INHIBITORS OF TYROSIN KINASES TO PREVENT AND TREAT BRAIN METASTASES

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Introduction

- Brain metastases are an important sequelae of many types of cancer, most commonly lung cancer.
- Breast cancer is the second most common cause of CNS metastases (1st for leptomenigeal metastases).
- The incidence of brain metastases is likely to increase as new systemic treatment options became available.

Prognosis

- Median survival of brain metastases patients is about 4 months after WBRT.
- Factors that predict better survival:
  - good performance status,
  - age < 65 yrs,
  - successful control of the primary tumor,
  - absence of extracranial metastases,
  - favorable tumor histology,
  - presence of a solitary brain metastasis.

Risk factors

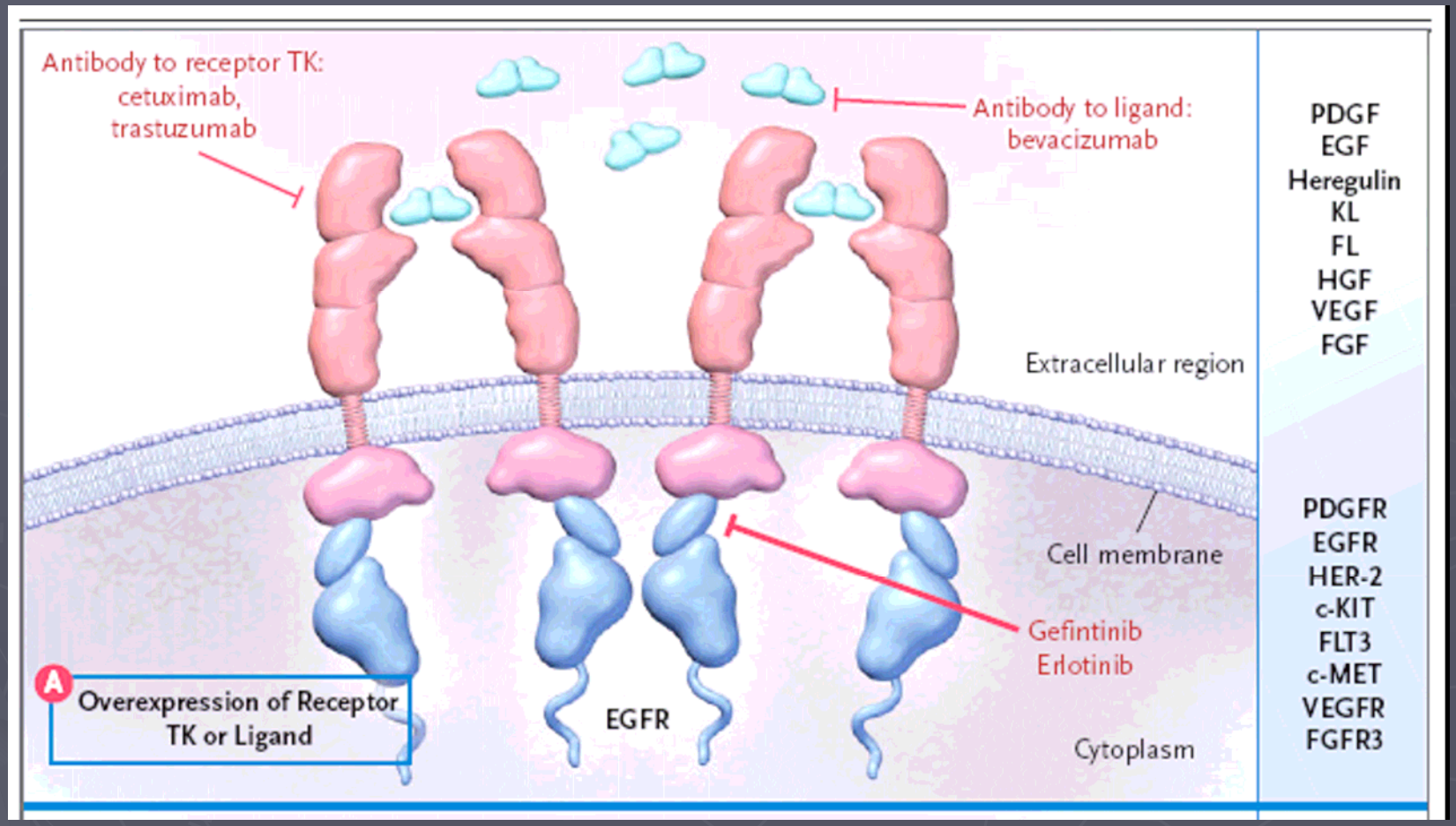
- Human epidermal growth factor receptor 2 (HER-2, ErbB-2) overexpression defines an aggressive subtype of breast cancer.
- HER-2 overexpression is the most significant indipendent risk factor associated with brain metastases.
- Other risk factors in breast cancer patients are younger age and hormone receptor status.
- 28-43% incidence of brain metastases among patients treated with trastuzumab for stage IV breast cancer.

