How soon will CRC patient management be driven by molecular factors ?

CONTRA

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My approach to the CONTRA position

1. What the title means
2. Today our management is already driven by K-RAS, then , why are we holding this controversy ?
3. My explanation of why the controversy makes sense
4. Why I think ….it will not be soon…
   - 4 specific reasons + 1 general reason

How soon will CRC patient management be driven by molecular factors ?

1. HOW SOON
2. WILL BE DRIVEN BY MOLECULAR FACTORS

WILL BE DRIVEN BY MOLECULAR FACTORS

1. Reliable assay available on large scale
2. Drugs available with substantial efficacy for ‘each’ specific condition
   - Moderate efficacy in high %
   - Outstanding efficacy even in low %

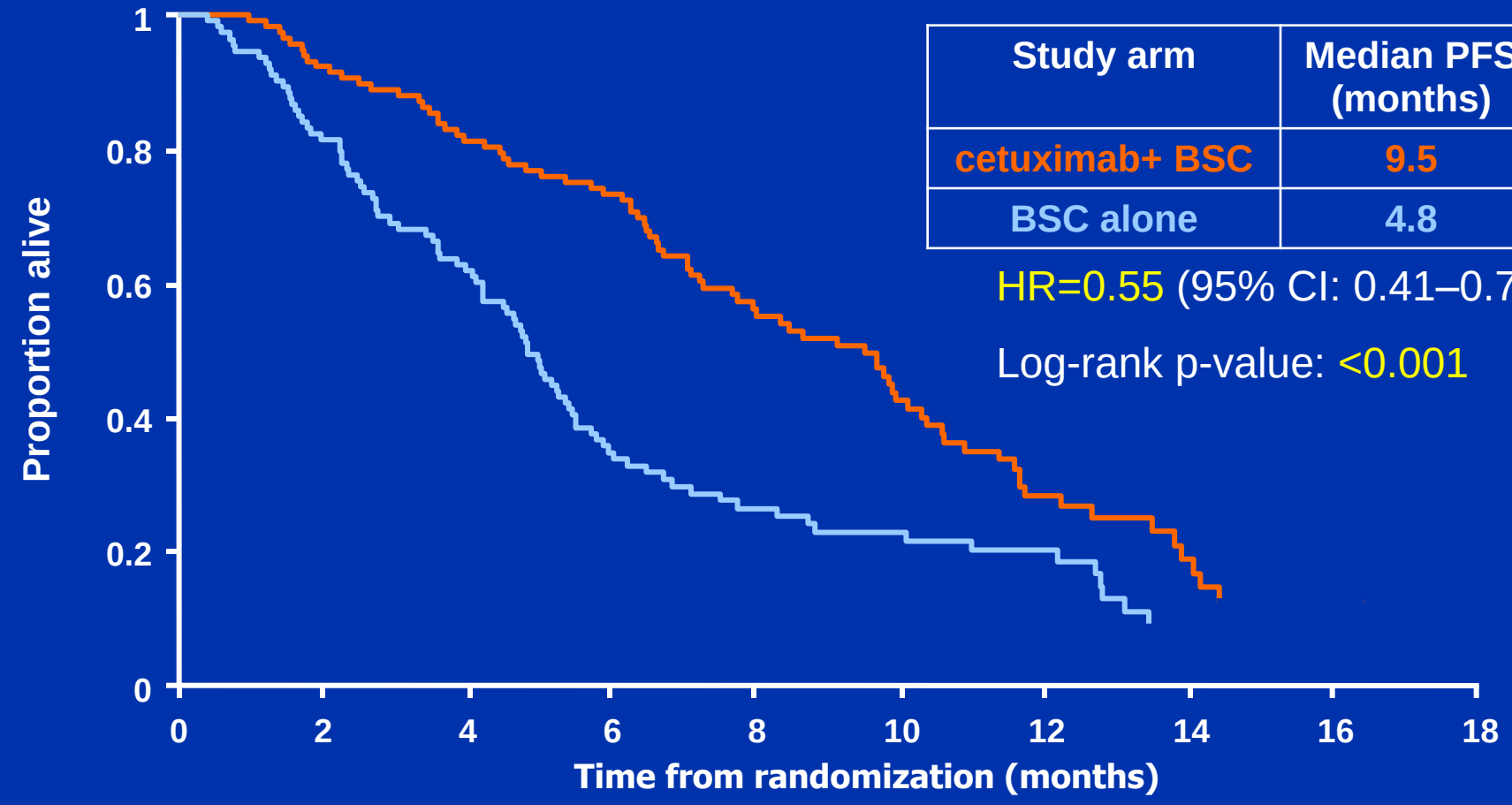
PARADIGM CHANGING

‘WILL BE DRIVEN BY MOLECULAR FACTORS’

1. **Breast cancer**
   - **ER, PGR** → **paradigm changing**
   - **HER-2**
2. **NSCLC**
   - **EGFR mutation** → **paradigm changing**
   - **MET-ALK translocation**
3. **Colorectal**

K-RAS	→ paradigm changing
B-RAF	……
MSI	……
Signatures	……

NCIC CTG CO.17: Overall survival in patients with KRAS wild-type tumors



Study arm	Median PFS (months)
cetuximab+ BSC	9.5
BSC alone	4.8

HR=0.55 (95% CI: 0.41–0.74)

Log-rank p-value: <0.001

Karapetis C, et al. N Engl J Med 2008;359:1757–1765

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Patient X

Male, 60 years : presentation

- 8 bilobar liver metastases and 5 bilateral lung metastases (≤3cm)
- Asymptomatic, PS 0
- No comorbidities
- Normal attitude
- *KRAS* wild-type

