Discussion LBA 20-21

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RELEVANCE

NORDIC 7

Large scale R phase III N=600

Impact on practice:

- cetuximab 1st line
- Duration of CT

HH GDC-0449

R phase II N = 200

Impact on drug development:

- go no-go in CRC

The results: NORDIC (n = 566)

	RR	PFS	OS	TOX
FLOX	41	7.9	20.4	
FLOX CET	49	8.3	19.7	more
maintenance	47	7.3	20.3	

no better outcome in the K-RAS wt population !!!

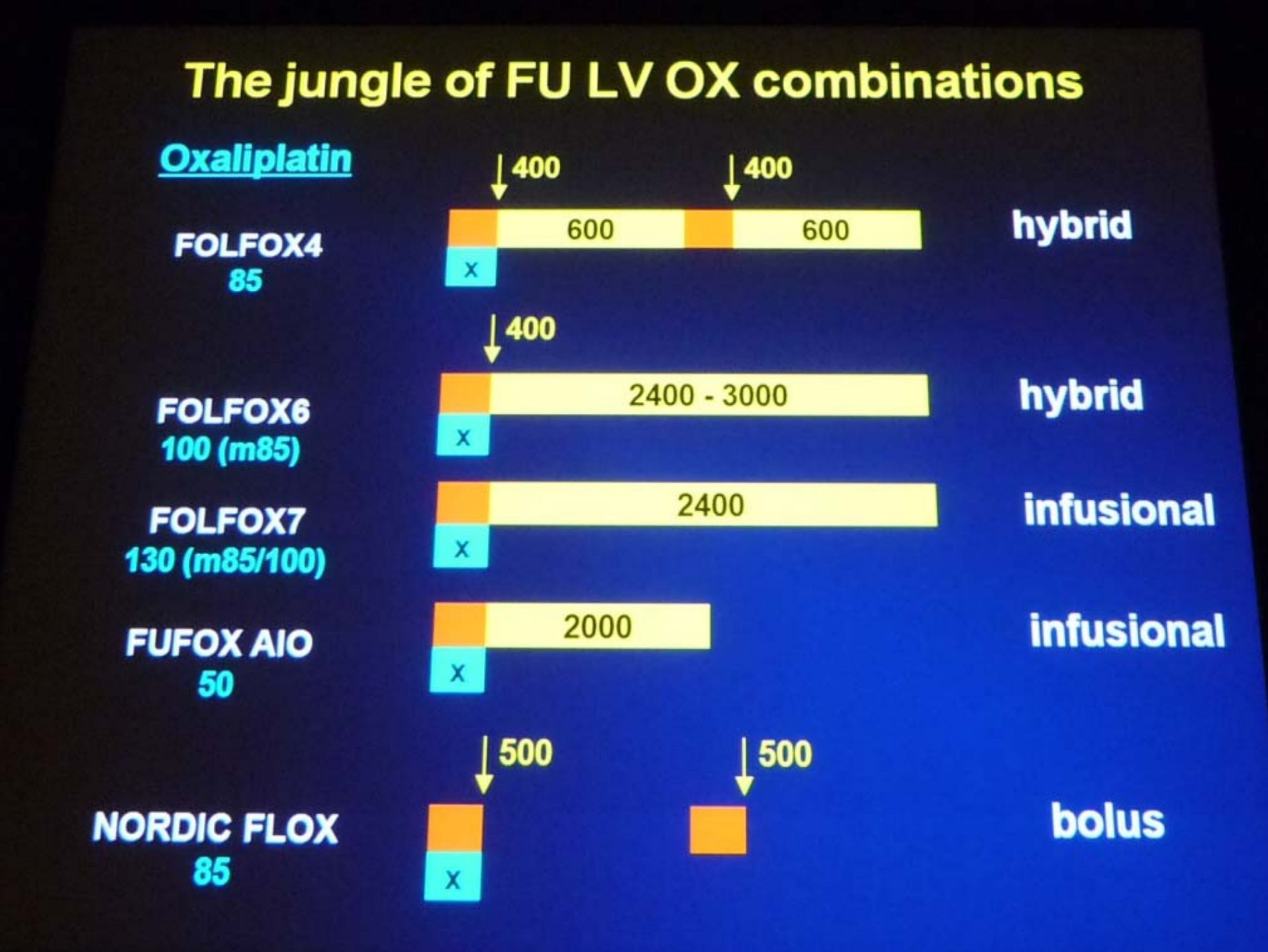
NORDIC major findings

- *Efficacy results*: overall, negative
- *K-RAS wt* : no benefit
- *Concept of intermittent CT reinforced*

NORDIC

- Underpowered for K-RAS
- Backbone CT regimen

The jungle of FU LV OX combinations



Why

1. Bias
2. Chance
3. True interaction

K-RAS STORY: NORDIC AGAINST ALL?

- *Only* NORDIC reported lower RR and *PFS in K-RAS* wt than in mut out of 11 *trials*

- *49% RR is the highest ever reported for K-RAS mut*

K-RAS results : Just chance ?

		OR	95% C.I.	
• RR				
• ITT	566	1.35	0.9	2.02
• Wt	303	0.96	0.55	1.69
• Mut	195	1.44	0.72	2.90

		HR	95% C.I.	
• PFS				
• ITT	566	0.89	0.7	1.11
• Wt	194	1.07	0.79	1.45
• Mut	130	0.71	0.5	1.03

True negative interaction between cetuximab and FU + oxaliplatin ?

The fact that the results in the K-Ras wt population are no better than ITT reinforces the possibility of a true negative interaction:

- *With bolus FU ?*
- *With oxaliplatin ?*

Does the administration mode of fluoropyrimidines play a role? (PFS) K-RAS wt population

	CT	CT + bio	HR	p
Continous infusion FU				
CRYSTAL	8.4	9.9	0.67	0.001
OPUS	7.2	8.3	0.57	0.006
