Case(s): How to Deal with Mixed Response

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Disclosures

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Consultant: Pfizer, Novartis

Background

Mixed response may be defined as the growth and/or the appearance of new lesions while disease control is noted in the remaining sites

Background

Why mixed responses?

Heterogeneity of the disease

Different activity of targeted therapies in various sites of disease

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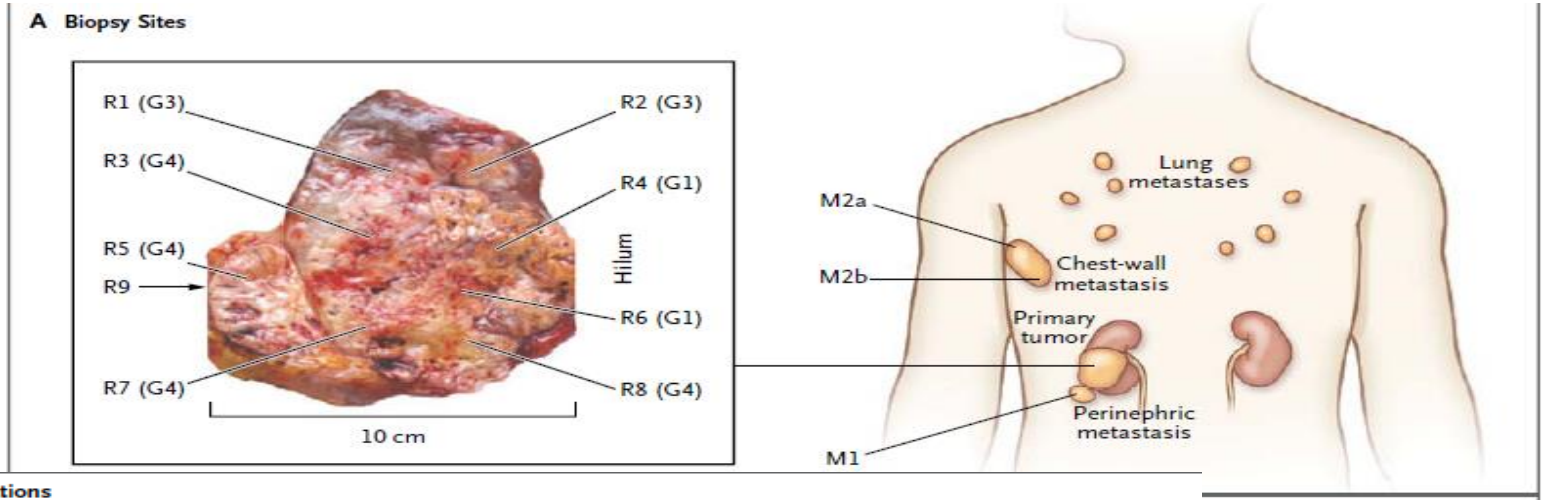
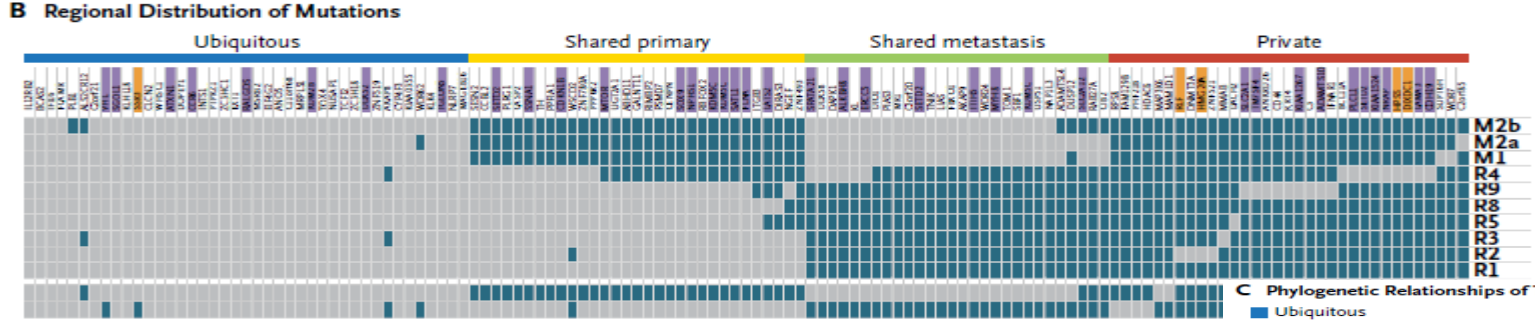
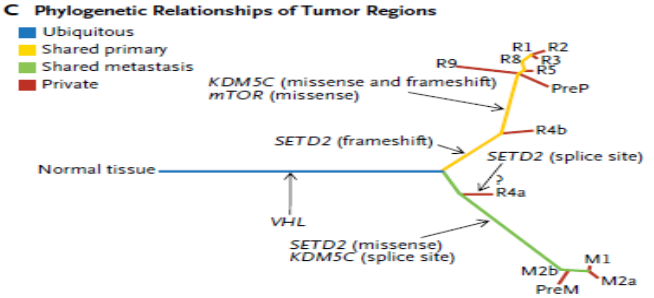
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

