ABSTRACT

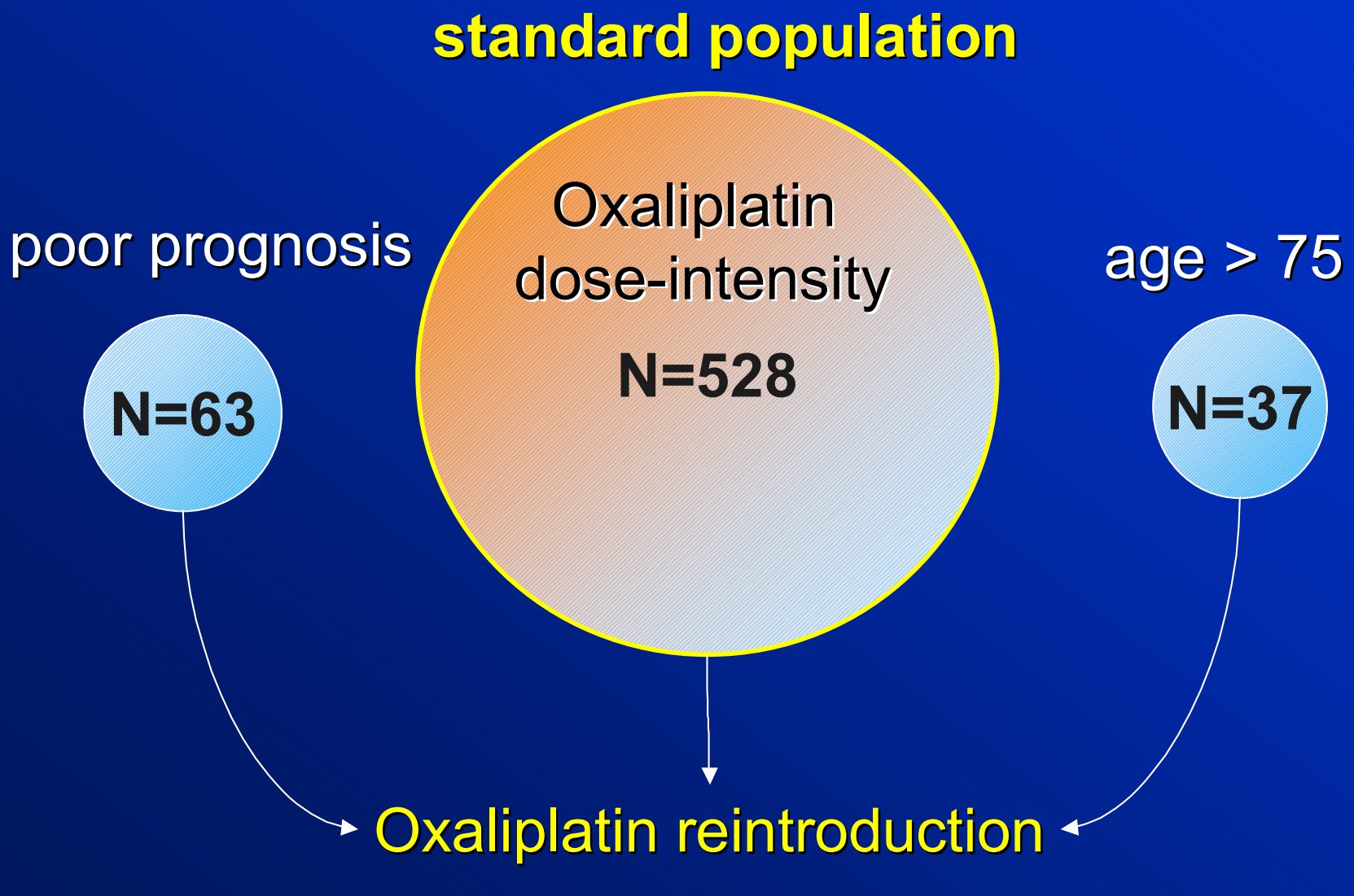
Background: FOLFOX4 has shown superiority over LV5FU2 in first line therapy of advanced colorectal cancer. FOLFOX7 combines a simplified (s) LV5FU2 regimen and high-dose oxaliplatin. The limiting toxicity of the FOLFOX4 regimen is a cumulative sensory neurotoxicity which imposes to stop therapy in patients still responding to therapy.

Methods: OPTIMOX study is a phase III trial comparing in first line therapy FOLFOX4 until progression (arm A) to FOLFOX7 x 6 cycles followed by simplified LV5FU2 x 12 cycles and FOLFOX7 reintroduction (arm B). 526 patients ≤ 75 years and with Alk Ph < 3-time the UNL were enrolled. Patients characteristics (%) are in arm A, 262 pts : M/F= 58/42, PS 0/1-2= 55/45, median age= 63 yrs(29-75) ; in arm B 264 pts : M/F= 62/38 , PS 0/1-2= 56/44, median age= 63yrs (32-75).

Results: Grade 3-4 toxicity (% of pts) was in arm A/B : neutrophils 31.7/21.5, platelets 2.7/10.3, nausea 5.8/10.0, mucositis 2.7/6.1, diarrhea 10.8/12.3, HFS 0.4/3.5, neurotoxicity 18.2/13.0. Response rate (ITT) was 58.5% in arm A and 58.3% in arm B. In arm A and B, median PFS were respectively 9.2 and 9.0 months (n.s.), median OS were respectively 20.0 and 21.6 months (n.s.). The primary endpoint of this study is the time of disease control (TDC). Median TDC was 9.2 months in arm A and 9.7 in arm B (n.s.). Oxaliplatin was reintroduced in 40% of the patients in arm B; responses were observed in 10.4% of the patients and stabilisation in 32.0% (ITT). 27 patients had oxaliplatin reintroduction in arm A and 52 received oxaliplatin-based therapy in subsequent lines. Overall 23.8% of patients in arm A and 48.7% in arm B received at least two oxaliplatin-based therapy. Not reintroducing oxaliplatin was protocol violation in 21% of the patients in arm B. In a multivariate analysis, prognostic factors were performance status, number of metastatic sites, LDH, alk phosphatases and oxaliplatin reintroduction.