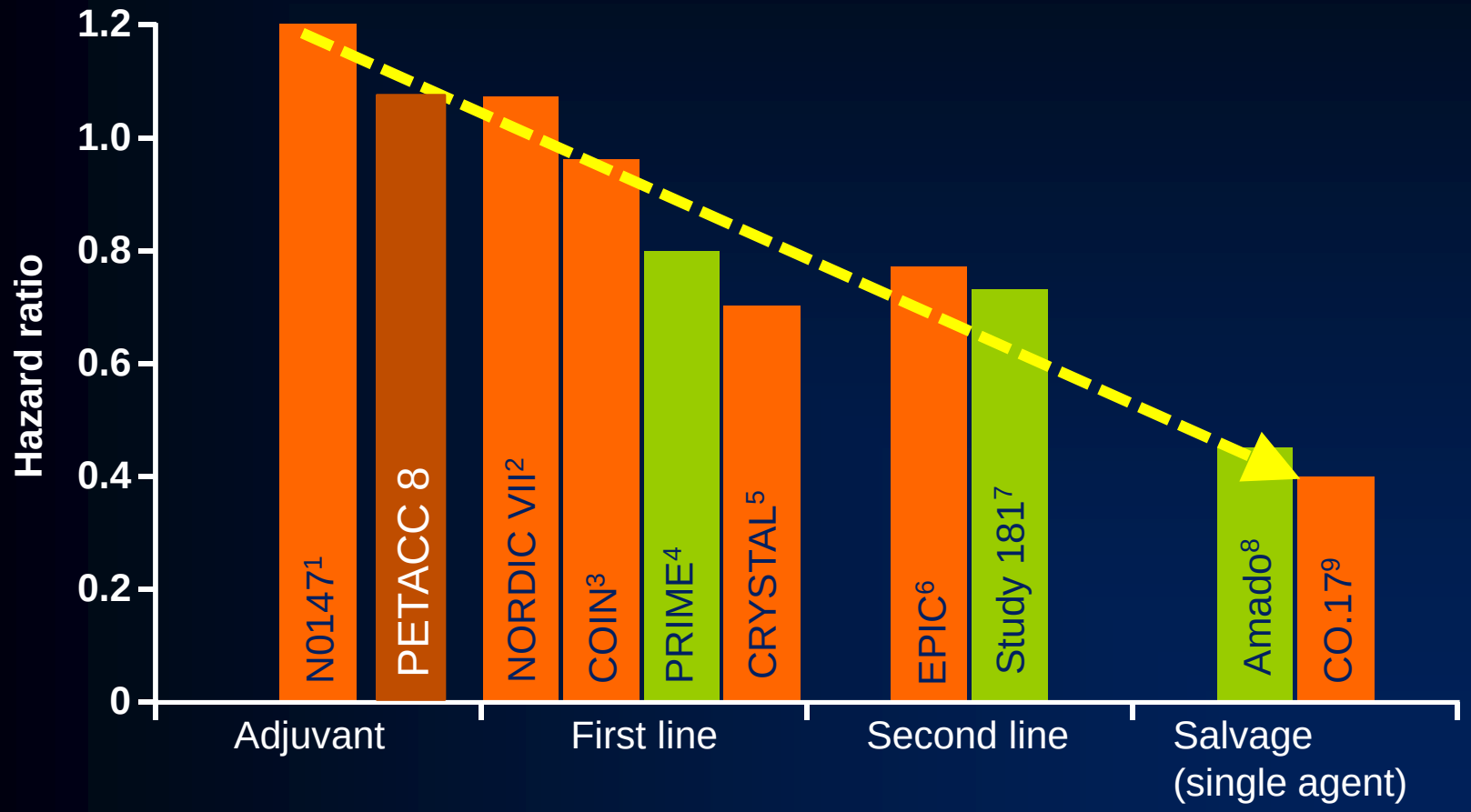
1. How do you treat this pt?
2. Do you need BRAF, MMR, etc…?

Why are we then holding this controversy session ?

- **Because today the initial management is not driven by the most popular known molecular markers**

1. **In early lines K-RAS driven anti EGFRs are incrementalists because K-RAS is a resistance (not a sensitivity) predictor**
2. **Anti VEGF are incrementalist without biomarker of efficacy**
3. **The other molecular factors , whether prognostic or predictive are not used in practice yet bacause too 'weak'**

PFS/DFS for EGFR inhibitors improves across lines of therapy in *KRAS* wild-type patients



Slide Courtesy of A Grothey

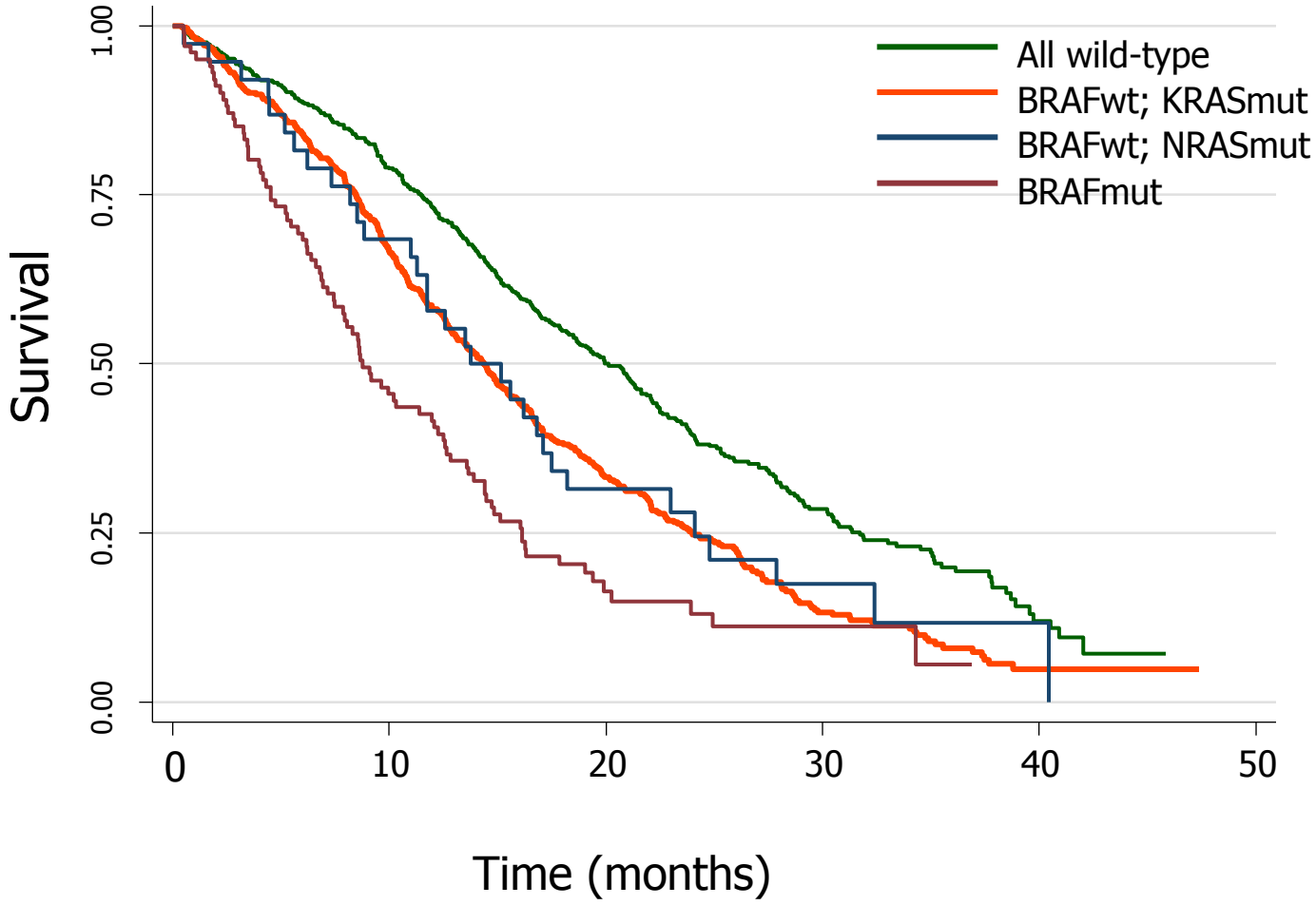
1. Alberts, et al. JAMA 2012; 2. Tveit, et al. JCO 2012; 3. Maughan, et al. Lancet 2011
4. Douillard, et al. ASCO 2011; 5. Van Cutsem, et al. JCO 2011; 6. Langer, et al. ESMO 2008
7. Sobrero, et al. ASCO GI 2012; 8. Amado, et al. JCO 2008; 9. Karapetis, et al. NEJM 2008

Why are we then holding this controversy session ?

