# *Preliminary results of the neratinib arm in the Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT): A phase II platform trial using Bayesian adaptive randomization.*

**Isabel Arrillaga-Romany,** *Lorenzo Trippa, Geffrey Fell, Eudocia Quant Lee, Rifaquat Rahman, Mehdi Touat, Christine McCluskey, Jennifer Bruno, Sarah Gaffey, Jan Drappatz, Andrew B. Lassman, Evanthia Galanis, Manmeet Ahluwalia, Howard Colman, L. Burt Nabors, Jaroslaw Hepel, Heinrich Elinzano, Thomas Kaley, Ingo Mellinghoff, David Schiff, Ugonma Chukwueke, Rameen Beroukhim, Lakshmi Nayak, Jose Riccardo Mcfaline-Figueroa, Tracy Batchelor, Christine Lu-Emerson, Wenya Linda Bi, Omar Arnaout, Pier Paulo Peruzzi, Daphne Haas-Kogan, Shyam Tanguturi, Daniel Cagney, Ayal Aizer, Mary Welch, Lisa Doherty, Maria Lavallee, Brittany Fisher-Longden, Shanna Dowling, Jack Geduldig, Fiona Watkinson, Sandro Santagata, David Meredith, E. Antonio Chiocca, David A. Reardon, Keith L. Ligon, Brian M. Alexander, Patrick Y Wen.*

*Massachusetts General Hospital, Boston, MA;, Dana-Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital, Boston, MA; Gustave Roussy Cancer Centre, Villejuif, France; University of Pittsburgh, Pittsburgh, PA; Columbia University, New York, NY; Mayo Clinic, Rochester, MN; Cleveland Clinic, Cleveland, OH; University of Utah, Salt Lake City, UT; University of Alabama, Birmingham, AL; Rhode Island Hospital, Providence, RI; University of Virginia, Charlottesville, VA; Memorial Sloan Kettering Cancer Center, New York, NY; Maine Medical Center, Portland, ME*

# DISCLOSURES

- Astex Pharmaceutics (contracted research)

- FORMA therapeutics (advisory board)

# Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT): A Bayesian Adaptive Platform Trial to Develop Precision Medicines for Patients With Glioblastoma

INSIGhT

Brian M. Alexander, PhD, MPH[1,3]; Lorenzo Trippa, PhD[1]; Sarah Gaffey[1]; Isabel C. Arrillaga-Romany, MD, PhD[2]; Eudocia Q. Lee, MD[1]; Mikael L. Rinne, MD, PhD[3,4]; Manmeet S. Ahluwalia, MD[5]; Howard Colman, MD, PhD[6]; Geoffrey Fell, MS[1]; Evanthia Galanis, MD[7]; John de Groot, MD[8]; Jan Drappatz, MD[9]; Andrew B. Lassman, MD[10]; David M. Meredith, MD, PhD[1,3]; L. Burt Nabors, MD[11]; Sandro Santagata, MD, PhD[1,3]; David Schiff, MD[12]; Mary R. Welch, MD[10]; Keith L. Ligon, MD, PhD[1,3]; and Patrick Y. Wen, MD[1]

**Brian Alexander**   **Keith Ligon**

**Lorenzo Trippa**   **Patrick Wen**

**(50-70 patients/arm)**

Molecular/Imaging biomarker assessment
(Whole exome sequencing, array CGH)

Newly diagnosed GBM

(ABC2)

Tissue

RANDOMIZE

4-6 weeks

RT + TMZ Adjuvant TMZ

RT/TMZ followed by Abemaciclb (CDK 4/6 inhibitor)

RT + CC115 (mTOR/DNA PK inhibitor)

RT/TMZ followed by Neratinib (EGFR Inhibitor)

Reoperation

PFS

OS

Adaptive design

Preclinical models

Co-clinical trials to generate biomarker/tx hypotheses

Preclinical surrogate endpoint development

**Arms can be dropped or added**

**DFCI
Columbia
Huntsman
Mayo
MGH
MSKCC
RIH
U Pittsburgh
UVA
U Alabama**

# Advantages of a Bayesian Adaptive Trial

- Patients are randomized to arms using an adaptive algorithm that will updated the randomization probabilities by biomarker grouping monthly.

- individual biomarker groups and PFS of enrolled pts is used to determine randomization probabilities

- This algorithm accelerates and provided a competitive advantage to those experimental arms associated with promising data early during the study.

