

Is Maintenance Therapy Useful in Head & Neck Cancer ?

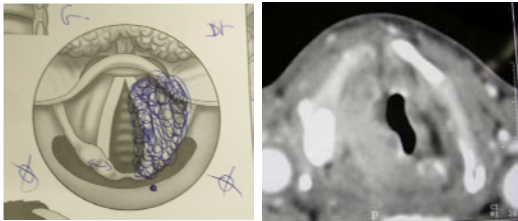


Pr. Sandrine Faivre

PRO

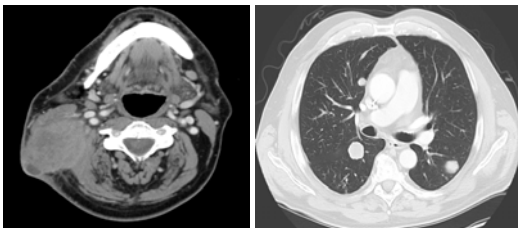
Oncology Unit, Beaujon Hospital, Clichy, France
Denis Diderot University Paris 7 – INSERM-U728
sandrine.faivre@bjn.aphp.fr

MAINTENANCE THERAPY ?



For LOCALIZED disease, adjuvant systemic treatment given after primary surgery/XRT failed to demonstrate benefit, mainly because of low dose-intensity delivered

MAINTENANCE THERAPY ?

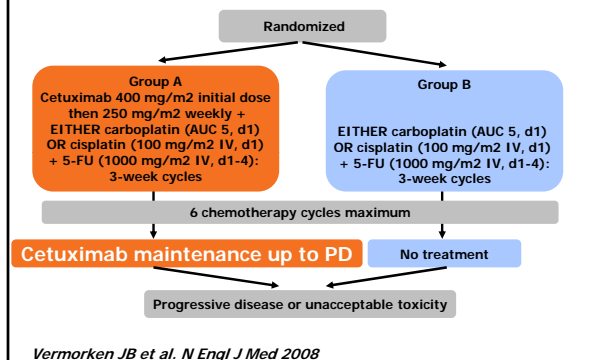


For ADVANCED disease, maintenance systemic therapy may be discussed in the case of residual disease = situations in which complete pathological response is unlikely to occur

Do we have much experience of maintenance therapy in H&N Cancer ?

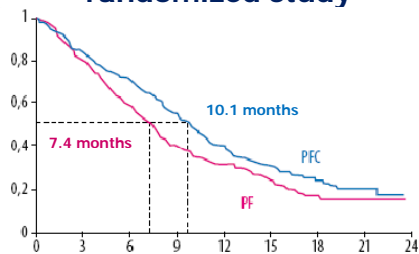
NO

EXTREME: Study design



Vermorken JB et al. N Engl J Med 2008

Results of EXTREME phase III randomized study



Improvement of Overall Survival with Cetuximab + platinum + 5FU versus platinum + 5FU

Vermorken JB et al. N Engl J Med 2008

WHY ?

1. LIMITED SURVIVAL (median OS 6-9 months):

initial response to treatment is rapidly followed by broad acquired resistance to several classes of conventional chemotherapy agents

2. LIMITING TOXICITY: Low therapeutic index with conventional cytotoxics

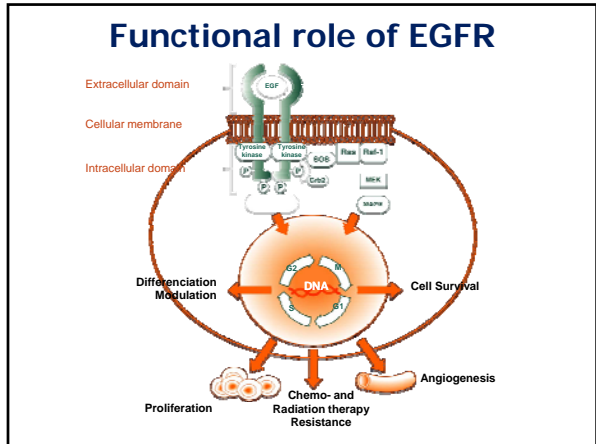
- general toxicity / comorbidities
- neurological/renal cumulative toxicity of cisplatin

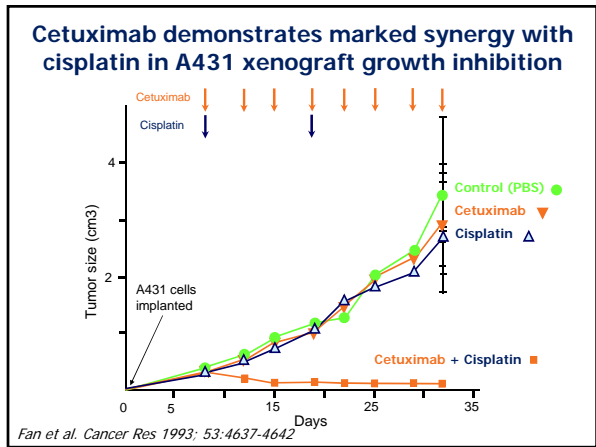
Can we prevent acquired resistance and improve therapeutic index ?