- Because today the initial management is not driven by the most popular known molecular markers

1. In early lines K-RAS driven anti EGFRs are just incrementalists because K-RAS is a resistance (not a sensitivity) predictor
2. Anti VEGF are just incrementalist without biomarker of efficacy
3. The other molecular factors , whether prognostic or predictive are not used in practice yet bacause too ‘weak’

Prognostic Effect of KRAS, NRAS and BRAF mutations on overall survival in metastatic CRC

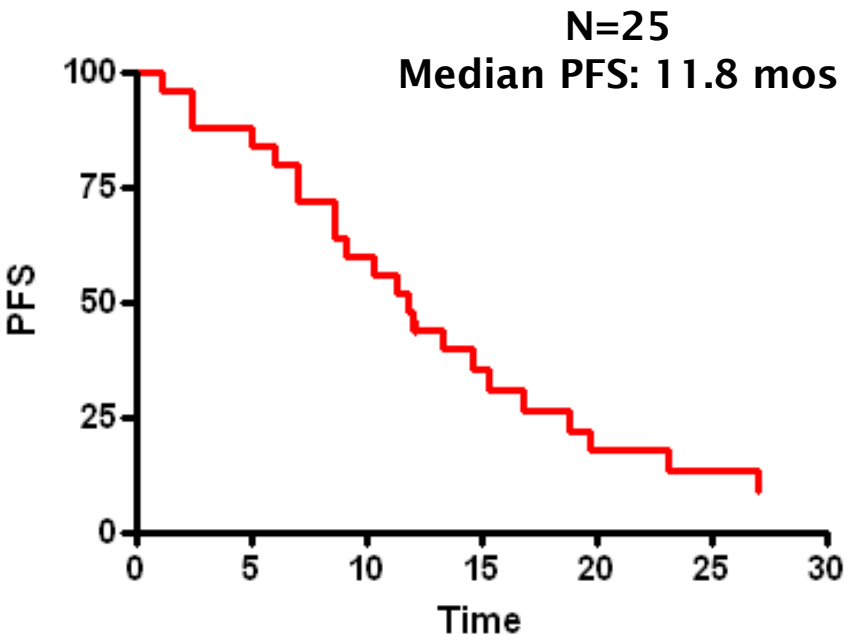


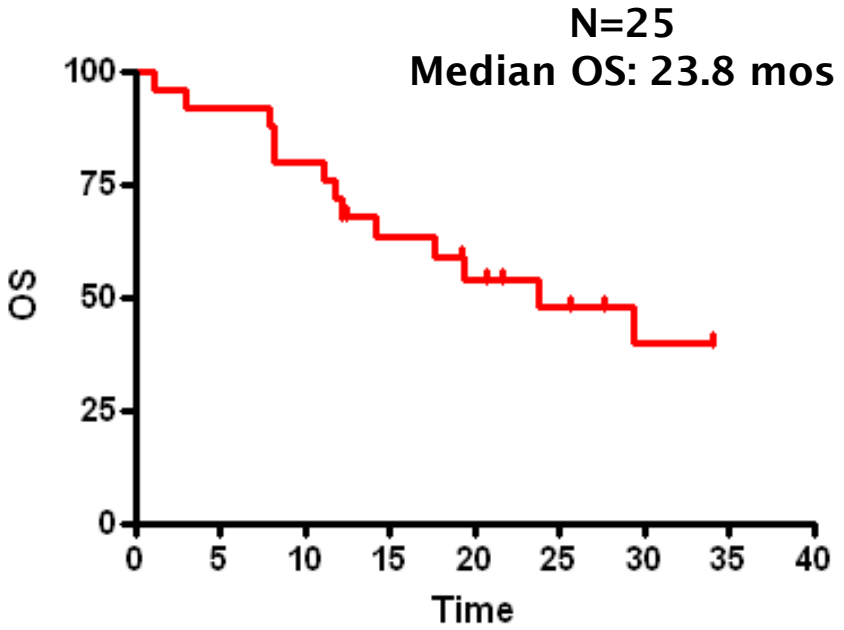
MRC COIN trial Maughan et al. Lancet 2011; 377: 2103–14

A less targeted approach

FOLFOXIRI plus Beva as first-line tx of *BRAF-mut* mCRC pts:

Pooled analysis of retrospectively and prospectively treated pts





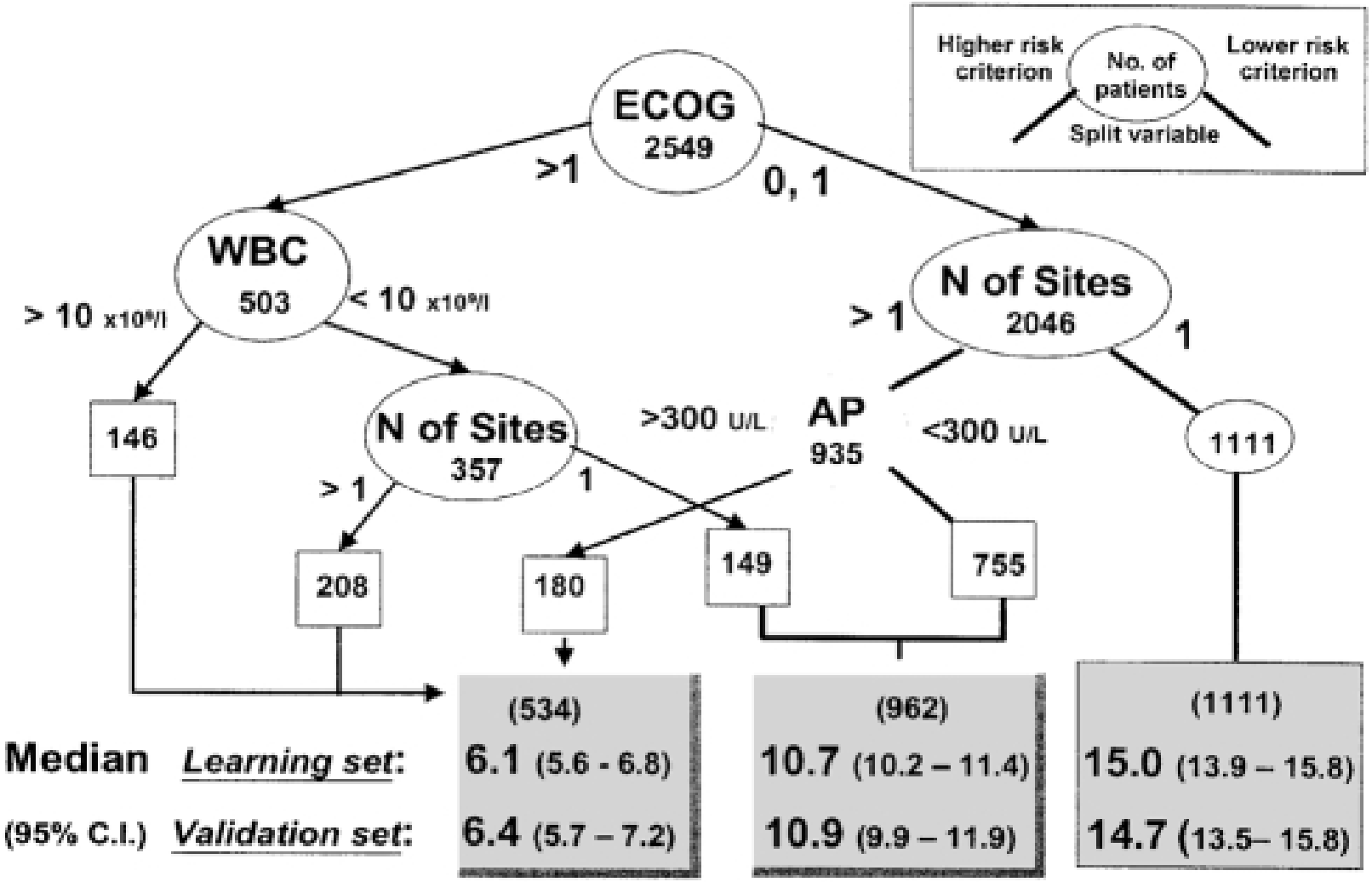
2012 ASCO Annual Meeting
June 1-5, 2012 | McCormick Place | Chicago, Illinois
Collaborating to Conquer Cancer

