

Raltitrexed and oxaliplatin plus  
radiotherapy as adjuvant treatment  
in stage II-III rectal cancer:  
a dose-finding study.

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# Background.

- ✓ Neoadjuvant radiotherapy  $\Rightarrow$  standard treatment in rectal cancer
- ✓ Adjuvant radio-chemotherapy evaluated in a subgroup of pts:
  - TN stage underestimated by diagnostic workup (cT2  $\Rightarrow$  pT3, cN0  $\Rightarrow$  N+)
  - Tumour perforation
  - Surgeons working in hospital outside RT Centre
  - p II-III intraperitoneal rectal cancer

# Background.

- ✓ Norway and HCOG trials: effectiveness of post-op RT-5FU x 2 cycles over surgery alone or post-op RT-5FU x 6 cycles

Tveit et al, Br J Surg 1997; Fountzilas et al, Ann Oncol 1999

- ✓ Post-op RT plus 5FU  $\Rightarrow$  suboptimal patients “compliance” (60-70%) and severe acute toxicity  $\geq$  grade III (20-65%)

GITSG, Mayo-NCCTG, INT 0114, INT 0144

# Dose escalation study design.

Stage II-III radically resected (R0) rectal cancer

- Weekly clinical evaluation and laboratory tests
- Acute toxicity assessment → RTOG scale
- Written informed consent
- Study approval by the local Ethics Committee

RT 54 Gy (45 Gy to the pelvis  
+ 9 Gy boost dose to the site  
of resected tumour)

Raltitrexed 3 mg/mq/iv, d 1, 22 RT

Oxaliplatin at four dose levels  
(**65-85-110-130** mg/mq/iv) d 1, 22 RT

# Primary endpoint.

- Determine the **recommended dose (RD)** of **oxaliplatin** in combination with fixed doses of raltitrexed and adjuvant RT according to a dose finding rules.
- **RD**: defined as the dose level of oxaliplatin below the Maximum Tolerated Dose (MTD)
  - **MTD**: defined as the dose of oxaliplatin causing limiting toxicity in  $\geq 50\%$  of pts treated (i.e. at least 3 of a 6-pt cohort)
- **DLT of oxaliplatin**: either grade 3-4 haematological or gastrointestinal or neurological toxicity



# Oxaliplatin dose levels: pts enrolment

<b>Dose Level</b>	<b>Oxaliplatin</b>	<b>Raltitrexed</b>	<b>RT dose</b>	<b>No. Pts</b>	<b>No. Pts with DLT</b>
<b>I</b>	65	3	50.4-54Gy	3	0
<b>II</b>	85	3	50.4-54Gy	3	0
<b>III</b>	110	3	50.4-54Gy	3	0
<b>IV</b>	130	3	50.4-54Gy	6	0

# Acute toxicity according to oxaliplatin dose levels.

<b>Toxicity</b>	<b>Grade RTOG</b>	<b>Level I</b>	<b>Level II</b>	<b>Level III</b>	<b>Level IV</b>
<b>Diarrhoea</b>	<b>1</b>	-	-	2	2
	<b>2</b>	3	3	-	3
<b>Leukopenia</b>	<b>1</b>	1	-	-	2
	<b>2</b>	1	2	1	2
<b>Liver</b>	<b>1</b>	1	2	1	2
	<b>2</b>	1	-	-	2
<b>Nausea / vomiting</b>	<b>1</b>	2	2	1	1
	<b>2</b>	-	-	-	-
<b>Proctitis</b>	<b>1</b>	-	-	2	2
	<b>2</b>	3	3	-	3

# Patient compliance.

- 93% (14/15) of patients **completed** treatment
- **Radiotherapy**: 100% (9 pts 54Gy; 6 pts 50.4Gy)
- **Chemotherapy**: 93% (1 pt did not received the second cycle due to grade 2 protracted leukopenia)

# Conclusions.

- ✓ Importance of methodology in exploring new combination therapies
- ✓ DLT of oxaliplatin not reached at the maximum dose level (IV)
- ✓ Recommended dose of oxaliplatin plus raltitrexed and RT → 130mg/mq/ev every 3 weeks
- ✓ Treatment regimen → feasible and well tolerated