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Leading a new era of precision oncology

Oncofocus®

Precision Oncology

ONCOFOCUS® TEST REPORT

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Patient demographics

Surname	-	**Requester**	-
Forename	-	**Contact details**	-
DOB	-	**Date requested**	-
Gender	-		
Histology #	-	**Tumour %**	95%
Primary site	Brain	**Tumour %**	-
Tumour subtype	Glioblastoma	**(macrodissected)**	
Tissue Type	Brain		

Comment

The DNA and RNA extracted from this sample were of optimal quality. The Oncofocus assay on which the sample was run met all assay specific quality metrics.

Oncofocus currently targets 505 genes covering oncogenes, fusion genes, genes susceptible to copy number variation and tumour suppressors. Actionable genetic variants detected by Oncofocus are currently linked to 764 anti-cancer targeted therapies/therapy combinations.

The clinically significant bio-markers identified in this case are summarised on page 2

Within the 'Current Clinical Trials Information' section of this report, starting on page 11, the NCT numbers are hyperlinks to the clinicaltrials.gov webpages which should be accessed to gain further trial specific information

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Clinically Significant Biomarkers

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
EGFR p.(A289V) c.866C>T	Clinical trials and/or off-label	afatinib dacomitinib erlotinib gefitinib gefitinib + chemotherapy bevacizumab + erlotinib bevacizumab + gefitinib atezolizumab + bevacizumab + chemotherapy	10
EGFR amplification	Clinical trials and/or off-label	Clinical trials and/or off-label	11
PDGFRA amplification	Clinical trials and/or off-label	Clinical trials and/or off-label	6
EGFR-SEPT14 fusion	Clinical trials and/or off-label	Clinical trials and/or off-label	3

Sources included in relevant therapies: EMA1, FDA2, ESMO, NCCN

Hotspot variants with >10% alternate allele reads are classified as 'detected' with an assay sensitivity and positive predictive value(PPV) of 99%. Copy number variants; amplifications of CN> 6 with the 5% confidence value of ≥4 after normalization and deletions with 95% CI ≤1 are classified as present when the tumour% >50% with a sensitivity of 80% and PPV 100%. Gene Fusions are reported when occurring in >40 counts and meeting the thresholds of assay specific internal RNA quality control with a sensitivity of 92% and PPV of 99%.Other mutations, copy number variations, or fusions that were detected but not classified by the Oncofocus Test as actionable by a known therapeutic targeted agent are not listed in the results section of this report. Supplementary technical information is available upon request.

Biomarker Descriptions

EGFR (epidermal growth factor receptor)

Background: The EGFR gene encodes the epidermal growth factor receptor (EGFR) tyrosine kinase, a member of the human epidermal growth factor receptor (HER) family. Along with EGFR/ERBB1/HER1, ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4 make up the HER protein family[1]. EGFR ligand induced dimerization results in kinase activation and leads to stimulation of oncogenic signaling pathways including the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways. Activation of these pathways promote cell proliferation, differentiation, and survival[2,3].

Alterations and prevalence: Recurrent somatic mutations in the tyrosine kinase domain of EGFR are observed in approximately 10-20% of lung adenocarcinoma and at higher frequencies in never-smoker, female, and in Asian populations with lung cancer[4,5,6,7]. The most common mutations occur near the ATP-binding pocket of the kinase domain and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 21[8]. These mutations constitutively activate the EGFR kinase resulting in downstream signaling and represent 80% of the EGFR mutations observed in lung cancer. A second group of recurrent activating mutations that are less common include E709K, G719X, S768I, L861Q, and short in-frame insertions in exon 20[9,10,11,12]. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations[13]. Although these variants are common in lung cancer, they are rare in other cancer types. In glioblastoma, recurrent activating EGFR mutations in the extracellular domain include R108K, A289V and G598V[8,14]. The recurrent focal amplification of the EGFR gene leads to an increase in expression in several cancer types. EGFR is amplified in up to 30% of glioblastoma, 12% of esophageal cancer, 10% of head and neck cancer, 5% of bladder cancer, and 5% of lung squamous cell carcinoma[5,6,7,14,15]. Deletion of exons 2-7 encoding the extracellular domain of EGFR (EGFRvIII) results in overexpression of a ligand-independent constitutively active protein which is frequently observed in glioblastoma and has been shown to lead to lung cancer development as well as sensitivity to TKIs[16,17,18].

