

Positioning Antiangiogenesis Drugs and Other Agents in Renal Cell Cancer Treatment

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Survival according to burden of disease

5-year survival rates

Localised disease (54% of patients)	89%
Regionally advanced (21% of patients)	61%
Distant metastasis (25% of patients)	9%

Adjuvant setting

- No effective adjuvant treatment after surgery has been established

Radiotherapy
Interferon- α (IFN- α)
Interleukin 2 (IL-2)



failed to improve PFS
and/or OS

Immunomodulatory therapies

- **Goal: to boost tumour antigenicity or host surveillance**
- **IFN- α \rightarrow 14% responses**
median duration of response: 6m
- **IL-2 \rightarrow high dose: 21% responses**
low dose: 13% responses
no impact in DFS and OS

Stem-cell transplantation

- **Allogeneic stem-cell transplantation**
- **After administration of non-myeloablative regimen**
- **Elicits a potent graft-versus-tumour effect**
- **Responses correlated well with:**
 - **development of graft-versus-host disease**
 - **conversion of T-cell chimerism to full donor origin**
- **44% responses in 1 study**
- **Acute graft-versus-host disease (grade II, III or IV) in 53%**
- **No conclusions yet : more studies are needed**

Therapies targeting VEGF(R) pathways

- **VEGF:**
 - overexpressed throughout renal-cell carcinoma tissue
 - the most important tumour angiogenic factor
- "Proof of principle" of the efficacy of anti-angiogenic therapy in renal cancer : **bevacizumab** (Avastin[®])

Bevacizumab = Monoclonal Antibody targeting VEGF

- **Randomized phase 2 trial**
- **Metastatic renal-cell carcinoma**
- **Dosing schedule (each given q 2 weeks):**
 - **Bevacizumab 3 mg/kg (n=37)**
 - **Bevacizumab 10 mg/kg (n=39)**
 - **Placebo (n=40)**
- **Primary end points: TTP and overall response rate**
- **Secondary end point : Survival**

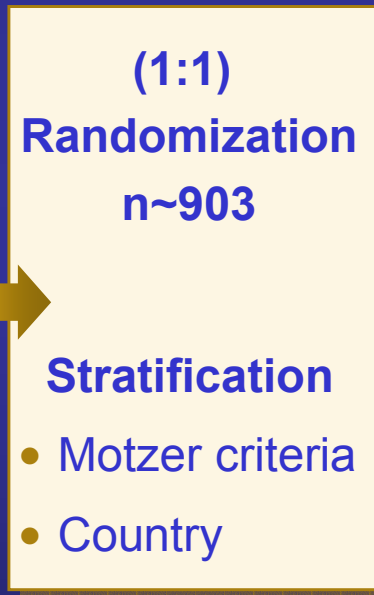
Bevacizumab

- **↑ PFS with high-dose bevacizumab (n=39) x placebo (4.8 x 2.5 months, HR=2.55, p<0.001)**

Randomized phase III trial of Sorafenib (BAY 43-9006) – an oral multi-kinase inhibitor – in patients with advanced RCC

Eligibility criteria

- Histologically/cytologically confirmed, unresectable and/ or metastatic disease
- Clear-cell histology
- Measurable disease
- Failed one prior systemic therapy in last 8 months
- ECOG PS 0 or 1
- Good organ function
- No brain metastasis
- Poor risk Motzer group excluded