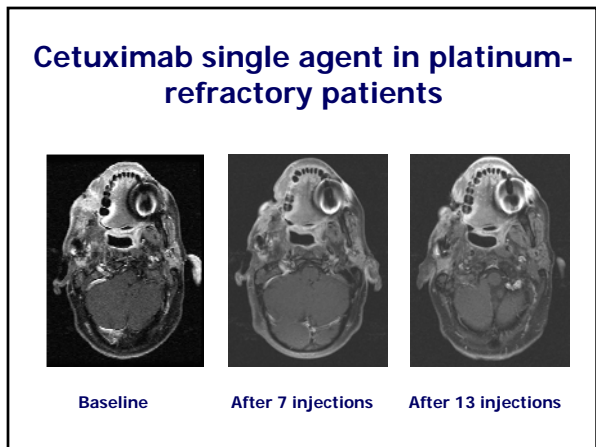
PROBABLY YES

1. Prevent acquired resistance

Select therapeutic agents that are active in the context of resistance to platinum







2. Improve therapeutic index

Decrease toxicity while improving efficacy

Therapies must take into account H&N patients characteristics...

- High blood pressure:** careful monitoring during hyperhydration for cisplatin administration
- Cardiac disease:** careful monitoring of blood pressure and respiratory status during hyperhydration for cisplatin administration
- Coronary disease:** if uncontrolled, contra-indication to 5FU administration
- Diabetes mellitus:** screening for impaired glucose tolerance during chemotherapy, particularly if corticosteroids are administered (+ occult symptoms of coronary insufficiency)
- Pulmonary disease:** high incidence of obstructive chronic bronchitis and infections (pneumonia)
- Renal insufficiency:** careful monitoring of biological renal function and potential side effects of nephrotoxic drugs (cisplatin +++)
- Alcohol addiction:** increased risk of acute syndrome (delirium tremens) and of gastrointestinal (gastric ulcer, bleeding, pancreatitis) or liver complications (steatosis or cirrhosis decompensation)

Limited side effects of EGFR inhibitors: Skin toxicity

Acne-like rash... 80% (including 5-20% severe)

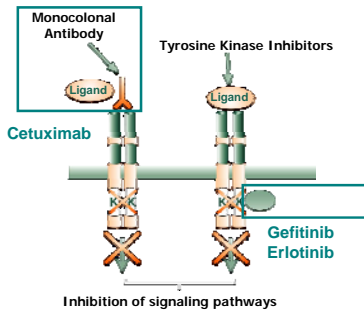
Topical treatments or systemic antibiotherapy

Positive correlation with efficacy

- No myelosuppression
- No infection
- No cardiovascular toxicity
- No renal toxicity
- No neurological toxicity



Antitumor agents inhibiting EGFR



Overcoming CYP1A1/1A2 Mediated Induction of Metabolism by Escalating Erlotinib Dose in Current Smokers

Andrew N. Hughes, Mary E.R. O'Brien, W. Jeffrey Petty, Jonathan B. Chick, Elaine Rankin, Penella J. Woll, David Dunlop, Marianne Nicolson, Ramesh Boinsally, Julie Wolf, and Allan Price

JOURNAL OF CLINICAL ONCOLOGY

J Clin Oncol 27:1220-1226. © 2009

"Steady-state trough plasma concentrations and incidence of rash and diarrhea in smokers at 300 mg were similar to those in former or never smokers receiving 150 mg in previous studies"

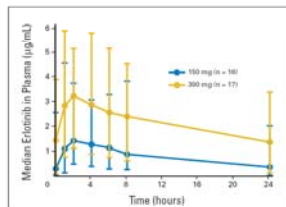


Fig 8. Median and range steady state erlotinib plasma concentrations after 150 or 300 mg oral dose of erlotinib in non-small-cell lung cancer patients who are current smokers.

Can we learn from other malignant diseases ?