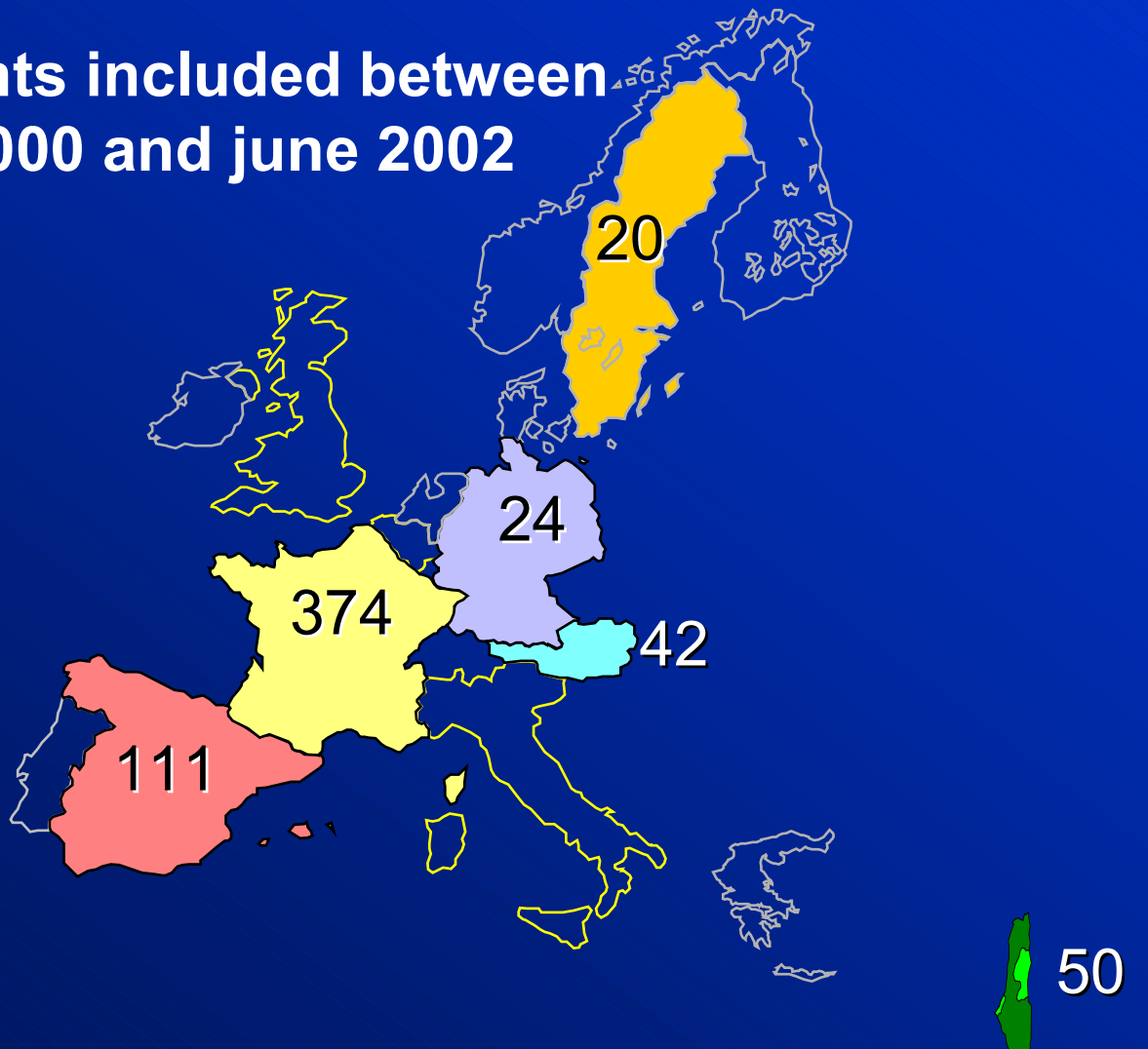
Conclusion: FOLFOX7 followed by sLV5FU2 has a similar toxicity and efficacy than FOLFOX4 but is more convenient. There was a large variation among centers on oxaliplatin reintroduction which appears as a major prognostic factor. These results allow us to start a new investigational study OPTIMOX2 comparing this OPTIMOX 1 strategy versus FOLFOX7x 6 cycles followed by a treatment break and reintroduction of FOLFOX7.

