Discussion

5200	PETACC 8 mut
5210	dMMR and BRAF
5190	RALTITREXED

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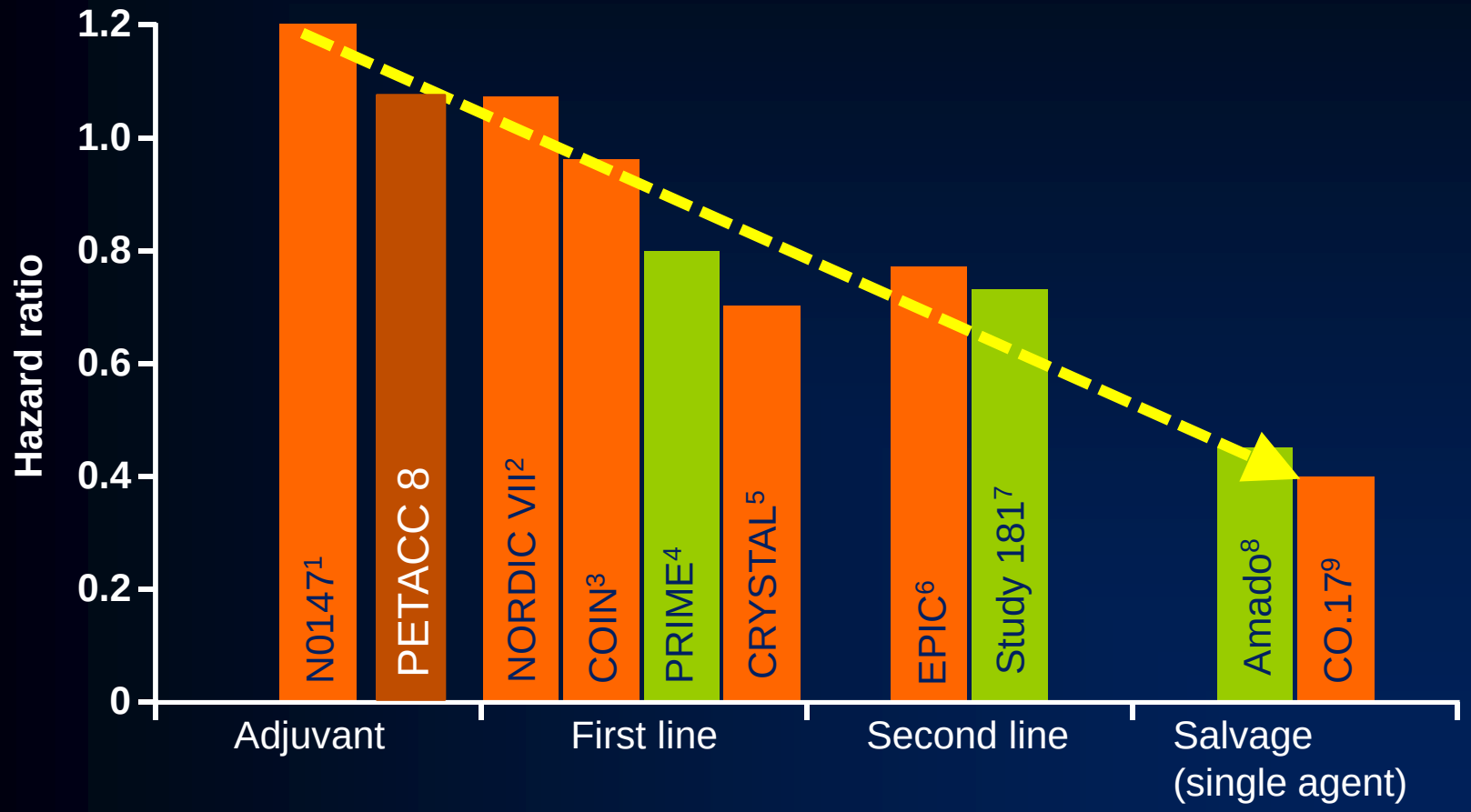
Adding Cetuximab to FOLFOX in high risk stage III K RAS mut (25% T4; 35% N2; 50% vascular invasion)

1. Efficacy not increased in mut
2. Efficacy not decreased in mut
3. Same efficacy results in K RAS mut and wt
4. K RAS mut marginal neg effect on prognosis (3-4%)
5. Gr 3-4 tox substantially increased
   - Skin tox x 30
   - Mucositis x 10
   - Feb. Neutro x 3
   - Asthenia x 2
   - Diarrhea x 1.5

   - Treatment discont. due to ‘tox’ doubled

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

Incremental Tumor Shrinkage afforded by antiEGFR in randomized trials

- **Cetuximab**
  - CRYSTAL FOLFIRI +18%
  - OPUS FOLFOX +23%
  - COIN FOLFOX XELOX +7%
  - NORDIC FLOX 0%
- **Panitumumab**
  - PRIME FOLFOX +9%
  - 181 II line FOLFIRI +25%
  - Piccolo IRI +22%

