generation, irreversible tyrosine kinase inhibitor of EGFR, HER2, and HER4, is FDA-approved as first-line therapy in patients with non-small cell lung cancer (NSCLC) whose tumors harbor EGFR exon 19 deletion or L858R, L861Q, G719, and/or S768I substitution mutations. FDA approval was based on the Phase II LUX-Lung 2 trial, which demonstrated an objective response rate of 61% in patients with EGFR-mutant lung cancer treated with afatinib (PMID: 22452895). In the Phase III LUX-Lung 3 trial, afatinib significantly improved progression-free survival (PFS) in patients with EGFR-mutant lung cancer compared to patients treated with chemotherapy comprised of cisplatin plus pemetrexed (13.6 months versus 6.9 months; HR=0.47; p=0.001) (PMID: 23816960). In a pooled analysis of the LUX-Lung 3 and 6 trials comparing overall survival in patients with EGFR mutation who were treated with afatinib versus those treated with chemotherapy, first-line treatment with afatinib significantly improved overall survival specifically in patients harboring exon 19 deletions compared to those treated with chemotherapy (31.7 versus 20.7 months; HR = 0.59; p = 0.0001) (PMID: 25589191).

Amivantamab+Chemotherapy

DrugBank

Amivantamab is an intravenously infused, EGFR-MET bispecific monoclonal antibody that is FDA-approved for the treatment of adult patients in combination with carboplatin and pemetrexed for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with an EGFR tyrosine kinase inhibitor. FDA approval is based on the results of the Phase III MARIPOSA-2 (NCT04988295) trial of amivantamab plus chemotherapy versus chemotherapy in 394 patients with NSCLC with EGFR L858R mutations or exon 19 deletions.

In the Phase III MARIPOSA-2 (NCT04988295) trial, the amivantamab plus chemotherapy cohort (n=131 [n=89, EGFR exon 19 deletions; n=42, EGFR L858R]) demonstrated an overall response rate (ORR) of 53% (95% CI=44-62), with a 0.8% complete response (CR) rate and 52% partial response (PR) rate (PMID: 37879444). In contrast, the chemotherapy cohort (n=263 [n=183, EGFR exon 19 deletions; n=79, EGFR L858R]) demonstrated an ORR of 29% (95% CI=23-35) (p<0.0001), with a 29% PR rate (PMID: 37879444). The amivantamab plus chemotherapy cohort demonstrated a median progression-free survival (PFS) of 6.3 months (95% CI=5.6-8.4) and a median duration of response (DOR) of 6.9 months (95% CI= 5.5–NE) while the chemotherapy cohort demonstrated a median PFS of 4.2 months (95% CI=4.0–4.4) (HR=0.48 [95% CI=0.36-0.64]; p<0.0001) and a median DOR of 5.6 months (95% CI=4.2–9.6) (PMID: 37879444).

Amivantamab+Lazertinib

DrugBank

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Amivantamab, an intravenously infused, EGFR-MET bispecific monoclonal antibody, and lazertinib, a small molecule, third-generation EGFR tyrosine kinase inhibitor, are FDA-approved in combination for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test. FDA approval was based on the results of the Phase III MARIPOSA (NCT04487080) trial of amivantamab plus lazertinib versus osimertinib monotherapy in 1074 patients with NSCLC with an EGFR exon 19 deletion or L858R mutation. In the Phase III MARIPOSA (NCT04487080) trial, the amivantamab plus lazertinib cohort (n=429) demonstrated an overall response rate (ORR) of 86% (95% CI=83-89), a median progression-free survival (PFS) of 23.7 months (95% CI=19.1-27.7), a median duration of response (DOR) of 25.8 months (95% CI=20.1-NE) and a 24-month overall survival (OS) rate of 74% (95% CI=69-78) while the osimertinib cohort (n=429) demonstrated an ORR of 85% (95% CI=81-88), a median PFS of 16.6 months (95% CI=14.8–18.5) (HR=0.70 [95% CI=0.58-0.85]; p<0.001), a median DOR of 16.8 months (95% CI=14.8-18.5) and a 24-month OS rate of 69% (95% CI=64-74) (PMID: 38924756).

Dacomitinib

DrugBank

Dacomitinib is a small molecule inhibitor of EGFR that is FDA-approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test. FDA approval was based on the Phase III ARCHER 1050 trial of dacomitinib versus gefitinib in 452 patients with advanced, EGFR-positive NSCLC in which the median progression-free survival (PFS) was 14.7 months for patients randomized to dacomitinib and 9.2 months for patients randomized to gefitinib (HR=0.59; 95% CI=0.47-0.74; p=0001) (PMID: 28958502). Overall survival was 34.1 months in the dacomitinib arm versus 26.8 months in the gefitinib arm (HR=0.760; 95% CI=0.582-0.993; P = .044) (PMID: 29864379).

Datopotamab Deruxtecan

DrugBank

Datopotamab deruxtecan (Dato-DXd) is an intravenously infused, TROP2-directed antibody drug conjugate that is FDA-approved for the treatment of patients with EGFR-mutated non-small cell lung cancer (NSCLC) who have received prior EGFR-directed therapy and platinum-based chemotherapy. FDA approval is based on the results of the Phase II TROPION-Lung05 (NCT04484142) and Phase III TROPION-Lung01 (NCT04656652) trials of Dato-DXd in patients with previously treated EGFR-mutated NSCLC.

In the Phase II TROPION-Lung05 (NCT04484142) trial of Dato-DXd in patients with NSCLC harboring actionable alterations progressing on or after targeted therapy and platinum-based chemotherapy, patients with EGFR-mutated NSCLC (n=78 [exon 19 deletion: 41 (29.9%); exon 20 T790M: 26 (19.0%); exon 21 L858R: 25 (18.2%); exon 18 G719: 5 (3.6%); exon 21 L861Q: 3 (2.2%); exon 20 insertion: 2 (1.5%)]) demonstrated an overall response rate (ORR) of 43.6% (95% CI=32.4-55.3), with a 5.1% (n=4) complete response (CR) rate, 38.5% (n=30) partial response (PR) rate and 34.6% (n=27) stable disease (SD) rate, a disease control rate (DCR) of 82.1% (95% CI=71.7-89.8), a median duration of response (DOR) of 7.0 months (95% CI=4.2-10.2) and a median progression-free survival (PFS) of 5.8 months (95% CI=5.4-8.3) (PMID: 39761483).
In the Phase III TROPION-Lung01 (NCT04656652) trial of Dato-DXd versus docetaxel in patients with pretreated NSCLC, patients treated with Dato-DXd (n=299 [EGFR mutations: 39 (13.0%)]) demonstrated an ORR of 26.4% (95% CI= 21.5-31.8), with a 1.3% (n=4) CR rate, 25.1% (n=75) PR rate and 49.8% (n=149) SD rate, a DCR of 77.3% (95% CI=72.1-81.9), a median DOR of 7.1 months (95% CI=5.6-10.9), a median PFS of 4.4 months (95% CI=4.2-5.6) and a median overall survival (OS) of 12.9 months (95% CI=11.0-13.9) (PMID: 39250535).

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George Nasioulas, PhD Molecular Biologist, Scientific Director, Medical ID:26025301255

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Patients treated with docetaxel (n=305 [EGFR mutations: 45 (14.8%)]) demonstrated an ORR of 12.8% (95% CI=9.3-17.1), with a 12.8% (n=39) PR rate and 50.2% (n=153) SD rate, a DCR of 64.9% (95% CI=59.3-70.3), a median DOR of 5.6 months (95% CI=5.4-8.1), a median PFS of 3.7 months (95% CI=2.9-4.2) (HR=0.75 [95% CI=0.62-0.91]; p=.004) and a median OS of 11.8 months (95% CI=10.1-12.8) (HR=0.94 [95% CI=0.78-1.14]; p=0.530) (PMID: 39250535).

Erlotinib

DrugBank

Erlotinib, a first-generation EGFR tyrosine kinase inhibitor (TKI), is approved with or without ramucirumab for the treatment of non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 (L858R) substitution mutations. Results of the Phase III EURTAC trial demonstrated that patients with NSCLC receiving erlotinib showed significant improvement in progression-free survival (PFS) (9.7 vs. 5.2 months; HR=0.37; p=0.0001) compared to those receiving platinum-based doublet chemotherapy (PMID: 22285168). The partial response rate with erlotinib was 56%, compared to 13% with chemotherapy, and was associated with a reduced toxicity profile (PMID: 22285168). The safety and efficacy of erlotinib have not been established in patients harboring EGFR mutations other than exon 19 deletion and exon 21 (L858R) substitution; however, the phase III IUNO trial demonstrated no difference in PFS between patients with NSCLC lacking EGFR exon 19 deletion or EGFR L858R mutation who were given erlotinib versus placebo as maintenance therapy (PMID: 27987585).