Chemotherapy for brain metastases

- Chemotherapy has traditionally played a limited role in the treatment of brain metastases.
- The integrity of Blood-Brain Barrier (BBB) was thougth to limit delivery of large and hydrophilic drugs.
- Inherent chemoresistance of brain metastases.
- Most sensitive brain metastases from SCLC, germ cell tumors and lymphoid malignancies.
- Agents with activity against breast cancer able to cross the BBB: liposomal doxorubicin, idarubicin, methotrexate, platinums, tamoxifen.

Tyrosin kinases as targets for cancer therapy

- Protein tyrosin kinases (TKs) are enzymes that catalyze the transfer of phosphate from ATP to tyrosine residues in polypeptides.
- The humane genome contains about 90 TK and 43 TK-like genes.
- TKs regulate cellular proliferation, survival, differentiation function, and motility.
- Imatinib mesylate, an inhibitor of the BCR-ABL TK in chronic myeloid leukemia (CML), proof-of-principle of targeted cancer therapy.

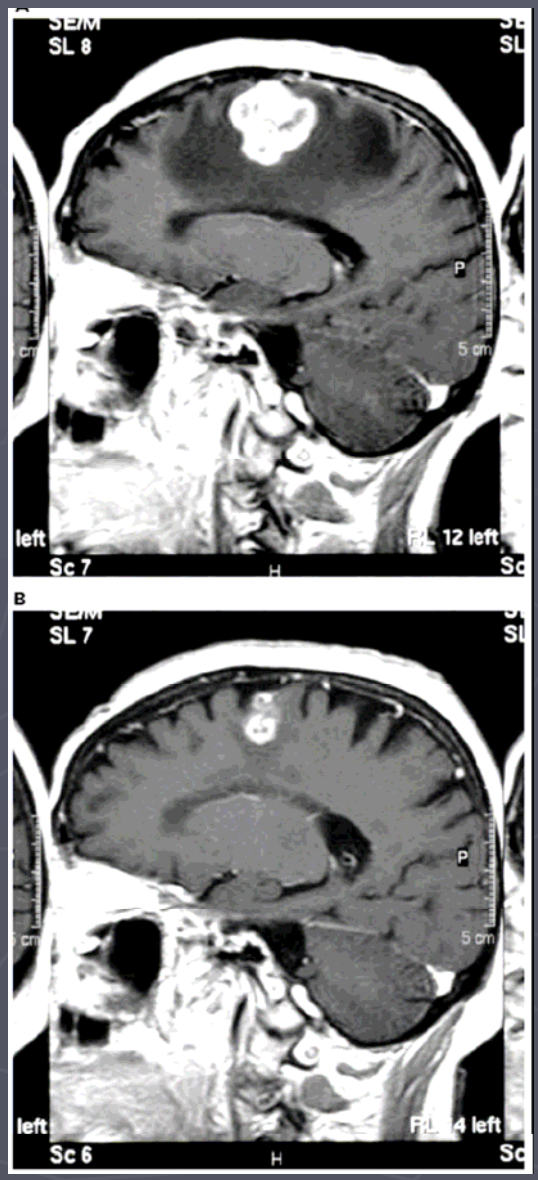


EGFR is overexpressed, mutated, or both in many solid tumors

specific, competitive inhibitors of ATP binding by EGFR

Gefitinib in NSCLC patients with brain metastases

- Gefitinib is an oral specific inhibitor of epidermal growth factor receptor-associated tyrosine kinase.
- Some activity in chemotherapy pretreated NSCLC.
- 41 consecutive NSCLC patients with measurable brain metastases.
- PR observed in four patients (10%), with stable disease (SD) in seven cases (17%).