Salvatore et al, 3585

Is this a convincing example of paradigm changing , molecularly driven strategy?

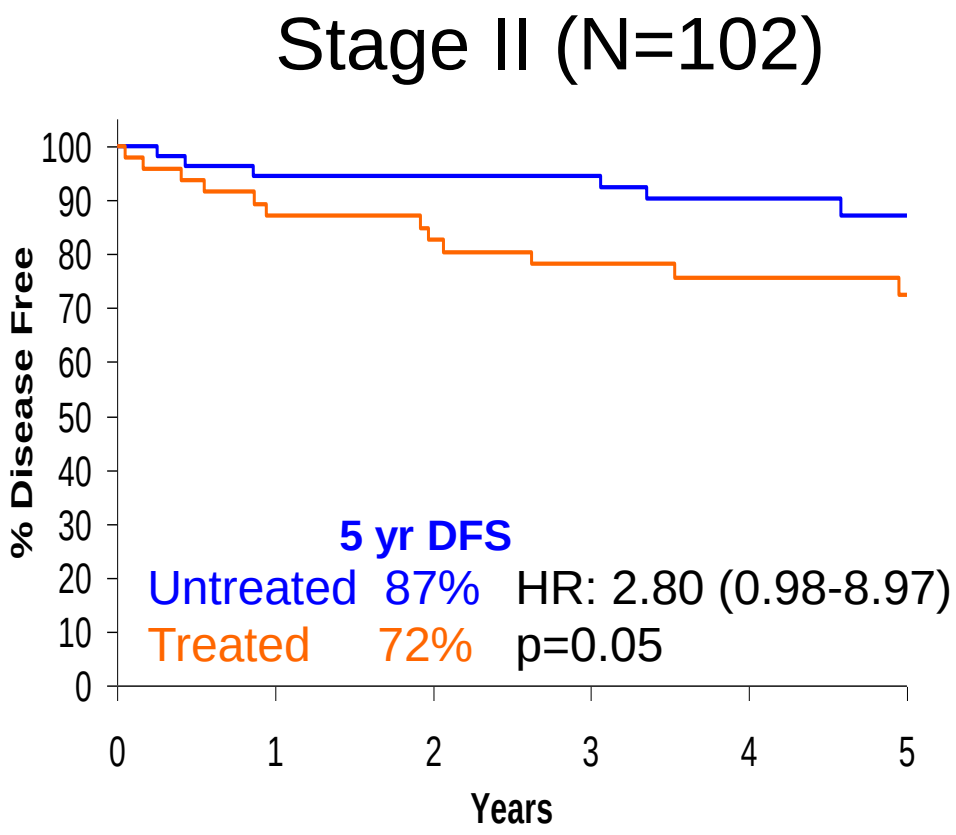
1. Therapy driven by potential risk , not molecularly targeted
2. 25 pts only
3. Results are good , but not outstanding
4. BRAF mut prevalence low (8%)
5. BRAF mut prognostically bad only in pMMR (5%)
6. Other much easier clinical parameters exists

Assessing prognosis



C.-H. Köhne, D. Cunningham, F. Di Costanzo et al. Clinical determinants of survival in patients with 5-fluorouracil based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients Annals of Oncology 13: 308–317, 2002

DFS in MMR-D patients



Sargent 2008

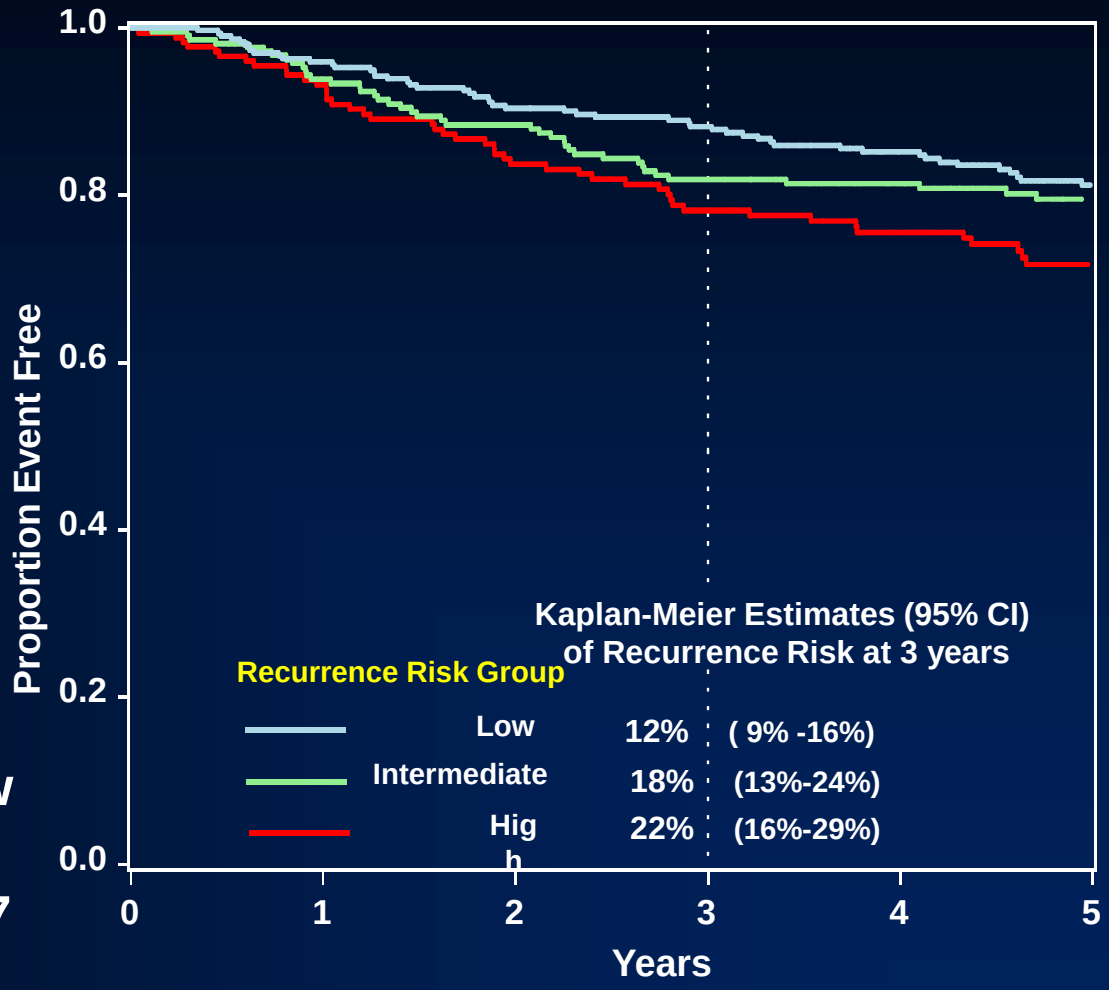
ESMO consensus guidelines for management of patients with colon and rectal cancer. A personalized clinical decision making. Schmoll et al Ann. Oncol 2012