Gefitinib

DrugBank

Gefitinib, a first-generation EGFR tyrosine kinase inhibitor (TKI), is FDA-approved as first-line therapy in patients with non-small cell lung cancer (NSCLC) whose tumors harbor EGFR exon 19 deletion or exon 21 (L858R) substitution mutations. FDA approval is based on multiple clinical trials that demonstrated the efficacy of gefitinib in EGFR-mutant NSCLC and includes IPASS (PMID: 19692680, 21670455), NEJ002 (PMID: 20573926), WJTOG3405 (PMID: 20022809) and First-SIGNAL (PMID: 22370314). Response rates in EGFR-mutant lung cancers in these studies ranged from 55% to 85%, with median progression-free survival (PFS) of 8 to 10.8 months (PMID: 19692680, 21670455, 20573926, 20022809, 22370314). In one study comparing gefitinib with standard chemotherapy in pulmonary adenocarcinoma, the response rate with gefitinib in patients with EGFR mutations (47%) was nearly double that of patients who were EGFR wildtype (24%) (PMID: 19692680). Additionally, in the biomarker analysis and final overall survival (OS) analysis of the Phase III IPASS study, though OS was not different between the gefitinib and carboplatin/paclitaxel groups, 64.3% of patients assigned to chemotherapy had crossed over to treatment with EGFR TKIs; PFS in this study was significantly longer with gefitinib than chemotherapy in patients with EGFR mutation (HR=0.48) (PMID: 21670455). In a Phase II trial, the addition of carboplatin plus pemetrexed to gefitinib increased progression-free survival (20.9 months vs 11.9 months; HR = 0.490, P < .001) in patients with EGFR-mutant NSCLC compared to gefitinib alone (PMID: 31682542).

Osimertinib

DrugBank

Osimertinib is an orally available, small molecule third-generation EGFR T790M tyrosine kinase inhibitor (TKI) that is FDA-approved for adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, the treatment of adult patients with locally advanced, unresectable (stage III) NSCLC whose disease has not progressed during or following concurrent or sequential platinum-based chemoradiation therapy and whose

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tumors have EGFR exon 19 deletions or exon 21 L858R mutations and the first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test. EGFR exon 19 deletions and exon 21 L858R mutations for treatment with osimertinib were detected by the cobas EGFR Mutation Test v2, FoundationOne CDx, FoundationOne Liquid CDx or Guardant360 CDx. FDA approvals were based on the results of the Phase III ADAURA (NCT02511106) trial for adjuvant treatment, the Phase III LAURA (NCT03521154) trial for locally advanced, unresectable NSCLC treatment and the Phase III FLAURA (NCT02296125) trial for first-line monotherapy treatment.

In the Phase III ADAURA (NCT02511106) trial of osimertinib versus placebo in 682 patients with completely resected EGFR mutation-positive stage IB to IIIA NSCLC, 89% (95% CI=85-92) of patients in the osimertinib cohort (n=339 [55%, EGFR exon 19 deletion; 45%, EGFR L858R; 1%, EGFR T790M]) and 52% (95% CI=46-58) of patients in the placebo cohort (n=343 [55%, EGFR exon 19 deletion; 45%, EGFR L858R; 1%, EGFR T790M]) were alive and disease-free at 24 months (HR=0.20 [99.12% CI=0.14-0.30]; p<0.001) (PMID: 32955177).

In the Phase III LAURA (NCT03521154) trial of osimertinib versus placebo in 216 patients with unresectable EGFR mutation-positive stage III NSCLC without progression during or after chemoradiotherapy, the osimertinib cohort (n=143 [n=74, EGFR exon 19 deletion; n=68, EGFR L858R]) demonstrated an objective response rate (ORR) of 57% (95% CI=49-66), with a 2% (n=3) complete response (CR) rate, 55% (n=79) partial response (PR) rate and 31% (n=45) stable disease (SD) rate, a median progression-free survival (PFS) of 39.1 months (95% CI=31.5-NC) and a median duration of response (DOR) of 36.9 months (95% CI=30.1-NC). In contrast, the placebo cohort (n=73 [n=43, EGFR exon 19 deletion; n=30, EGFR L858R]) demonstrated an ORR of 33% (95% CI=22-45) (OR=2.77 [95% CI=1.54-5.08]), with a 1% (n=1) CR rate, 32% (n=23) PR rate and 47% (n=34) SD rate, a median PFS of 5.6 months (95% CI=3.7-7.4) (HR=0.16 [95% CI=0.10-0.24]; p<0.001) and a median DOR of 6.5 months (95% CI=3.6-8.3) (PMID: 38828946).

In the Phase III FLAURA (NCT02296125) trial of osimertinib versus standard EGFR TKI (gefitinib or erlotinib) in 556 patients with previously untreated, EGFR mutation-positive advanced NSCLC, the osimertinib cohort (n=279 [n=175, EGFR exon 19 deletion; n=104, EGFR L858R]) demonstrated an ORR of 80% (95% CI=75-85), with a 3% (n=7) CR rate, 77% (n=216) PR rate and 17% (n=47) SD rate, a median PFS of 18.9 months (95% CI=15.2-21.4), a median DOR of 17.2 months (95% CI=13.8-22.0) and a median overall survival (OS) could not be calculated (95% CI=NC-NC). In contrast, the standard EGFR TKI cohort (n=277 [n=174, EGFR exon 19 deletion; n=103, EGFR L858R]) demonstrated an ORR of 76% (95% CI=70-81), with a 1% (n=4) CR rate, 74% (n=206) PR rate and 17% (n=46) SD rate, a median PFS of 10.2 months (95% CI=9.6-11.1) (HR=0.46 [95% CI=0.37-0.57]; p<0.001), a median DOR of 8.5 months (95% CI=7.3-9.8) and a median OS that could not be calculated (95% CI=NC-NC) (HR=0.63 [95% CI=0.45-0.88]; p=0.007) (PMID: 29151359). In the final analysis of the OS in the Phase III FLAURA (NCT02296125) trial, the osimertinib cohort and standard EGFR TKI cohort demonstrated a median OS of 38.6 months (95% CI=34.5-41.8) and 31.8 months (95% CI=26.6-36.0), respectively (HR=0.80 [95.05% CI=0.64-1.00]; p=0.046) (PMID: 31751012).

Osimertinib+Chemotherapy DrugBank

Osimertinib is an orally available, small molecule third-generation EGFR T790M tyrosine kinase inhibitor (TKI) that is FDA-approved in combination with pemetrexed and platinum-based chemotherapy, the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations,

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as detected by an FDA-approved test. EGFR exon 19 deletions and exon 21 L858R mutations for treatment with osimertinib were detected by the cobas EGFR Mutation Test v2, FoundationOne CDx, FoundationOne Liquid CDx or Guardant360 CDx.

FDA approval is based on the results of the Phase III FLAURA2 (NCT04035486) trial of osimertinib plus chemotherapy (pemetrexed plus cisplatin or carboplatin) versus single-agent osimertinib in 557 patients with previously untreated, EGFR mutation-positive advanced NSCLC. In the Phase III FLAURA2 (NCT04035486) trial, the osimertinib plus chemotherapy cohort (n=279 [n=169, EGFR exon 19 deletion; n=106, EGFR L858R; n=3, both; n=1, unknown]) demonstrated a median progression-free survival (PFS) of 25.5 months (95% CI=24.7-NC), a median duration of response (DOR) of 24.0 months (95% CI=20.9-27.8) and an objective response rate (ORR) of 83% (95% CI=78-87), with an 83% partial response (PR) rate and <1% complete response (CR) rate. The osimertinib monotherapy cohort (n=278 [n=168, EGFR exon 19 deletion; n=106, EGFR L858R; n=3, both; n=2, unknown]) demonstrated a median PFS of 16.7 months (95% CI=14.1-21.3) (HR=0.62 [95% CI=0.49–0.79]; p<0.001), a median DOR of 15.3 months (95% CI=12.7–-9.4) and an ORR of 76% (95% CI=70-80), with a 75% PR rate and 1% CR rate (PMID: 37937763).