Ceresoli GL, et al. *Ann Oncol* 2004

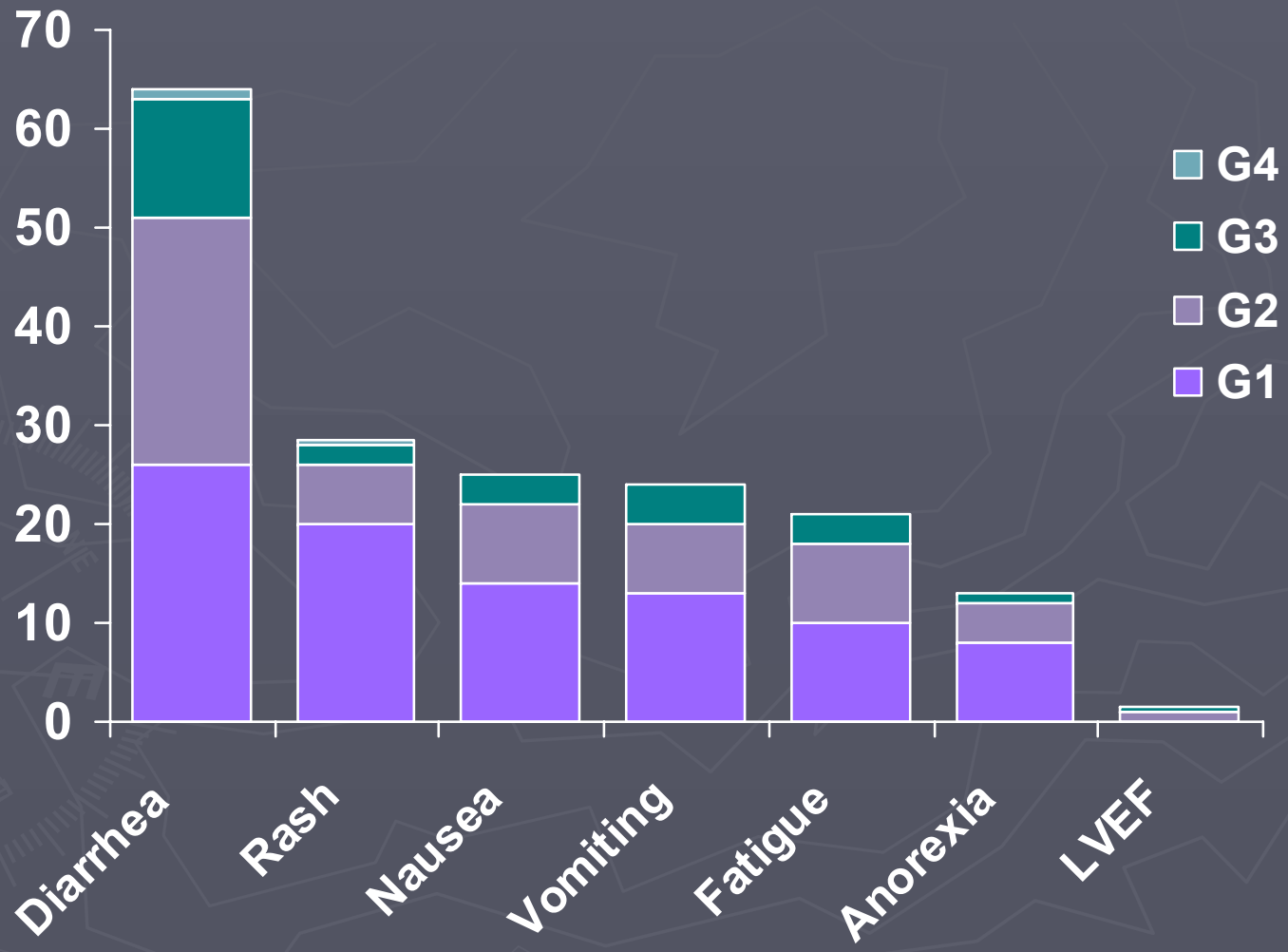
Lapatinib

- Lapatinib is an orally active small molecule that inhibits the tyrosine kinases of HER2 and epidermal growth factor receptor type 1 (EGFR).
- In preclinical studies, lapatinib was not cross-resistant with trastuzumab.
- A phase III study provide support for the use of lapatinib and capecitabine in women with progression of HER2-positive breast cancer after treatment with trastuzumab.
- NCI pilot study of lapatinib in 39 patients with recurrent HER2-positive brain metastases:
  - 1 PR (2.6%), 7 SD (18%) >16 weeks. (Lin NU, et al. *J Clin Oncol* 2008)

EGF 105084

- Multi-center, international phase II trial:
  - accrual 241 patients with HER-2 positive breast cancer
- Key Eligibility Criteria:
  - Radiographically documented progressive CNS disease
  - Prior cranial radiotherapy (WBRT and/or SRS)
  - Target brain lesion (≥ 10 mm diameter)
  - Prior trastuzumab
- Primary objective:
  - CNS objective response rate including centrally reviewed volumetric MRI.