Sorafenib
400 mg bid

Placebo

Major endpoints

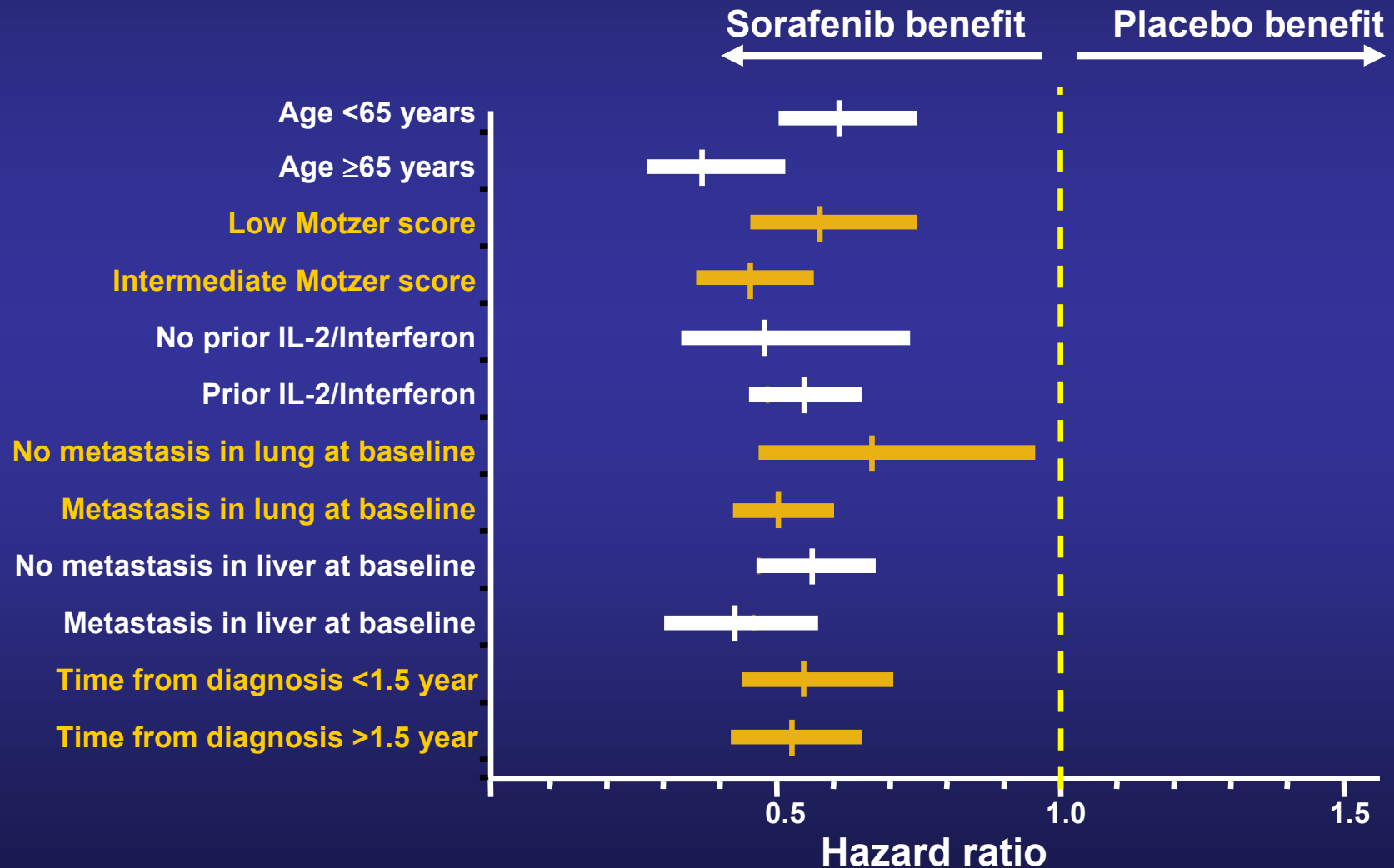
- Survival (alpha=0.04)
- PFS (alpha=0.01)

Randomized phase III trial of Sorafenib (BAY 43-9006) Results

Best Response (RECIST)	Sorafenib (n=335)	Placebo (n=337)
Partial Response	7 (2%)	0
Stable Disease	261 (78%)	186 (55%)
Progressive Disease	29 (9%)	102 (30%)
Missing	38 (11%)	49 (15%)