OPTIMOX 1 Study



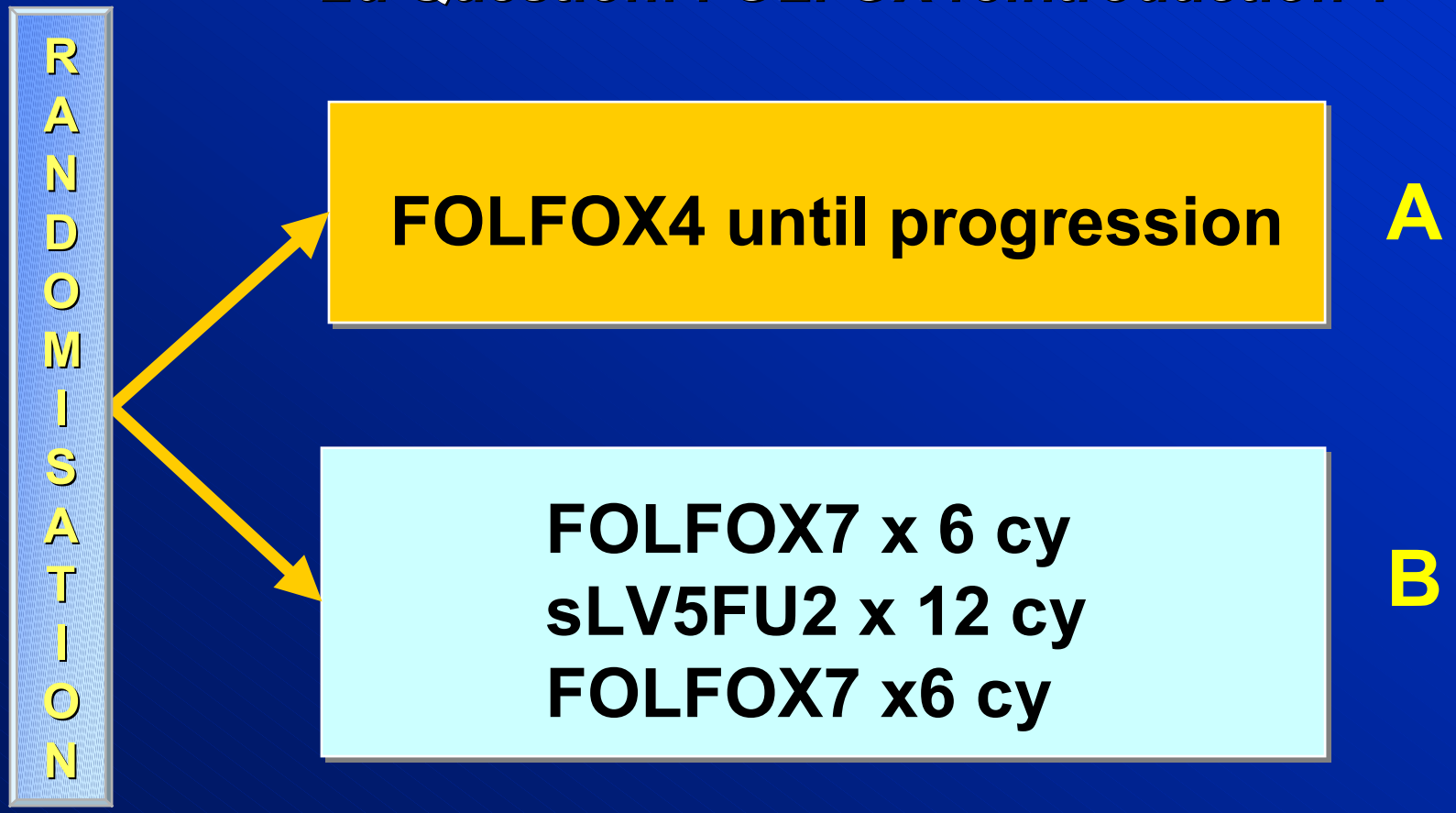
OPTIMOX 1 Countries

623 patients included between january 2000 and june 2002

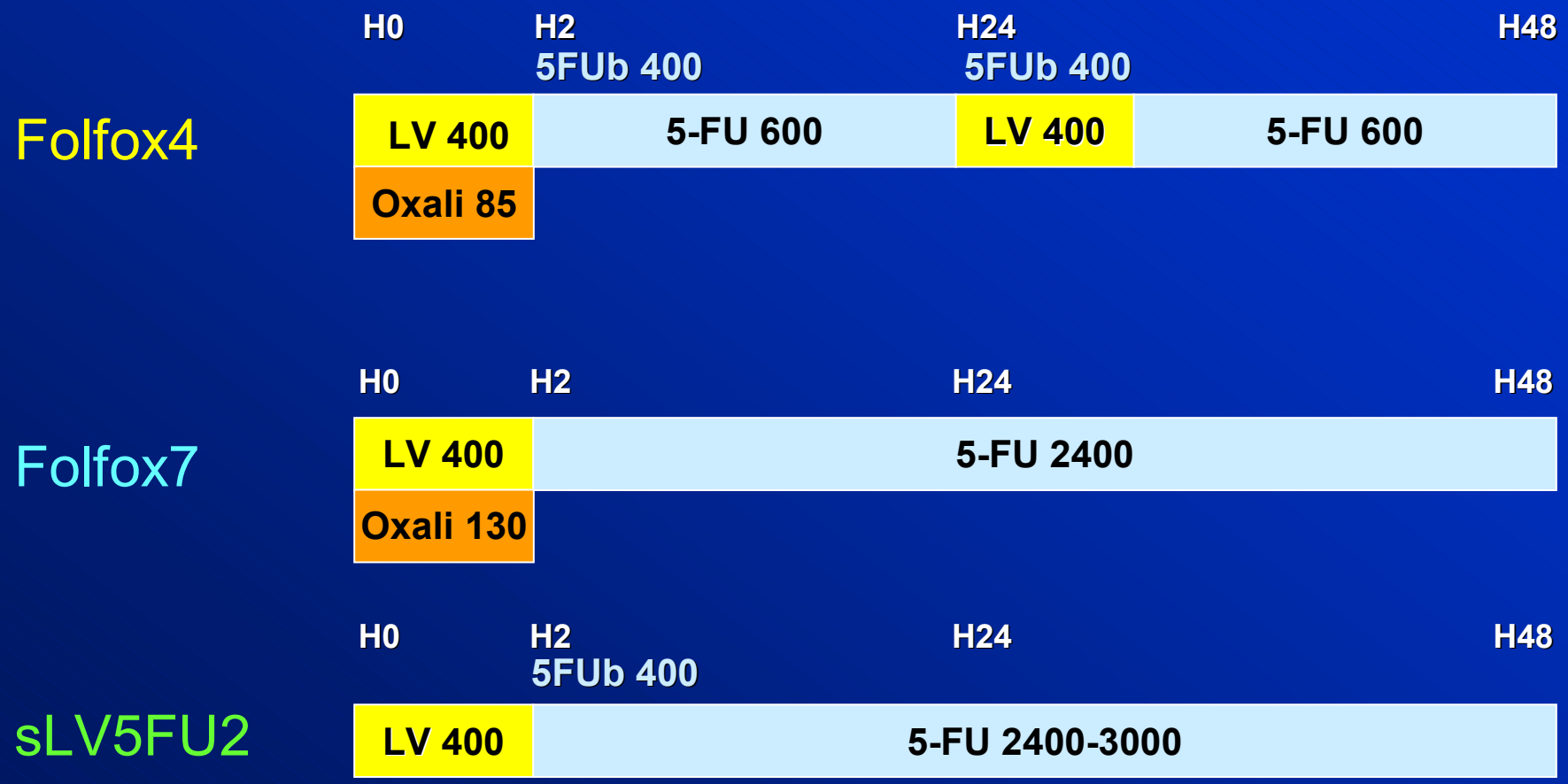


OPTIMOX 1 Study design

- Ist Question: FOLFOX4 or FOLFOX7 ?
- 2d Question: FOLFOX reintroduction ?



CHEMOTHERAPY



Cycles every 14 days

Dose mg/m²

Inclusion criteria

- Histologically proven colorectal cancer
- Unresectable metastases
- No prior CT except adjuvant CT if ended $\geq$ 6 months before study entry