Adverse Events

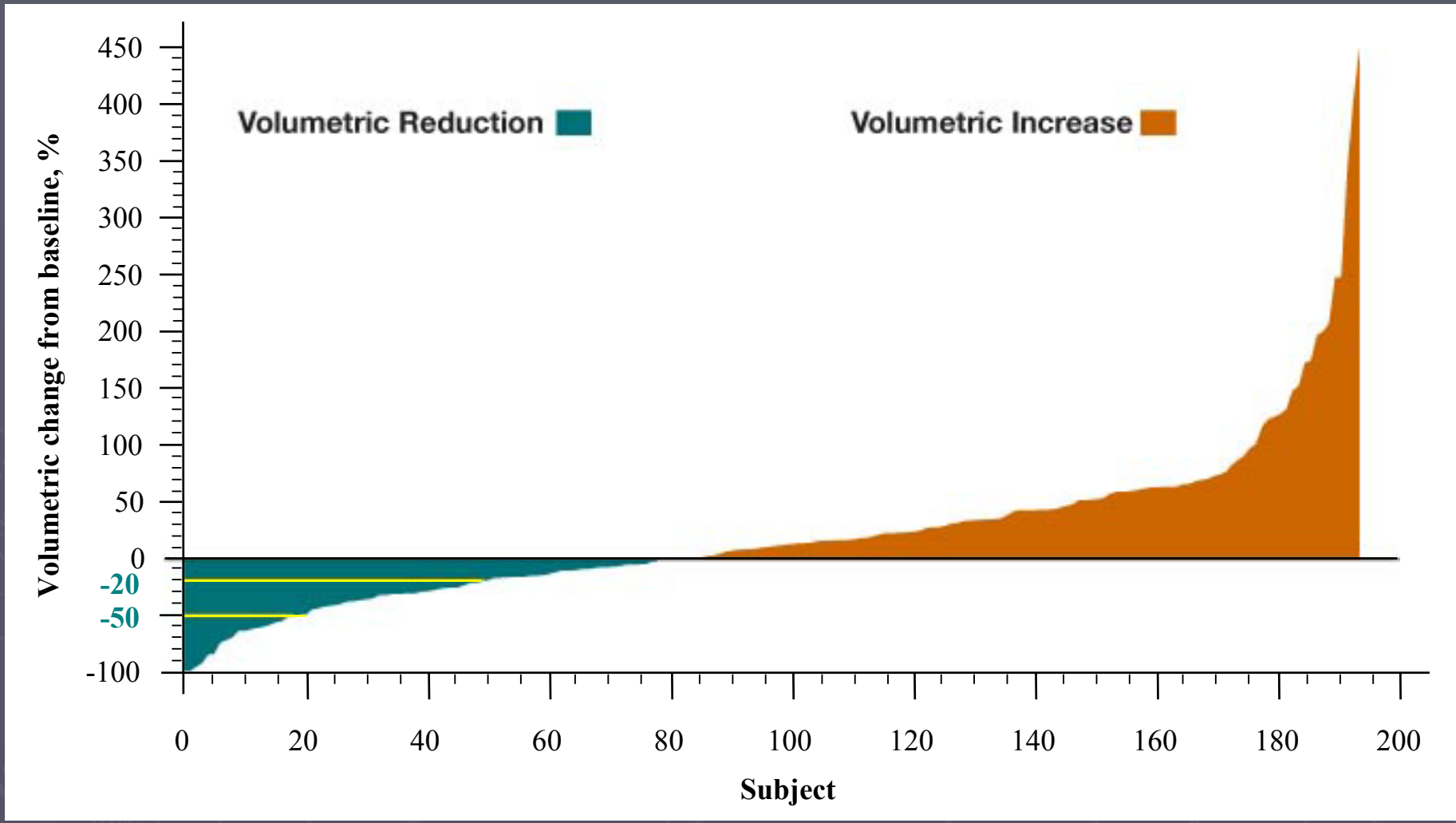


Volumetric Reduction in CNS Lesions (Lapatinib Monotherapy)

	n (%) Median (range), cm^3
≥ 50% CNS volumetric tumor reduction Absolute tumor volumetric reduction	19/241 (7) 3.1 (0.17-29.7)
≥ 20%* CNS volumetric tumor reduction Absolute tumor volumetric reduction	46/241 (19) 1.9 (0.08-29.7)

