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Neratinib with or without temsirolimus in patients with non-small cell lung cancer carrying *HER2* somatic mutations: An international randomized phase II study

Benjamin Besse,[1] Soria J-C,[1] Bin Yao,[2] Mark G Kris,[3] Bo Chao,[4] Alexis Cortot,[5] Julien Mazieres,[6] Mark A. Socinski[7] Leora Horn,[8] Saiama N Waqar,[9] Fabrice Barlesi,[10] Jhanelle E. Gray,[11] Denis Moro-Sibilot,[12] Ana Oton[13] Elisabeth Quoix,[14] Alshad S. Lalani,[2] Leanne McCulloch,[2] Richard Bryce,[2] Leena Gandhi[15]

1. Gustave Roussy, Villejuif, France; 2. Puma Biotechnology Inc., Los Angeles, CA, USA; 3. Memorial Sloan Kettering, New York, NY, USA; 4. Ohio State University, Columbus, Ohio, USA; 5. CHRU de Lille - Hôpital Calmette, Lille, France; 6. CHU de Toulouse Hôpital Larrey, Toulouse, France; 7. University of Pittsburgh, Pittsburgh, PA, USA; 8. Vanderbilt University, Nashville, TN, USA; 9. Washington University, St Louis, MO, USA; 10. Hôpital Nord, Marseille, France; 11. Moffitt Cancer Center, Tampa, FL, USA; 12. CHU de Grenoble, Grenoble, France; 13. University of Colorado, Aurora, CO, USA; 14. Hôpitaux Université de Strasbourg, Strasbourg, France; 15. Dana Farber Institute, Boston, MA, USA

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- Benjamin Besse has research grants from:
  - Puma Biotechnology
  - Pfizer

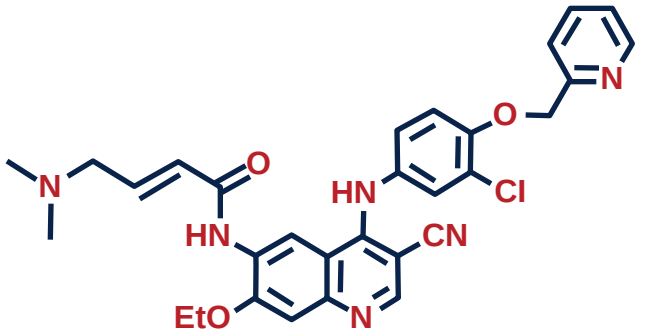
HER2 Mutations in Lung Cancer

- Somatic *HER2* (*ERBB2*) mutations occur in approximately 2% of patients with non-small cell lung cancer (NSCLC)[1,2]
  - Most *HER2* mutations are observed in tumors with adenocarcinoma histology[2,3]
- Comprehensive molecular profiling suggests that *HER2* mutations are mutually exclusive to other driver aberrations in NSCLC, including KRAS, EGFR and ALK[4]
- The most common type of *HER2* mutations are in-frame insertions (e.g. 775_776insYVMA) within the kinase domain (exon 20)[1]

1. Cancer Genome Atlas Research Network. Nature 2014;511:543–50
2. Mazières et al. J Clin Oncol 2013;31:1997–2003
3. Shigematsu et al. Cancer Res 2005;65:1642–4
4. Cancer Genome Atlas Research Network. Nature 2014;511:543–50