- 18 - 75 years and WHO PS $\leq$ 2
- Adequate hematological, renal and liver functions

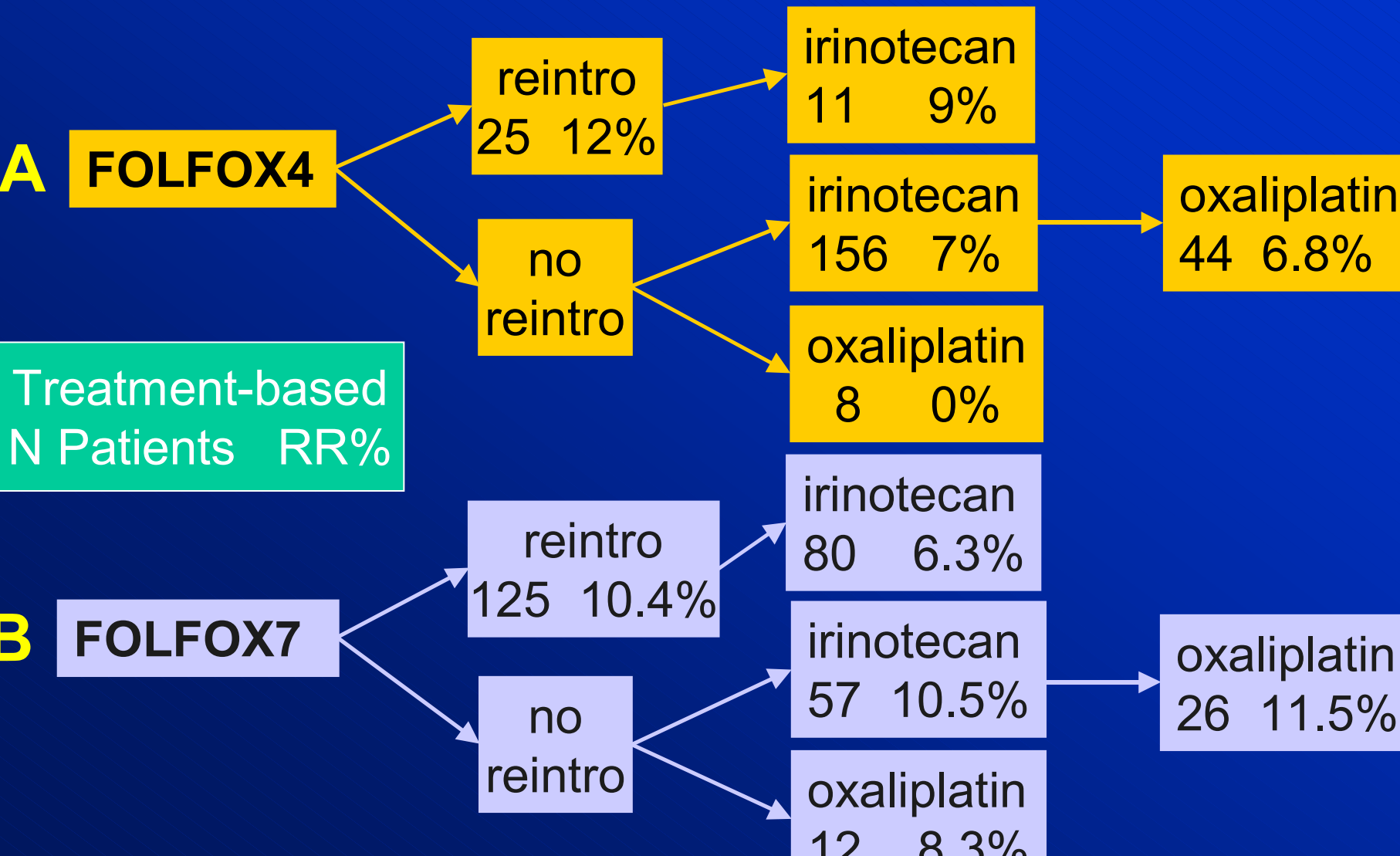
Statistics

- Randomisation using minimization technique
- Stratification by center, PS (0-1 vs 2), number of sites (1 vs > 1) age (18 - 50 vs 51-75 vs 76 - 80) Alk Ph. (< 3x UNL vs ≥ 3 - 5 ULN)
- Sample size calculated to demonstrate the test treatment extends the Duration of Disease Control (DDC) by a median of 3 months in comparaison to the reference treatment.