PROBABLY YES

LUNG (chemotherapy)
COLORECTAL Cancer (CT)
GIST (imatinib)

Example of Lung Cancer

The Oncologist

Lung Cancer

The Oncologist 2007;12:451-464

Sequential, Alternating, and Maintenance/Consolidation
Chemotherapy in Advanced Non-Small Cell Lung Cancer:
A Review of the Literature

FRANCESCO GROSSI,¹ MARIANNA ATTA,² ALESSANDRO FOLLADORI,³ CARLOTTA DEFFERRARI,⁴
ANNALISA BRIANTI,⁵ GRAZIELLA SINACCO,⁶ ORNELLA BELVEDERE³

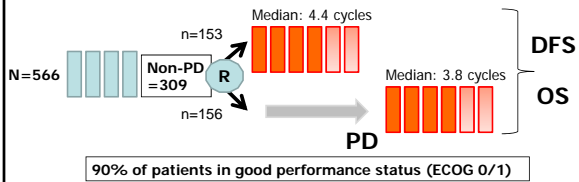
“- Consolidation/maintenance chemotherapy may provide additional benefit
for patients achieving disease control after standard first-line chemotherapy
- Better results are seen when maintenance consists of an agent that has
proven active in the induction phase”

Example of Lung Cancer

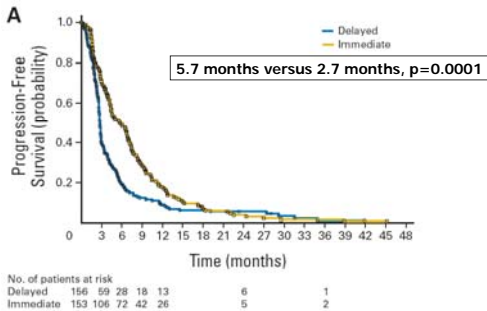
Phase III Study of Immediate Compared With Delayed
Docetaxel After Front-Line Therapy With Gemcitabine Plus
Carboplatin in Advanced Non-Small-Cell Lung Cancer

Panos M, Fidas, Shaker R, Dakhlil, Alan P, Lys, David M, Loesch, David M, Waterhouse, Jane L, Bromund,
Ruqin Chen, Maria Hristova-Kazmierki, Joseph Treat, Coleman K, Obasaju, Martin Marcinia, John Gill,
and Joan H. Schiller

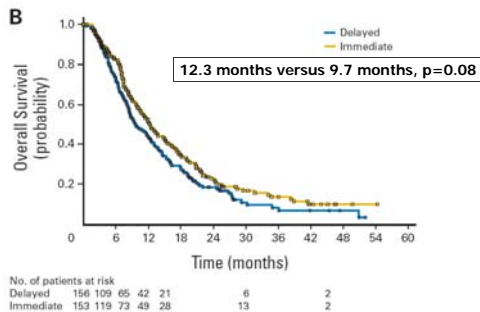
JOURNAL OF CLINICAL ONCOLOGY J Clin Oncol 27:591-598. © 2008



Significant improvement of Progression-Free Survival with maintenance docetaxel after platinum-based CT



Non-significant improvement of Overall Survival with maintenance docetaxel after platinum-based CT



Example of Lung Cancer

Phase III Study of Immediate Compared With Delayed Docetaxel After Front-Line Therapy With Gemcitabine Plus Carboplatin in Advanced Non-Small-Cell Lung Cancer

Panos M. Fidiias, Shaker R. Dakhlil, Alan P. Lys, David M. Loesch, David M. Waterhouse, Jane L. Bromund, Ruqin Chen, Maria Hristova-Kazmierki, Joseph Treat, Coleman K. Obasaju, Martin Marciniak, John Gill, and Joan H. Schiller

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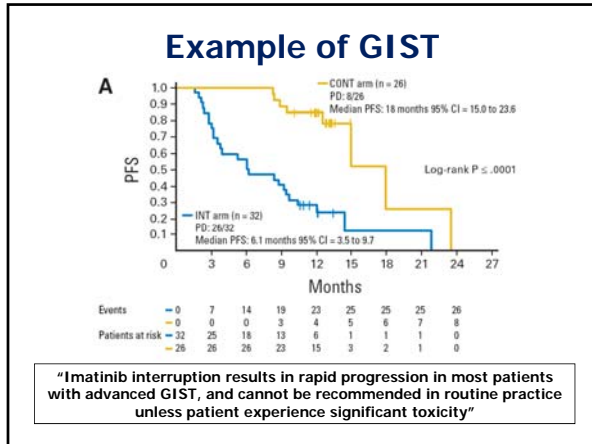
In patients with good PS, maintenance treatment with docetaxel (efficient doses 75 mg/m² q 3weeks):
 - statistically significant improved PFS
 - nonstatistically significant increased OS
 after front-line platinum-based regimen, without increasing toxicity or decreasing QOL