Potential clinical relevance: Erlotinib[19] (2004), afatinib[20] (2013), gefitinib[21] (2015), osimertinib[22] (2015), and dacomitinib[23] (2018) are small molecule TKIs that are FDA approved for non-small cell lung cancer (NSCLC) patients with sensitizing exon 19 deletions and exon 21 L858R mutations. Acquired secondary mutations often confer resistance to first line TKI therapy with the T790M amino acid substitution accounting for 50-60% of cases[8]. Osimertinib is also indicated for NSCLC patients harboring EGFR T790M mutations whose disease has progressed on or after treatment with a first line TKI. EGFR targeting antibodies including cetuximab[24] (2004), panitumumab[25] (2006), and necitumumab[26] (2016) are also under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations. The use of cetuximab in combination with afatinib is currently recommended by the NCCN for patients who have progressed after receiving erlotinib, afatinib, dacomitinib, or gefitinib and chemotherapy[27].

PDGFRA (platelet derived growth factor receptor alpha)

Background: The PDGFRA gene encodes the platelet derived growth factor receptor alpha, a member of the PDGF receptor type III receptor tyrosine kinase family, which includes PDGFRB, CSF1R, FLT1, FLT3, FLT4, KDR, and KIT[28,29]. PDGFRA is a receptor for platelet derived growth factors, which are mitogens for cells of mesenchymal origin[30]. PDGFRA may function as a homodimer or heterodimer with PDGFRB depending on the ligand[31]. The PDGFRA gene is physically adjacent to KIT and KDR on chromosome 4q12. Ligand binding to PDGFRA results in kinase activation and stimulation of downstream pathways including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways promoting cell proliferation and survival.

Alterations and prevalence: Recurrent somatic PDGFRA alterations are observed in both solid and hematological cancers and include activating mutations, gene amplification, and translocations generating PDGFRA gene fusions. Recurrent PDGFRA activating mutations, including D842V, V561D, N659K, and in-frame deletions in exon 18, are common in 30-40% of KIT negative gastrointestinal stromal tumors (GISTs) and approximately 7% overall[32,33,33,34,35]. PDGFRA recurrent mutations are also described in adult and pediatric glioblastoma and high-grade gliomas[14,35]. In these cases, PDGFRA amplification is common (about 10% of cases) and recurrent mutations frequently co-occur with gene amplification[6,7]. PDGFRA fusions are observed in gliomas and glioblastomas as well as eosinophilic leukemias, of which the FIP1L1-PDGFRA fusion defines approximately half of patients with hypereosinophilic syndrome[36,37,38].

Potential clinical relevance: The small molecule kinase inhibitor, imatinib[39], is approved for patients diagnosed with chronic eosinophilic leukemia harboring FIP1L1-PDGFRA fusions. Additionally, the NCCN recommends imatinib (category 1) for the treatment of GISTs harboring PDGFRA mutations with the exception of D842V[40]. Dasatinib is recommended (category 2A) by the NCCN for the treatment of GISTs harboring a PDGFRA D842V mutation following disease progression on imatinib, sunitinib, or regorafenib[40].

Tier Criteria Met

Genomic Alteration	Tier Classification for Glioblastoma
EGFR p.(A289V) c.866C>T Tier: IIC	IIC: Biomarker is included in ESMO or NCCN guidelines that predict response or resistance to therapies in other cancer types IIC: Biomarker is an inclusion criteria for clinical trials
EGFR amplification Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials
PDGFRA amplification Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials
EGFR-SEPT14 fusion Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials

Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

EGFR p.(A289V) c.866C>T

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
afatinib	✖	✖	○	✖	● (II)
erlotinib	✖	✖	○	✖	● (II)
atezolizumab + bevacizumab + carboplatin + paclitaxel	✖	✖	○	✖	✖
bevacizumab + erlotinib	✖	✖	○	✖	✖
bevacizumab + gefitinib	✖	✖	○	✖	✖
dacomitinib	✖	✖	○	✖	✖
gefitinib	✖	✖	○	✖	✖
gefitinib + carboplatin + pemetrexed	✖	✖	○	✖	✖
afatinib, osimertinib	✖	✖	✖	✖	● (II)
neratinib	✖	✖	✖	✖	● (II)
TAK788	✖	✖	✖	✖	● (I/II)
cetuximab + FATE-NK100	✖	✖	✖	✖	● (I)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

EGFR p.(A289V) c.866C>T (continued)

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
everolimus + neratinib, neratinib + palbociclib, neratinib + trametinib	✖	✖	✖	✖	● (I)
LZM-009	✖	✖	✖	✖	● (I)
pirotinib	✖	✖	✖	✖	● (I)