Erlotinib+Ramucirumab

DrugBank

Erlotinib, a first-generation EGFR tyrosine kinase inhibitor (TKI), is approved with or without ramucirumab for the treatment of non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 (L858R) substitution mutations. Results of the Phase III EURTAC trial demonstrated that patients with NSCLC receiving erlotinib showed significant improvement in progression-free survival (PFS) (9.7 vs. 5.2 months; HR=0.37; p=0.0001) compared to those receiving platinum-based doublet chemotherapy (PMID: 22285168). The partial response rate with erlotinib was 56%, compared to 13% with chemotherapy, and was associated with a reduced toxicity profile (PMID: 22285168). The safety and efficacy of erlotinib have not been established in patients harboring EGFR mutations other than exon 19 deletion and exon 21 (L858R) substitution; however, the phase III IUNO trial demonstrated no difference in PFS between patients with NSCLC lacking EGFR exon 19 deletion or EGFR L858R mutation who were given erlotinib versus placebo as maintenance therapy (PMID: 27987585).

Patritumab Deruxtecan

DrugBank

Patritumab deruxtecan (HER3-DXd) is an antibody-drug conjugate consisting of a HER3 antibody attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker. HER3 is the preferred heterodimeric partner for EGFR (PMID: 34084213, 30057690). In a phase I dose-escalation/expansion study (NCT03260491) of HER3-DXd in 57 patients with locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC) (n=33 with Exon 19 deletion), the objective response rate (ORR) was 39% (95% CI=26.0–52.4) and median progression-free survival (PFS) was 8.2 (95% CI=4.4–8.3) months (PMID: 34548309). In the phase II HERTHENA-Lung01 trial of HER3-DXd in 225 patients with previously treated EGFR-mutated NSCLC, the median PFS was 5.5 months (95% CI=5.1-5.9) and an objective response was observed in 67 patients (29.8%; 95% CI=23.9-36.2), with complete response observed in one patient (PMID: 37689979). In preclinical studies, in vitro and in vivo models containing HER3-expressing CM-3 cancer cells treated with U3-1402 (HER3-DXd) exhibited reduced cell viability and tumor volume, respectively (PMID: 31661465). In the Phase I U31402-A-U102 (NCT03260491) trial of HER3-DXd in 97 patients with EGFR-mutated NSCLC who had received prior EGFR tyrosine kinase inhibitor therapy and platinum-based chemotherapy (n=64, exon 19 deletion; n=29, L858R; n=4, G719A; n=2, L861Q; n=1, exon 19 insertion), the cohort demonstrated an ORR of 39.2% (n=38) (95% CI=29.4-49.6), with a 1% (n=1) complete response rate, 38.1% (n=37) partial

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response rate, 40.2% (n=39) stable disease rate and 12.4% (n=12) progressive disease rate, a median duration of response of 9.6 months (95% CI=6.9-15.4), a median PFS of 6.4 months (95% CI=4.9-8.3) and a median overall survival of 15.8 months (95% CI=10.8-21.5) (PMID: 38369013).

Genetic Variation:	*TP53*: c.832C>G (p.P278A)	VAF*: 22.5%	OncoKB

Gene information

TP53 encodes the p53 tumor suppressor protein, a transcription factor that responds to cellular stresses, including DNA damage and oncogenic activation, by inducing downstream anti-tumor responses such as DNA repair and apoptosis (PMID: 11099028). p53 levels are kept low in healthy cells due to negative regulation by MDM2/4, Cop1 and Trim24 and constant degradation by the ubiquitin-proteasome system (PMID: 36859359, 36207426). When DNA is damaged, a network of pathways is activated to detect and repair lesions in a cell- and context-specific manner (PMID: 36207426). p53 is rapidly phosphorylated by upstream regulators such as ATM, ATR, and CHL1/2, which results in the accumulation of stable p53 (PMID: 36207426). p53 then binds to specific DNA sequences to direct the expression of a wide variety of genes, including those involved in apoptosis, cell cycle arrest, DNA repair, senescence, stem cell differentiation, autophagy, cellular metabolism, and others (PMID: 27141080, 36859359, 36207426). Oncogenic mutations of TP53 often result in the dysregulation of p53 function, usually due to structural changes in the DNA binding domain (PMID: 36859359). Loss of p53 function can have various outcomes including tumorigenesis, invasion and metastasis, drug resistance, metabolic reprogramming, immune evasion and overall genomic instability (PMID: 36859359). TP53 is the most commonly mutated gene in human cancers, and germline mutations occur in the cancer predisposition syndrome Li-Fraumeni (PMID: 22713868, 21765642). Clinical and preclinical research into drugs that target TP53 is ongoing, notably with MDM2 inhibitors that aim to restore p53 function and are being tested in combination with other cancer therapies (PMID: 36859359, 37818252).

Variant Information

The TP53 P278A mutation is likely oncogenic. The TP53 P278A mutation is located in the DNA binding domain of the protein. In vitro studies have demonstrated that this mutation is likely inactivating, as evidenced by failure to transactivate p53-dependent genes in the mutant compared to wildtype (PMID: 24076587). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with TP53 P278A mutant non-small cell lung cancer.

*VAF: Variant Allele Frequency

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7. Clinical Trials to consider

TP53 associated clinical trials

NCT06739395	PHASE2
Title	Precision Medicine Trial Based on Molecular Matching Therapy for Patients With Standard Treatment Exhaustion
Treatment	Olaparib tablet | Temozolomide capsule | Anlotinib | Trametinib tablet | Dabrafenib | Vebreltinib Enteric Capsules | Alpelisib Pill | Sacituzumab Govitecan-Hziy 180 MG | Lenvatinib Capsules | Pazopanib Pill | Palbociclib Pill | Chidamide | PD-1/PD-L1/PD-1&CTLA4 inhibitor | Target Gene
Location	China

NCT06329206	PHASE1
Title	A Phase Ia/Ib Study of GH2616 Tablet in Subjects With Advanced Solid Tumors
Treatment	GH2616 Tablets
Location	China

Press here for a live search of clinical trials for TP53

EGFR associated clinical trials

NCT05748093	PHASE4
Title	Improving Osimertinib Exposure and Cost-effectiveness Using Pharmacokinetic Boosting With Cobicistat
Treatment	Cobicistat
Location	Netherlands

NCT06561620	PHASE4
Title	Befotertinib Adjuvant Therapy in Stage IA2-IB NSCLC Patients
Treatment	Befotertinib
Location	China

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NCT06838273	PHASE3
Title	A Study of BL-B01D1 in Combination With Osimertinib Versus Osimertinib as First-Line Treatment in Patients With EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer(PANKU-Lung04)
Treatment	BL-B01D1 | Osimertinib | Osimertinib
Location	China

NCT05382728	PHASE3
Title	Phase III Study of TY-9591 in Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer (FLETEO)
Treatment	TY-9591 | placebo Osimertinib | Osimertinib | placebo TY-9591
Location	China

NCT06674343	PHASE3
Title	Furmonertinib 160mg as First-line Treatment in Locally Advanced or Metastatic NSCLC With EGFR Classical Mutations
Treatment	Furmonertinib
Location	China

NCT05624996	PHASE3
Title	Testing the Addition of High Dose, Targeted Radiation to the Usual Treatment for Locally-Advanced Inoperable Non-Small Cell Lung Cancer
Treatment	Carboplatin | Cisplatin | Computed Tomography | Durvalumab | Etoposide | Image Guided Radiation Therapy | Nab-paclitaxel | Osimertinib | Paclitaxel | Pemetrexed | Positron Emission Tomography | Questionnaire Administration | Stereotactic Body Radiation Therapy
Location	Canada, United States

NCT06927986	PHASE3
Title	Phase III Trial of SYS6010 Versus Platinum-based Chemotherapy for EGFR-mutated NSCLC（SYNSTAR01）
Treatment	SYS6010 | Pemetrexed | Cisplatin | Carboplatin

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Location	China

NCT07100080	PHASE2 | PHASE3
Title	Study of Izalontamab Brengitecan (BMS-986507) Versus Platinum-Pemetrexed for EGFR-mutated Non-small Cell Lung Cancer After Failure of EGFR TKI Therapy (IZABRIGHT-Lung01)
Treatment	Iza-bren | Carboplatin | Cisplatin | Pemetrexed
Location	Argentina, Belgium, Canada, Chile, China, Colombia, France, Germany, Greece, India, Italy, Japan, Mexico, Netherlands, Norway, Poland, Romania, Singapore, South Korea, Spain, Switzerland, Taiwan, Thailand, United Kingdom, United States