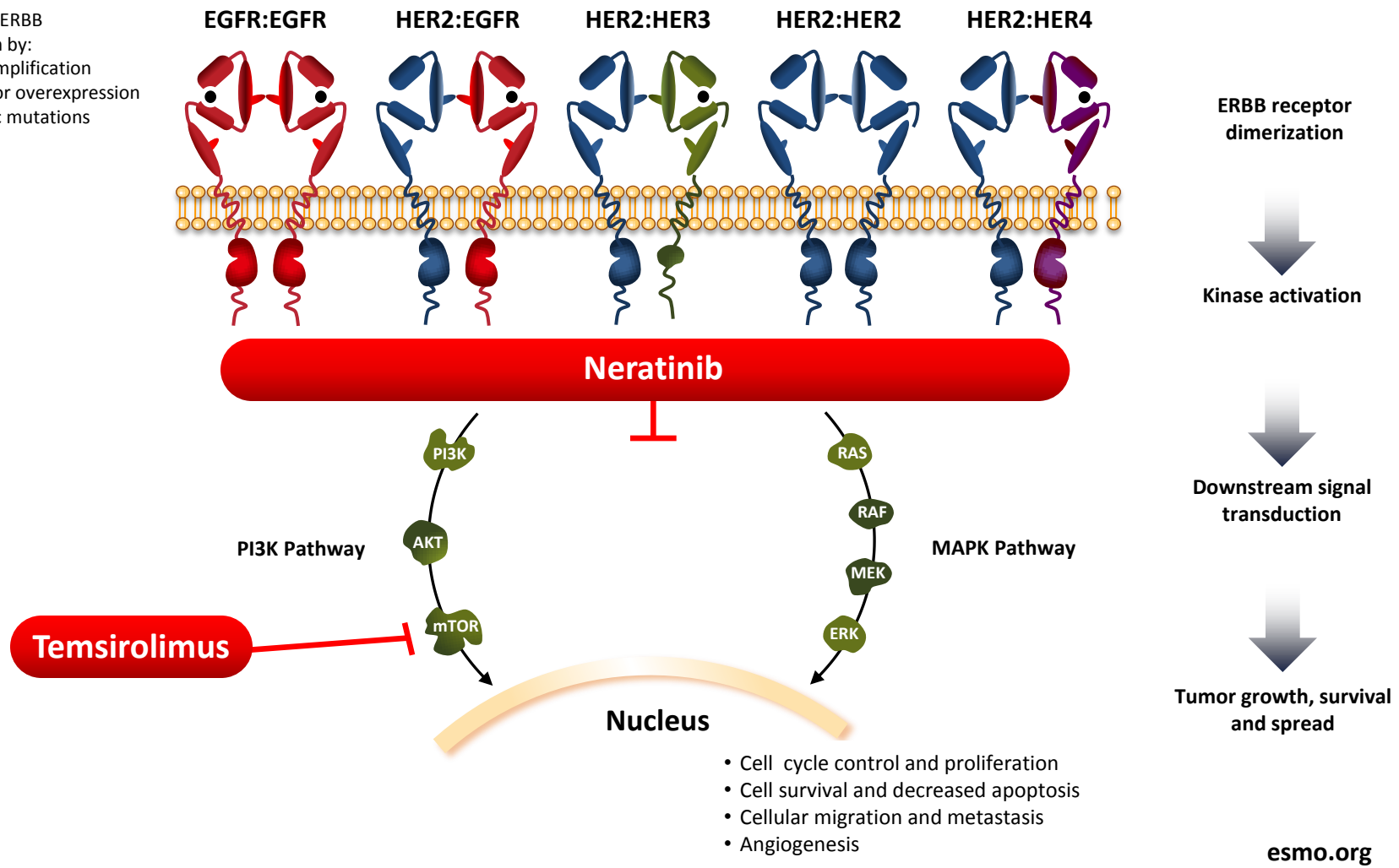
Neratinib (PB272)

- Potential, irreversible, pan-ERBB (HER) tyrosine kinase inhibitor
  - High affinity, covalent binding to EGFR (ERBB1), HER2 (ERBB2) and HER4 (ERBB4) receptor tyrosine kinases
  - Blocks downstream ERBB signal transduction pathways and cell proliferation
  - Inhibits growth of tumor xenografts that have aberrant ERBB pathway activation
- Administered orally, once daily 240 mg



Mechanism of Action

Aberrant ERBB activation by:
- Gene amplification
- Receptor overexpression
- Somatic mutations