- **Adjuvant therapy should not be routinely recommended for unselected stage II colon cancer patients. However, stage II patients must be separated into high and low risk, according to the presence of at least one of the following tumour-related risk factors [93, 94] [IV, B]:**

1. **lymph nodes sampling <12,**
2. **poorly differentiated tumour,**
3. **vascular or lymphatic or perineural invasion,**
4. **pT4 stage,**
5. **clinical presentation with intestinal occlusion or perforation**

QUASAR Results: Recurrence Risk in Pre-specified Recurrence Risk Groups (n=711)

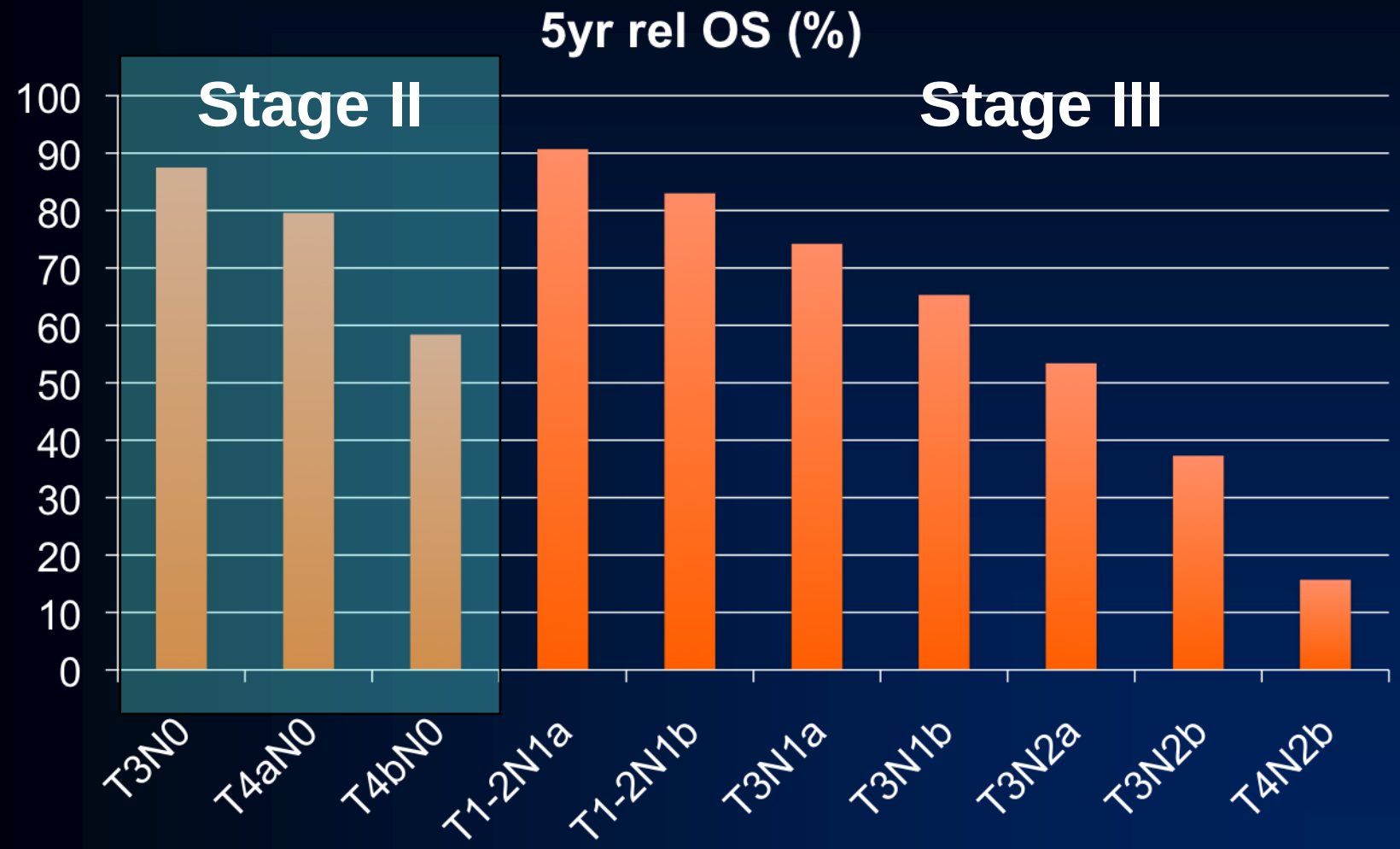
Recurrence Risk Group	Range of RS	Proportion of patients
Low	<30	43.7%
Intermediate	30-40	30.7%
High	≥41	25.6%



Comparison of High vs. Low Recurrence Risk Groups using Cox Model: HR = 1.47 (p=0.046)

Kerr et al., ASCO 2009, abstr. 4000
Gray , JCO 2011

AJCC v7



Gunderson et al, JCO 2009

Impact of signatures today

Would you spend 3000 E to get the signature results in order to give adjuvant CT to a T3 N0 (0/25) G1 if the recurrence score is high ?

or

refrain from prescribing it to a T3, G3, N0 (0/11) LVI if the recurrence score is low ?

Why are we then holding this controversy session ?

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2. **Anti VEGF are incrementalist without biomarker of efficacy**
3. **The other molecular factors , whether prognostic or predictive are not used in practice yet bacause too 'weak'**

Thus therapy will be ‘driven by molecular factors’ when

1. we find predictors of efficacy for anti-EGFR
2. we find predictors of efficacy for BEV
3. we find predictors of efficacy for CT