EGFR amplification

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
erlotinib	✖	✖	✖	✖	● (II)
GC1118A	✖	✖	✖	✖	● (II)
gefitinib	✖	✖	✖	✖	● (II)
neratinib	✖	✖	✖	✖	● (II)
epitinib	✖	✖	✖	✖	● (I/II)
afatinib	✖	✖	✖	✖	● (I)
anti-EGFR-IL-dox	✖	✖	✖	✖	● (I)
cetuximab + FATE-NK100	✖	✖	✖	✖	● (I)
everolimus + neratinib, neratinib + palbociclib, neratinib + trametinib	✖	✖	✖	✖	● (I)
lapatinib + surgical intervention	✖	✖	✖	✖	● (I)
pirotinib	✖	✖	✖	✖	● (I)

PDGFRA amplification

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
crenolanib	✖	✖	✖	✖	● (II)
dasatinib, sunitinib	✖	✖	✖	✖	● (II)
nilotinib, pazopanib	✖	✖	✖	✖	● (II)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

PDGFRA amplification (continued)

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
ponatinib	✖	✖	✖	✖	● (II)
DCC-2618	✖	✖	✖	✖	● (I)
sitravatinib	✖	✖	✖	✖	● (I)

EGFR-SEPT14 fusion

Relevant Therapy	EMA	FDA	ESMO	NCCN	Clinical Trials*
erlotinib	✖	✖	✖	✖	● (II)
afatinib	✖	✖	✖	✖	● (I)
cetuximab + FATE-NK100	✖	✖	✖	✖	● (I)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Relevant Therapy Details

Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated 👎 Not recommended 🛡 Resistance

ESMO information is current as of 2019-02-14. For the most up-to-date information, search www.esmo.org.

EGFR p.(A289V) c.866C>T

○ afatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Stage IV Non-Squamous Cell Non Small Cell Lung Cancer; PS 0-2 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

○ dacomitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Stage IV Non-Squamous Cell Non Small Cell Lung Cancer; PS 0-2 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

○ erlotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Stage IV Non-Squamous Cell Non Small Cell Lung Cancer; PS 0-2 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

EGFR p.(A289V) c.866C>T (continued)

○ gefitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Stage IV Non-Squamous Cell Non Small Cell Lung Cancer; PS 0-2 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

○ gefitinib + carboplatin + pemetrexed

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: I / B

Population segment (Line of therapy):
- Advanced Non-Small Cell Lung Cancer (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

○ bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: II / B

Population segment (Line of therapy):
- Stage IV Non-Squamous Cell Carcinoma; ESMO-Magnitude of Clinical Benefit Scale version 1.1 score: 3 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

○ bevacizumab + gefitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: II / B

Population segment (Line of therapy):
- Stage IV Non-Squamous Cell Carcinoma; ESMO-Magnitude of Clinical Benefit Scale version 1.1 score: 3 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

EGFR p.(A289V) c.866C>T (continued)

○ afatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):
- Stage IV Non-Small Cell Lung Cancer; PS 3-4 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

○ atezolizumab + bevacizumab + carboplatin + paclitaxel

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):
- Metastatic Non-Squamous Non Small Cell Lung Cancer; Without contraindications to use immunotherapy after targeted therapies have been exploited (Second-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

○ dacomitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):
- Stage IV Non-Small Cell Lung Cancer; PS 3-4 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

○ erlotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):
- Stage IV Non-Small Cell Lung Cancer; PS 3-4 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

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EGFR p.(A289V) c.866C>T (continued)

gefitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):
- Stage IV Non-Small Cell Lung Cancer; PS 3-4 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

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Current Clinical Trials Information

Clinical Trials information is current as of 2019-03-01. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers'.

EGFR p.(A289V) c.866C>T

NCT01953926
An Open-Label, Phase II Study Of Neratinib In Patients With Solid Tumors With Somatic Human Epidermal Growth Factor Receptor (EGFR, HER2, HER3) Mutations Or EGFR Gene Amplification

Cancer type: Glioblastoma

Variant class: EGFR mutation

Other identifiers: 13-140, 13-615, 2013-0904, 20150716, CTA733, EudraCT Number: 2013-002872-42, IRAS ID: 171670, NCI-2014-00495, PUMA-NER-5201, REec-2014-0843, SUMMIT, SUMMIT basket

Population segments: EGFR, Estrogen receptor positive, First line, Fourth line or greater, HER2 negative, HER2 positive, Progesterone receptor positive, Second line, Stage IV, Third line, Triple receptor negative

Phase: II

Therapy: neratinib

Locations: Australia, Belgium, Canada, Denmark, France, Ireland, Israel, Italy, Republic of Korea, Spain, United States

US States: AZ, CA, FL, IL, LA, MA, MN, MO, NY, OH, PA, TN, TX, WI

Contact: Puma Biotechnology Clinical Operations Senior Director [424-248-6500; ClinicalTrials@pumabiotechnology.com]

NCT02423525
A Phase I Dose Escalation and Central Nervous System (CNS) Pharmacokinetic Study of the ErbB Family Inhibitor Afatinib in Patients with Recurrent or Progressive Brain Cancer

