Patient demographics

Surname - Requester -
Forename - Contact details -
DOB - Date requested -
Gender -
Histology # -
Primary site -
Tumour subtype -
Tissue Type -

Glioblastoma
Brain
Brain

Tumour % 95%
Tumour % -

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

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

**Sources included in relevant therapies:** EMA, FDA, 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 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. 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.

**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. 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. 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. EGFR activating mutations in lung cancer lead to mutually exclusive to KRAS activating mutations. 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, A2987 and G538V. 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. 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.

**Potential clinical relevance:** Erlotinib (2004), afatinib (2013), gefitinib (2015), osimertinib (2015), and dacomitinib (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. 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 (2004), panitumumab (2006), and necitumumab (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.

PDGFRA (platelet derived growth factor receptor alpha)

**Background:** The PDGFRA gene encodes the platelet derived growth factor receptor alpha, a member of the PDGFR type III receptor tyrosine kinase family, which includes PDGFRB, CSF1R, FLT1, FLT3, FLT4, KDR, and KIT. PDGFRA is a receptor for platelet derived growth factors, which are mitogens for cells of mesenchymal origin. PDGFRA may function as a homodimer or heterodimer with PDGFRB depending on the ligand. 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 19, are common in 30-40% of KIT negative gastrointestinal stromal tumors (GISTs) and approximately 7% overall. PDGFRA recurrent mutations are also described in adult and pediatric glioblastoma and high-grade gliomas. In these cases, PDGFRA amplification is common (about 10% of cases) and recurrent mutations frequently co-occur with gene amplification. 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.

**Potential clinical relevance:** The small molecule kinase inhibitor, imatinib, 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. 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.
**Tier Criteria Met**

<table>
<thead>
<tr>
<th>Genomic Alteration</th>
<th>Tier Classification for Glioblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>EGFR p.(A289V) c.866C&gt;T</em></td>
<td>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</td>
</tr>
<tr>
<td><em>EGFR amplification</em></td>
<td>IIC: Biomarker is an inclusion criteria for clinical trials</td>
</tr>
<tr>
<td><em>PDGFRA amplification</em></td>
<td>IIC: Biomarker is an inclusion criteria for clinical trials</td>
</tr>
<tr>
<td><em>EGFR-SEPT14 fusion</em></td>
<td>IIC: Biomarker is an inclusion criteria for clinical trials</td>
</tr>
</tbody>
</table>


**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*

<table>
<thead>
<tr>
<th>Relevant Therapy</th>
<th>EMA</th>
<th>FDA</th>
<th>ESMO</th>
<th>NCCN</th>
<th>Clinical Trials*</th>
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<td>○</td>
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<td>(II)</td>
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<td>✗</td>
<td>○</td>
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<td>(II)</td>
</tr>
<tr>
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<td>✗</td>
<td>○</td>
<td>✗</td>
<td></td>
</tr>
<tr>
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<td>✗</td>
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<td>(I)</td>
</tr>
</tbody>
</table>

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

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### Relevant Therapy Summary (continued)

<table>
<thead>
<tr>
<th>EGFR p.(A289V) c.866C&gt;T (continued)</th>
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<th>FDA</th>
<th>ESMO</th>
<th>NCCN</th>
<th>Clinical Trials*</th>
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</thead>
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### EGFR amplification

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<th>ESMO</th>
<th>NCCN</th>
<th>Clinical Trials*</th>
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<td>(II/II)</td>
</tr>
<tr>
<td>afatinib</td>
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<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>(I)</td>
</tr>
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<td>anti-EGFR-IL-dox</td>
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<td>✗</td>
<td>✗</td>
<td>(I)</td>
</tr>
<tr>
<td>cetuximab + FATE-NK100</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>(I)</td>
</tr>
<tr>
<td>everolimus + neratinib, neratinib + palbociclib, neratinib + trametinib</td>
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<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>(I)</td>
</tr>
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<td>(I)</td>
</tr>
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<td>pirotinib</td>
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<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>(I)</td>
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</table>

### PDGFRA amplification

<table>
<thead>
<tr>
<th>PDGFRA amplification</th>
<th>EMA</th>
<th>FDA</th>
<th>ESMO</th>
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<th>Clinical Trials*</th>
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<tbody>
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<td>(II)</td>
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</tbody>
</table>

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---

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### Relevant Therapy Summary (continued)

<table>
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<th>Relevant Therapy</th>
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</table>

### PDGFRA amplification (continued)

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<thead>
<tr>
<th>Relevant Therapy</th>
<th>EMA</th>
<th>FDA</th>
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<th>Clinical Trials*</th>
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<tbody>
<tr>
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<td>(I)</td>
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<td>afatinib</td>
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<td>(I)</td>
</tr>
<tr>
<td>cetuximab + FATE-NK100</td>
<td>x</td>
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<td>x</td>
<td>x</td>
<td>(I)</td>
</tr>
</tbody>
</table>