Adapted from Hurwitz H, et al. N Engl J Med 2004;350:2335-42;Hochster HS, et al. ASCO 2006; Giantonio BJ, et al. J Clin Oncol 2007;25:1539-44; Sobrero AF, et al. AACR 2007 Annual Meeting; Van Cutsem E, et al. ASCO 2007 Maugham 2010, Tveit 2010, Siena 2011, Douillard 2011, Seymour Ecco 2011

Empirical evidence for dogma # 1

Approximate absolute benefit of adjuvant treatment in common solid tumors (stage III)

- Breast 25%
- Ovarian 25%
- Colon 20%
- Gastric 12%
- Pancreas 8%
- NSCLC 5%

In <u>all</u> these cases the regimens accounting for this benefit was derived from regimens with efficacy in the advanced setting

Empirical evidence for dogma #1 in CRC

REGIMEN	GAIN IN ADVANCED SETTING			ADJUVANT SETTING
	MST	PFS	RR	DFS
FU vs BSC	5	4	15%	10%
Best FU LV vs FU	2	2	5%	5%
DOUBLET vs FU LV	3	2	15%	5%

HOWEVER

ADVANCED = ADJUVANT: NOT ALWAYS TRUE

TRUE

- FU
- CAPE
- FU LV
- MTX → FU
- FOLFOX
- FLOX

FALSE

- IFL
- …FOLFIRI…
- CETUXIMAB
- BEVACIZUMAB

Is the game over with adjuvant cet ?

STUDY	N	HR DFS	HR OS
NO 147 wt	1847	1.20	1.30

definitely YES. YES, even if PETACC-8 is POS.

However,

if POS AND translational research identifies a new sizable target population with a huge benefit, then the game may be re- opened

BRAF and dMMR

	BRAF MUT		dMMR	
	prevalence	px impact	prevalence	px impact
Early	8%	bad	15%	good
Advanced	8%	bad	4%	uncertain (bad?)
Advanced	8.6 %	bad	5%	uncertain (PFS)
Advan. dMMR	34.6%%	uncertain		
Advan. pMMR	7.2%	bad		

BRAF and dMMR

Opposite to the Raltitrexed story :

- **high ‘internal validity’ ,**
- **excellent science,**
- **right direction for future advances ,**
- **but limited practical relevance**

BRAF and dMMR

The prognostic value of dMMR and BRAF by themselves turn out weakened by this excellent report

- **low prevalence of both parameters in the advanced setting**
- **What promised to be granitic molecular px factors need further distinction**

a) BRAF (8%) is px only in pMMR tumors (65%) = 5%

b) dMMR (5%) is not so px in the advanced setting

c) dMMR prognostic only in R sided tumors in the early stages (Sinicrope ASCO 2012)

United States Patent Office

2,802,005

Patented Aug. 6, 1957

2,802,005

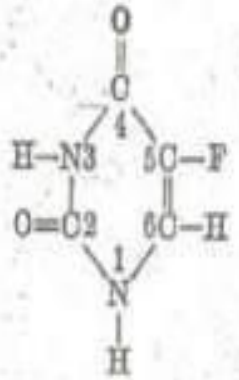
5-FLUOROURACIL

Charles Heidelberger, Madison, Wis., and
Robert Duschinsky, Essex Fells, N. J.

No Drawing. Application September 26, 1956,
Serial No. 612,088

12 Claims. (Cl. 260—260)

This invention relates to novel chemical compounds and to novel processes and novel intermediates useful in preparing the same. More particularly, the invention relates to 5-fluorouracil and salts thereof; to methods of preparing said 5-fluorouracil and salts; and to interme-



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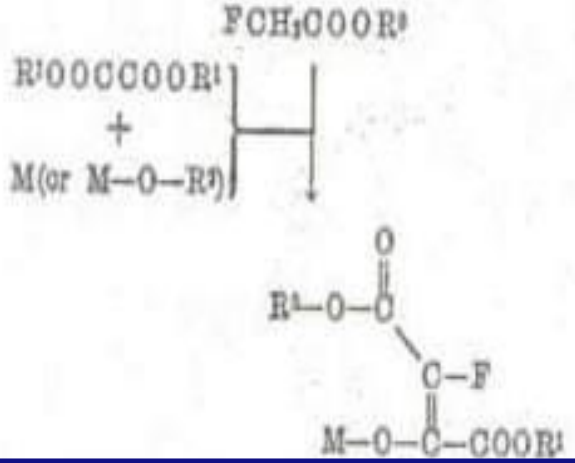
FLOW SHEET—PROCESS II



Cardiac tox of FP

- Very low incidence, poorly quantified
- Definitely occurs (time of onset) 1-4 %.
- 1° cycle, 24 hrs, recurs
- Infusional and cape > bolus (x2)
- Most due to coronary spasm
- Can be lethal

When cardiac tox develops

1. Avoid FP
2. Switch schedule
3. Switch FP
4. Use preventive cardiac meds
5. Use raltitrexed (3 case reports)

Why are we discussing a single arm , retrospective audit trial on 42 pts ?