- Arms can be dropped

- New arms can be added

- Efficiency from sharing a control arm

# Background
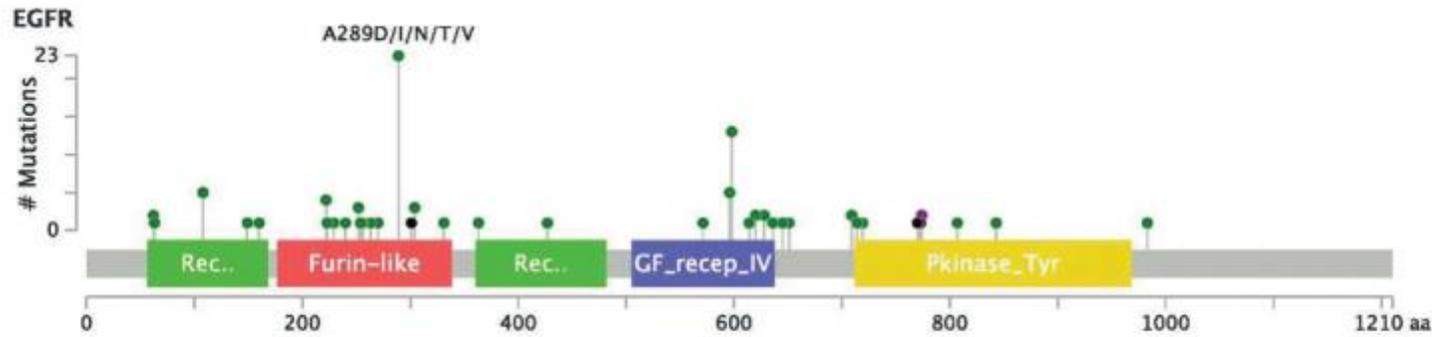


Source: cBioPortal for Cancer Genomics, accessed: 21OCT2013.

- EGFR is a receptor tyrosine kinase that regulates cell growth and differentiation

- ~ 40% of GBMs show amplification of the *EGFR* gene locus

- ~ half of *EGFR*-gene amplified cases express the constitutively active mutant receptor *EGFRvIII*

- EGFR is a compelling therapeutic target in GBM, though a number of trials in unselected patients with GBM (or selected but using archival tissue for patients with rGBM) report limited efficacy with EGFR-selective TKIs

- First biomarker-driven prospective controlled study of an EGFR small molecule inhibitor in newly diagnosed GBM

# Neratinib (HKI-272)

- Orally available potent irreversible small molecule inhibitor of EGFR, HER2, and HER4

- Successful in clinical trials of HER2 positive breast cancer; FDA approved

- Has shown activity in controlling and delaying CNS progression of breast cancer metastases (Awada A, et al: JAMA Oncol 2:1557-1564, 2016).

- Selectively cause cell death in GBM cell lines harboring genetic activation of *EGFR* (Vivanco I, et al: Cancer Discov 2:458-471, 2012)

- More effective than other EGFR inhibitors in lines harboring the extracellular domain mutations seen in GBM (Vivanco I, et al: Cancer Discov 2:458-471, 2012)
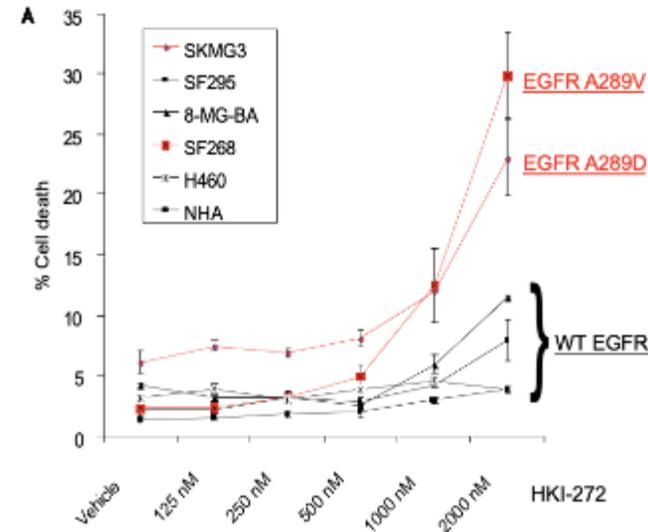


*HKI-272 induces cell death in GBM cells with EGFR EC mutation (SKMG3, SF268) but not EGFR wild-type (WT EGFR) cancer cell lines or astrocytes (NHA)*
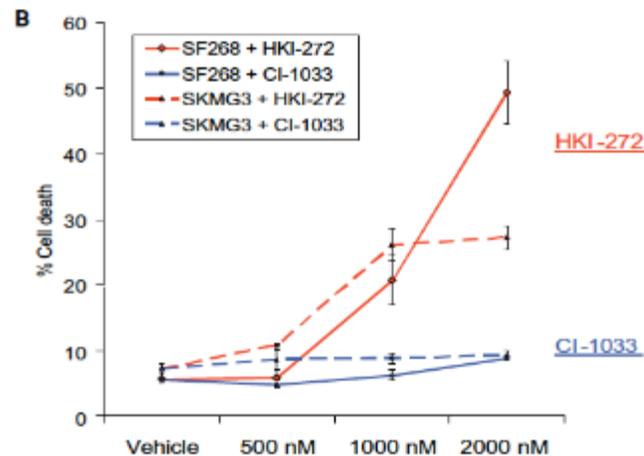
*Cell death in GBM cell lines harboring extracellular domain mutations using neratinib (HKI-272) vs. another irreversible EGFRi (CI-1033)*

Vivanco I, et al: Cancer Discov 2:458-471, 2012

# Neratinib: potent inhibitor of EGFRvII and EGFRvIII GBM cell lines

Neratinib has also been shown to exhibit potential for potent inhibition of *EGFRvII* and *EGFRvII* expressing GBM patient-derived cell-line models

Out of a various EFFR inhibitors, the irreversible inhibitors afatinib and neratinib exhibited the lowest IC50 for both EGFRVII and VIII expressing cells.