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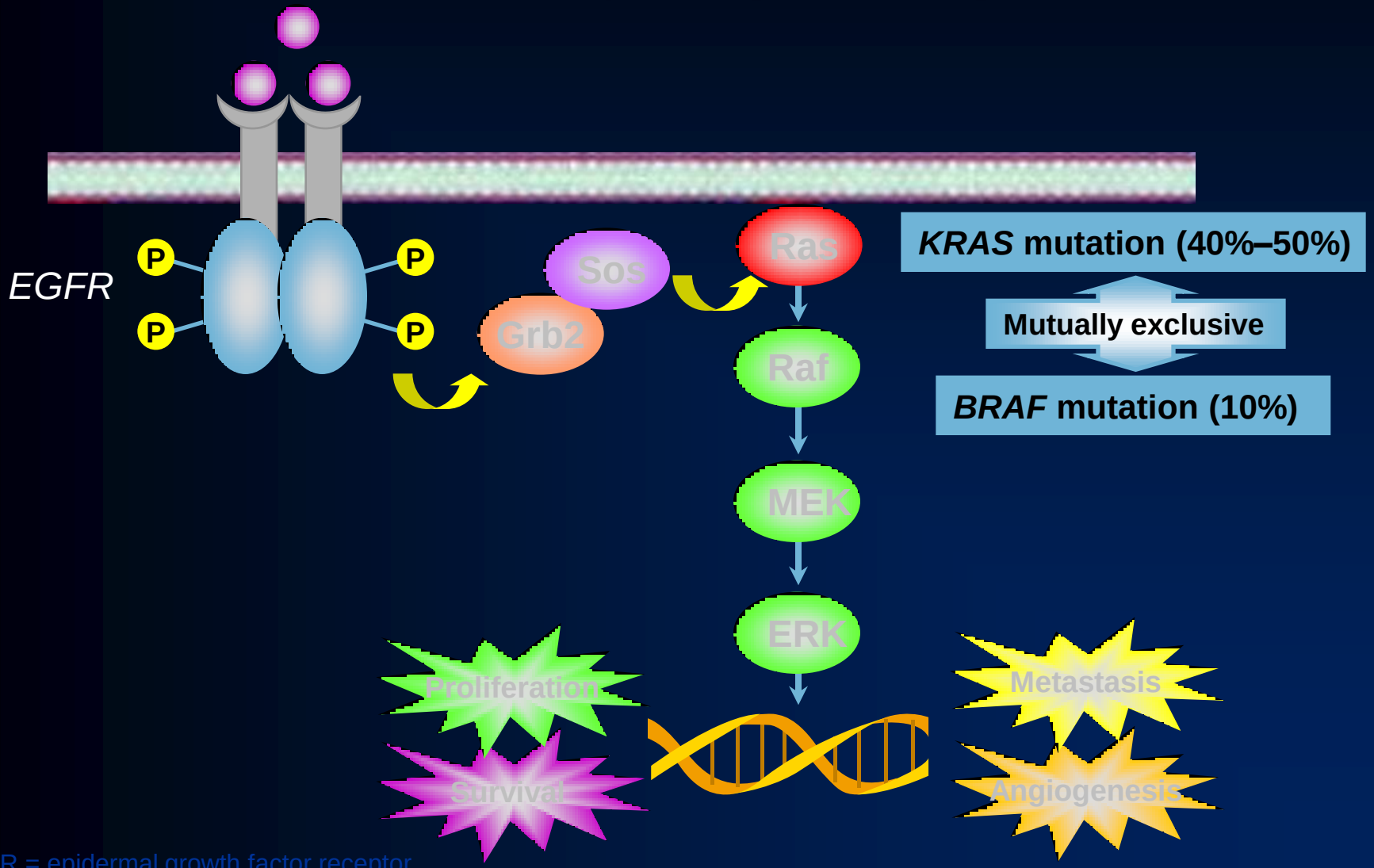
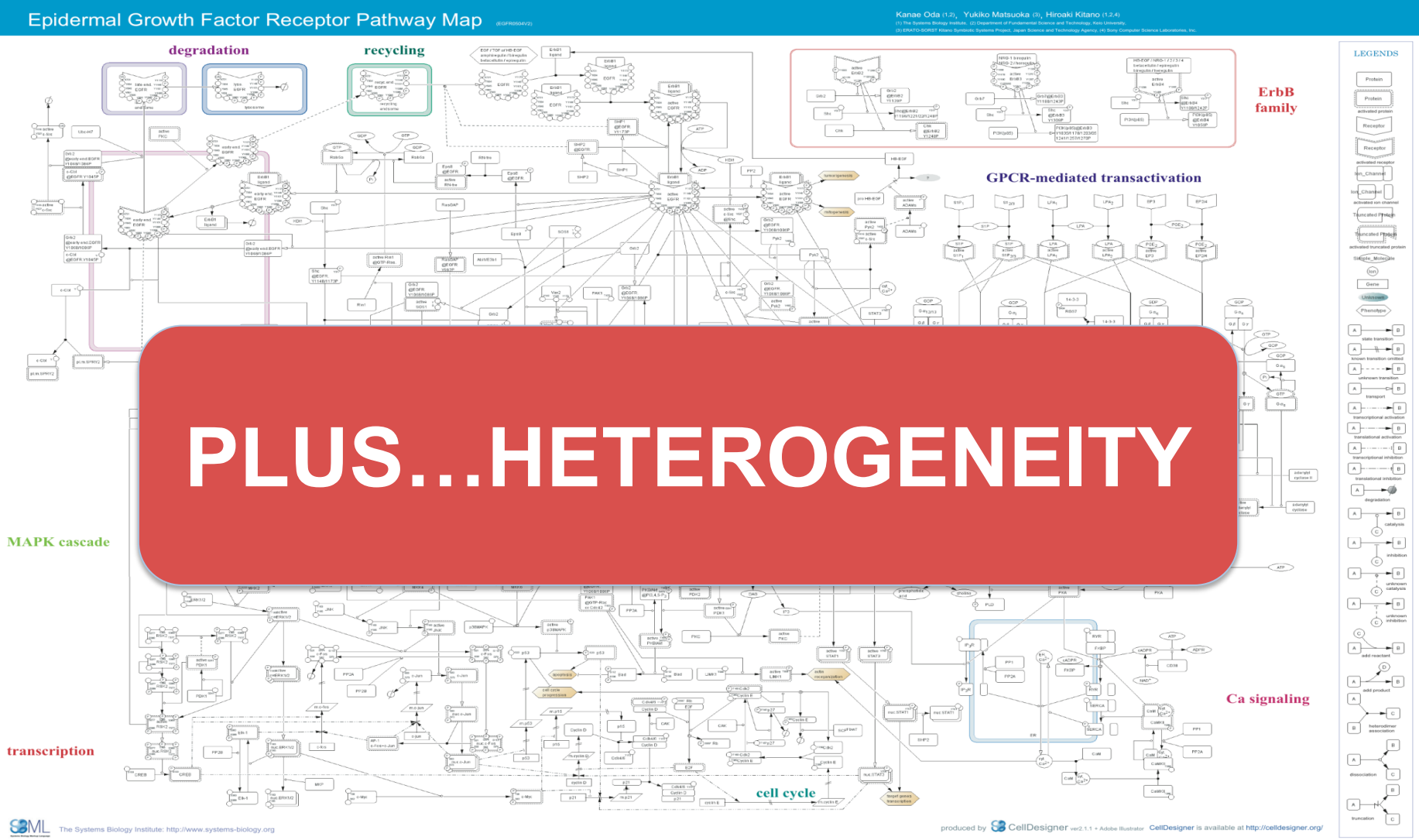
EGFR Pathway Signaling in CRC



EGFR = epidermal growth factor receptor.