*Exploratory analysis

Best Volumetric Response



n = 194

Maximum percent reduction of brain target lesions by patient, centrally reviewed

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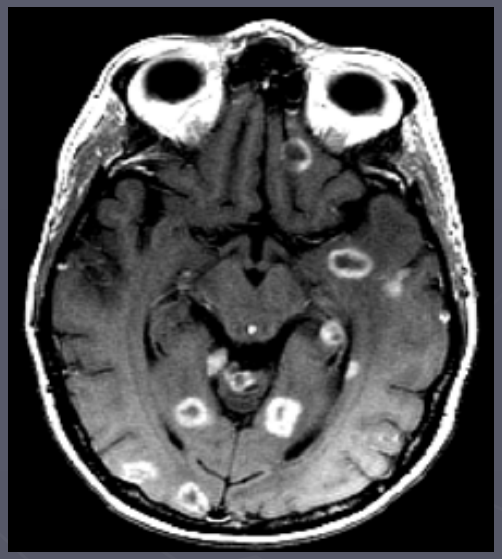
Brain MRI

Baseline

Week 8



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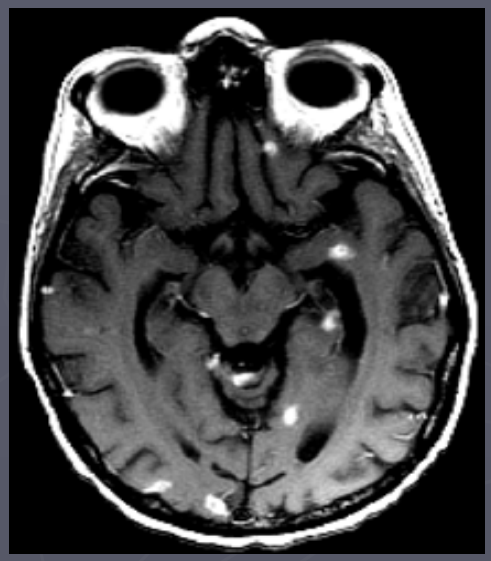