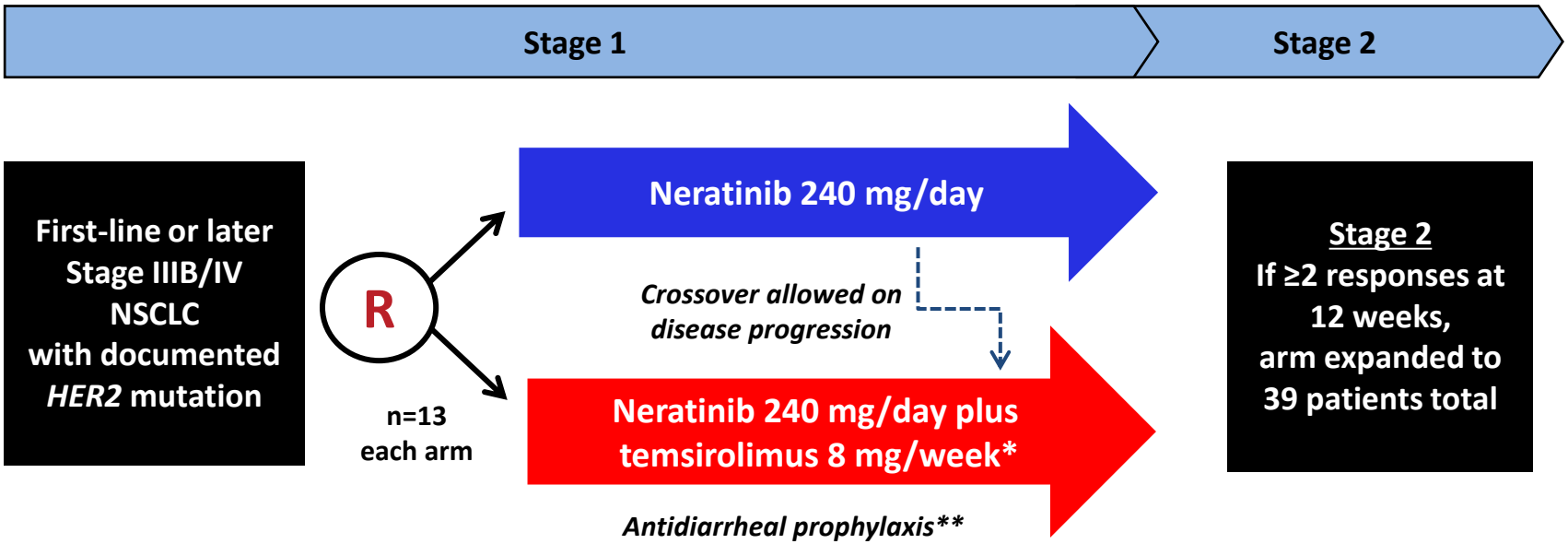


Combined HER2/mTOR Inhibition: Rationale

- Preclinical data suggest synergistic efficacy of combined HER2 and mTOR inhibition in *HER2* mutation-positive NSCLC[1,2]
- In a phase I study, neratinib plus temsirolimus showed promising efficacy in patients with *HER2*-mutated NSCLC[3]
- The effects of neratinib monotherapy in NSCLC have not been characterized previously
- A 2-stage multicenter phase II study compared neratinib with or without temsirolimus against historical controls in patients with advanced or metastatic NSCLC with somatic *HER2* mutations

1. Perera et al. Proc Natl Acad Sci USA 2009;106:474–9
2. Puma Biotechnology Inc, data on file
3. Gandhi et al. J Clin Oncol 2014;32:68–75

PUMA-NER-4201: Study design



STUDY OBJECTIVES:

- 1º endpoint: Objective Response Rate (ORR)
- 2º endpoints: Clinical benefit rate, duration of response, PFS, OS, safety, health outcomes
- Exploratory: PK, correlative studies (tumor tissue and plasma), exposure-response relationship

*Temsirolimus dose escalated to 15 mg IV weekly after 1st cycle if tolerated
**Mandatory primary antidiarrheal prophylaxis with a 21-day regimen of high-dose loperamide