1. Why it is unlikely that we find molecular markers of anti EGFR 'soon'



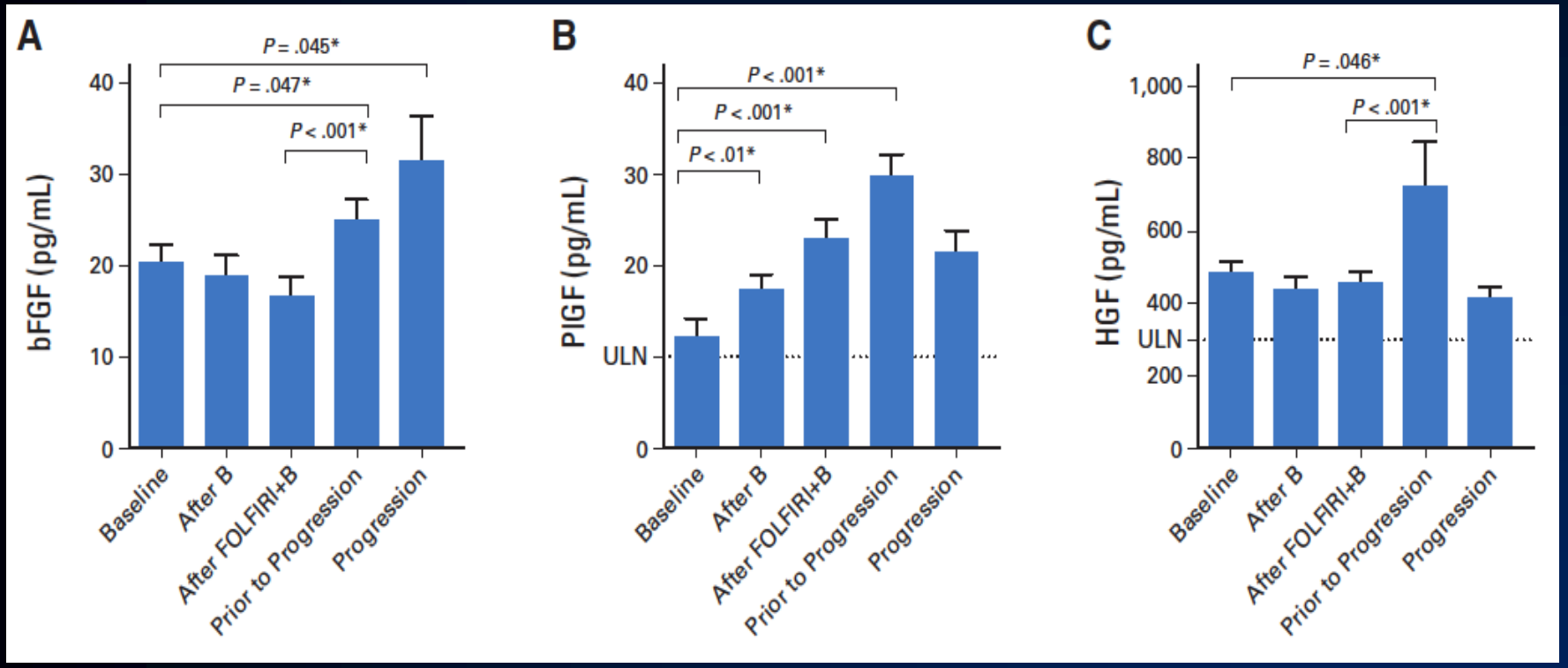
2 Why it is unlikely that we find molecular markers of BEV ‘soon’

- Longer than 10 yrs of search….
- The nature of the target
- ‘Everybody benefits’

2 Why it is unlikely that we find molecular markers of BEV ‘soon’

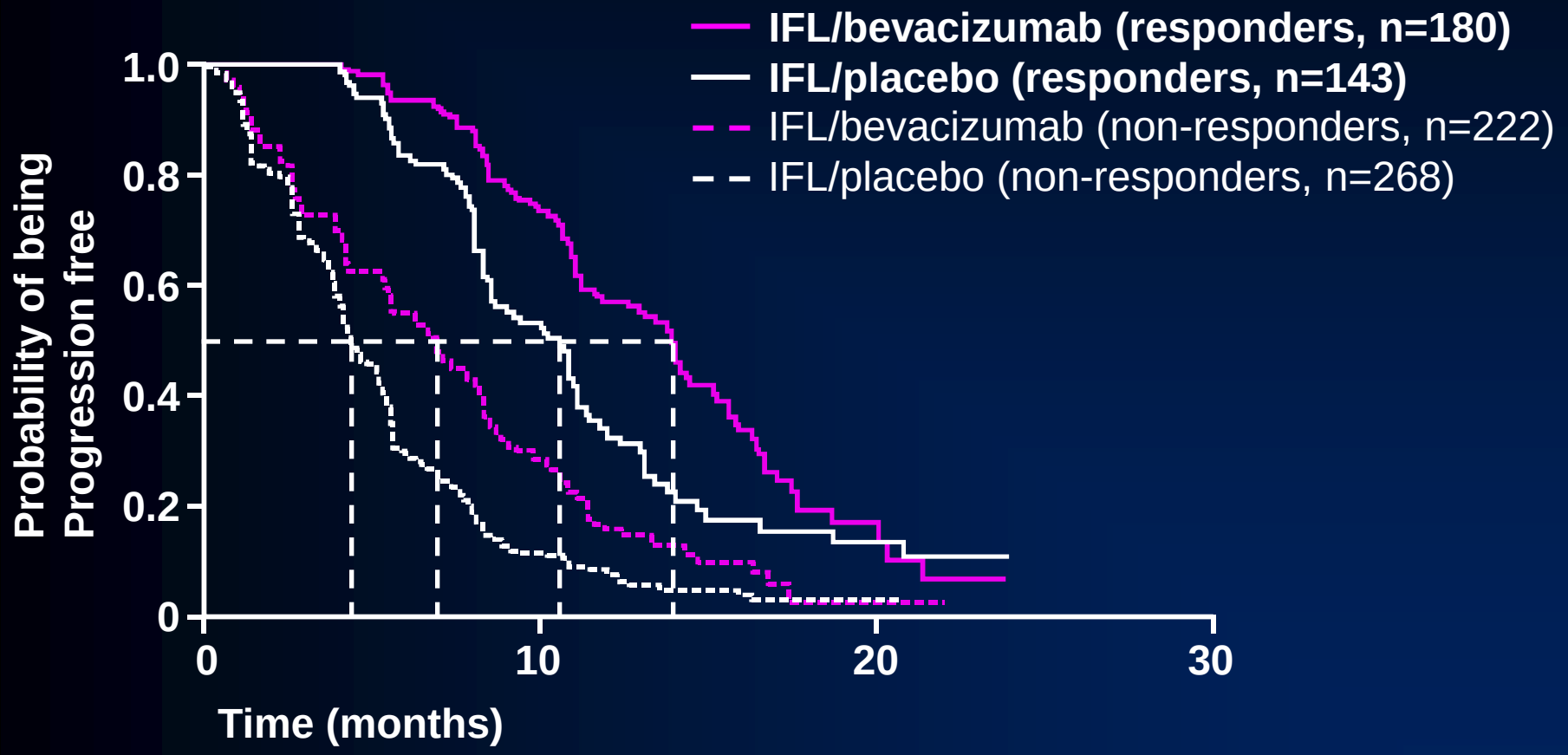
- Longer than 10 yrs of search….
  - It is much more likely that we find where or when BEV will no longer be effective than where it is particularly effective (negative predictors).
- The nature of the target
  - Microenvironment, not the tumor
- ‘Everybody benefits’

Cytokines Increased Prior to Progression On FOLFIRI + Bev



Kopetz JCO 2009

Progression-free survival during first-line therapy



Mass R, et al. Eur J Cancer Suppl 2005;3:182 (Abstract 643)

3 Why it is unlikely that biochemical and molecular factors will drive our decisions on chemotherapy 'soon'

EUROPEAN JOURNAL OF CANCER 45 (2009) 1935–1949

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Review

A review on the use of molecular markers of cytotoxic therapy for colorectal cancer, what have we learned?