NCT06417008	PHASE2 | PHASE3
Title	A Study of HS-20117 Combined With Aumolertinib in Participants With Advanced Non-Squamous Non-Small Cell Lung Cancer
Treatment	HS-20117 | Aumolertinib
Location	China

NCT04951635	PHASE3
Title	A Phase III Study to Assess the Effects of Almonertinib Following Chemoradiation in Patients With Stage III Unresectable Non-small Cell Lung Cancer
Treatment	Almonertinib | Placebo Almonertinib
Location	China

NCT06745908	PHASE3
Title	Clinical Trial of N-803 Plus Tislelizumab or Prior Failed Immune Checkpoint Inhibitor and Docetaxel Versus Docetaxel Monotherapy in Participants With Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Acquired Resistance to Immune Checkpoint In
Treatment	N-803 | Tislelizumab | Docetaxel | Prior failed checkpoint inhibitor
Location	Canada, United Kingdom, United States

NCT07005102	PHASE2 | PHASE3

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Title	A Study to Assess Adverse Events, Change in Disease Activity of Intravenous Telisotuzumab Adizutecan in Combination With Osimertinib as First-Line Treatment in Adult Participants With Locally Advanced Unresectable or Metastatic EGFR-Mutated Non-Squamous Non-Small Cell Lung Cancer
Treatment	Standard of Care | Telisotuzumab Adizutecan | Osimertinib (Osi) | Cisplatin | Carboplatin | Pemetrexed
Location	Australia, Belgium, Canada, China, Israel, Italy, Japan, Portugal, Singapore, South Korea, Spain, Taiwan, United States

NCT06486142	**PHASE3**
Title	EGFR-mutated Lung Cancer in Randomized Investigator-Initiated Study
Treatment	Afatinib/Dacomitinib | Osimertinib
Location	Sweden

NCT06829459	**PHASE3**
Title	A Study to Evaluate the Efficacy and Safety of Glumetinib Combined With Osimertinib Mesylate Versus Platinum-based Doublet Chemotherapy in Non-Small Cell Lung Cancer Patients After Resistance to EGFR-TKIs
Treatment	Glumetinib | Osimertinib mesylate | Pemetrexed | Cisplatin or carboplatin
Location	China

NCT04928846	**PHASE3**
Title	A Study to Assess Disease Activity and Adverse Events of Intravenous (IV) Telisotuzumab Vedotin Compared to IV Docetaxel in Adult Participants With Previously Treated Non-Squamous Non-Small Cell Lung Cancer (NSCLC)
Treatment	Telisotuzumab Vedotin | Docetaxel
Location	Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Czechia, Denmark, France, Germany, Greece, Israel, Italy, Japan, Mexico, Netherlands, Poland, Portugal, Romania, Slovakia, South Africa, South Korea, Spain, Sweden, Taiwan, Turkey (Türkiye), United Kingdom, United States

NCT04853342	**PHASE3**

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Name	-	Report No	26xxxxxxGR

Title	To Assess the Efficacy and Safety of Furmonertinib Versus Placebo, in Patients With Epidermal Growth Factor Receptor Mutation Positive Stage II-IIIA Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy
Treatment	Drug: Furmonertinib 80 mg | Furmonertinib 80 mg placebo
Location	China

NCT06970639	**PHASE3**
Title	A Study Evaluating Furmonertinib Plus Platinum-based Doublet Chemotherapy Versus Osimertinib in Patients With Epidermal Growth Factor Receptor (EGFR) Sensitizing Mutation-Positive Non-squamous Non-Small Cell Lung Cancer (NSCLC) and Brain Metastases
Treatment	Furmonertinib Mesilate Tablets | Carboplatin Injection | Cisplatin for injection | Pemetrexed Disodium for Injection | Osimertinib Mesylate Tablets
Location	China

NCT04181060	**PHASE3**
Title	Osimertinib With or Without Bevacizumab as Initial Treatment for Patients With EGFR-Mutant Lung Cancer
Treatment	Bevacizumab | Biospecimen Collection | Computed Tomography | Echocardiography Test | Magnetic Resonance Imaging | Multigated Acquisition Scan | Osimertinib
Location	United States

NCT06041776	**PHASE3**
Title	Adjuvant Befotertinib in Stage IB-IIIB Non-small Cell Lung Cancer With Positive EGFR Sensitive Mutations
Treatment	Befotertinib + Icotinib placebo | Icotinib + Befotertinib placebo
Location	China

NCT06043973	**PHASE3**
Title	Almonertinib Combined With Anlotinib as First-line Treatment for Advanced Non-small Cell Lung Cance
Treatment	almonertinib

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Name	-	Report No	26xxxxxxGR

Location	China

NCT06735391	PHASE3
Title	A Clinical Study of JMT101 in Combination With Osimertinib Versus Osimertinib Alone as First-Line Treatment for Patients With Locally Advanced or Metastatic Non-Squamous Non-Small Cell Lung Cancer (NSCLC) Harboring Epidermal Growth Factor Receptor (EGFR) Sensitive Mutations
Treatment	JMT101 | Osimertinib
Location	China

NCT06080776	PHASE3
Title	SH-1028 Tablets Versus Placebo as Adjuvant Therapy in Resected Stage II-IIIB NSCLC With Sensitizing EGFR Mutations
Treatment	SH-1028 tablets | Placebo SH-1028 tablets
Location	China

NCT06350097	PHASE3
Title	Phase III, Open-label Study of First-line Osimertinib With or Without Datopotamab Deruxtecan for EGFRm Locally Advanced or Metastatic Non-small Cell Lung Cancer
Treatment	Osimertinib | Datopotamab Deruxtecan
Location	Australia, Brazil, Canada, China, France, Germany, Hong Kong, India, Italy, Japan, Poland, Puerto Rico, South Korea, Spain, Taiwan, Thailand, Turkey (Türkiye), United States, Vietnam

NCT03297606	PHASE2
Title	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)
Treatment	Olaparib | Dasatinib | Nivolumab plus Ipilimumab | Axitinib | Bosutinib | Crizotinib | Palbociclib | Sunitinib | Temsirolimus | Erlotinib | Trastuzumab plus Pertuzumab | Vemurafenib plus Cobimetinib | Vismodegib | Tucatinib
Location	Canada

NCT07231068	PHASE1 | PHASE2

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Name	-	Report No	26xxxxxxGR

Title	A Dose-escalation and Dose-expansion Phase I/Phase II Clinical Study of Dositinib Mesylate Tablets (90-1408) in the Treatment of Locally Advanced or Metastatic Non-small Cell Lung Cancer With Positive EGFR Mutation
Treatment	Dositinib mesylate tablets
Location	China

NCT06071013	**PHASE1 | PHASE2**
Title	Nintedanib Plus EGFR TKI In EGFR-mutated Non-small Cell Lung Cancer Patients
Treatment	Nintedanib, gefitinib, erlotinib, afatinib, osimertinib
Location	Taiwan

NCT06222489	**PHASE2**
Title	Whole Body HER3 Quantification With Radiolabelled Patritumab Deruxtecan (HER3-DXd) PET/CT
Treatment	89Zr-Patritumab deruxtecan
Location	Netherlands

NCT05456256	**PHASE2**
Title	A Study of LP-300 With Carboplatin and Pemetrexed in Never Smokers With Advanced Lung Adenocarcinoma
Treatment	LP-300 | Pemetrexed | Carboplatin
Location	Japan, Taiwan, United States

NCT05536505	**PHASE2**
Title	Adjuvant Treatment Based on MRD for EGFR Mutant NSCLC
Treatment	Adjuvant treatment for MRD positivity
Location	China

NCT06348927	**PHASE2**

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Name	-	Report No	26xxxxxxGR

Title	Sunvozertinib Plus Anlotinib as 1L Treatment in EGFR-Sensitive Mutations Combined With Co-Mutations Advanced NSCLC
Treatment	sunvozertinib in combination with Anlotinib
Location	China

NCT04777084	**PHASE2**
Title	The Efficacy and Safety of the Bispecific Anti-PD-1/PD-L1 Antibody IBI318 Combined with Lenvatinib in NSCLC.
Treatment	IBI318
Location	China