Francis JM, et al: Cancer Discov 4:956-971, 2014
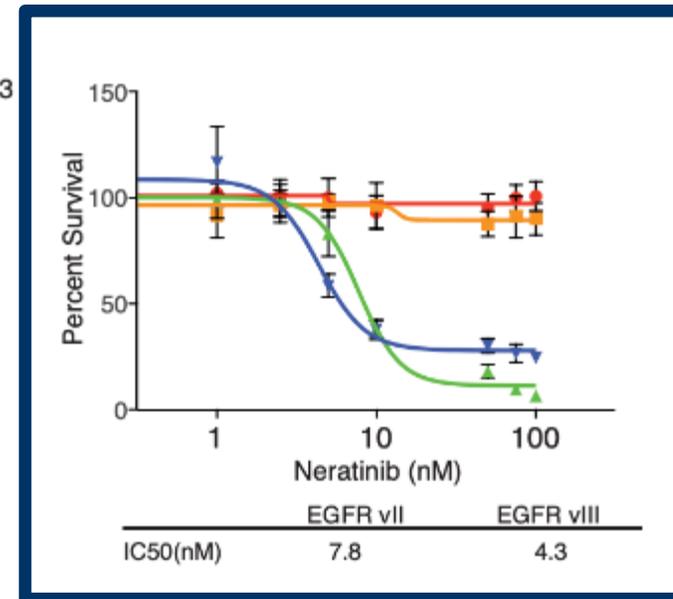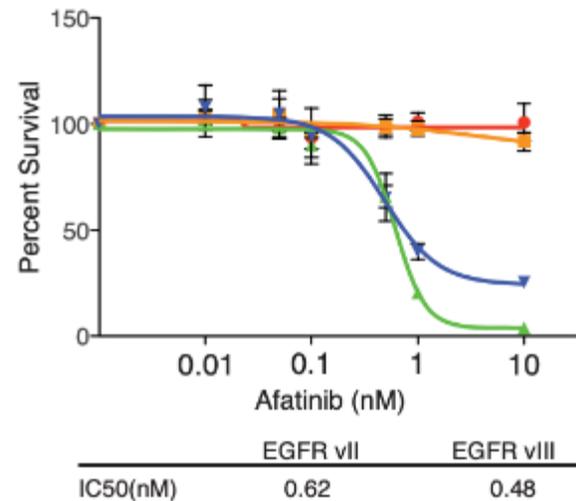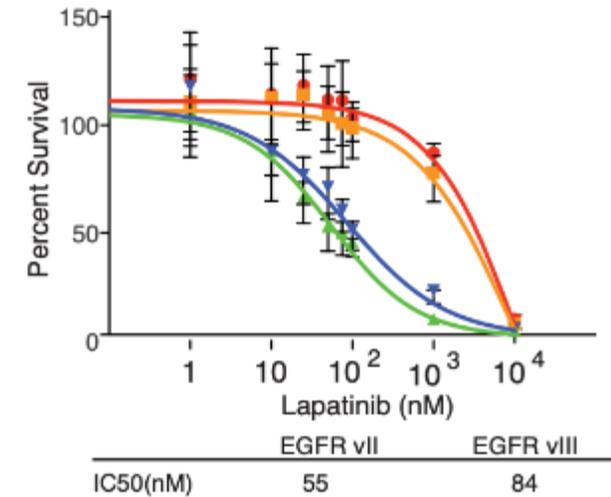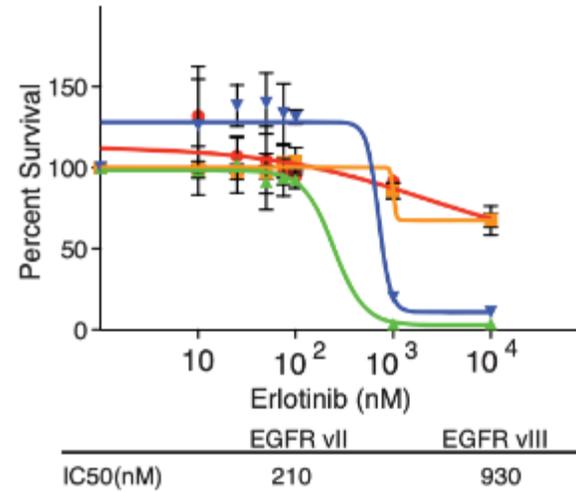
# Study Objectives

Primary Objective

To determine whether experimental arms improve overall survival (OS) in patients with GBM harboring unmethylated MGMT promoters compared with standard therapy

Secondary Objectives

- To determine whether specific a priori defined biomarkers predict the benefit from experimental therapy

- To assess the toxicity of experimental arms

- To assess progression-free survival (PFS) among experimental arms and biomarker groups