- Tumor-biopsy samples from four consecutive patients with mRCC (E-PREDICT)
- Pretreatment biopsy
- 6 weeks treatment (everolimus)
- nephrectomy





Pt.1



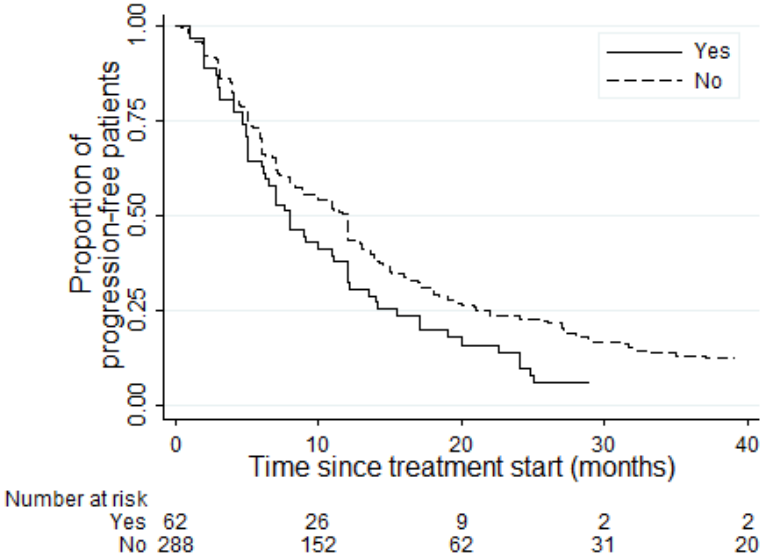
128 mutations, 40 ubiquitous, 31 shared primary, 28 shared M+, 29 private in specific regions

Grey: presence of mutation

Targeted therapies and sites of disease

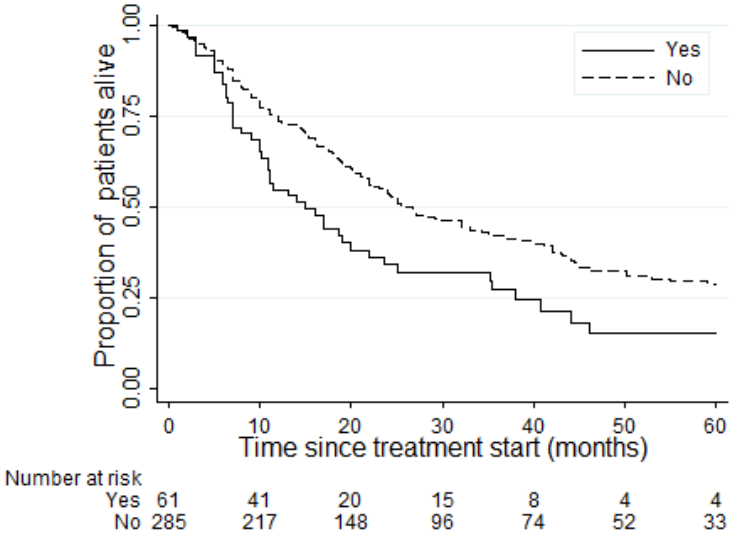
Best activity of TTs in lung and lymphnodes, less in liver and bone