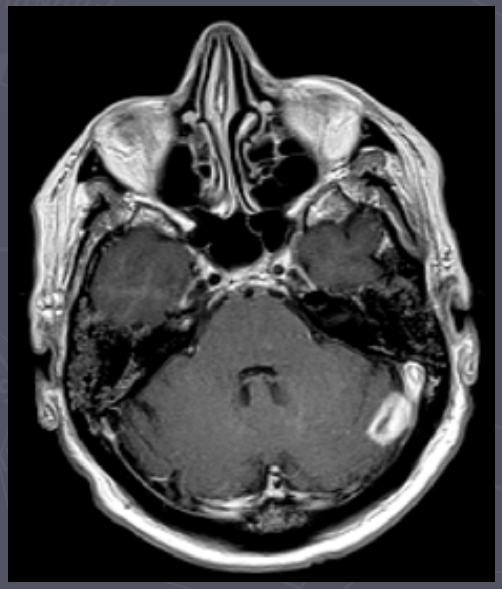

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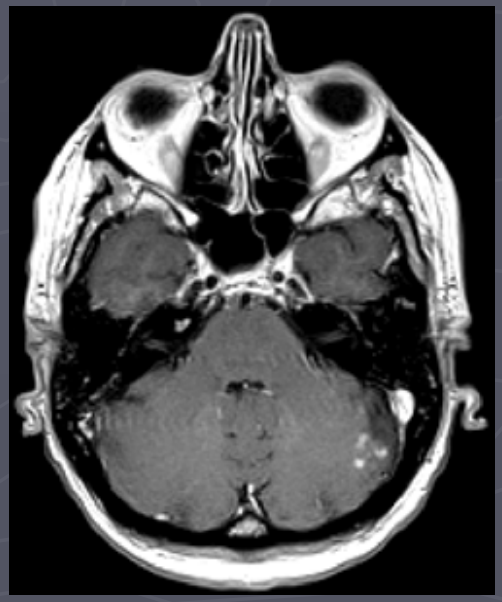
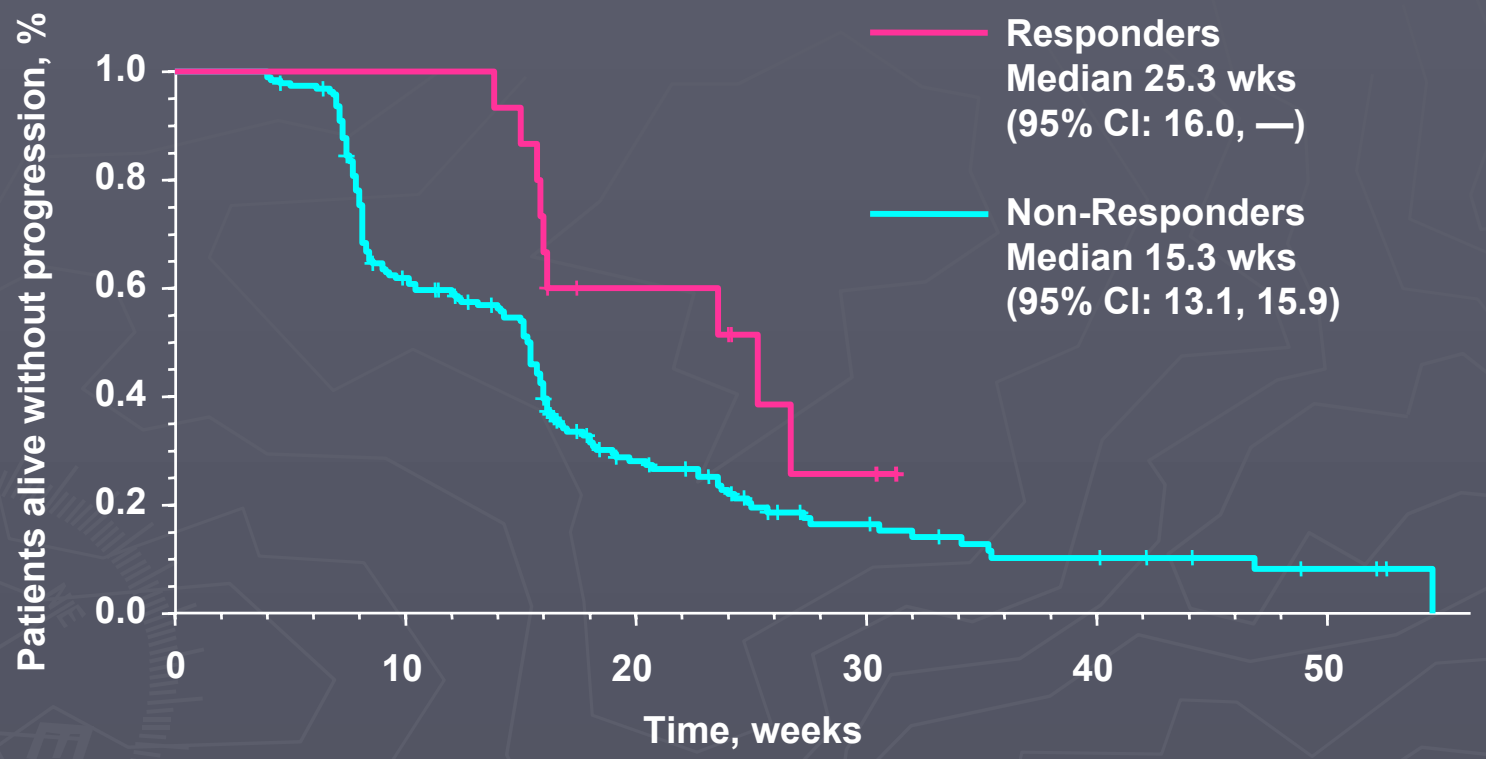