- To assess OS among experimental arms and biomarker groups

- To determine the association between PFS and OS effects of experimental agents

# Treatment Plan
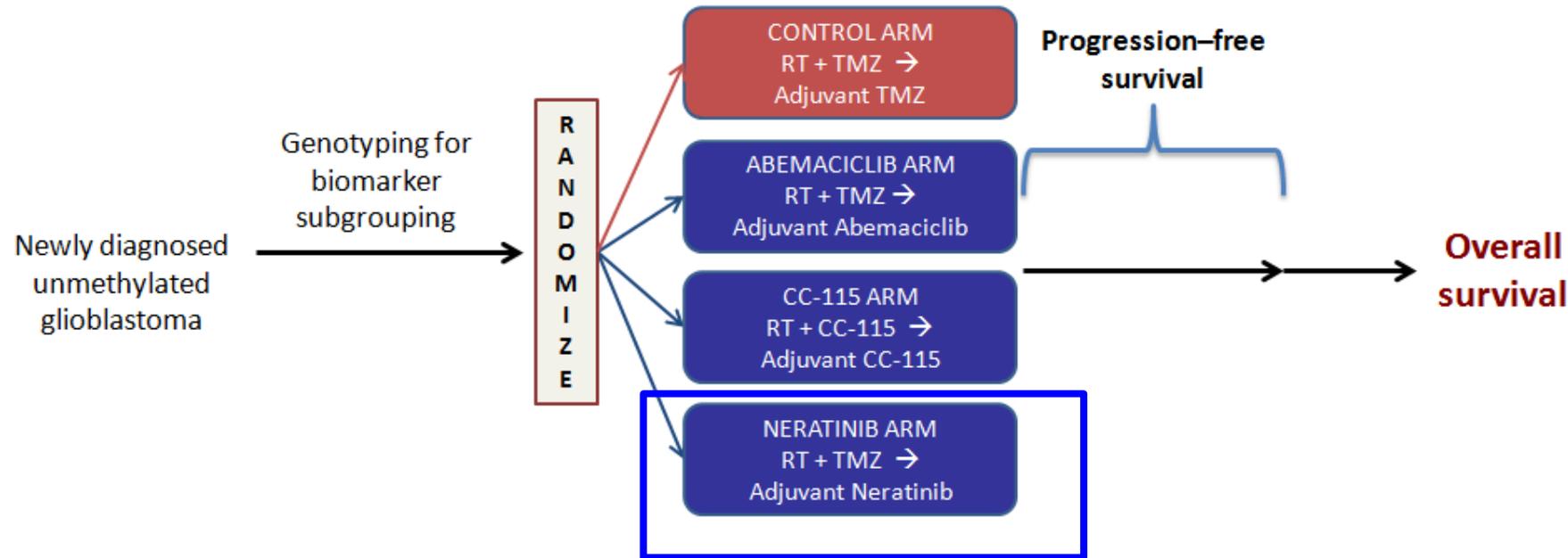


- **Chemoradiation:** RT (6000 cGy) + Temozolomide (75mg/m2/d x 42 days)→ 4-week break

- **Study Arm:** neratinib (240 mg daily)in 28-day cycles until progression or unacceptable tox

- **Control arm:** Temozolomide 150-200mg/m2/d x 5 for 6 cycles

# Inclusion Criteria

- Histologically confirmed intracranial glioblastoma or gliosarcoma

- Age ≥ 18 years.

- Karnofsky performance status ≥60

- Normal organ and marrow function

- Participants must plan to begin radiation therapy 14-42 days after surgical resection.

- Immunohistochemically negative for IDH1 R132H mutation.

- Evidence that the tumor MGMT promoter is unmethylated by standard of care assays.

- Genotyping data available or in process

- Ability to understand and the willingness to sign a written informed consent document.

# Exclusion Criteria

- Prior therapy apart from surgery

- History of a different malignancy, unless disease-free for at least 2 years and are deemed by the investigator to be at low risk for recurrence of that malignancy

- Significant intratumoral hemorrhage

- Taking EIAED

- > 4mg decadron

- Uncontrolled intercurrent illness

- Impairment of GI function

# Statistical Design and Analysis

- Analysis was based on an ITT population.

-  OS and PFS were calculated using the the Kaplan-Meier method and the Log-Rank test was conducted to compare between the study arms

- Max # of patients per arm, 70,  maintains the power of detecting a positive treatment effect for a specific experimental arm stable with respect to the presence or absence of treatment effects on the remaining arms.

- With OS-HR equal to 0.6 (0.7) on the overall population, the power of rejecting the null hypothesis at completion of the study is 0.89 (0.77)

- With an PFS-HR equal to 0.6 (0.7) on the overall population, the power of rejecting the corresponding primary null hypothesis (overall population PFS-HR ≥ 1) at completion of the study is 0.9 (0.79).

# Demographics
## 149 patients (68 control; 81 neratinib)

|  |  | Neratinib | Control |
|---|---|---|---|
| N |  | 81 | 68 |
| Age | Median | 60 | 59 |
|  | Range | [24 - 78] | [24 -75] |
| Sex | Male | 46 | 41 |
|  | Female | 35 | 27 |
| Race | Caucasion | 74 | 63 |
|  | African American | 2 | 0 |
|  | Other | 5 | 5 |
| Ethnicity | Hispanic | 2 | 3 |
|  | Non-Hispanic | 79 | 65 |
| KPS | 100 | 14 | 4 |
|  | 90 | 31 | 40 |
|  | 80 | 25 | 20 |
|  | 70 | 11 | 4 |
| EGFR | + | 43 | 30 |
|  | - | 38 | 38 |
| CDK | + | 64 | 49 |
|  | - | 17 | 19 |
| PI3K | + | 53 | 39 |
|  | - | 28 | 29 |