Randomized phase III trial of Sorafenib (BAY 43-9006)

Progression-free survival across patients subgroups



Sunitinib

- **SU11248**
- **Inhibits multiple split kinase domain receptor tyrosine kinases (RTKs), including:**
 - VEGFR 1 and 2
 - PDGFR a and b
 - KIT receptor
 - FLT3 receptor

Sunitinib

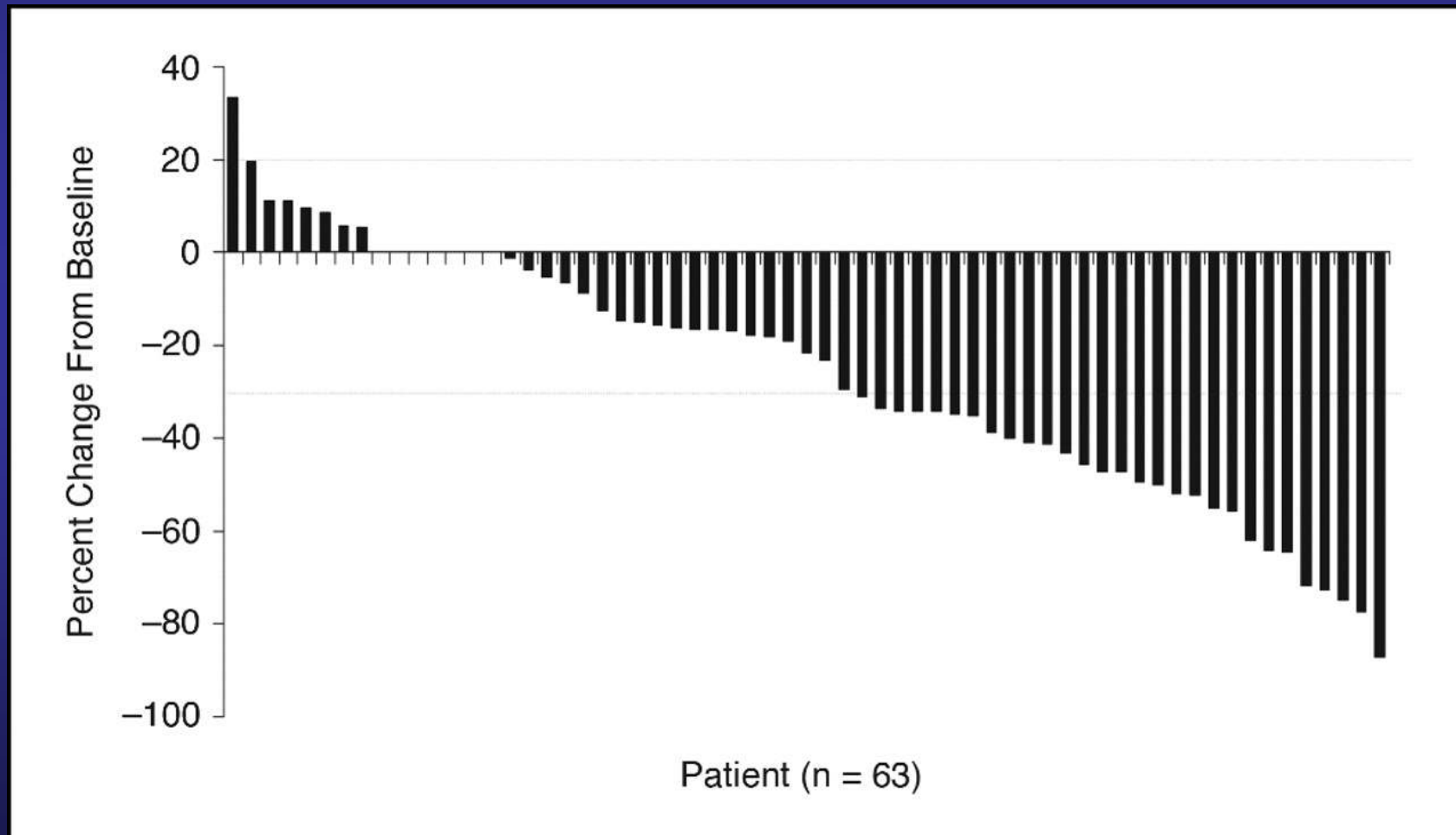
- **Phase I trial***: partial response in RCC
- **Phase II****:
 - 63 cytokine-refractory metastatic RCC patients
 - 40% partial response
 - 27% stable disease for at least 3 months
 - median time to progression: 8.7 months