PATIENTS CHARACTERISTICS

	Arm A Folfox4 N = 262	Arm B Folfox7 N = 264
Median age, years (range)	63 (29 - 75)	63 (32 - 75)
Male/Female (%)	58% / 42%	62% / 38%
WHO PS 0/1-2 (%)	55%/ 45%	56%/ 44%
LDH N / > ULN/ Missing (%)	45%/37%/18%	44%/ 38%/18%
Colon/Rectum/Both (%)	66%/32%/1%	60%/38%/0.5%
Prior adjuvant CT/RT (%)	24%	22%
Synchronous metastasis (%)	29%	31%
Nb metastatic sites 1/≥ 2 (%)	57% / 43%	57% / 43%
Liver	69.5	65.5
Lung	27	25

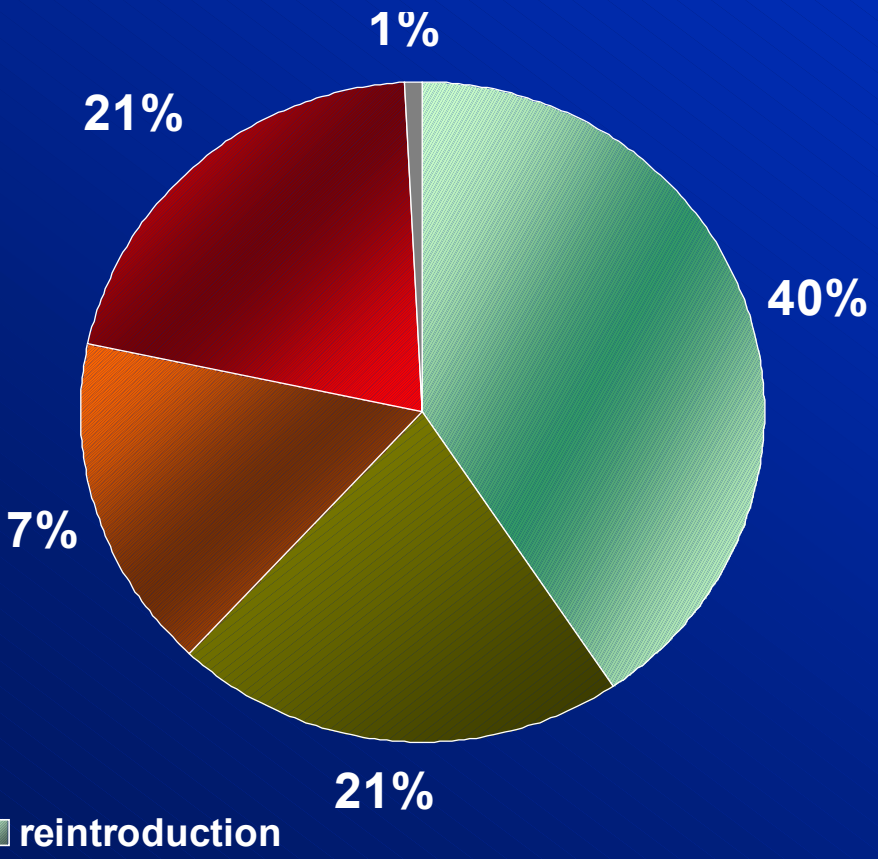
OPTIMOX 1 Reintroduction and Second-Lines



OPTIMOX 1 Number of Cycles

	Folfox4 N = 262	Folfox7 sLV5FU2 N = 264
Nb of cycles with oxaliplatin	2938	2076
Nb of all cycles (with or without oxaliplatin)	3514	4107
Median nb of cycles with oxaliplatin (range)	*11 [1- 24]*	*6 [1- 20]*
Median DI/w (6 cy)	41.9 mg	62.2 mg
Median nb of cycles with or without oxaliplatin (range)	*12 [1 - 30]*	*14 [1- 46]*

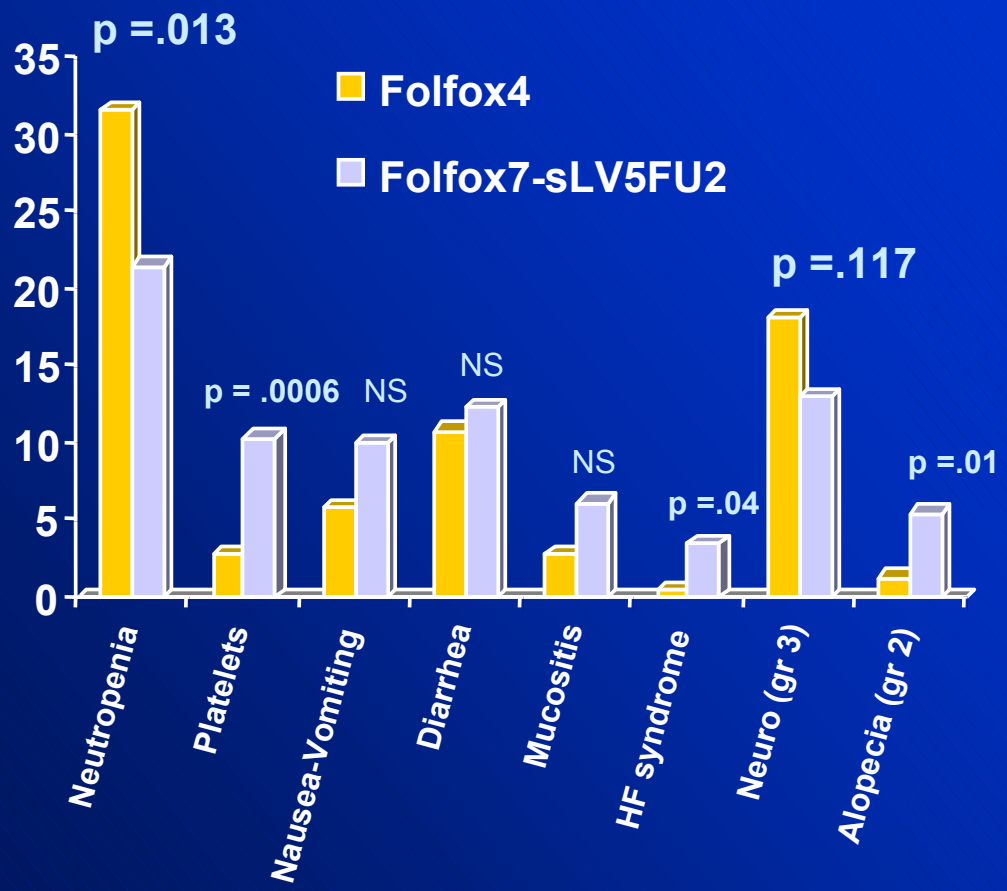
OPTIMOX 1 Reintroduction (all patients)



reintroduction: 125
oxaliplatin toxicity: 59
neurological: 42
5FU toxicity: 7
progression or death: 51
progression:32
death: 19
other: 3
no therapy:1,
hemangioma: 1
liver cancer:1
no reason, protocole violation: 6