Cancer type: Glioblastoma

Variant class: EGFR mutation

Other identifiers: 1200.229, 20161975

Population segments: (N/A), Second line

Phase: I

Therapy: afatinib

Location: United States

US State: CA

Contact: Trial Team [310-829-8265; neuro.oncology@providence.org]

NCT03810872
An Open Explorative Phase II, Open Label Study of Afatinib in the Treatment of Advanced Cancer Carrying an EGFR, a HER2 or a HER3 Mutation

Cancer type: Unspecified Cancer

Variant class: EGFR activating mutation

Other identifiers: 1200.264, EudraCT Number: 2016-003411-34, Precision 2, Precision 2 - 1200.264

Population segments: HER2 positive, Second line, Stage III, Stage IV

Phase: II

Therapy: afatinib

Location: Belgium

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EGFR p.(A289V) c.866C>T (continued)

NCT02465060
Molecular Analysis for Therapy Choice (MATCH)

Cancer type: Unspecified Solid Tumor

Variant class: EGFR activating mutation

Other identifiers: 15-7002, 16-750, CTSU/EAY131, EAY131, EAY131- K1, EAY131- K2, EAY131- Z1K, EAY131-A, EAY131-B, EAY131-C1, EAY131-C2, EAY131-E, EAY131-F, EAY131-G, EAY131-H, EAY131-I, EAY131-J, EAY131-L, EAY131-M, EAY131-MATCH, EAY131-N, EAY131-P, EAY131-Q, EAY131-R, EAY131-S1, EAY131-S2, EAY131-T, EAY131-U, EAY131-V, EAY131-W, EAY131-X, EAY131-Y, EAY131-Z1A, EAY131-Z1B, EAY131-Z1C, EAY131-Z1D, EAY131-Z1E, EAY131-Z1F, EAY131-Z1G, EAY131-Z1H, EAY131-Z1I, EAY131-Z1J, EAY131-Z1L, EAY131-Z1M, ECOGEAY131-M, MATCH, MATCH, NCI-2015-00054, NCI-MATCH

Population segments: Aggressive, Classical, Fourth line or greater, HER2 positive, Indolent, Nodular lymphocyte-predominant, Pulmonary, Second line, Stage III, Stage IV, Third line, Unspecified

Phase: II

Therapies: afatinib, osimertinib

Locations: Puerto Rico, United States

US States: AK, AL, AR, AZ, CA, CO, CT, DC, DE, FL, GA, HI, IA, ID, IL, IN, KS, KY, LA, MA, MD, ME, MI, MN, MO, MS, MT, NC, ND, NE, NH, NJ, NM, NV, NY, OH, OK, OR, PA, RI, SC, SD, TN, TX, UT, VA, VT, WA, WI, WV, WY

Contact: Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

NCT03297606
Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial

Cancer type: Unspecified Solid Tumor

Variant class: EGFR aberration

Other identifiers: CA209-9DL, CAPTUR, ESR-17-12831, ML39800, PM1, WI233446

Population segments: Aggressive, Diffuse large B-cell lymphoma (DLBCL), Extranodal marginal zone B-cell lymphoma (MALT), First line, Follicular lymphoma (FL), Indolent, Lymphoblastic lymphoma (LBL), Mantle cell lymphoma (MCL), Other subtype, Second line, Stage III, Stage IV, Waldenstrom's macroglobulinemia (WM)

Phase: II

Therapy: erlotinib

Location: Canada

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EGFR p.(A289V) c.866C>T (continued)

NCT02716116
A Phase I/II Study Of The Safety, Pharmacokinetics, And Anti-Tumor Activity Of The Oral EGFR/HER2 Inhibitor AP32788 In Non-Small Cell Lung Cancer

Cancer type: Unspecified Solid Tumor

Variant class: EGFR mutation

Other identifiers: 16-143, 16-447, 2016-1030, AP32788-15-101, LUN0082, NCI-2016-00587, U1111-1217-7205

Population segments: CNS mets, EGFR, First line, Fourth line or greater, Second line, Stage III, Stage IV, Third line

Phase: I/II

Therapy: TAK788

Location: United States

US States: CA, CO, IL, MA, MI, NY, TN, TX, VA, WA

Contact: Takeda Study Registration Call Center [866-835-2233; globaloncologymedinfo@takeda.com]

NCT03286296
A First-in-Human, Multicenter, Open-label, Phase I Dose-Escalation Study of LZM009 in Subjects With Advanced Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: EGFR activating mutation