PFS*



Liver
HR (95%CI): 1.409 (1.056-1.880)
Chi2, p-value: 5.416, 0.020

OS*



Liver
HR (95%CI): 1.707 (1.238-2.354)
Chi2, p-value: 10.643-0.001

Grassi P., Unpublished data

Case: 1

56 year old male, who lives near Milan

Past medical history

- Hypertension
- Colelitiasis

Specific medical history

- April 2005 ematuria

Work up: right renal tumor

- May 2005 right nephrectomy: clear cell carcinoma pT3 G2 pN0

Case 1

March 2007 during follow-up evidence of relapse on lung and lymphonodes

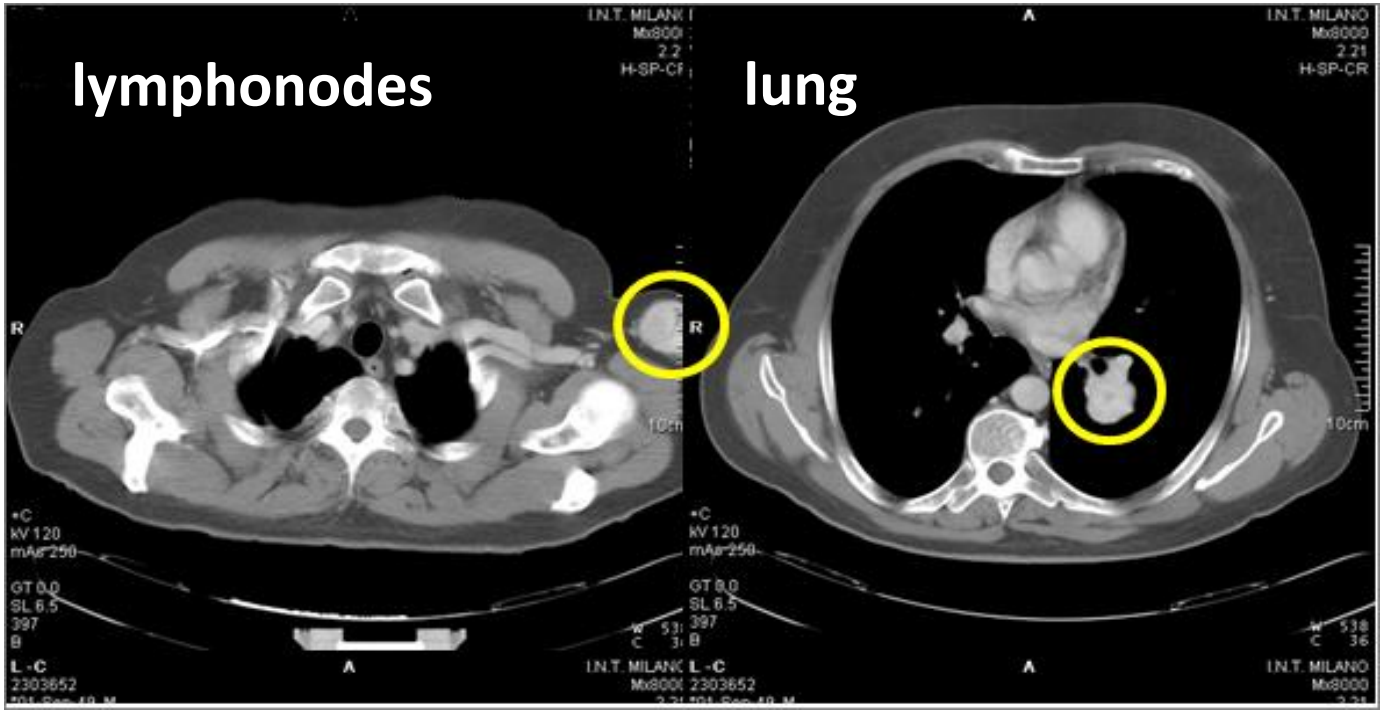
No symptoms

ECOG PS 100%

low risk according to MSKCC and Heng criteria

Case 1

CT scan



Treatment strategy in 2007

Cytokines, sunitinib or sorafenib

Patient was randomized in a clinical trial (ROSORC) evaluating sorafenib + IL-2 vs sorafenib alone