NCT05579366	**PHASE1 | PHASE2**
Title	Rinatabart Sesutecan (Rina-S, PRO1184, GEN1184) for Advanced Solid Tumors (GCT1184-01/ PRO1184-001)
Treatment	Rina-S | Carboplatin | Bevacizumab | Pembrolizumab
Location	China, Japan, United States

NCT05271916	**PHASE1 | PHASE2**
Title	First-line Treatment With Dacomitinib Plus Anlotinib for Patients With Advanced NSCLC With EGFR 21L858R Mutations
Treatment	Dacomitinib+Anlotinib | Dacomitinib
Location	China

NCT06014827	**PHASE2**
Title	Biologically Guided Radiation Therapy (BgRT) and Stereotactic Body Radiation Therapy (SBRT) to Tyrosine Kinase Inhibitor in Oligoprogressive Oncogenic Positive Non-Small Cell Lung Carcinoma
Treatment	Biospecimen Collection | Computed Tomography | Osimertinib | Positron Emission Tomography | Stereotactic Body Radiation Therapy | Survey Administration
Location	United States

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Name	-	Report No	26xxxxxxGR

NCT07070440	PHASE1 | PHASE2
Title	DZD6008 Combination Therapy in Patients With Locally Advanced or Metastatic NSCLC With EGFR Mutation (TIAN-SHAN7)
Treatment	DZD6008 | Pemetrexed | Carboplatin | Docetaxel
Location	China

NCT06276283	PHASE2
Title	DZD9008 In Combination With Bevacizumab in Locally Advanced or Metastatic NSCLC Patients With EGFR Mutation (WU-KONG29)
Treatment	DZD9008 plus Bevacizumab
Location	China

NCT06431243	PHASE1 | PHASE2
Title	A Clinical Study of Purinostat Mesylate for Injection in Patients With Advanced Solid Tumors
Treatment	A0/B0 group Purinostat Mesylate 11.2mg/m2 | A0/B0 group Purinostat Mesylate 15mg/m2 | A group Purinostat Mesylate 6mg/m2 | A group Purinostat Mesylate 8.4mg/m2 | A group Purinostat Mesylate 11.2mg/m2 | A group Purinostat Mesylate 15 mg/m2 | B group Purinostat Mesylate 6 mg/m2 | B group Purinostat Mesylate 8.4 mg/m2 | B group Purinostat Mesylate 11.2mg/m2 | B group Purinostat Mesylate 15mg/m2
Location	China

NCT05686434	PHASE2
Title	Osimertinib Therapy After Resection in High-risk Stage I EGFRm NSCLC (OSTAR)
Treatment	Osimertinib
Location	China

NCT05785741	PHASE1 | PHASE2
Title	A Study of DB-1310 in Advanced/Metastatic Solid Tumors
Treatment	DB-1310 | Trastuzumab | Osimertinib | capecitabine
Location	China, United States

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Name	-	Report No	26xxxxxxGR

NCT05104788	PHASE2
Title	A Study of Icotinib With Chemotherapy as Neoadjuvant Therapy for Patients With EGFRm Positive Resectable Non-Small Cell Lung Cancer
Treatment	Icotinib | Cisplatin | Carboplatin | Pemetrexed
Location	China

NCT06667076	PHASE2
Title	A Study of Amivantamab in Combination With Lazertinib, or Amivantamab in Combination With Platinum-Based Chemotherapy, for Common Epidermal Growth Factor Receptor (EGFR)-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)
Treatment	Amivantamab | Lazertinib | Chemotherapy: Pemetrexed | Chemotherapy: Carboplatin
Location	Belgium, Finland, France, Germany, Greece, Israel, Italy, Poland, Portugal, Puerto Rico, Saudi Arabia, Spain, United Kingdom, United States

NCT06668103	PHASE2
Title	A Phase 2 Clinical Study of Combination Therapy With ABSK043 and Firmonertinib
Treatment	ABSK043 in combination with Firmonertinib
Location	China

NCT06924398	PHASE2
Title	Postoperative EGFR-TKI Therapy forContralateral Pulmonary Nodules in Patients With EGFR-Mutant NSCLC（ARMOR2501）
Treatment	Postoperative EGFR-TKI Therapy
Location	China

NCT04486833	PHASE1 | PHASE2
Title	Quaratusugene Ozeplasmid (Reqorsa) and Osimertinib in Patients With Advanced Lung Cancer Who Progressed on Osimertinib
Treatment	quaratusugene ozeplasmid | osimertinib | Platinum-Based Chemotherapy

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Name	-	Report No	26xxxxxxGR

Location	United States

NCT06709859	PHASE2
Title	Afatinib Combined With Chemotherapy as Conversion Therapy in Unresectable EGFR Sensitive Mutation-positive Stage III NSCLC
Treatment	Afatinib plus chemotherapy as conversion treatment
Location	China

NCT06951464	PHASE2
Title	A Study of BL-B01D1 and Almonertinib in Patients With Resectable EGFR+ Stage II-IIIB NSCLC
Treatment	BL-B01D1 | Almonertinib
Location	China

NCT06355609	PHASE2
Title	Sunvozertinib Plus Anlotinib as 1L Treatment in EGFR Mutant Advanced NSCLC-RW
Treatment	sunvozertinib in combination with Anlotinib
Location	China

NCT06618287	PHASE1 | PHASE2
Title	A Study to Evaluate the Safety, Tolerability, Drug Levels, and Preliminary Efficacy of BMS-986507 Combinations in Adult Participants With Advanced Solid Tumors
Treatment	BMS-986507 | Osimertinib | Pembrolizumab | Nivolumab | Pumitamig
Location	Australia, Canada, Chile, France, Italy, Netherlands, Spain, United Kingdom, United States

NCT06755684	PHASE2
Title	Neoadjuvant Befotertinib Combined Bevacizumab or Platinum-based Double Chemotherapy for Resectable Locally-advanced EGFR Mutation-positive Non-Small Cell Lung Cancer
Treatment	Befotertinib combined Bevacizumab | Befotertinib combined platinum-based double chemotherapy

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Name	-	Report No	26xxxxxGR

Location	China

NCT05351788	PHASE2
Title	SKB264 Combinatiton Therapy in Patients With Advanced or Metastatic Non-small Cell Lung Cancer.
Treatment	SKB264 | KL-A167 | Carboplatin | Cisplatin
Location	China

NCT05498428	PHASE2
Title	A Study of Amivantamab in Participants With Advanced or Metastatic Solid Tumors Including Epidermal Growth Factor Receptor (EGFR)-Mutated Non-Small Cell Lung Cancer
Treatment	Amivantamab | Lazertinib | Carboplatin | Pemetrexed | Direct Oral Anticoagulant (DOAC) | Low Molecular Weight Heparin (LMWH)
Location	Brazil, China, France, Germany, Israel, Italy, Japan, Malaysia, South Korea, Spain, United Kingdom, United States

NCT05011487	PHASE2
Title	Neoadjuvant Osimertinib + Chemotherapy for EGFR-mutant Stage III NSCLC
Treatment	Osimertinib | Cisplatin | Pemetrexed
Location	China

NCT05394831	PHASE1 | PHASE2
Title	A Phase 1/2 Study to Evaluate the Safety, Tolerability and PK of JIN-A02 in Patients With EGFR Mutant Advanced NSCLC
Treatment	JIN-A02
Location	South Korea, Thailand, United States

NCT06483555	PHASE1 | PHASE2
Title	Basal-like PDAC Treated With Gemcitabine, Erlotinib, and Nab-paclitaxel

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Name	-	Report No	26xxxxxxGR

Treatment	Gemcitabine | Nab paclitaxel | Erlotinib | NALIRIFOX | Folfirinox
Location	United States

NCT06295432	**PHASE2**
Title	A Phase II Clinical Trial of DZD9008 in Combination With AZD4205 in Standard Treatment Failed NSCLC Patients With EGFR Mutations (WU-KONG21)
Treatment	DZD9008+AZD4205
Location	China

NCT06706076	**PHASE1 | PHASE2**
Title	A Study of BH-30643 in Subjects With Locally Advanced or Metastatic NSCLC Harboring EGFR and/or HER2 Mutations
Treatment	BH-30643 | BH-30643 combo therapy with Carboplatin/Pemetrexed | BH-30643
Location	Australia, Canada, Hong Kong, Japan, Malaysia, Singapore, South Korea, Taiwan, United States

NCT04591002	**PHASE2**
Title	Osimertinib to Suppress the Progression of GGN(EGFR Mutation-positive)
Treatment	Osimertinib 80 MG
Location	South Korea