PRIME	8.0	9.6	0.80	0.02
Bolus FU				
NORDIC VII	8.7	7.9	1.07	0.66

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PRIME	8.0	9.6	0.80	0.02
COIN MdG	n.a	n.a	0.77	0.056
COIN xelox	n.a	n.a	1.06	0.5
Bolus FU				
NORDIC VII	8.7	7.9	1.07	0.66

Is Irinotecan a better partner for cetuximab than oxali in 1st line?

		FOLFOX plus cetuximab	FOLFIRI plus cetuximab
CELIM[1] *ITT (n=106)*	RR	68%	57%
CALGB 80203[2] *ITT (n=108)*	RR	60%	44%
	PFS	8.2	10.6
CECOG *KRAS wt (n=62)*	RR	56%	50%
	PFS	9.1	8.4

[1] Folprecht et al., Lancet Oncol 2010; 11: 38-47
[2] Venook et al, ASCO 2006 , oral presentation, abstract no.3509
[3] Ocvirk et al., World J Gastroenterol 2010; 16:3133-3143

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Direct comparison very weak → whole story

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Is Irinotecan a better partner for cetuximab than oxali ?

IRINOTECAN

- III line ++ BOND (MLE)
- II line ++ EPIC
- I line +++ CRYSTAL

- No detrimental effect mut

OXALIPLATIN

- III line no data
- II line - little data
- I line ++ OPUS
  + COIN
  - NORDIC
- Adjuvant - NO146
- Detrimental effect in mut

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	+	COIN
	-	NORDIC
• Adjuvant	-	NO146
• Detrimental effect in mut		

Very solid

shaky

Why

1. Bias	no…
2. Chance	hmm…
3. True interaction	likely

CONCLUSIONS

- *NORDIC*
  - *Impact on practice : yes*
    - *Iri-based CT should be the partner of cet*
    - *Another piece of evidence against continuing CT untill progression*
- *HH GDC-0449*
  - *Impact on drug development in CRC: yes*
    - *no-go*