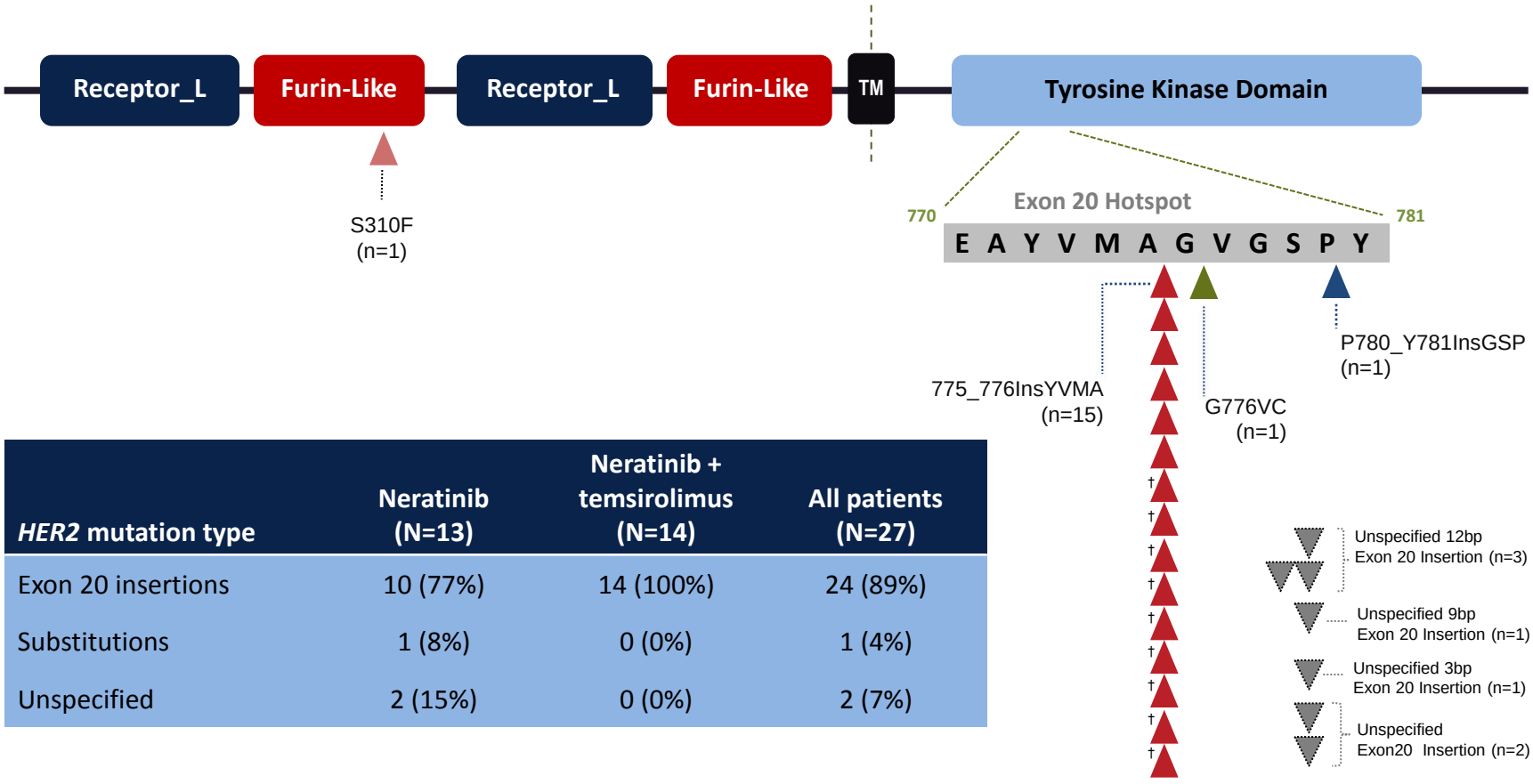
ClinicalTrials.gov Identifier: NCT01827267
EudraCT Identifier: 2012-004743-68

Patient Characteristics

	Neratinib (N=13)	Neratinib + temsirolimus (N=14)
Age, years		
Median (range)	66 (45–76)	64 (36–74)
Gender, n (%)		
Male	8 (62)	6 (43)
Female	5 (38)	8 (57)
Smoking status, n (%)		
Never smokers	7 (54)	10 (71)
Prior anticancer medications, n (%)		
Yes	13 (100)	12 (86)
No	0	2 (14)
Mutation status, n		
HER2 mutation	13	14
EGFR mutation	0	0
KRAS mutation	1	0
ALK translocation	0	0