* Raymond et al, ASCO 2003 (768)

** Motzer et al, JCO 2006

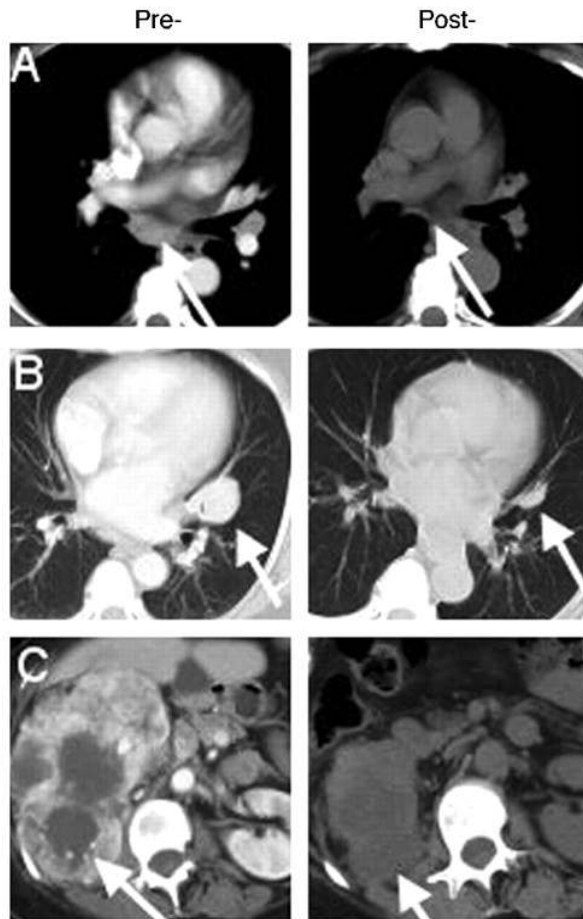
Sunitinib: phase II study

Maximal percentage of tumor reduction for target lesions by Response Evaluation Criteria in Solid Tumors (RECIST)

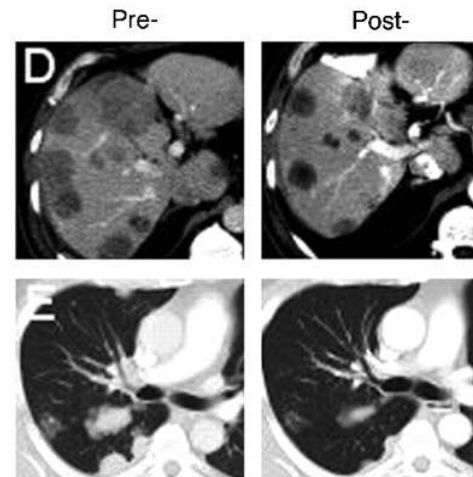


Sunitinib: Tumor responses of hepatic metastases CT scan images (liver) after one cycle of treatment