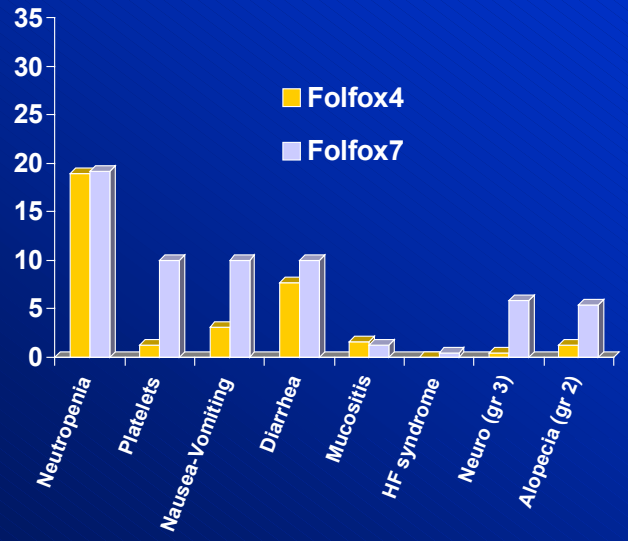
Toxicity Grade 3-4 (%) per Patient, (N = 524)

All Cycles

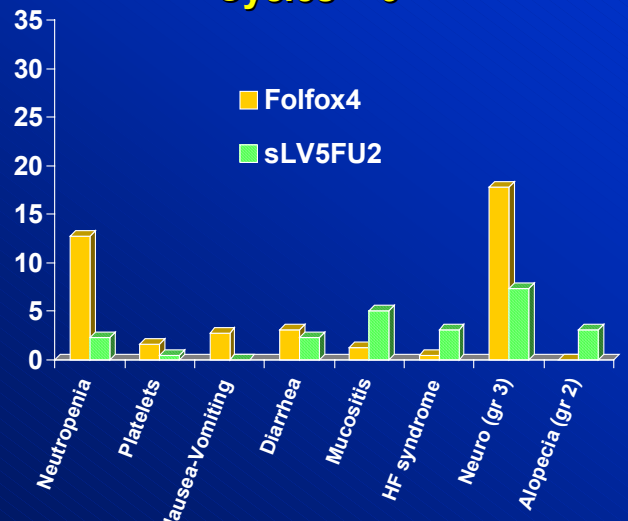


Death within 60 days
- **Folfox4: 6 pts**
- **Folfox7: 7 pts**

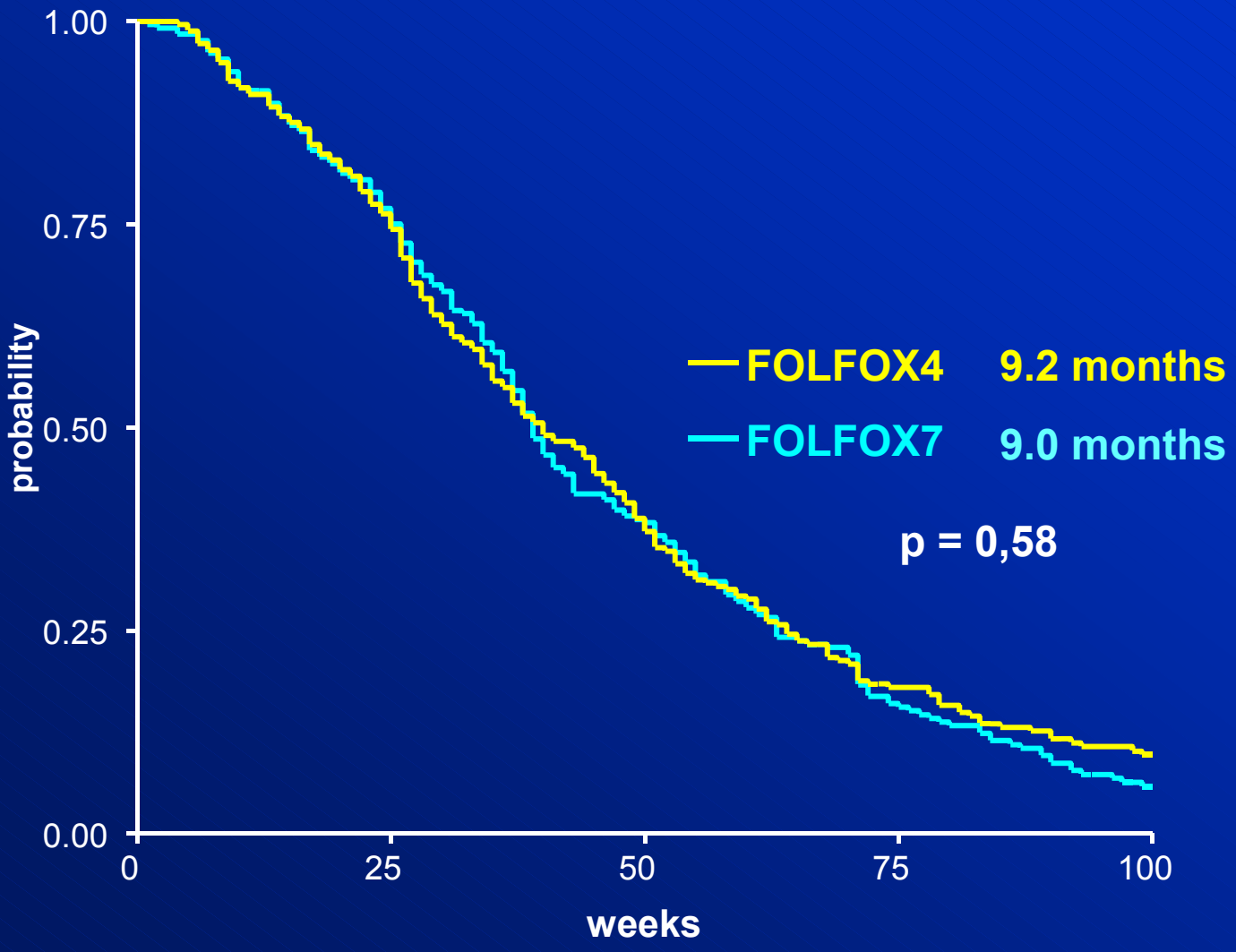
6 first cycles