Started Sorafenib in May 2007

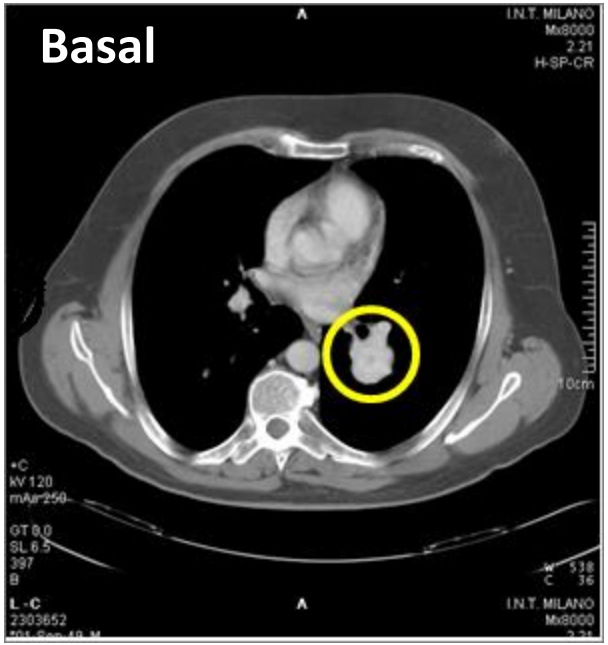
Treatment

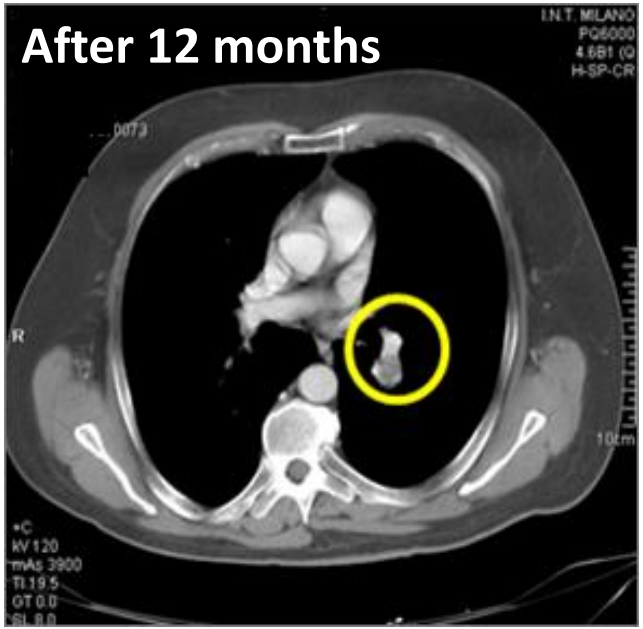
After 8 weeks, tumor shirinkage was noted

Good safety profile (hypertension and hand foot syndrome grade 1)

Shrinkage was confirmed up to 12 months

CT scan image





Treatment

After 12 months of sorafenib, a tumefaction on left testicle was noted.

No other changes were reported

Treatment

The overall disease was controlled, but a new lesion formed and the treatment was well tolerated.

Which approach?

- a 2nd line with sunitinib?
- Surgery?

Which role for metastasectomy in mRCC?

Resection of single or solitary metastastis: selection criteria*

- disease free interval > 1 y (55% vs 9% 5 year OS)
- single site metastatic foci (54% vs 29% e years OS)
- **complete metastasectomy**

***Kavolius et al, JCO 1998**

Treatment

Patient underwent left orchiectomy and continued sorafenib for additional 19 months with overall disease control (October 2010).

At that time, due to appearance of bone disease, started sunitinib.

Up to now patient is still alive and has received 4 lines of therapy

Case 2

39 year old female without comorbidities

Medical history

- Jan 2009: right nephrectomy
  - Clear cells pT3 G 3 N0

Case 2

October 2009 during follow-up evidence of lung metastases

Intermediate risk due to anemia and short time from nephrectomy

Treatment strategy in 2009

Sunitinib or bevacizumab + IFN?