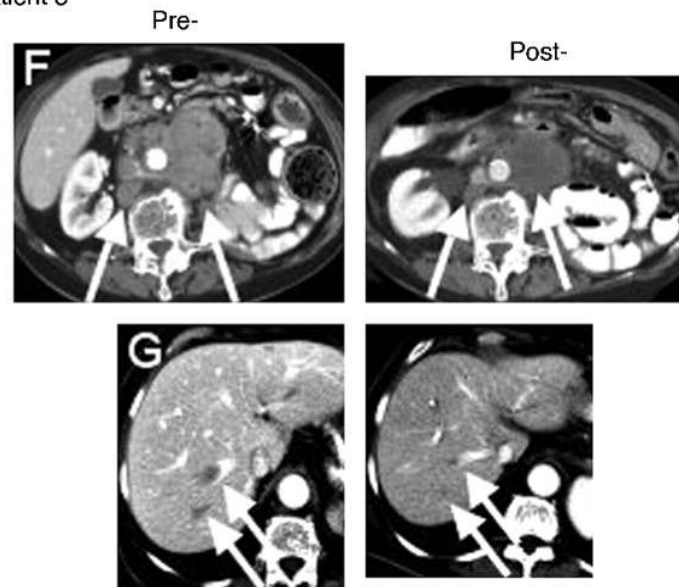
Patient 1



Patient 2



Patient 3

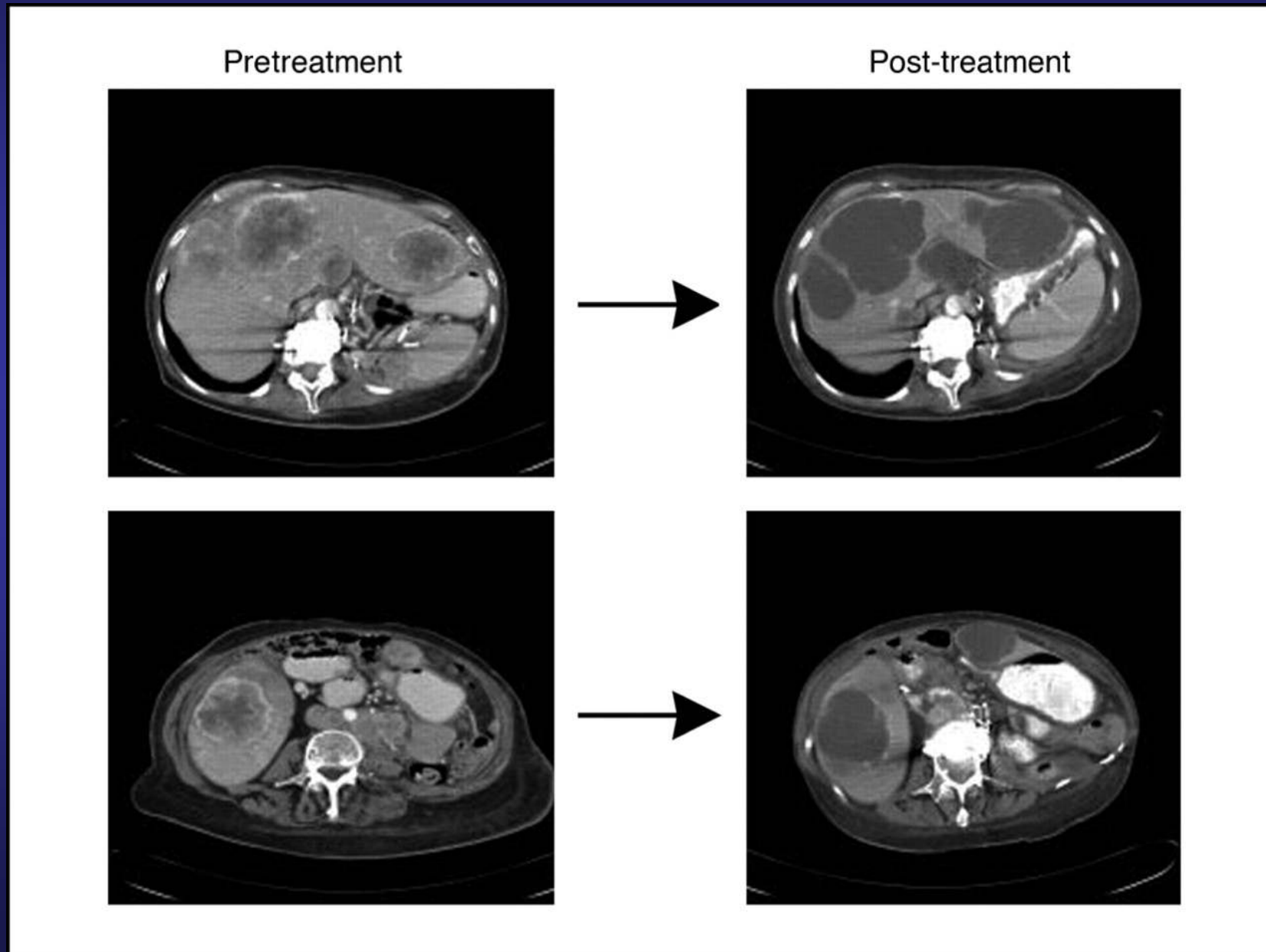


A,B,C: responses in patient with multiple metastatic sites from a large primary RCC after treatment;

D,E: responses in patient 2 with multiple hepatic, lung, and pleural metastases;