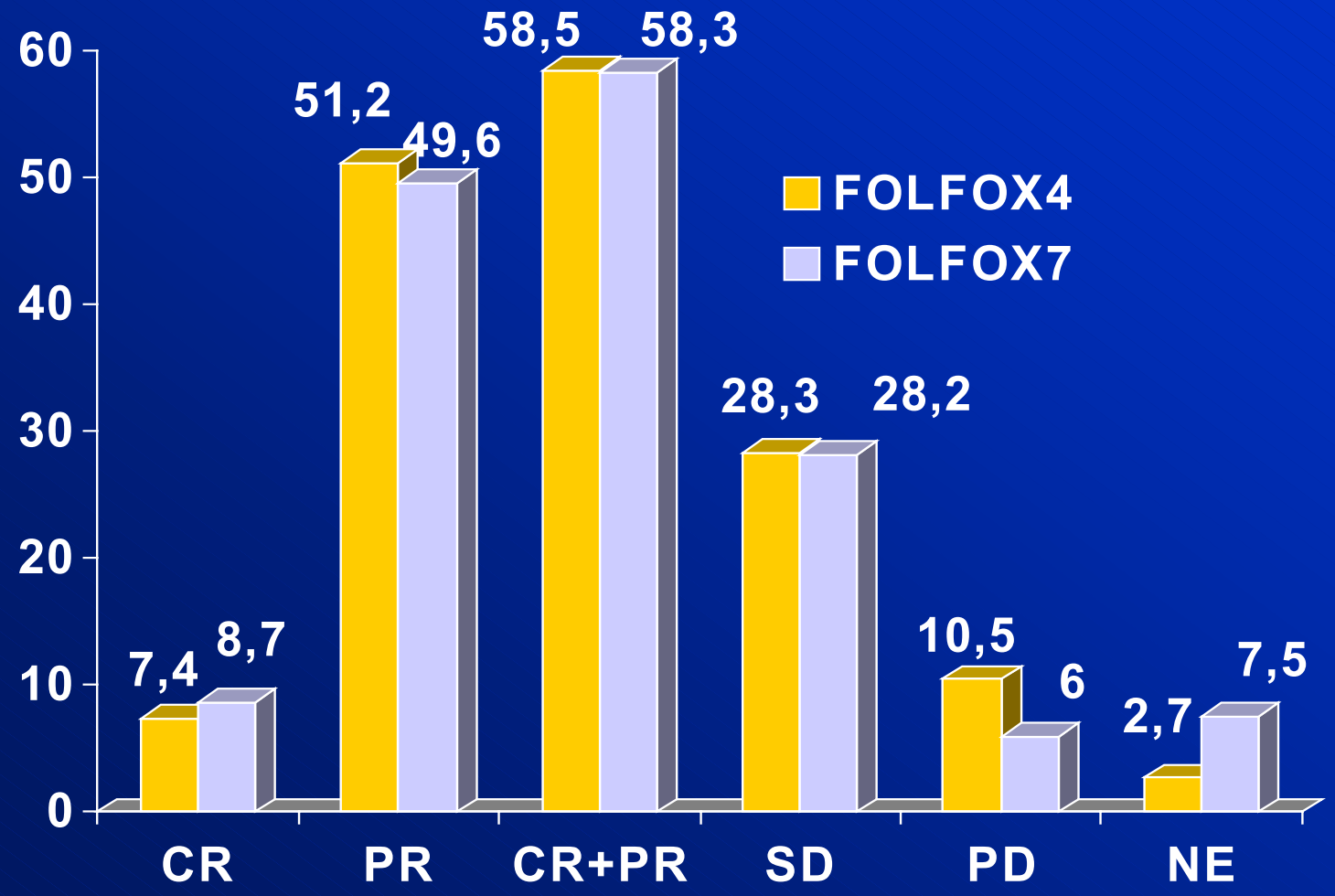
Cycles > 6



OPTIMOX 1 Progression-free Survival

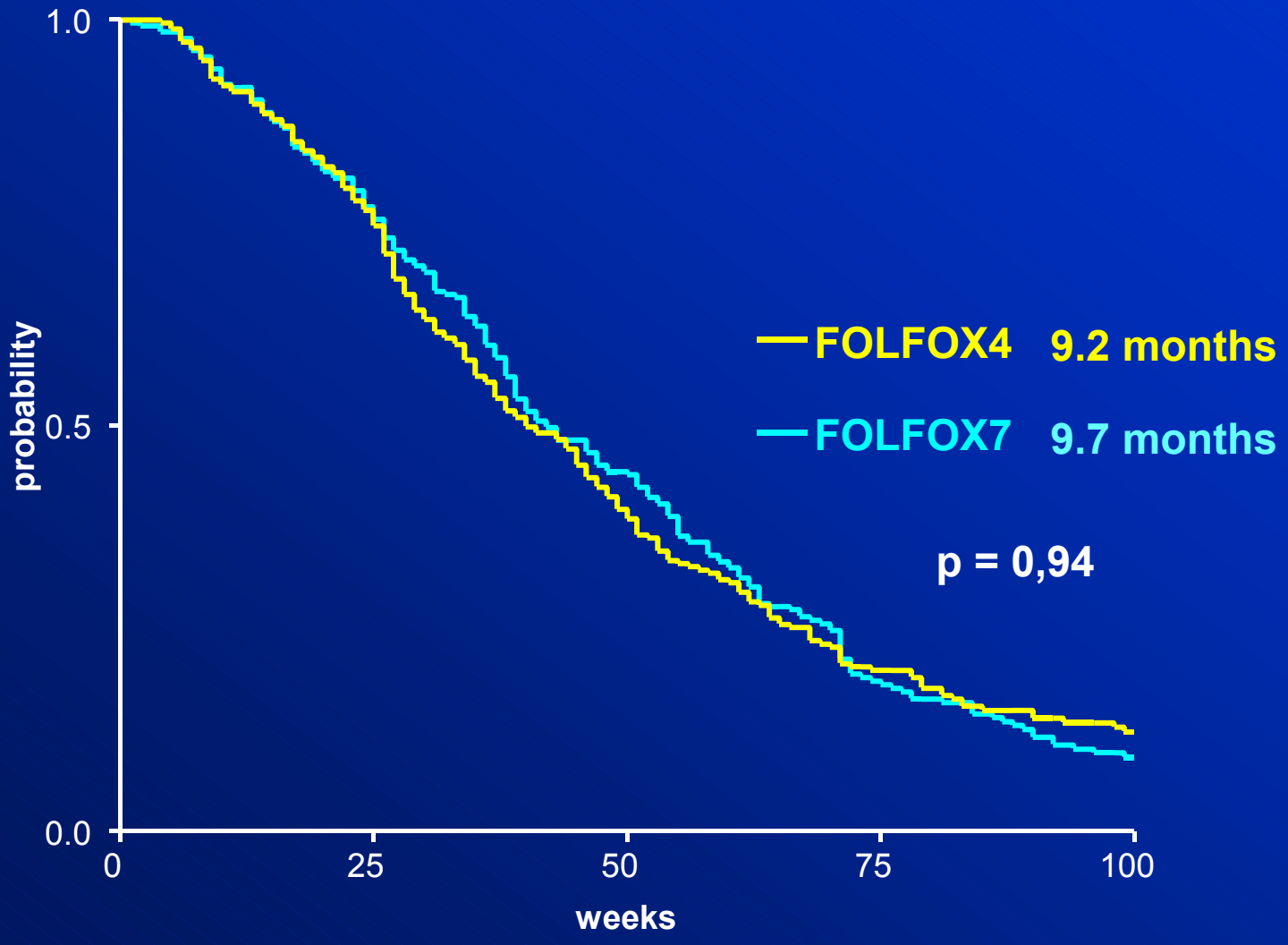


OPTIMOX 1 Responses

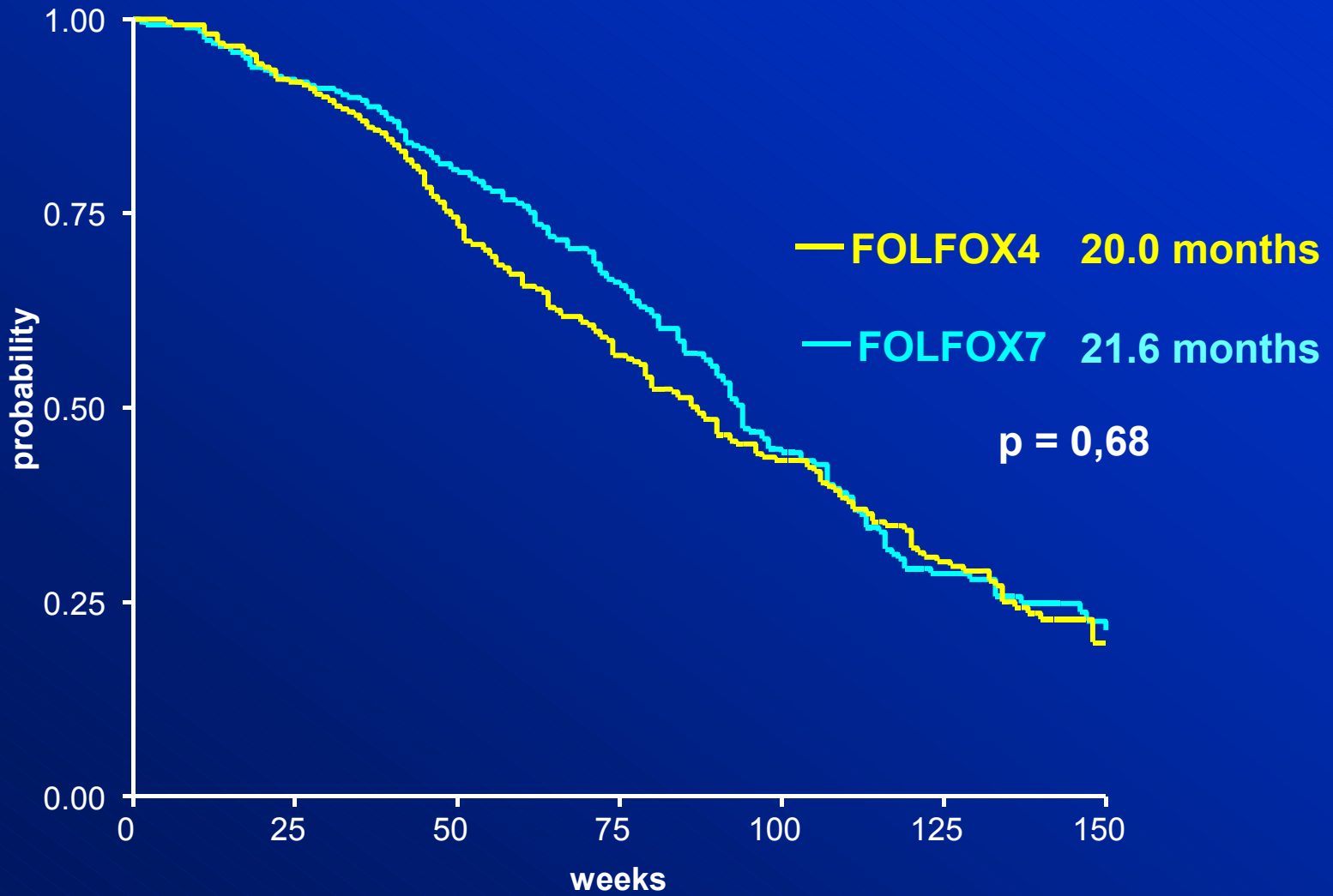


Response was evaluated at 4 and 6 cycles then every 3 months.