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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)

- **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)

- **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)

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

- **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)  

- **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)  

- **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)  

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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)

- **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)

- **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)

- **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)

---

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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)

# 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](http://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

<table>
<thead>
<tr>
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<th>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</th>
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<tbody>
<tr>
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<tr>
<td>Variant class:</td>
<td>EGFR mutation</td>
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</tr>
<tr>
<td>Contact:</td>
<td>Puma Biotechnology Clinical Operations Senior Director [424-248-6500; <a href="mailto:ClinicalTrials@pumabiotechnology.com">ClinicalTrials@pumabiotechnology.com</a>]</td>
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<table>
<thead>
<tr>
<th>NCT02423525</th>
<th>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</th>
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<tr>
<td>Cancer type:</td>
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<tr>
<td>Variant class:</td>
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</tr>
<tr>
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<tr>
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<tr>
<td>Therapy:</td>
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<td>Location:</td>
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<tr>
<td>US State:</td>
<td>CA</td>
</tr>
<tr>
<td>Contact:</td>
<td>Trial Team [310-829-8265; <a href="mailto:neuro.oncology@providence.org">neuro.oncology@providence.org</a>]</td>
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<tr>
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NCT02465060
Molecular Analysis for Therapy Choice (MATCH)
Cancer type: Unspecified Solid Tumor
Variant class: EGFR activating mutation


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

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<td>United States</td>
<td>CA, CO, IL, MA, MI, NY, TN, TX, VA, WA</td>
<td>Takeda Study Registration Call Center [866-835-2233; <a href="mailto:globaloncologymedinfo@takeda.com">globaloncologymedinfo@takeda.com</a>]</td>
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<td>NCT03286296</td>
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<td>LZM-009</td>
<td>United States</td>
<td>MI, TX</td>
<td>Dr. Changdong Liu [756-813-5099; <a href="mailto:liuchangdong@livzon.cn">liuchangdong@livzon.cn</a>]</td>
</tr>
<tr>
<td>NCT03065387</td>
<td>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</td>
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<td>everolimus + neratinib, neratinib + palbociclib, neratinib + trametinib</td>
<td>United States</td>
<td>TX</td>
<td>Dr. Sarina Piha-Paul [713-563-1930; <a href="mailto:spihapau@mdanderson.org">spihapau@mdanderson.org</a>]</td>
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**EGFR p.(A289V) c.866C>T (continued)**

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<tr>
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<th>Therapy</th>
<th>Location</th>
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<td>EGFR, HER2 positive, Second line, Stage III, Stage IV</td>
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**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, NC1-2014-00495, 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, 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

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**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

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]
| NCT02029001 | Other identifiers: ET12-081, EudraCT number: 2012-004510-34, MOST, ProfiLER  
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  
Cancer type: Unspecified Solid Tumor  
Variant class: PDGFRA amplification | Population segments: Maintenance/Consolidation, Second line, Stage III, Stage IV, Third line  
Phase: II  
Therapies: nilotinib, pazopanib  
Location: France |
| NCT03297606 | Other identifiers: CA209-9DL, CAPTUR, ESR-17-12831, ML39800, PM1, WI233446  
Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial  
Cancer type: Unspecified Solid Tumor  
Variant class: PDGFRA aberration | 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 | Other identifiers: 14078, 2014C0143, NCI-2014-01499, OSU-14078  
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 | 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] |
### 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, AAA00006, 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
### EGFR-SEPT14 fusion (continued)

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<tr>
<th>NCT03319459</th>
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<tbody>
<tr>
<td>FATE-NK100 as Monotherapy and in Combination With Monoclonal Antibody in Subjects With Advanced Solid Tumors</td>
<td>Population segments: HER2 positive, Pulmonary, Second line, Stage III, Stage IV</td>
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<tr>
<td>Cancer type: Unspecified Solid Tumor</td>
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<td>Variant class: EGFR positive</td>
<td>Therapy: cetuximab + FATE-NK100</td>
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<td></td>
<td>US States: MN, TX</td>
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<td>Contact: Sara Weymer [858-875-1800; <a href="mailto:clinical@fatetherapeutics.com">clinical@fatetherapeutics.com</a>]</td>
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</table>

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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

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<th>Variant Class</th>
<th>Evidence Items</th>
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### EGFR amplification

<table>
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### PDGFRA amplification

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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

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<th>Variant Class</th>
<th>Evidence Items</th>
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## Variant Details

### DNA Sequence Variants

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<td>EGFR</td>
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References


References (continued)


32. Lasota et al. KIT and PDGFR mutations in gastrointestinal stromal tumors (GISTs). Semin Diagn Pathol. 2006 May;23(2):91-102. PMID: 17193822