The neratinib and control groups are overall well balanced

# Grade 3 or greater toxicity related to study drug

Neratinib was generally well tolerated

Toxicities for neratinib were similar that previously described

No new toxicity signal identified

| Toxicity | Grade | |
|---|---|---|
| | 3 | 4 |
| Colitis | 1 | 0 |
| Diarrhea | 6 | 0 |
| Fatigue | 2 | 0 |
| Sepsis | 1 | 0 |
| UTI | 1 | 0 |
| ALT increased | 1 | 0 |
| Platelet count decreased | 1 | 0 |
| Anorexia | 1 | 0 |
| Dehydration | 1 | 0 |
| Hypokalemia | 1 | 0 |
| Generalized Muscle Weakness | 1 | 0 |
| Hypertension | 1 | 0 |
| Surgical and Medical Procedures | 1 | 0 |

# Progression Free Survival
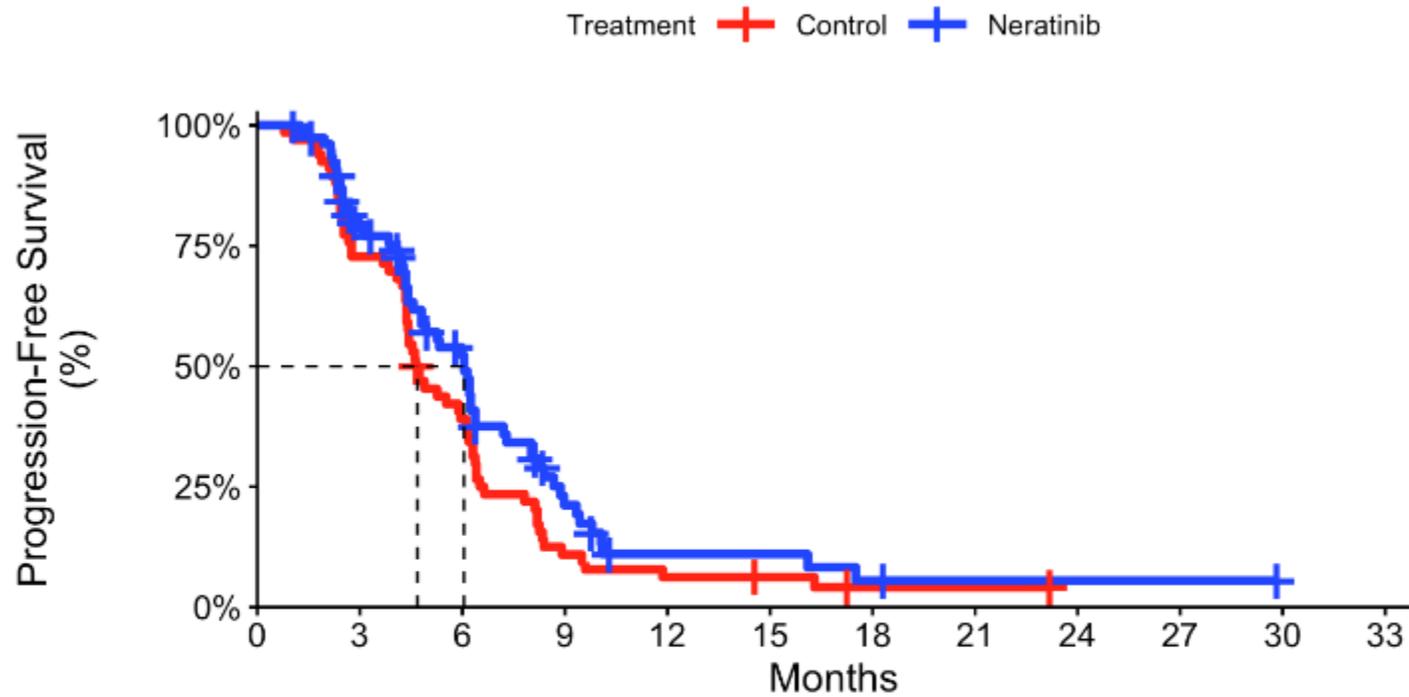


**PFS was not significantly longer** (HR 0.75; p=0.12, logrank test) with neratinib (median 6.0 mo) vs control arm (median 4.7 mo).
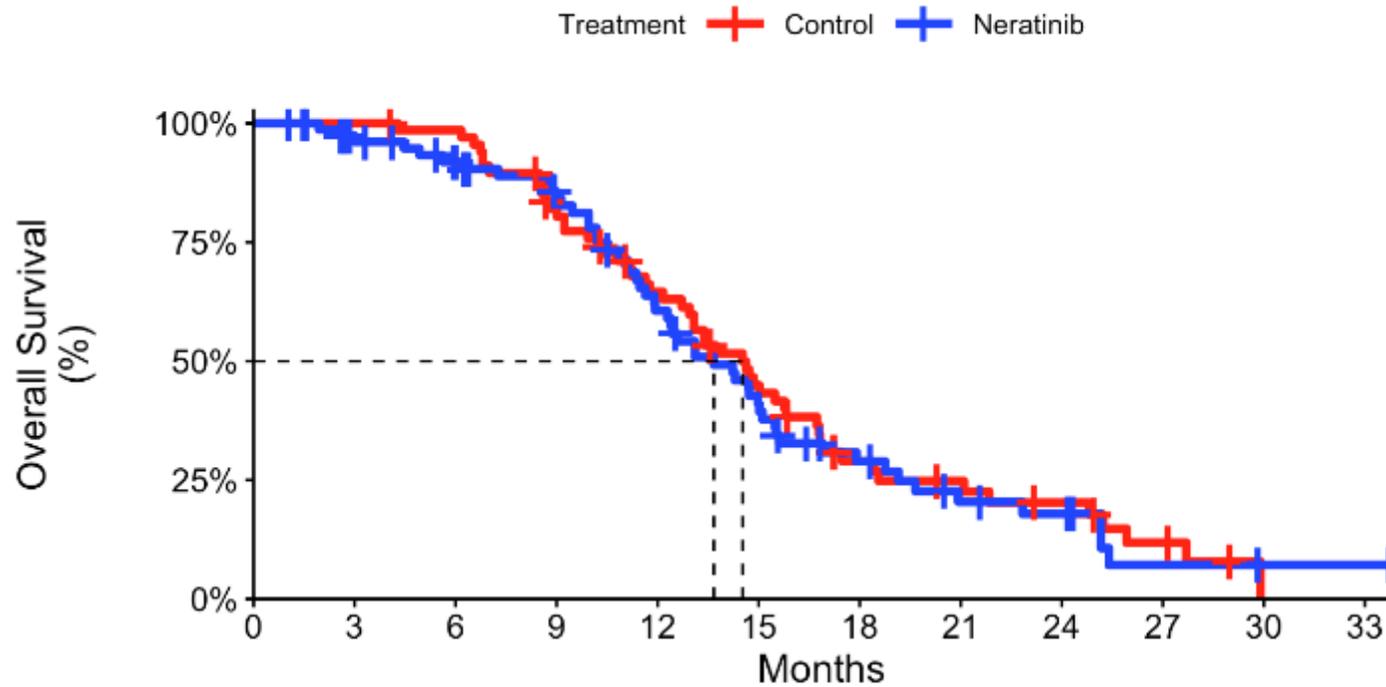
# Overall Survival



**No significant improvement in overall survival** (HR 1.01; p=0.75) between neratinib (median 13.8 mo) vs control arm (median 14.7 mo).
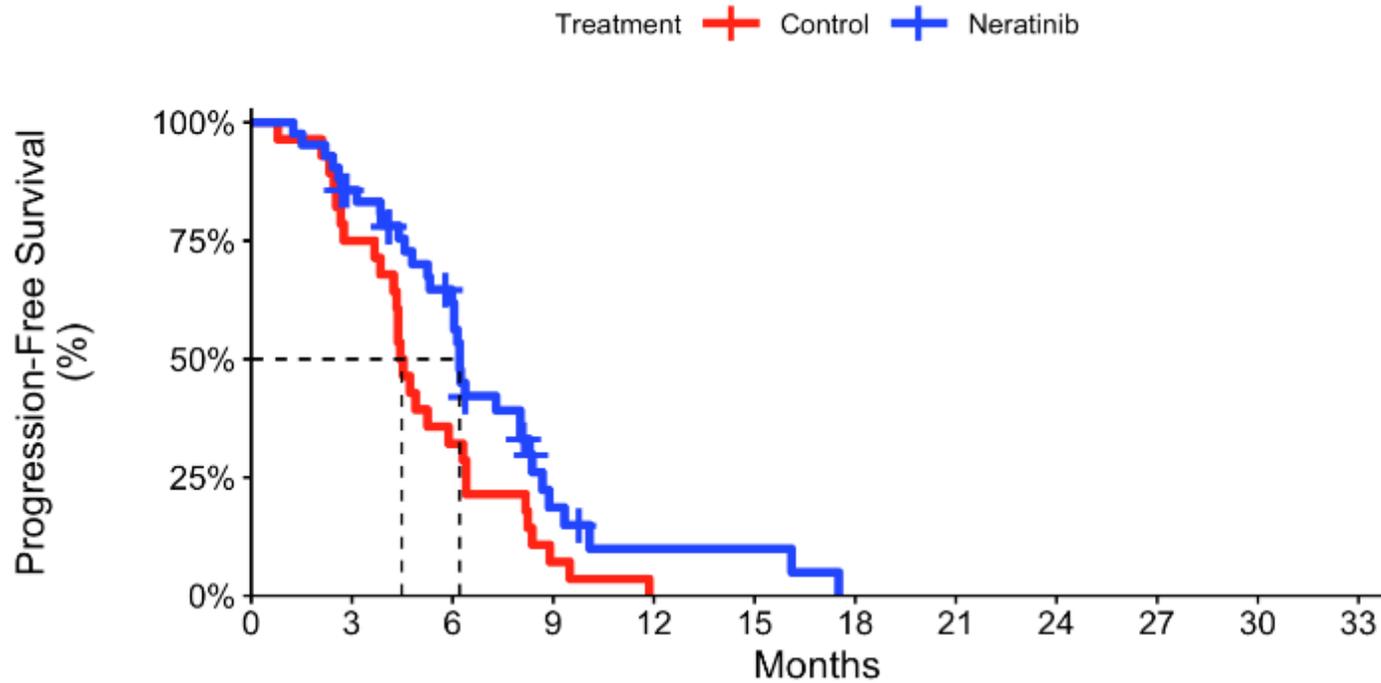
# PFS in the EGFR positive subpopulation (N=73)



For patients with activation of the EGFR pathway:
**PFS was significantly longer** (HR 0.58; p=0.04, logrank test) with neratinib (median 6.3 mo) vs control arm (median 4.6 mo).