OPTIMOX 1 Duration of Disease Control with oxaliplatin

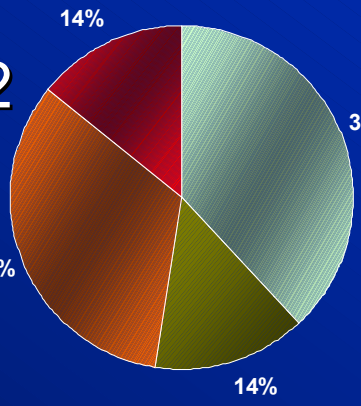


OPTIMOX 1 Overall Survival

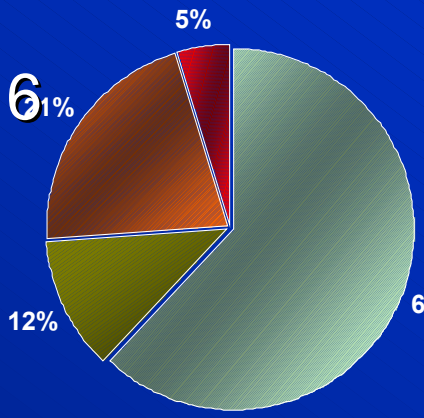


OPTIMOX 1 Reintroduction among Centres

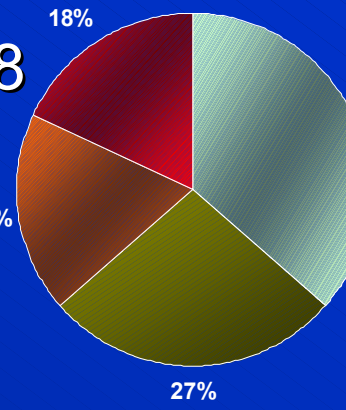
centre 2
N=40
A 22%
B 39%



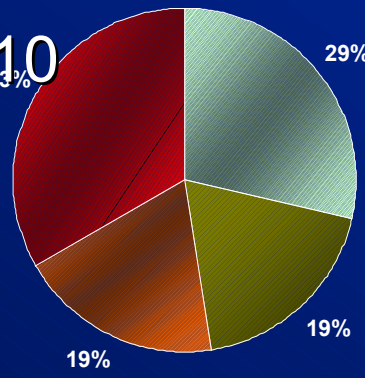
centre 6
N=85
A 50%
B 62%



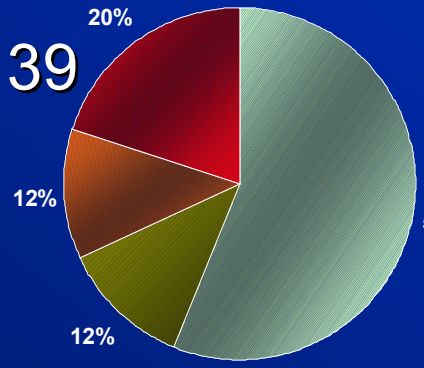
centre 8
N=42
A 20%
B 37%



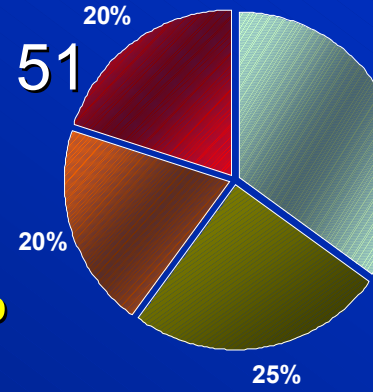
centre 10
N=45
A 42%
B 29%



centre 39
N=48
A 17%
B 56%

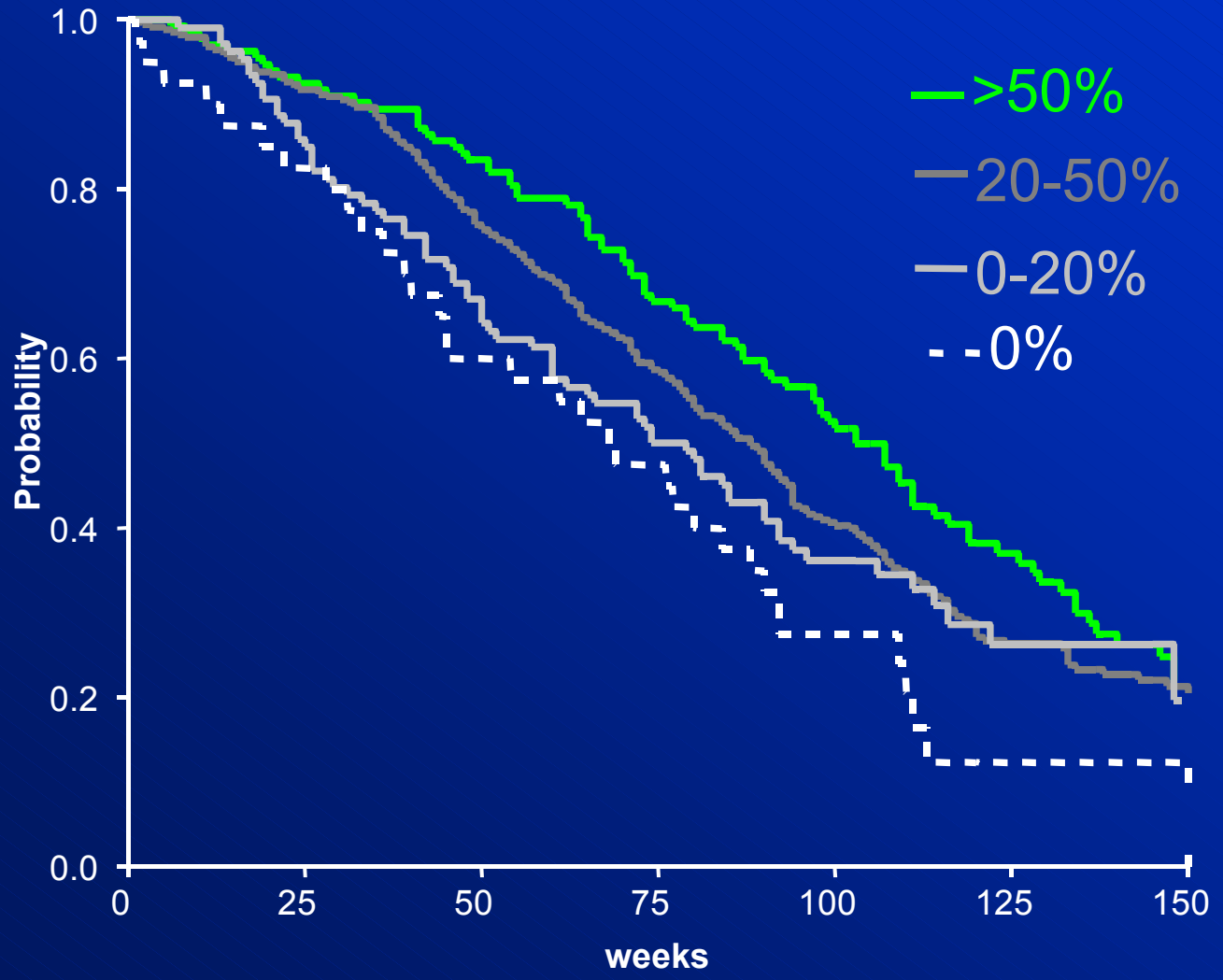


centre 51
N=48
A 4%
B 35%

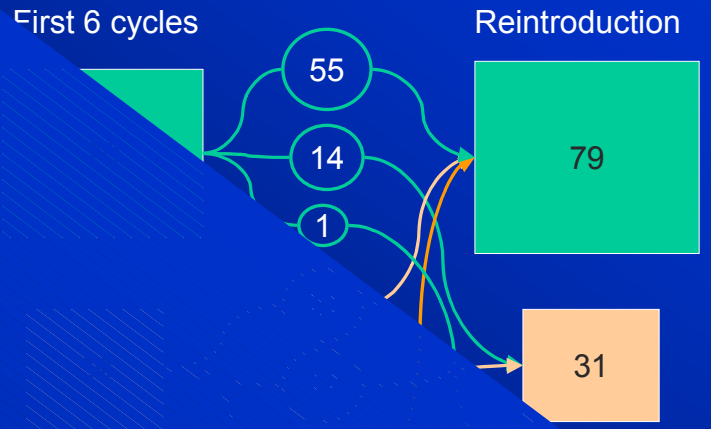


Arm B ■ reintroduction ■ toxicity ■ prog or death ■ no reason

OPTIMOX 1 Survival according to % of reintroduction into centers



Reintroduction and neurotoxicity



SURGERY

FOLFOX4				FOLFOX7			
all	%	RO	%	all	%	RO	%
39	14.9%	20	7.6%	43	16.3%	23	8.7%

OPTIMOX 1 Multivariate Analysis

- Performance status
- No. metastatic sites
- LDH
- Alk phosphatases
- Reintroduction

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Dr P. ARAMBURU	
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Dr C. BOAZIZ	Sa…
Dr D. BARBERAU	Tours, …
Dr J.R. BARCELO	Barakaldo, …
Dr M. BENNAMOUN	Montfermeil, Fra…
Dr C. BOREL	Strasbourg, France
Dr O. BOULAT	Avignon, France
Dr B. BRUN	Paris, France
Dr B. CALLET	Neuilly s/ S, France
Dr E. CAROLA	Senlis, France
Dr S. CATTAN	Paris, France
Dr A. CERVANTES	Valencia, Spain
Pr M. CLEMENS	Trier, Germany
Dr P. COLIN	Reims, France
Dr M.A. COULON-SFAIRI	Le Mans, France
Pr A. de GRAMONT	Paris, France
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Dr G. GANEM	Le Mans, France
Dr F. GUINET	Paris, France
Dr J. HANSEN	Vasteras, Sweden
Dr …	…
Dr J.R.	…
Dr P. MEY…	…
Dr L. MINEUR	…
Dr R. MOSER	…
Dr J. NEUMANN	…
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Dr S. SKULLMAN	Skovde, Sweden
Dr G. STEGER	Wien, Austria

OPTIMOX 1 Conclusions

- 6 cycles of FOLFOX7 followed by simplified LV5FU2 achieved identical response rate and progression-free survival than FOLFOX4. Oxaliplatin high dose-intensity is not a major issue in first-line therapy. Less neutropenia but more thrombocytopenia were observed with FOLFOX7. However, patients benefited from a less demanding regimen and from less toxicity after the 6 first cycles.
- Duration of disease control and overall survival were not improved with the new strategy. However, this might be due to a lower oxaliplatin reintroduction rate than expected (56%: 46% per protocol and 10% later) in the FOLFOX7 arm, in part explained by protocol violations (21%), and a high reintroduction rate in the FOLFOX4 arm (27%).
- Oxaliplatin reintroduction did not increase the incidence of neuropathy.
- A different attitude towards reintroduction was found between centers which can explain a strong center effect and suggests that oxaliplatin reintroduction (early or late) prolongs survival. Analyses are ongoing to further evaluate oxaliplatin reintroduction.