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<tr>
<td>Clonal: Polyclonal ratio</td>
<td>Up to 55% polyclonal</td>
<td>53%</td>
</tr>
<tr>
<td>Low Quality</td>
<td>≤26% approximately.</td>
<td>22%</td>
</tr>
<tr>
<td>Usable reads</td>
<td>≥30%</td>
<td>36%</td>
</tr>
<tr>
<td>Aligned bases</td>
<td>≥80% Can be less if base coverage, and % reads on target is high</td>
<td>91%</td>
</tr>
<tr>
<td>Unaligned bases</td>
<td>≤20%</td>
<td>9%</td>
</tr>
<tr>
<td>Mean raw accuracy</td>
<td>This value should be as close to 100% as possible</td>
<td>99%</td>
</tr>
<tr>
<td>Overall read length histogram</td>
<td>Median read length 98-115bp for DNA only, 65-90bp RNA only, DNA &amp; RNA 100bp ±20</td>
<td>105</td>
</tr>
<tr>
<td>DNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of mapped reads</td>
<td>&gt;4.5 million</td>
<td>4,843,885</td>
</tr>
<tr>
<td>Percent reads on target</td>
<td>&gt;90%</td>
<td>92.23%</td>
</tr>
<tr>
<td>Average base coverage depth</td>
<td>&gt;1200</td>
<td>1,243</td>
</tr>
<tr>
<td>Uniformity of amplicon (base) coverage</td>
<td>&gt;90% (degraded 85-90%)</td>
<td>93.10%</td>
</tr>
<tr>
<td>Percent assigned amplicon reads</td>
<td>&gt;90%</td>
<td>92.23%</td>
</tr>
<tr>
<td>Amplicons with no strand bias</td>
<td>&gt;90%</td>
<td>96.68%</td>
</tr>
<tr>
<td>Amplicons reading end to end</td>
<td>&gt;80%</td>
<td>86.25%</td>
</tr>
<tr>
<td>% base reads on target</td>
<td>&gt;85%</td>
<td>90.77%</td>
</tr>
<tr>
<td>coverage at 1X</td>
<td>&gt;90% coverage is required at 500X for samples with tumour percentages below 40%</td>
<td>99.92%</td>
</tr>
<tr>
<td>coverage at 20X</td>
<td>&gt;99%</td>
<td>99.31%</td>
</tr>
<tr>
<td>coverage at 100X</td>
<td>&gt;97%</td>
<td>97.52%</td>
</tr>
<tr>
<td>coverage at 500X</td>
<td>&gt;80%</td>
<td>80.35%</td>
</tr>
<tr>
<td>MAPD value</td>
<td>In the presence of a copy number variant, this value should be &lt;0.5</td>
<td>0.272</td>
</tr>
<tr>
<td>RNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mapped reads</td>
<td>&gt;40,000 for software to call a fusion, (should be over 500,000)</td>
<td>987,225</td>
</tr>
<tr>
<td>Expression Control Genes MYC</td>
<td>&gt;15 read counts indicates the gene is present (5 out of 6 genes should be present to accept the presence of a fusion)</td>
<td>5783</td>
</tr>
<tr>
<td>Expression Control Genes HMBS</td>
<td></td>
<td>530</td>
</tr>
<tr>
<td>Expression Control Genes TBP</td>
<td></td>
<td>151,595</td>
</tr>
<tr>
<td>Expression Control Genes LRP1</td>
<td></td>
<td>100,490</td>
</tr>
<tr>
<td>Expression Control Genes ITGB7</td>
<td></td>
<td>5418</td>
</tr>
<tr>
<td>Expression Control Genes MRPL13</td>
<td></td>
<td>105,921</td>
</tr>
</tbody>
</table>
PD-L1 test

Anti-PD-1/PD-L1 directed immunotherapies are an important group of agents used in the treatment of a range of different cancer types. These immunotherapies include pembrolizumab, atezolizumab, avelumab, nivolumab, and durvalumab.

The immunofocus test is used to help identify those patients most likely to benefit from anti-PD-L1 directed immunotherapies. The immunofocus test assesses the proportion of tumour cells that express PD-L1 (Tumour Proportion Score) and the area occupied by tumour infiltrating PD-L1 positive immune cells. A range of cut-off/threshold values for tumour proportion scores (>1%, >25%, >50%) and PD-L1 positive immune cells (>10%) have been identified as predictors of response to anti-PD-L1 directed therapies. These cut offs vary according to tumour type, whether the drug is being used in first or second line therapy and according to which immunotherapy is selected.

The Oncologist will use the Immunofocus test results together with other clinicopathological parameters as a guide to determine whether a patient’s tumour is likely to benefit from anti-PD-L1 directed therapies.

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