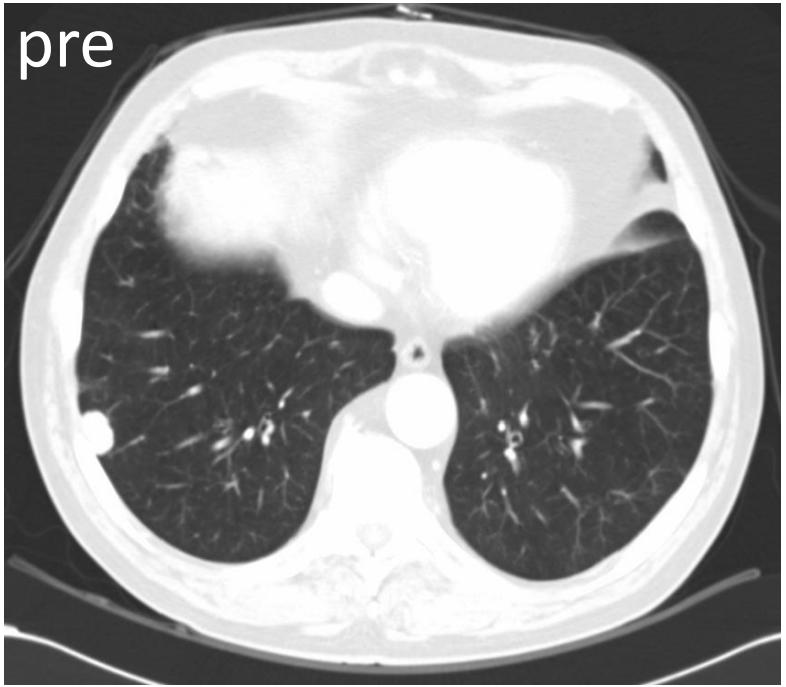
Patient started sunitinib

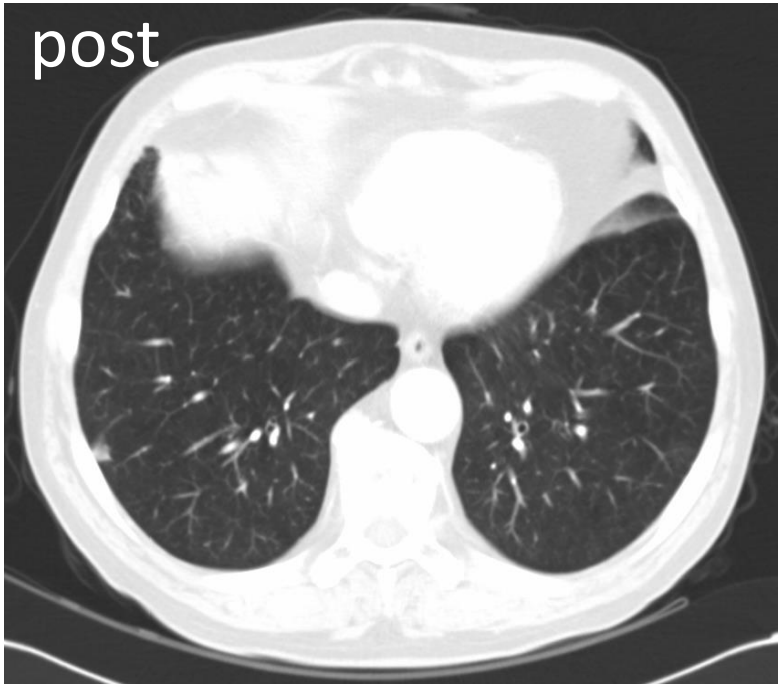
Treatment

After 8 weeks partial response

AE: hypothiroidism, hypertension and G1 diarrhoea

CT scan





Treatment

After 9 months, disease was responding, but a mediastinum lymphonode was noted

What is the best approach?

- Sorafenib?
- Everolimus?
- Metastasectomy?

Treatment

Patient received radiotherapy and continued sunitinib

After 12 months dosage was reduced due to diarrhoea and G2 mucositis

Patient is currently alive and continues with sunitinib 37.5 mg on an intermittent schedule

Key points

No guidelines or prospective data in cases having mixed response

Before changing ongoing treatment I suggest considering the following parameters:

- Type of progression (new lesion or increase of preexisting disease) Site of progression
- Related symptoms
- Availability of locoregional approach
- Tolerability and duration of treatment

Treatment approach in mixed response

My personal point of view:
don't change ongoing treatment if

- only one lesion progressing
- site: lung or lymphnode
- no symptoms
- feasibility of locoregional approach
- good tolerability

Treatment approach in mixed response

My personal point of view:
Change ongoing treatment if

- more lesions progressing
- site: liver or bone
- symptoms
- bad tolerability

Conclusion

No standard approach in cases having mixed response.

Physicians should tailor their decision making according to patient and disease characteristics.