All patients had adenocarcinoma histology

Distribution of Somatic *HER2* Mutations



HER2 mutation type	Neratinib (N=13)	Neratinib + temsirolimus (N=14)	All patients (N=27)
Exon 20 insertions	10 (77%)	14 (100%)	24 (89%)
Substitutions	1 (8%)	0 (0%)	1 (4%)
Unspecified	2 (15%)	0 (0%)	2 (7%)

†Confirmed by central NGS testing (FoundationOne®)

Treatment Exposure

Neratinib exposure	Neratinib (N=13)	Neratinib + temsirolimus (N=14)
Median treatment duration, weeks	9.1	17.5
Median prescribed dose, mg/day	240	230
Dose reductions, n	2	4
Doses withheld, n	4	9
Crossover to combination therapy, n	5	NA
Temsirolimus exposure		
Median treatment duration, weeks	NA	17.1
Median prescribed dose, mg/week	NA	8.3
Dose increase (8 to 15 mg/week), n	NA	7
Dose reductions, n	NA	0
Doses withheld, n	NA	9

Table shows dosing data prior to crossover by neratinib monotherapy patients; NA = not applicable

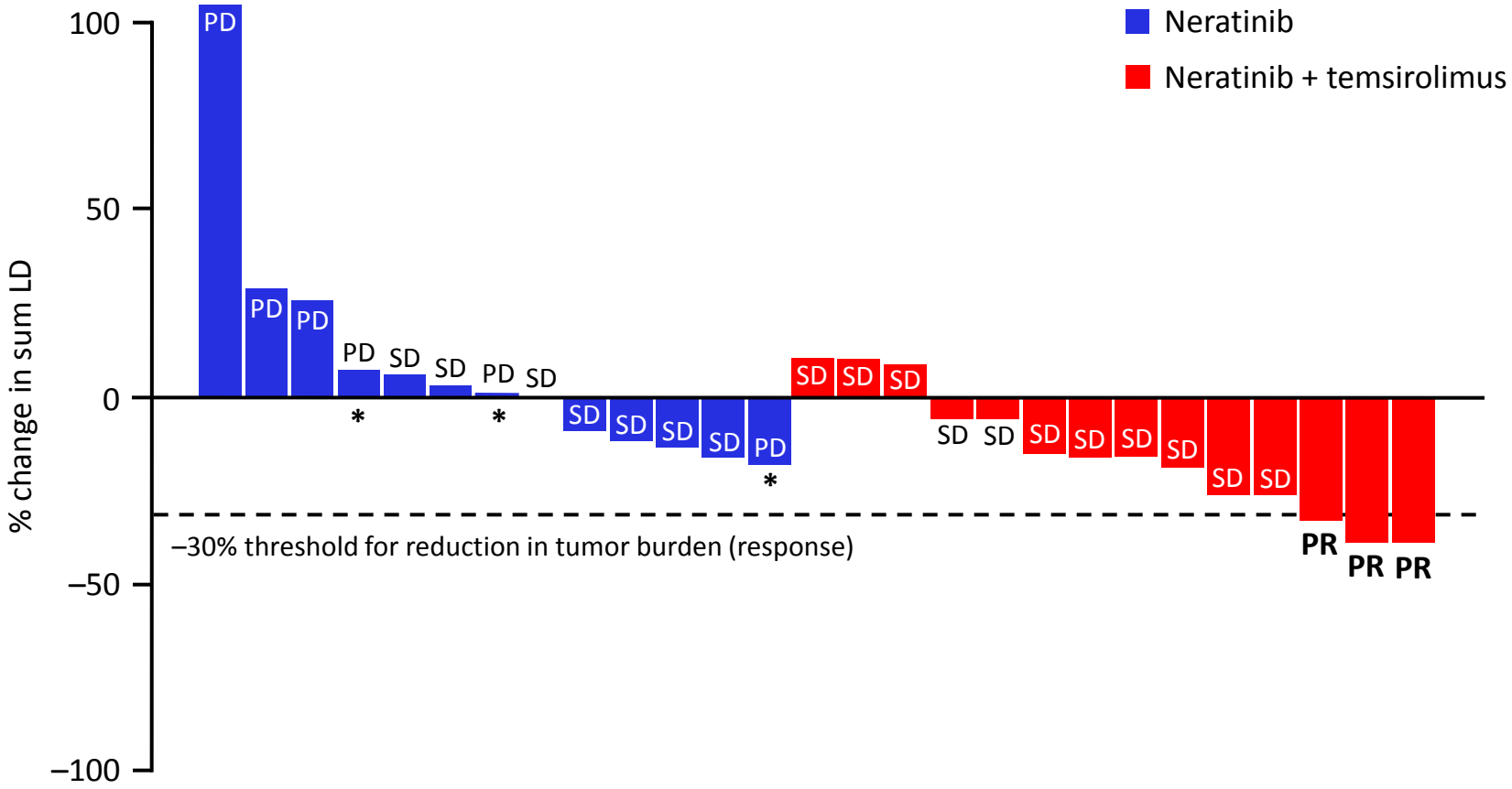
Efficacy – Stage I Analysis

	Neratinib (N=13)	Neratinib + temsirolimus (N=14)
Best overall response, n (%)		
Partial response	0 (0)	3 (21)*
Stable disease	7 (54)	11 (79)
Progressive disease	6 (46)	0 (0)
Onset of response, days	–	39, 41, 43
Clinical benefit rate**, n (%)	4 (31)	9 (64)
Median duration of follow-up, months	2.2	3.9

*2 of 3 responses were confirmed. **Including responders and those with SD ≥12 weeks
Data cut for stage 1 analysis: 2 June 2014

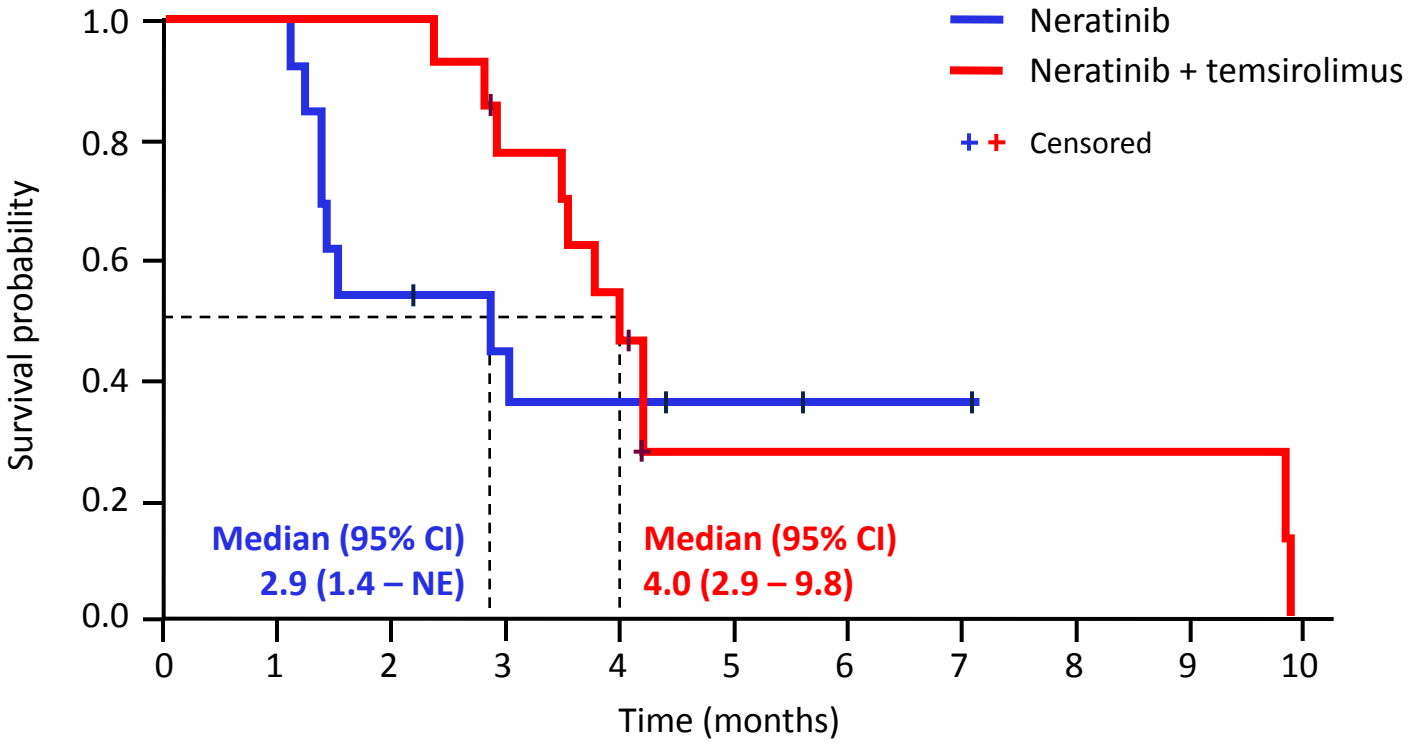
- No apparent correlation observed between *HER2* mutation type and response
- Outcome in crossover patients: stable disease and still on treatment (n=1); disease progression (n=4)