Other identifiers: CTR20180494, LZM009-001, LZM009-CH-I

Population segments: Second line, Stage III, Stage IV

Phase: I

Therapy: LZM-009

Location: United States

US States: MI, TX

Contact: Dr. Changdong Liu [756-813-5099; liuchangdong@livzon.cn]

NCT03065387
Phase I Study of the Pan-ERBB Inhibitor Neratinib Given in Combination With Everolimus, Palbociclib or Trametinib in Advanced Cancer Subjects With EGFR Mutation/Amplification, HER2 Mutation/ Amplification, HER3/4 Mutation or KRAS Mutation

Cancer type: Unspecified Solid Tumor

Variant class: EGFR mutation

Other identifiers: 2016-0430, NCI-2018-01218

Population segments: HER2 negative, HER2 positive, Second line, Stage III, Stage IV

Phase: I

Therapies: everolimus + neratinib, neratinib + palbociclib, neratinib + trametinib

Location: United States

US State: TX

Contact: Dr. Sarina Piha-Paul [713-563-1930; spihapau@mdanderson.org]

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EGFR p.(A289V) c.866C>T (continued)

No NCT ID - see other identifier(s)
Phase I Clinical Study With Advanced Solid Tumors KBP-5209 Treatment

Cancer type: Unspecified Solid Tumor

Variant class: EGFR mutation

Other identifiers: 5209-CPK-1002, CTR20150792

Population segments: EGFR, HER2 positive, Second line, Stage III, Stage IV

Phase: I

Therapy: pirotinib

Location: China

NCT03319459
FATE-NK100 as Monotherapy and in Combination With Monoclonal Antibody in Subjects With Advanced Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: EGFR positive

Other identifiers: DIMENSION, NCI-2017-02242, NK-101

Population segments: HER2 positive, Pulmonary, Second line, Stage III, Stage IV

Phase: I

Therapy: cetuximab + FATE-NK100

Location: United States

US States: MN, TX

Contact: Sara Weymer [858-875-1800; clinical@fatetherapeutics.com]

EGFR amplification

NCT03618667
A Phase II Clinical Study of GC1118 in Recurrent Glioblastoma Patients With High Epidermal Growth Factor Receptor (EGFR) Amplification

Cancer type: Glioblastoma

Variant class: EGFR amplification

Other identifier: SMC2017-06-111

Population segments: (N/A), Second line

Phase: II

Therapy: GC1118A

Location: Republic of Korea

EGFR amplification (continued)

NCT01953926
An Open-Label, Phase II Study Of Neratinib In Patients With Solid Tumors With Somatic Human Epidermal Growth Factor Receptor (EGFR, HER2, HER3) Mutations Or EGFR Gene Amplification

Cancer type: Glioblastoma

Variant class: EGFR amplification

Other identifiers: 13-140, 13-615, 2013-0904, 20150716, CTA733, EudraCT Number: 2013-002872-42, IRAS ID: 171670, NCI-2014-00495, PUMA-NER-5201, REec-2014-0843, SUMMIT, SUMMIT basket

Population segments: EGFR, Estrogen receptor positive, First line, Fourth line or greater, HER2 negative, HER2 positive, Progesterone receptor positive, Second line, Stage IV, Third line, Triple receptor negative

Phase: II

Therapy: neratinib

Locations: Australia, Belgium, Canada, Denmark, France, Ireland, Israel, Italy, Republic of Korea, Spain, United States

US States: AZ, CA, FL, IL, LA, MA, MN, MO, NY, OH, PA, TN, TX, WI

Contact: Puma Biotechnology Clinical Operations Senior Director [424-248-6500; ClinicalTrials@pumabiotechnology.com]

NCT03231501
A Phase Ib, Multi-center, Open-label Study of Epitinib Succinate (HMPL-813) in Treating Patients With Glioblastoma.

Cancer type: Glioblastoma

Variant class: EGFR amplification

Other identifiers: 2016-813-00CH3, CTR20170170

Population segments: (N/A), First line

Phase: I/II

Therapy: epitinib

Location: China

NCT02423525
A Phase I Dose Escalation and Central Nervous System (CNS) Pharmacokinetic Study of the ErbB Family Inhibitor Afatinib in Patients with Recurrent or Progressive Brain Cancer

Cancer type: Glioblastoma

Variant class: EGFR amplification

Other identifiers: 1200.229, 20161975

Population segments: (N/A), Second line

Phase: I

Therapy: afatinib

Location: United States

US State: CA

Contact: Trial Team [310-829-8265; neuro.oncology@providence.org]

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EGFR amplification (continued)

NCT03603379
A Pharmacokinetic Phase I Study of Anti-epidermal Growth Factor Receptor (EGFR) -Immunoliposomes Loaded With Doxorubicin in Patients With Relapsed or Refractory High-grade Gliomas