Progression-Free Survival
CNS Objective Responders Versus Non-Responders



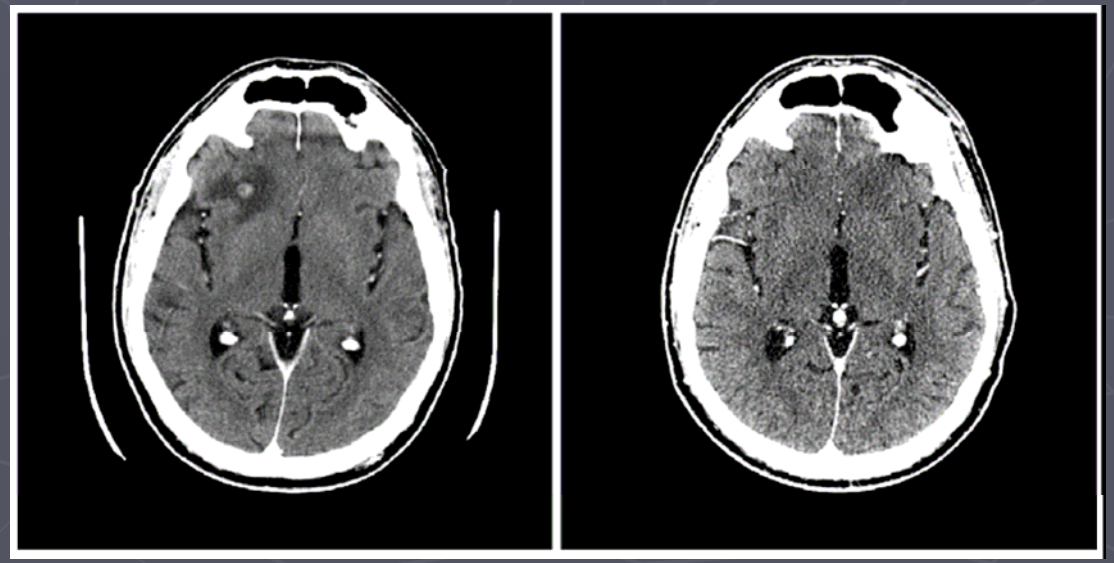
Subjects at risk						
Nonresponder	189	113	40	15	8	3
Responder	15	15	7	2		

- Lapatinib activity was modest in patients with recurrent brain metastases from HER2+ breast cancer.

- Some patients derived durable volumetric reductions in brain tumor burden, with improvement or stabilization of CNS symptoms.