Example of GIST

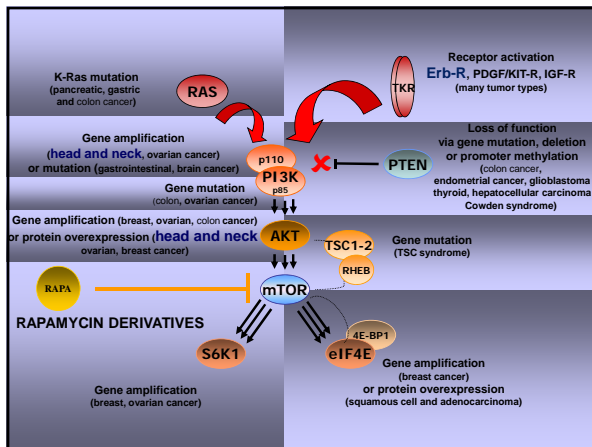
Prospective Multicentric Randomized Phase III Study of Imatinib in Patients With Advanced Gastrointestinal Stromal Tumors Comparing Interruption Versus Continuation of Treatment Beyond 1 Year: The French Sarcoma Group

Jean-Yves Blay, Axel Le Cesne, Isabelle Ray-Coquard, Binh Bui, Florence Duffaud, Catherine Delbaldo, Antoine Adenis, Patrice Viens, Maria Rios, Emmanuelle Bompas, Didier Capisoul, Cecile Guillemet, Pierre Kerbrat, Jerome Fayette, Sylvie Chabaud, Patrice Berthaud, and David Perel

JOURNAL OF CLINICAL ONCOLOGY J Clin Oncol 25:1107-1113. © 2007



What is the next targeted therapy that could be an attractive candidate in H&N cancer ?

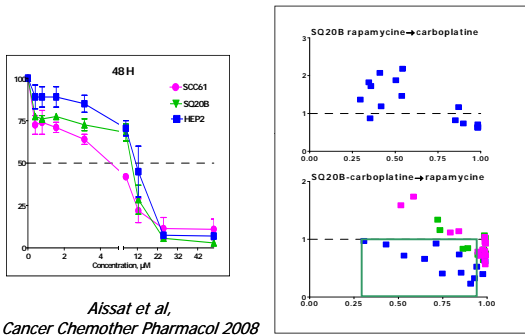


RAPAMYCIN-COMBINATIONS WITH CONVENTIONAL AGENTS

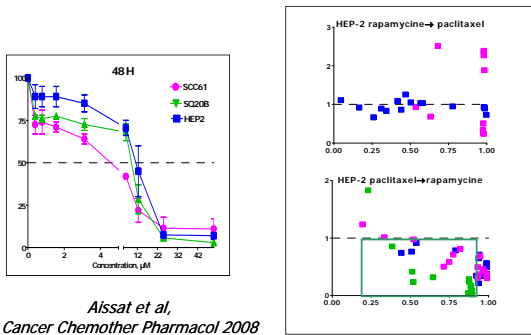
- To provide strong demonstration of synergistic effects
- To study the possible role of sequence exposure to respective agents

Rapamycin + Carboplatin } In HNSCC cell lines
 Rapamycin + Paclitaxel }

CARBOPLATIN AND RAPAMYCIN IN HNSCC CELL LINES

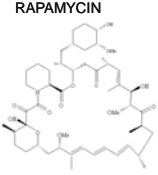
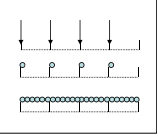



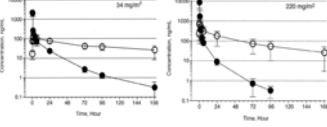
PACLITAXEL AND RAPAMYCIN IN HNSCC CELL LINES



Rapamycin derivatives

RAPAMYCIN

Raymond et al, 2004 JOURNAL OF CLINICAL ONCOLOGY

CONCLUSIONS

- The investigation of maintenance therapy in H&N cancers with conventional cytotoxics was impaired by limited survival and low therapeutic index
- EGFR inhibitors represent promising drugs since they are active in platinum-resistant patients and display good toxicity profile
- The role of maintenance therapy with EGFR inhibitors needs to be assessed in controlled trials
- Other targeted therapies including mTOR inhibitors may be attractive agents for initial combinations followed by maintenance therapy

YES

Maintenance therapy
with **targeted agents**
will be useful
in advanced H&N Cancer



Medical Oncology Unit: Sandrine Faivre, Chantal Dreyer, Eric Raymond
Oncology laboratory (INSERM U728): Maria Serova, Lucile Astorgues-Xerri,
Sébastien Albert, Sophie Deneuve, Sandrine Faivre, Eric Raymond
Surgery Unit (Bichat): Sébastien Albert, Sophie Deneuve, Béatrix Barry
Radiation Unit (La Pitié, Hartmann): Philippe Lang, Alain Toledano