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Editorial Comment

Molecular markers of chemotherapy in advanced colorectal cancer: Back to square one

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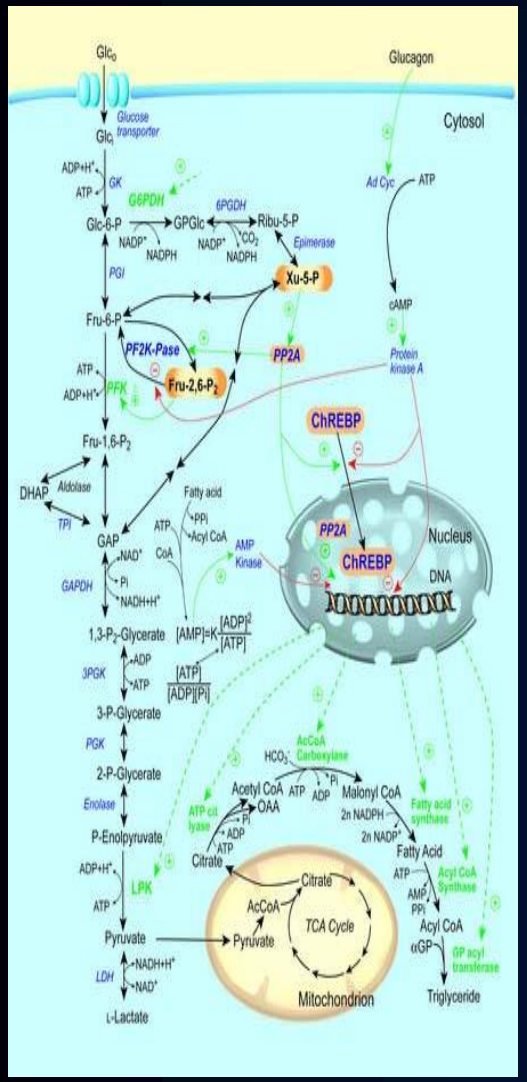
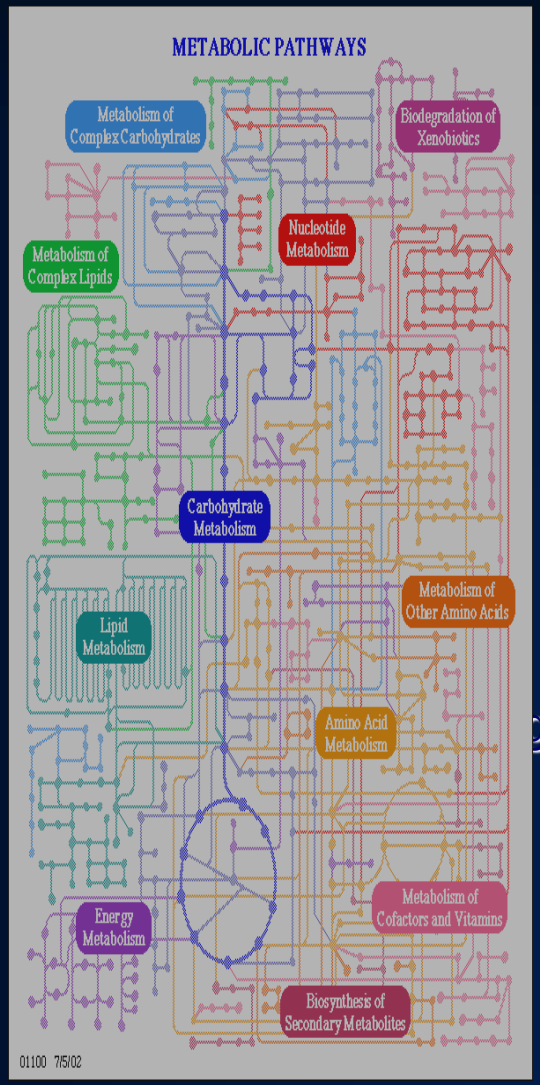
Systems biology of cancer: Integration of networks (Yarden et al)

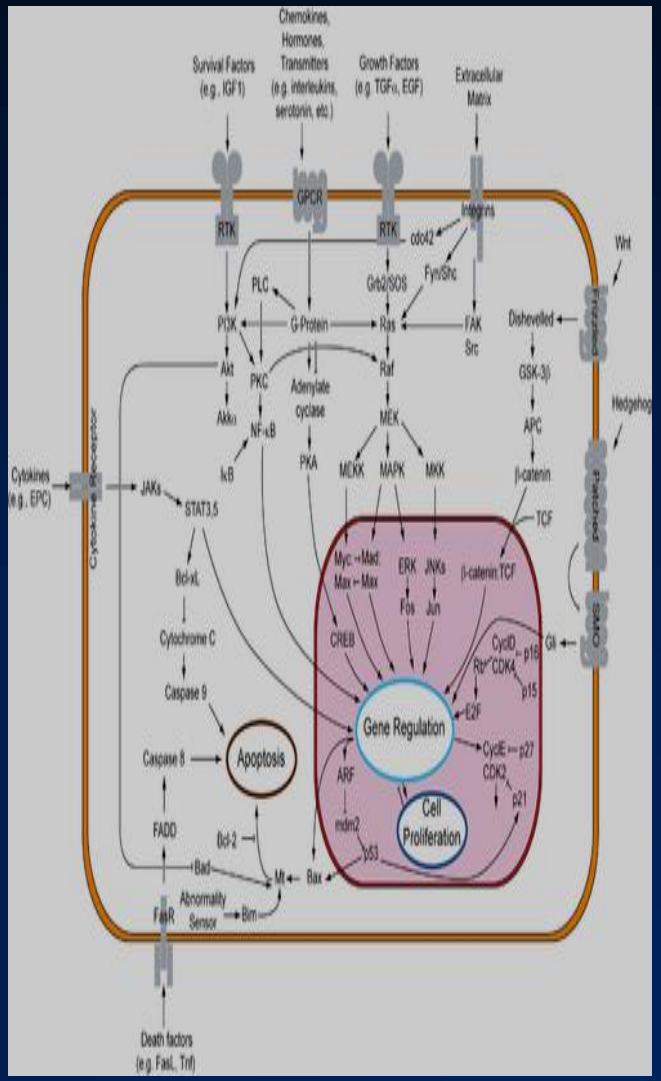
Energy



Metabolism



Information/signaling



CONCLUSION

Progress relies upon the continued search of potential drivers of this disease , but their identification among the passengers is not easy and will not be that ‘soon’