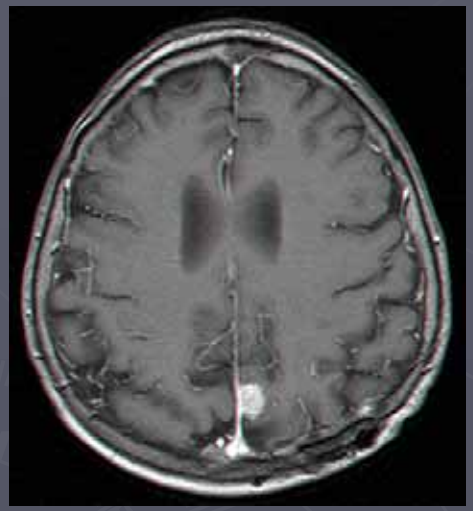
- Sunitinib and sorafenib are small-molecule VEGF and PDGF receptor TK inhibitors with significant clinical activity in advanced renal cell carcinoma.

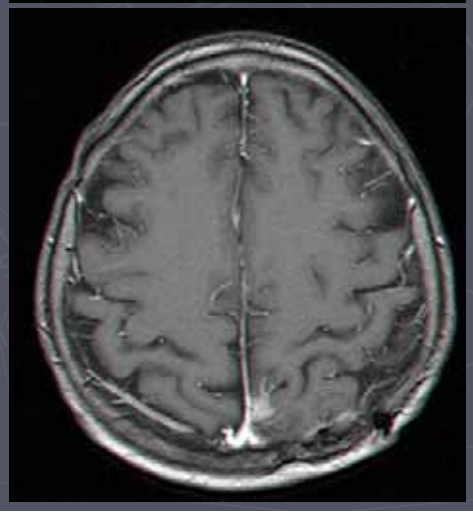
Complete cerebral response with sunitinib for metastatic renal cell carcinoma



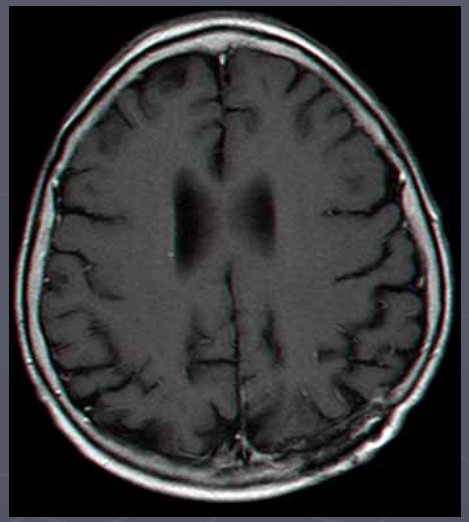
•75-year old woman with advanced RCC
•March 2007: brain MRI evidenced a new cerebral lesion at the top left of *falx cerebri, start* sorafenib 400 mg twice daily.
• July 2007: brain MRI showed 95%-volumetric regression of cerebral metastasis CT scan evidenced a substantial stationary disease at the other sites.
• April 2008: after 13 months of sorafenib treatment, brain MRI confirmed the almost complete cerebral response.

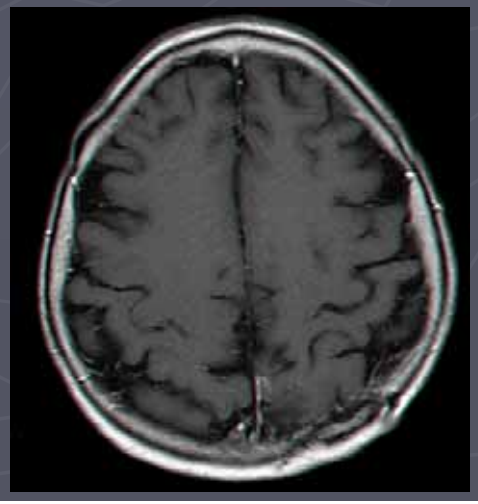
March 2007





July 2007





Conclusions

- Antitumor activity of TKIs in brain metastases has been reported with different drugs (lapatinib, gefitinib, sunitinib, sorafenib).
- Ongoing studies are evaluating the feasibility and activity of TKIs in combination with cranial radiotherapy.
- Ongoing randomized studies with lapatinib and chemotherapy (capecitabine or topotecan).
- Lapatinib-based combination regimens in early breast cancer (ALTTO trial).