Best Change in Tumor Burden



*Patients had <20% increase in tumor burden but were considered PD due to the appearance of new lesions

Progression-Free Survival



No. of patients											
Neratinib	13	13	7	5	4	3	2	2	0		
Neratinib + temsirolimus	14	14	14	10	7	2	2	2	2	2	0

Treatment-Emergent AEs (All Grades)

All-grade events (>40% patients), n (%)	Neratinib (N=13)	Neratinib + temsirolimus (N=14)
Diarrhea	10 (77)	14 (100)
Asthenia	6 (46)	5 (36)
Nausea	6 (46)	7 (50)
Abdominal pain	5 (38)	3 (21)
Constipation	5 (38)	8 (57)
Dyspnea	4 (31)	7 (50)
Rash	4 (31)	3 (21)
Vomiting	3 (23)	8 (57)
Anemia	3 (23)	6 (43)
Decreased appetite	3 (23)	6 (43)

Treatment-Emergent AEs (Grade 3–5)

n (%)	Neratinib (N=13)	Neratinib + temsirolimus (N=14)
Grade 3 events (>10% patients)		
Vomiting	0	3 (21)
Diarrhea*	1 (8)	2 (14)
Dyspnea	1 (8)	2 (14)
Nausea	0	2 (14)
Grade 4 events**		
Dyspnea	1 (8)	0
Blood uric acid increased	1 (8)	0
Cardio-respiratory arrest	1 (8)	0
Grade 5 events**		
Pleural effusion	1 (8)	0
Cerebrovascular accident	1 (8)	0
Respiratory failure	0	1 (8)

*2 of the 3 patients experiencing grade 3 diarrhea were not compliant with the loperamide prophylaxis regimen during cycle 1 and had stopped prophylaxis prior to diarrhea onset; **All grade 4 and 5 events were considered to be unrelated to neratinib

Conclusions

- In this predefined stage 1 analysis of the 4201 study in patients with advanced / metastatic NSCLC with somatic *HER2* mutations:
  - Inhibition of both *HER2* and PI3K pathways appeared to be superior to *HER2* pathway blockade alone
  - An ORR of 21% and median PFS of 4 months was observed with neratinib plus temsirolimus
  - Neratinib plus temsirolimus met pre-specified criteria for continuing to stage 2 (enrollment into this arm is ongoing)
  - Exon 20 insertions (775_776insYVMA) were the predominant *HER2* variant detected
- No unexpected safety signals were reported
- With upfront management (loperamide prophylaxis), diarrhea was not a limiting toxicity, no grade 4 diarrhea was reported and no patients discontinued study treatment due to diarrhea