NCT06081907	**PHASE1 | PHASE2**
Title	The Efficacy and Safety of IBI363 in Solid Tumors
Treatment	IBI363 | IBI363 | IBI363 | IBI363 | IBI363
Location	China

NCT05284539	**PHASE2**
Title	Efficacy of Platinum-based Chemotherapy Plus Immune Checkpoint Inhibitors for EGFR/ALK/ROS1 Mutant Lung Cancer

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Name	-	Report No	26xxxxxxGR

Treatment	Pemetrexed, Cisplatin, Bevacizumab Plus Pembrolizumab
Location	China

NCT04335292	PHASE2
Title	Osimertinib Then Chemotherapy in EGFR-mutated Lung Cancer with Osimertinib Third-line Rechallenge
Treatment	Osimertinib First-Line | Platinum + Pemetrexed Chemotherapy Second-Line | Osimertinib Third-Line
Location	Canada

NCT04423185	PHASE2
Title	PLATFORM Study of Precision Medicine for Rare Tumors
Treatment	Almonertinib 110 MG | Dacomitinib 45 MG | Alectinib 150 MG | Crizotinib 250 MG | Pyrotinib 160/80 MG | Imatinib 400 MG | Niraparib 200/300 MG | Palbociclib 125mg | Vemurafenib 240 MG | Sintilimab 100MG | Atezolizumab 1680 MG
Location	China

NCT06631989	PHASE1 | PHASE2
Title	A Study to Assess the Efficacy and Safety of WSD0922-FU in Patients With EGFRm+ Advanced Non-small Cell Lung Cancer
Treatment	WSD0922-FU
Location	China

NCT04410796	PHASE2
Title	Osimertinib Alone or With Chemotherapy for EGFR-Mutant Lung Cancers
Treatment	Osimertinib | Carboplatin | Pemetrexed
Location	United States

NCT06758557	PHASE1 | PHASE2

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Name	-	Report No	26xxxxxxGR

Title	A Study to Evaluate the Safety and Efficacy of HB0025 Injection in Patients With Advanced Solid Tumor
Treatment	HB0025 | Pemetrexed | Paclitaxel | Carboplatin
Location	China

NCT06363734	**PHASE2**
Title	Osimertinib Plus Dalpiciclib in Patients With EGFR-mutant, CDK4/6 Pathway Aberrant, Advanced Non-small Cell Lung Cancer Following Acquired Resistance to Third-generation EGFR TKI: a Phase II Trial
Treatment	Osimertinib plus Dalpiciclib
Location	China

NCT06109558	**PHASE1 | PHASE2**
Title	The Efficacy and Safety of LMV-12 Combined With Osimertinib in NSCLC
Treatment	LMV-12(HE003)
Location	China

NCT07070232	**PHASE1 | PHASE2**
Title	A Clinical Study to Test if an Investigational Treatment Called BNT326 is Safe and Potentially Beneficial When Used Alone or in Combination With Other Investigational Treatments Such as BNT327, for People With Advanced Malignant Tumors
Treatment	BNT326 | Pumitamig | Itraconazole | Paroxetine
Location	Australia, Belgium, Germany, Italy, Spain, Turkey (Türkiye), United Kingdom, United States

NCT07206498	**PHASE1 | PHASE2**
Title	A Study to Evaluate Safety and Efficacy of WSD0922-FU Combo With Osimertinib for NSCLC
Treatment	Osimertinib (Tagrisso®) | WSD0922-FU
Location	China

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Name	-	Report No	26xxxxxxGR

NCT06394674	PHASE2
Title	High-dose Furmonertinib in the Treatment in Patients With Advanced, Metastatic NSCLC With Progressed After First- or Second-line Treatment With Osimertinib
Treatment	Furmonertinib
Location	China

NCT05528458	PHASE2
Title	Osimertinib to Suppress the Progression of Remaining GGN for EGFR Mutation-positive Stage IB-IIIA Lung Adenocarcinoma
Treatment	Osimertinib 80Mg Tab
Location	South Korea

NCT05533697	PHASE1 | PHASE2
Title	Study of mRNA-4359 Administered Alone and in Combination With Immune Checkpoint Blockade in Participants With Advanced Solid Tumors
Treatment	mRNA-4359 | Pembrolizumab | Ipilimumab | Nivolumab
Location	Australia, Germany, Italy, Poland, Spain, United Kingdom, United States

NCT04322890	PHASE2
Title	Treatment Strategies and Survival Outcome for Non-small Cell Lung Cancer With Oncogenic Mutation
Treatment	Osimertinib | Alectinib 150 MG | Crizotinib 250 MG | Savolitinib, Crizotinib. | Chemotherapy
Location	China

NCT06306456	PHASE1 | PHASE2
Title	A Phase Ib/II Clinical Study of GH21 Capsules Combined With Osimertinib Mesylate Tablets in Patients With NSCLC
Treatment	GH21 | Tagrisso
Location	China

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Name	-	Report No	26xxxxxxGR

NCT07181499	PHASE2
Title	Sequential Chemotherapy With Befotertinib in Non-Small Cell Lung Cancer (NSCLC) Patients With Resistance to Third-Generation EGFR-TKI
Treatment	Befotertinib | Pemetrexed + Carboplatin
Location	China

NCT06784791	PHASE2
Title	Preoperative Amivantamab or Amivantamab and Carboplatin/Pemetrexed Treatment in Patients With Resectable Non-small-cell Lung Cancer Harboring Oncogenic EGFR Mutations (NEOpredict-EGFR)
Treatment	Amivantamab Intravenous | Carboplatin/Pemetrexed
Location	Belgium, Germany, Netherlands

NCT05442060	PHASE2
Title	To Evaluate OBI-833/OBI-821 in Combination With First-Line Erlotinib in Patients With EGFR-Mutated, Globo H-Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer
Treatment	30 µg OBI-833/100 µg OBI-821 | Erlotinib (150 mg daily)
Location	Taiwan

NCT06652048	PHASE2
Title	High-dose Furmonertinib or Combined With Chemotherapy in EGFR-mutant Advanced NSCLC After Disease Progression on Third-generation EGFR-TKI
Treatment	Furmonertinib 160mg QD | Furmonertinib 240mg QD | Furmonertinib 160mg QD plus Chemotherapy
Location	China

NCT07073365	PHASE2
Title	Bolstering Outcomes After Induction With Osimertinib Plus Chemotherapy Through Optimized Site-Directed Primary Tumor Therapy (BOOST Trial)
Treatment	Local Therapy (Surgery or Radiotherapy)
Location	South Korea

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Name	-	Report No	26xxxxxxGR

NCT07110883	PHASE1
Title	A Clinical Study of SYS6023 in Patients With Advanced Solid Tumors
Treatment	SYS6023
Location	China

NCT06046495	PHASE1
Title	A Study of the Oral EGFR Inhibitor PLB1004 in Non-Small Cell Lung Cancer
Treatment	PLB1004
Location	United States

NCT06210815	PHASE1
Title	A Study of HLX42 in Advanced/Metastatic Solid Tumors
Treatment	HLX42
Location	China

NCT04429542	PHASE1
Title	Study of Safety and Tolerability of BCA101 Monotherapy and in Combination Therapy in Patients With EGFR-driven Advanced Solid Tumors
Treatment	BCA101 | Pembrolizumab
Location	Australia, Canada, United States

NCT06905197	PHASE1
Title	A Multinational Study Assessing an Oral EGFR Inhibitor, DZD6008 in Patients Who Have Advanced NSCLC With EGFR Mutations (TIAN-SHAN1)
Treatment	DZD6008 | Sunvozertinib
Location	Australia, United States

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Name	-	Report No	26xxxxxGR

NCT06431594	PHASE1
Title	A Study to Evaluate the Safety,Tolerability, Pharmacokinetics and Clinical Activity of Mocertatug Rezetecan for Injection in Participants With Advanced Solid Tumors (BEHOLD-1)
Treatment	Mocertatug rezetecan
Location	Argentina, Australia, Belgium, Brazil, Canada, Finland, France, Italy, Japan, Netherlands, South Korea, Spain, Sweden, United Kingdom, United States

NCT05401110	PHASE1
Title	Study of Osimertinib With Carotuximab in Advanced, EGFR-mutated Non-Small Cell Lung Cancer
Treatment	Osimertinib | Carotuximab
Location	United States