Cancer type: Glioblastoma

Variant class: EGFR amplification

Other identifiers: 2018-01160, GBM-LIPO, me17Kasenda

Population segments: (N/A), Second line

Phase: I

Therapy: anti-EGFR-IL-dox

Location: Switzerland

NCT02101905
Drug Distribution and Pharmacodynamic Study of Pulsatile Lapatinib in Surgically Accessible EGFR-Amplified Recurrent High-Grade Glioma

Cancer type: Glioblastoma

Variant class: EGFR amplification

Other identifiers: 14-297, ABTC-1302, NCI-2014-00634

Population segments: (N/A), Neoadjuvant, Second line

Phase: I

Therapy: lapatinib + surgical intervention

Location: United States

US States: MA, MI, NC, PA

Contact: Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

NCT02447419
Study to Evaluate the Safety and Efficacy of Gefitinib, in Subjects With EFGR Amplification Refractory Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: EGFR amplification

Other identifier: 2014-10-029

Population segments: (N/A), Second line

Exclusion criteria variant classes: BRAF V600 mutation, KRAS G12 mutation, KRAS G13 mutation

Phase: II

Therapy: gefitinib

Location: Republic of Korea

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EGFR amplification (continued)

NCT03297606
Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial

Cancer type: Unspecified Solid Tumor

Variant class: EGFR aberration

Other identifiers: CA209-9DL, CAPTUR, ESR-17-12831, ML39800, PM1, WI233446

Population segments: Aggressive, Diffuse large B-cell lymphoma (DLBCL), Extranodal marginal zone B-cell lymphoma (MALT), First line, Follicular lymphoma (FL), Indolent, Lymphoblastic lymphoma (LBL), Mantle cell lymphoma (MCL), Other subtype, Second line, Stage III, Stage IV, Waldenstrom's macroglobulinemia (WM)

Phase: II

Therapy: erlotinib

Location: Canada

NCT03065387
Phase I Study of the Pan-ERBB Inhibitor Neratinib Given in Combination With Everolimus, Palbociclib or Trametinib in Advanced Cancer Subjects With EGFR Mutation/Amplification, HER2 Mutation/Amplification, HER3/4 Mutation or KRAS Mutation

Cancer type: Unspecified Solid Tumor

Variant class: EGFR amplification

Other identifiers: 2016-0430, NCI-2018-01218

Population segments: HER2 negative, HER2 positive, Second line, Stage III, Stage IV

Phase: I

Therapies: everolimus + neratinib, neratinib + palbociclib, neratinib + trametinib

Location: United States

US State: TX

Contact: Dr. Sarina Piha-Paul [713-563-1930; spihapau@mdanderson.org]

No NCT ID - see other identifier(s)
Phase I Clinical Study With Advanced Solid Tumors KBP-5209 Treatment

Cancer type: Unspecified Solid Tumor

Variant class: EGFR amplification

Other identifiers: 5209-CPK-1002, CTR20150792

Population segments: EGFR, HER2 positive, Second line, Stage III, Stage IV

Phase: I

Therapy: pirotinib

Location: China

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EGFR amplification (continued)

NCT03319459
FATE-NK100 as Monotherapy and in Combination With Monoclonal Antibody in Subjects With Advanced Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: EGFR positive

Other identifiers: DIMENSION, NCI-2017-02242, NK-101

Population segments: HER2 positive, Pulmonary, Second line, Stage III, Stage IV

Phase: I

Therapy: cetuximab + FATE-NK100

Location: United States

US States: MN, TX

Contact: Sara Weymer [858-875-1800; clinical@fatetherapeutics.com]

PDGFRA amplification

NCT02626364
Phase II Study of Single-agent Crenolanib in Recurrent/Refractory Glioblastoma With PDGFRA Gene Amplification

Cancer type: Glioblastoma

Variant class: PDGFRA amplification

Other identifiers: 2015-0864, ARO-015, NCI-2016-00257

Population segments: (N/A), Second line

Phase: II

Therapy: crenolanib

Location: United States

US State: TX

Contact: Dr. Sujata Jha [214-593-0510; sjha@arogpharma.com]

NCT02571036
A Multicenter Phase I, Open-Label Study of DCC-2618 to Assess Safety,Tolerability, and Pharmacokinetics in Patients With Advanced Malignancies

Cancer type: Glioblastoma

Variant class: PDGFRA amplification

Other identifiers: 103123, 15-495, 17-467, 2015-0621, 20170452, DCC-2618-01-001, EudraCT Number: 2016-001324-60, IRAS ID 229068, NCI-2015-01805

Population segments: (N/A), Fourth line or greater, Locally advanced, Metastatic, MPN-O, Second line, Third line