F,G: responses in patient 3 with large retroperitoneal lymphadenopathy and hepatic metastases

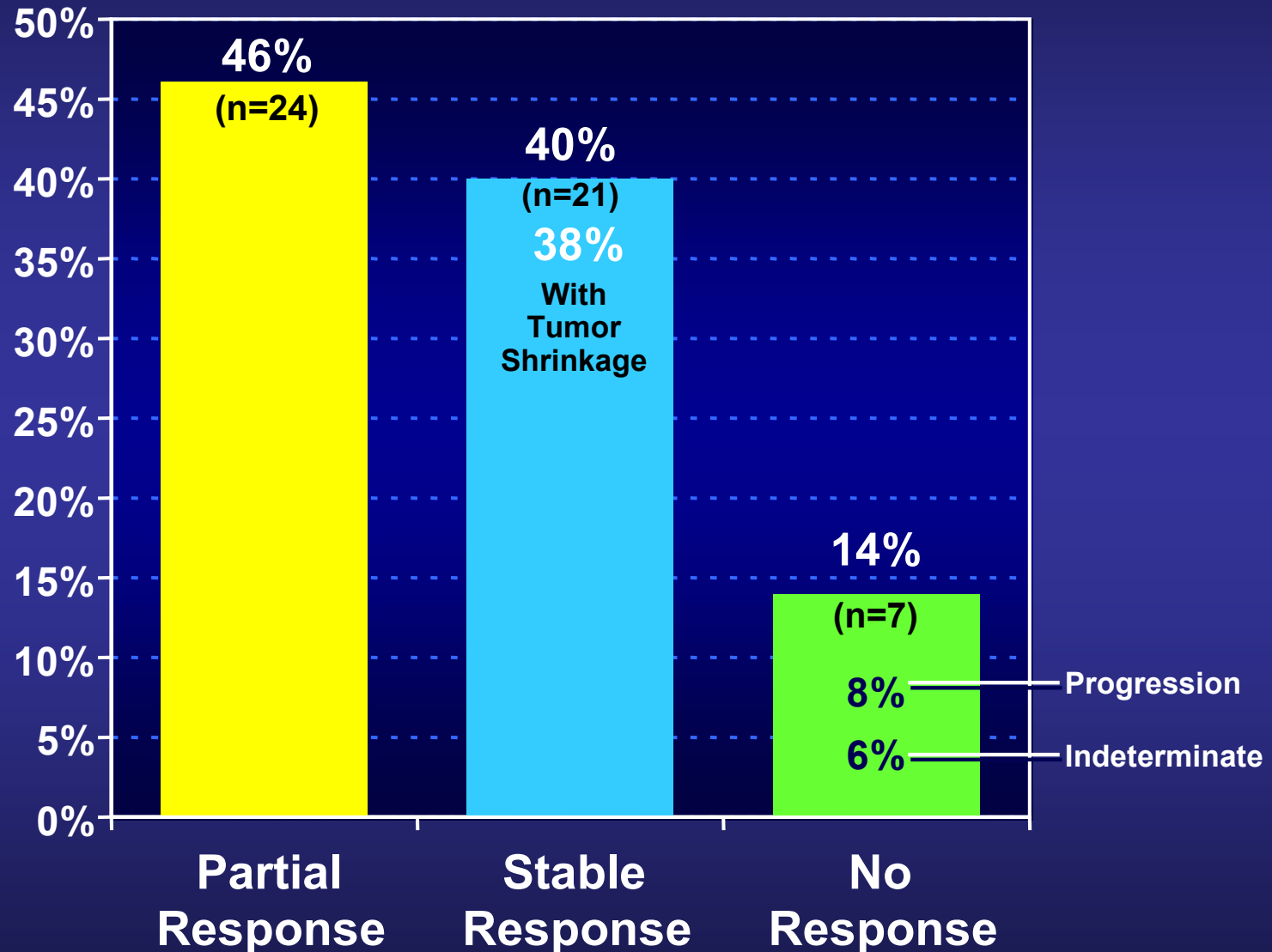
Sunitinib: CT scan images of responding lesions from three patients who achieved partial responses