NCT05948865	PHASE1
Title	A Phase 1 Study of CPO301 in Adult Patients With Advanced or Metastatic Solid Tumors
Treatment	CPO301
Location	Canada, United States

NCT04412616	PHASE1
Title	ZZ06 in Adult Patients With Advanced Solid Tumor Malignancies
Treatment	ZZ06
Location	China, United States

NCT07130916	PHASE1
Title	A Study of Aumolertinib in European Participants With Non-Small Cell Lung Cancer
Treatment	Aumolertinib
Location	Bosnia and Herzegovina, Bulgaria, Moldova

NCT04780568	PHASE1

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Name	-	Report No	26xxxxxxGR

Title	Osimertinib and Tegavivint as First-Line Therapy for the Treatment of Metastatic EGFR-Mutant Non-small Cell Lung Cancer
Treatment	Osimertinib | Tegavivint | Echocardiography Test | Multigated Acquisition Scan | Computed Tomography | FDG-Positron Emission Tomography | Biospecimen Collection
Location	United States

NCT05983432	**PHASE1**
Title	Evaluate BL-B01D1 in Patients With Metastatic or Unresectable Non-Small Cell Lung Cancer (NSCLC) and Other Solid Tumors
Treatment	BL-B01D1
Location	France, Italy, Japan, Spain, United States

NCT06926413	**PHASE1**
Title	A Study Evaluating the Effect of Aumolertinib on the Pharmacokinetics of Midazolam in Patients With NSCLC
Treatment	Aumolertinib ; midazolam
Location	China

NCT07085091	**PHASE1**
Title	A First in Human Study of ALX2004 With Advanced or Metastatic Selected Solid Tumors
Treatment	ALX2004 | ALX2004 | ALX2004
Location	United States

NCT06813365	**PHASE1**
Title	Assessing an Oral EGFR Inhibitor, DZD6008 in Patients Who Have Advanced NSCLC With EGFR Mutations (TIAN-SHAN2)
Treatment	DZD6008
Location	China

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Name	-	Report No	26xxxxxxGR

NCT04762199	PHASE1
Title	MRX-2843 and Osimertinib for the Treatment of Advanced EGFR Mutant Non-small Cell Lung Cancer
Treatment	Flt3/MerTK Inhibitor MRX-2843 | Osimertinib
Location	United States

NCT06621563	PHASE1
Title	Phase Ib Trial of HS-20117 in Combination With Other Drugs in Advanced Solid Tumors
Treatment	HS-20117 combined HS-20093 | HS-20117 combined Platinum-containing chemotherapy | HS-20117 combined HS-20093 and 5-FU | HS-20117+CAPEOX | HS-20117+FOLFIRI | HS-20117+mFOLFOX6
Location	China

Press here for a live search of clinical trials for EGFR

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Name	-	Report No	26xxxxxxGR

8. Appendix

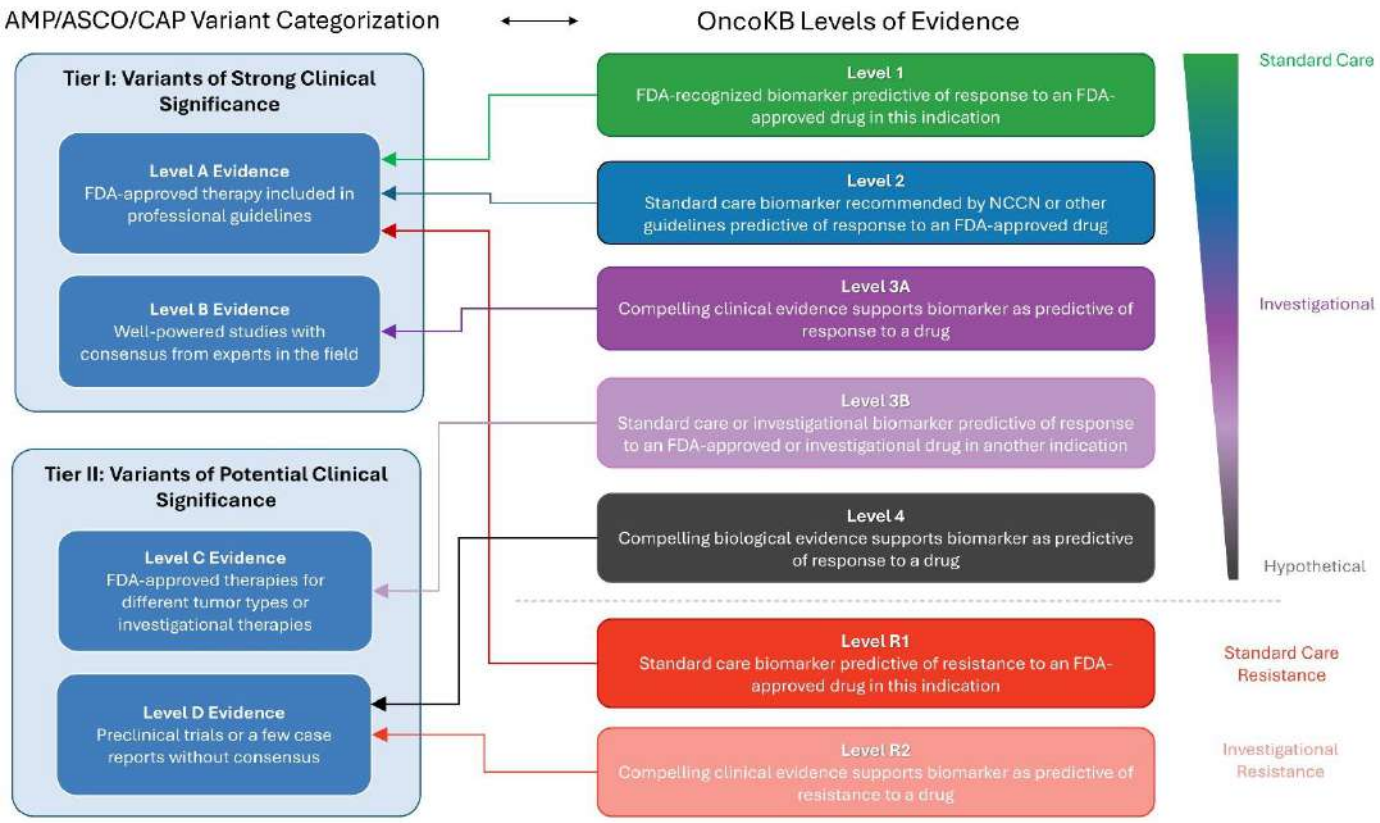

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

1. Li MM, Datto M, Duncavage EJ, et al. J Mol Diagn. 2017 Jan;19(1):4-23.
2. Leichsenring J, Horak P, Kreutzfeldt S, et al. Int J Cancer. 2019 Dec 1;145(11):2996-3010.

ERBB2 (HER2) expression by IHC

ERBB2, a receptor tyrosine kinase, is altered by mutation, amplification and/or overexpression in various cancer types, most frequently in breast, esophagogastric and endometrial cancers. FDA has granted approval to several anti-ERRB2 regimens, either as single or combination therapy for various cancer types. In addition, recently FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki, for adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

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Name	-	Report No	26xxxxxxGR

Table S1. ERBB2 Biomarkers associated with treatment response (LoE)