# OS in EGFR positive subpopulation (N=73)
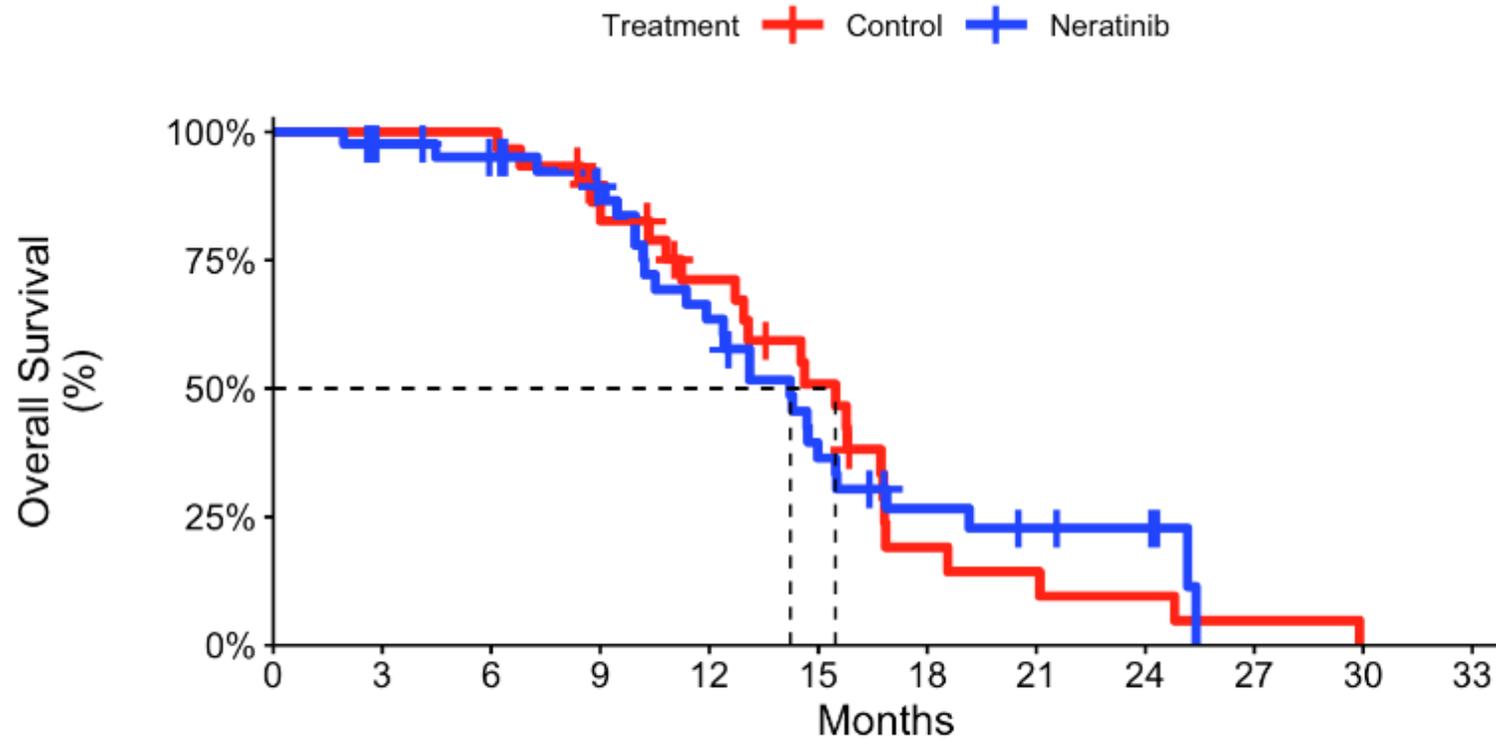


**No significant improvement in overall survival** (HR 0.97; p= 0.94) between neratinib (median 14.4 mo) vs control arm (median 15.3 mo).