42 pts with prior cardiac tox during FP (32/1 9/2 2/3)

42 pts treated with R: if > 13 R worse than FP

if < 4 R better than FP

RESULTS : 0/42

Rare example of

'weak methodology', but high impact anyway due to

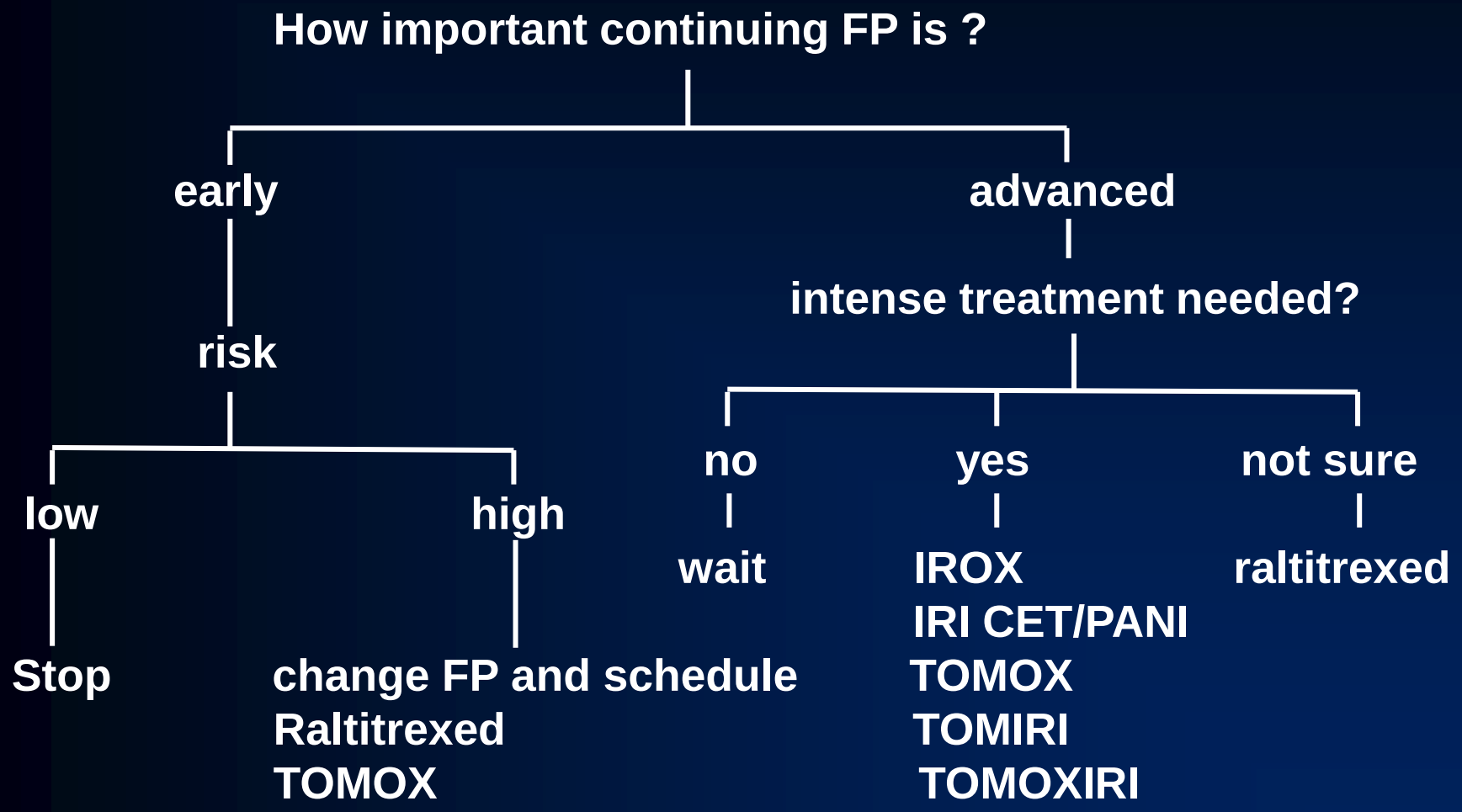
- Strength of findings
- High prevalence of FP treatment

Raltitrexed , clinical results in mCRC

R vs FU bolus N = 439	same eff, less tox	Cunningham EJC 95
R vs 3 infusional FU reg. N=294	lower eff, more tox	Ducreux Oncol 2006
R vs 2 infusional FU reg, N=905	same eff, more tox	Maugham Lancet 2002
R vs IROX N = 92	less eff, less tox	Sheithauer JCO 2002

TOMOX vs FOLFOX N=183	same eff, less tox	Gravalos C.T. Onc 2012
TOMOX vs TOMIRI N=94	same eff, PFS > 8 mo	Feliu BJC 2005
TOMOX N= 71	RR 40%	Seitz Ann. Onc. 2002
TOMOXIRI N = 30	RR 56%	NCIC EJC 2006

When FP-related cardiac toxicity develops



Discussion

		ORIGINALITY	VALIDITY	RELEVANCE
5190	**RALTITREXED**	**+++**	**+**	**+++**
5200	**PETACC 8**	**+**	**+++**	**+**
5210	**dMMR and BRAF**	**+++**	**+++**	**+**