AG-013736

- **Phase II trial**
- **Design**
 - Single-arm, multicenter, IRB-approved trial
 - Primary end point of ORR ($H_0=5\%$, $H_a=15\%$)
 - 2-stage design, target accrual of 52 patients
- **Treatment**
 - 5 mg orally twice daily (fasted) continuously until disease progression or unacceptable toxicity
 - Radiographic assessment at baseline and q 8 weeks
 - Response assessed by RECIST criteria

AG-013736: phase II trial



CCI-779 = An Inhibitor of the AKT/mTOR Pathway

- **Derivative of the immunosuppressive agent rapamycin**
- **Phase II trial:**
 - 111 patients with refractory metastatic RCC
- **Patients randomized to receive CCI-779:**
 - 25 mg weekly infused over 30 minutes
 - 75 mg weekly infused over 30 minutes
 - 250 mg weekly infused over 30 minutes

CCI-779

- **7% PR**
- **Clinical benefit rate for at least 24 weeks: 51%**
- **Median time to progression: 5.8 months**

CCI-779 + IFN-alpha

- Phase I/II trial (71 patients with metastatic RCC)
- 11% PR, 30% SD
- Median time to progression:
- Common side effects:
 - leukopenia (25%)
 - hyperlipidaemia (15%)
 - asthenia (13%)
 - AST increase (8%)
 - mucositis (6%)
 - anaemia (6%)
 - thrombocytopenia (6%)
 - rash (6%)

Erlotinib

- **OSI-774**
- **EGFR tyrosine kinase inhibitor**
- **Phase I trial:**
 - **only 1 CR**
 - **Disappointing!**

Erlotinib + Bevacizumab

- **2% CR, 23% PR, 61% SD, 14% Progression**
- **Median time to progression: 11 months**
- **Most significant reported side effects:**
 - **Hypertension, proteinuria, diarrhea, acnelike rash**

Erlotinib + Bevacizumab

- Phase II trial combining 2 agents that inhibit VEGF and EGFR pathways simultaneously

Perspectives

- **Should we continue to give cytokine therapy to RCC?**
- **Should we add molecular therapy in combination or in sequence to cytokines?**
- **Should we go on performing nephrectomy in metastatic RCC?**
- **Should we combine different antiangiogenic agents?**
- **What are the predictors of response in RCC?**