Phase: I

Therapy: DCC-2618

Locations: Canada, Italy, Netherlands, United Kingdom, United States

US States: AZ, CA, FL, MA, NY, OR, TX, UT

Contact: Jama Pitman [clinicaltrials@deciphera.com]

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PDGFRA amplification (continued)

NCT02029001
A Two-period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients With Progressive Locally-advanced or Metastatic Solid Tumors MOST: My own specific treatment

Cancer type: Unspecified Solid Tumor

Variant class: PDGFRA amplification

Other identifiers: ET12-081, EudraCT number: 2012-004510-34, MOST, ProfiLER

Population segments: Maintenance/Consolidation, Second line, Stage III, Stage IV, Third line

Phase: II

Therapies: nilotinib, pazopanib

Location: France

NCT03297606
Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial

Cancer type: Unspecified Solid Tumor

Variant class: PDGFRA aberration

Other identifiers: CA209-9DL, CAPTUR, ESR-17-12831, ML39800, PM1, WI233446

Population segments: Aggressive, Diffuse large B-cell lymphoma (DLBCL), Extranodal marginal zone B-cell lymphoma (MALT), First line, Follicular lymphoma (FL), Indolent, Lymphoblastic lymphoma (LBL), Mantle cell lymphoma (MCL), Other subtype, Second line, Stage III, Stage IV, Waldenstrom's macroglobulinemia (WM)

Phase: II

Therapies: dasatinib, sunitinib

Location: Canada

NCT02272998
Phase II Study Of Ponatinib For Advanced Cancers With Genomic Alterations In Fibroblastic Growth Factor Receptor (FGFR) And Other Genomic Targets (KIT, Pdgfra, RET FLT3, ABL1)

Cancer type: Unspecified Solid Tumor

Variant class: PDGFRA aberration

Other identifiers: 14078, 2014C0143, NCI-2014-01499, OSU-14078

Population segments: Advanced, Second line, Stage IV

Phase: II

Therapy: ponatinib

Location: United States

US States: MI, OH

Contact: The Ohio State University Comprehensive Cancer Center [800-293-5066; Jamesline@osumc.edu]

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PDGFRA amplification (continued)

NCT02219711
A Phase I/Ib Study of MGCD516 in Patients With Advanced Solid Tumor Malignancies

Cancer type: Unspecified Solid Tumor

Variant class: PDGFRA amplification

Other identifiers: 14-308, 16071502, 2014-1005, 20150094, 516-001, 76853, AAAO0006, NCI-2014-01866, Study 516-001, UMCC 2015.040, USOR Number: 17038, UW15054

Population segments: Adenocarcinoma, EGFR, Hormone refractory, Line of therapy N/A, Second line, Stage III, Stage IV, Third line, Unresectable

Phase: I

Therapy: sitravatinib

Locations: Republic of Korea, United States

US States: AL, CA, CO, FL, IL, LA, MA, MD, MI, NE, NM, NY, OH, PA, SC, TN, TX, UT, VA, WA, WI

Contact: Mirati Therapeutics Study Locator Services [844-893-5530; miratistudylocator@emergingmed.com]

EGFR-SEPT14 fusion

NCT02423525
A Phase I Dose Escalation and Central Nervous System (CNS) Pharmacokinetic Study of the ErbB Family Inhibitor Afatinib in Patients with Recurrent or Progressive Brain Cancer

Cancer type: Glioblastoma

Variant class: EGFR aberration

Other identifiers: 1200.229, 20161975

Population segments: (N/A), Second line

Phase: I

Therapy: afatinib

Location: United States

US State: CA

Contact: Trial Team [310-829-8265; neuro.oncology@providence.org]

NCT03297606
Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial

Cancer type: Unspecified Solid Tumor

Variant class: EGFR aberration

Other identifiers: CA209-9DL, CAPTUR, ESR-17-12831, ML39800, PM1, WI233446

Population segments: Aggressive, Diffuse large B-cell lymphoma (DLBCL), Extranodal marginal zone B-cell lymphoma (MALT), First line, Follicular lymphoma (FL), Indolent, Lymphoblastic lymphoma (LBL), Mantle cell lymphoma (MCL), Other subtype, Second line, Stage III, Stage IV, Waldenstrom's macroglobulinemia (WM)

Phase: II

Therapy: erlotinib

Location: Canada

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EGFR-SEPT14 fusion (continued)

NCT03319459
FATE-NK100 as Monotherapy and in Combination With Monoclonal Antibody in Subjects With Advanced Solid Tumors

Cancer type: Unspecified Solid Tumor

Variant class: EGFR positive

Other identifiers: DIMENSION, NCI-2017-02242, NK-101

Population segments: HER2 positive, Pulmonary, Second line, Stage III, Stage IV

Phase: I

Therapy: cetuximab + FATE-NK100

Location: United States

US States: MN, TX

Contact: Sara Weymer [858-875-1800; clinical@fatetherapeutics.com]

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Evidence Summary by Variant Class

A variant class hierarchy was created to summarize gene variants with associated clinical evidence. Evidence items refers to citations across the different global data sources.