Cancer Type	3+ IHC	2+ IHC & ≥2 FISH	ERBB2 amplification by NGS	IHC 1+ or IHC 2+/ISH -ve
Breast Cancer	Trastuzumab Deruxtecan (A) Trastuzumab (A) Ado-Trastuzumab Emtansine (A) Lapatinib + Capecitabine (A) Lapatinib + Letrozole (A) Margetuximab + Chemotherapy (A) Neratinib (A) Neratinib + Capecitabine (A) Trastuzumab + Tucatinib + Capecitabine (A) Trastuzumab + Chemotherapy (A) Trastuzumab + Pertuzumab + Chemotherapy (A)	Trastuzumab Deruxtecan (A) Ado-Trastuzumab Emtansine (A) Lapatinib + Capecitabine (A) Lapatinib + Letrozole (A) Margetuximab + Chemotherapy (A) Neratinib (A) Neratinib + Capecitabine (A) Trastuzumab + Tucatinib + Capecitabine (A) Trastuzumab + Chemotherapy (A) Trastuzumab + Pertuzumab + Chemotherapy (A) Trastuzumab (C)	Trastuzumab Deruxtecan (C) Trastuzumab (C) Ado-Trastuzumab Emtansine (C) Lapatinib + Capecitabine (C) Lapatinib + Letrozole (C) Margetuximab + Chemotherapy (C) Neratinib (C) Neratinib + Capecitabine (C) Trastuzumab + Tucatinib + Capecitabine (C) Trastuzumab + Chemotherapy (C) Trastuzumab + Pertuzumab + Chemotherapy (C)	Trastuzumab Deruxtecan (A)
Colorectal Cancer	Trastuzumab Deruxtecan (A) Tucatinib + Trastuzumab (A) Lapatinib + Trastuzumab (A) Trastuzumab + Pertuzumab (A)	Tucatinib + Trastuzumab (A) Lapatinib + Trastuzumab (A) Trastuzumab + Pertuzumab (A) Trastuzumab Deruxtecan (C)	Tucatinib + Trastuzumab (A) *(RAS/BRAF wild type)* Trastuzumab Deruxtecan (C) Lapatinib + Trastuzumab (C) *(RAS/BRAF wild type)* Trastuzumab + Pertuzumab (C) *(RAS/BRAF wild type)*	N/A
Gastric/GEJ	Trastuzumab Deruxtecan (A) Trastuzumab + Chemotherapy (A) Pembrolizumab + Trastuzumab + Chemotherapy (A) *(PD-L1 with CPS>1% required)*	Pembrolizumab+ Trastuzumab + Chemotherapy (A) *(PD-L1 with CPS>1% required)* Trastuzumab + Chemotherapy (A) Trastuzumab Deruxtecan (A)	Pembrolizumab+ Trastuzumab + Chemotherapy (C) *(PD-L1 with CPS>1% required)* Trastuzumab + Chemotherapy (C) Trastuzumab Deruxtecan (C)	N/A
Billiary Tract	Trastuzumab Deruxtecan (A) Zanidatamab-hrii (A) Trastuzumab + Pertuzumab (A) Tucatinib + Trastuzumab (A)	Trastuzumab Deruxtecan (C) Zanidatamab-hrii (C) Trastuzumab + Pertuzumab (A) Tucatinib + Trastuzumab (A)	Trastuzumab Deruxtecan (C) Zanidatamab-hrii (C) Trastuzumab + Pertuzumab (C) Tucatinib + Trastuzumab (C)	N/A
Uterine Serous Carcinoma/ Papillary Serous	Trastuzumab Deruxtecan (A) Trastuzumab + Carboplatin-Taxol Regimen (A)	Trastuzumab Deruxtecan (C) Trastuzumab + Carboplatin-Taxol Regimen (C)	Trastuzumab Deruxtecan (C) Trastuzumab + Carboplatin-Taxol Regimen (C)	N/A
Lung Cancer	Trastuzumab Deruxtecan (A)	Trastuzumab Deruxtecan (C)	Trastuzumab Deruxtecan (C)	N/A
All tumors	Trastuzumab Deruxtecan (A)	Trastuzumab Deruxtecan (C)	Trastuzumab Deruxtecan (C)	N/A

Table S2. PD-L1 interpretation and cut-offs.

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Cancer type	Therapy	PD-L1	Cut-off	We report
Non-Small Cell Lung Cancer (NSCLC)	Anti-PD-1 [1-4]	VENTANA (SP263)	1L TPS ≥ 50% 2L TPS ≥ 1%	%TPS
	Anti-PD-L1 [5-7]	VENTANA (SP263)	2L TPS ≥ 1%	%TPS
		VENTANA (SP263)	1L TPS ≥ 50%	%TPS
		VENTANA (SP142)	1L TC ≥ 50% or IC ≥ 10%	%TC/%IC
	Anti-PD-1 + Anti-CTLA-4 [8]	VENTANA (SP263)	1L TPS ≥ 1%	%TPS
Urothelial Cancer (UC)	Anti-PD-1 [9]	Dako 22C3	1L CPS ≥ 10	CPS
	Anti-PD-1 [19]	VENTANA (SP263)	1L TC≥ 1%	%TC
	Anti-PD-L1 [10]	VENTANA (SP142)	2L IC ≥ 5%	%IC
Triple Negative Breast Cancer (TNBC)	Anti-PD-L1 [11]	VENTANA (SP142)	1L IC ≥ 1%	%IC
	Anti-PD-1 [12] + chemotherapy	Dako 22C3	1L CPS ≥ 10	CPS
Cervical cancer	Anti-PD-1 [16]	Dako 22C3	2L CPS ≥ 1	CPS
Head and Neck Squamous Cell Carcinoma (HNSCC)	Anti-PD-1 [14,15]	Dako 22C3	1L CPS ≥ 1 2L TPS ≥ 50%	CPS and %TPS
Gastric cancer (adenocarcinoma) (HER-2 Positive)	Anti-PD-1 [13,20]	Dako 22C3	1L CPS ≥ 1	CPS
Gastric cancer (adenocarcinoma) (HER-2 Negative)	Anti-PD-1 [18, 20]	Dako 22C3	1L CPS ≥5	CPS
Oesophageal (Adenocarcinoma and squamous carcinoma)	Anti-PD-1 [17]	Dako 22C3	1L CPS ≥ 10	CPS
Oesophageal (squamous carcinoma)	Anti-PD-1 [17]	Dako 22C3	1L TC ≥ 1%	%TC
Oesophageal (Adenocarcinoma) (HER-2 Negative)	Anti-PD-1 [17]	Dako 22C3	1L CPS ≥ 5	CPS
Gastro-oesophageal junction Adenocarcinoma (HER-2 Negative)	Anti-PD-1 [17,20] *Depending on PD-L1 inhibitor	Dako 22C3	1L CPS ≥ 5 or* 1L CPS ≥ 10	CPS
Gastro-oesophageal junction Adenocarcinoma (HER-2 Positive)		Dako 22C3	1L CPS ≥ 1	

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TPS: Tumor Proportion Score = $\frac{\#PD-L1 \text{ positive tumor cells}}{Total\ \#PD-L1\ positive+PD-L1\ negative\ tumor\ cells} \times 100$

TC: tumor cell

CPS: Combined Positive Score = $\frac{\#PD-L1 \text{ staining cells (tumor cells,lymphocytes,macrophages)}}{Total\ \#\ of\ viable\ tumor\ cells} \times 100$

IC: immune cell

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c-MET expression by IHC

The c-MET proto-oncogene, encoding the hepatocyte growth factor receptor (HGFR), plays a critical role in cellular proliferation, survival, motility, and morphogenesis. c-MET overexpression, is a common oncogenic mechanism implicated in a variety of solid tumors, including gastric, hepatocellular, colorectal, breast, and non-small cell lung cancer (NSCLC), often correlating with poor prognosis and resistance to conventional therapies. On May 14, 2025, the Food and Drug Administration granted accelerated approval to telisotuzumab vedotin-tllv, a c-Met-directed antibody and microtubule inhibitor conjugate, for adults with locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC) with high c-Met protein overexpression [≥50% of tumor cells with strong (3+) staining], as determined by an FDA-approved test, who have received a prior systemic therapy.

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9. Biomarker findings across all Levels of evidence (A-D)

Biomarker	Result	Therapies with strong clinical significance		Therapies with potential significance		Therapies with potential resistance
		Approved/ Standard of care therapies (Level A)	Therapies in well powered studies (Level B)	Off label/ Investigational therapies (Level C)	Therapies in pre-clinical trials (Level D)	
EGFR	Exon 19 c.2236_2250del (p.E746_A750del) VAF: 30.5%	Afatinib Amivantamab+Chemotherapy Amivantamab+Lazertinib Dacomitinib Datopotamab Deruxtecan Erlotinib Gefitinib Osimertinib Osimertinib+Chemotherapy Erlotinib+Ramucirumab	Patritumab Deruxtecan	-	-	-
TP53	Exon 8 c.832C>G (p.P278A) VAF: 22.5%	-	-	-	-	-

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10. Treatment Table for NSCLC non metastatic setting based on the NCCN guidelines (acc. June 2025)		
Phase	**Indication**	**Treatment**
Neoadjuvant	Patients with tumors ≥4 cm or node positive should be evaluated for preoperative therapy, with strong consideration for an immune checkpoint inhibitor + chemotherapy EGFR wild-type ALK wild-type	Eligible for immunotherapy
Adjuvant	EGFR (Exon 19 Del/L858R)	Osimertinib (A)
	ALK rearrangement	Alectinib (A)

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