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 30 | 30 | 30 | 24 | 18 | 12 | 4 | 3 | 2 | 1 | 0 | 0 |
| Neratinib | 43 | 39 | 36 | 31 | 22 | 12 | 7 | 5 | 4 | 0 | 0 | 0 |

# PFS and OS in the EGFRVIII mutant subpopulation (N=28)
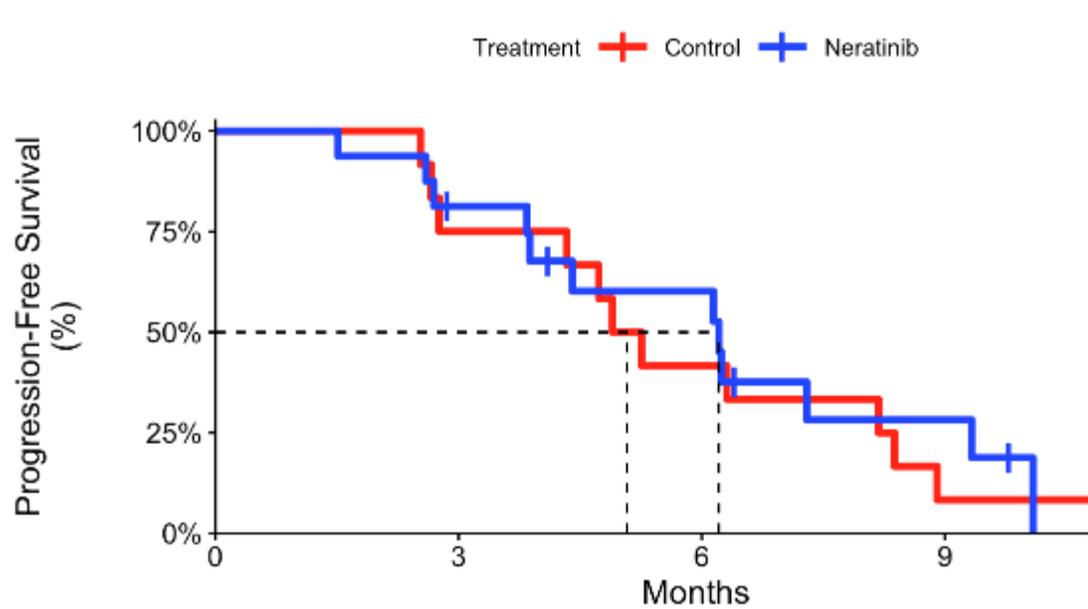


**PFS: No significant improvement in progression free survival** (HR 0.88; p= 0.77) between neratinib (median 6.2 mo) vs control arm (median 5.1 mo).
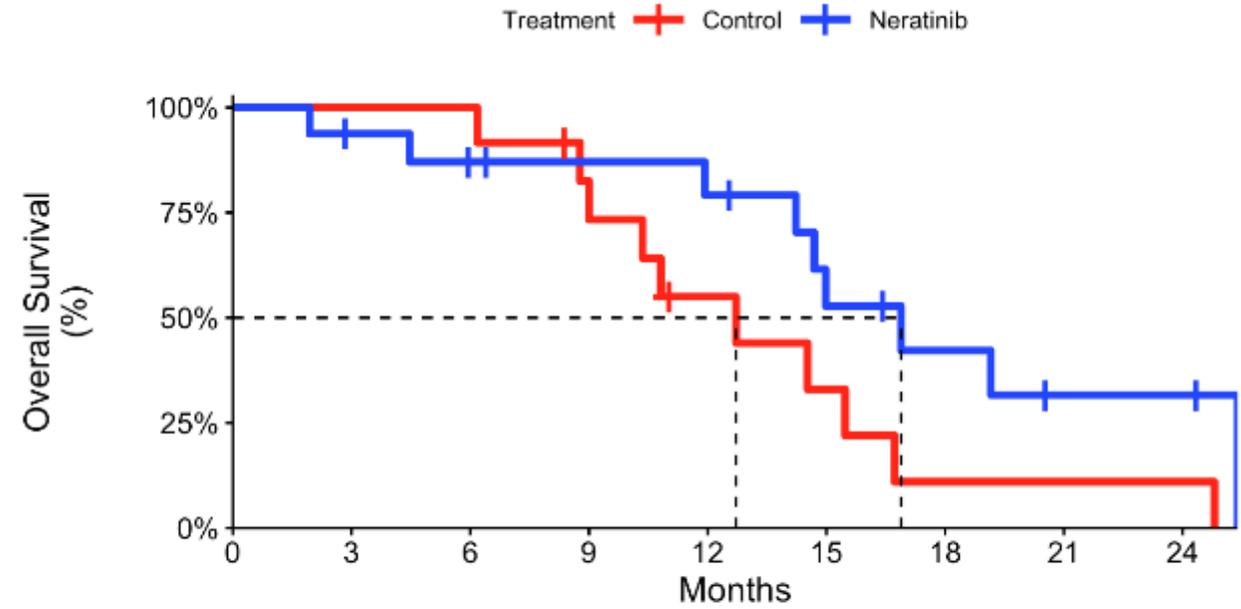
**OS: No significant improvement in overall survival** (HR 0.44; p= 0.09 between neratinib (median 16.9 mo) vs control arm (median 12.7 mo).

## Conclusions

- First biomarker-driven prospective controlled study of an EGFR TKI in newly diagnosed GBM

- We showed that a multicenter platform trial with Bayesian adaptive randomization in newly diagnosed GBM is feasible

  - Efficiency from sharing control arm

  - Rapid accrual

  - Potential to add additional arms

- Neratinib was well-tolerated

- Neratinib prolonged PFS in the EGFR positive subpopulation but there was no overall PFS benefit, or any OS improvement.

# Acknowledgements

- Study investigators and staff at each site

- Accelerated Brain Cancer Cure

- National Brain Tumor Society

- Patients and their family