EGFR p.(A289V) c.866C>T

Variant Class	Evidence Items
ERBB aberration	0
↳ EGFR aberration	4
↳ EGFR positive	3
↳ EGFR mutation status	0
↳ EGFR mutation	5
↳ EGFR activating mutation	15

EGFR amplification

Variant Class	Evidence Items
ERBB aberration	0
↳ EGFR aberration	4
↳ EGFR positive	3
↳ EGFR amplification	9

PDGFRA amplification

Variant Class	Evidence Items
PDGFR aberration	0
↳ PDGFRA aberration	2
↳ PDGFRA amplification	4

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Evidence Summary by Variant Class (continued)

A variant class hierarchy was created to summarize gene variants with associated clinical evidence. Evidence items refers to citations across the different global data sources.

EGFR-SEPT14 fusion

Variant Class	Evidence Items
ERBB aberration	0
↳ EGFR aberration	4
↳ EGFR positive	3
↳ EGFR fusion	0

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Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Allele Frequency	Transcript	Variant Effect	Gene Class	Variant Class
EGFR	p.(A289V)	c.866C>T	COSM21687	13.11%	NM_005228.4	missense	Gain of Function	Hotspot

Gene Fusions (RNA)

Genes	Variant ID
EGFR-SEPT14	EGFR-SEPT14.E24S10

Copy Number Variations

Gene	Locus	Copy Number
PDGFRA	chr4:55141007	6.41
EGFR	chr7:55211010	38.37

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PD-1/PD-L1 TESTING

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Surname	-	**Requester**	-
Forename	-	**Contact details**	-
DOB	-	**Date requested**	-
Gender	-		
Histology #	-	**Tumour %**	95%
Primary site	Brain	**Tumour %**	-
Tumour subtype	Glioblastoma	**(macrodissected)**	
Tissue Type	Brain		

PD-L1 test

PD-L1 IHC assays are used to help identify those patients most likely to benefit from anti-PD-1/PD-L1 directed immunotherapies. Assessment involves the determination of a range of cut-off/threshold values for PD-L1 positive tumour cells and PD-L1 positive immune cells. These cut off values are identified as predictors of response to anti-PD-L1 directed therapies used in the treatment of a range of different cancer types and include pembrolizumab, atezolizumab, avelumab, nivolumab, and durvalumab. The established cut off values for tumour proportion scores (>1%, >25%, >50%) and PD-L1 positive immune cells (10%), which vary according to immunotherapy, tumour type and whether first or second line therapy is to be used.

The Oncologica® Immunofocus PD-L1 immunocytochemistry assay quantifies the proportion of tumour cells that express PD-L1 (Tumour Proportion Score) and the area occupied by tumour infiltrating PD-L1 positive immune cells.

The Oncologica® Immunofocus PD-L1 immunocytochemistry assay is a Laboratory Developed Test utilising the RUO rabbit monoclonal antibody clone E1L3N (Cell Signalling Technologies) and Leica Bond III instrumentation. The performance of the Immunofocus assay is continually assessed by involvement in recognised External Quality Assessment schemes and returns performance levels commensurate with approved the PD-L1 diagnostic assays. All Immunofocus assay testing is performed within the scope of UKAS/ISO 15189:2012 accreditation. Clone E1L3N is not licensed and approved for use in clinical testing to direct the use of PD-1/PD-L1 therapies. The PD-L1 protein expression levels in tumour cells generated by the Immunofocus PD-L1 assay should therefore be interpreted within the context of these facts.

PD-L1 Result

The tumour shows a heterogeneous pattern of PD-L1 expression. In many areas a high proportion of tumour cells (60-100%) show PD-L1 expression. Tumour cells exhibit strong or moderate intensity immunostaining for PD-L1 with partial and complete patterns of surface membrane expression. In other areas a smaller population of tumour cells show PD-L1 expression. Taken together the proportion of PD-L1 expressing tumour cells amounts to around 35-40% of the total tumour cell population. The tumour is associated with a focal patchy PD-L1 expressing immune cell (IC) infiltrate. PD-L1 expressing tumour infiltrating immune cells (ICs) cover 2-3% of the tumour area occupied by tumour cells, intratumoural and contiguous peritumoural stroma.

Summary; PD-L1 Tumour Proportion Score 35-40% ; PD-L1 positive ICs 2-3% of tumour area

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