# Preventive effect of Carbamazepine for neurotoxicity of modified FOLFOX6 of metastatic colorectal cancer (mCRC) : a prospective phase II study (OGSG 0603 study)

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SCIENCE AND MULTIDISCIPLINARY MANAGEMENT OF GI MALIGNANCIES

# Background

- FOLFOX (oxaliplatin plus 5-fluorouracil and leucovorin) is a standard first-line therapy for mCRC[1,2]
- The main dose-limiting toxicity of oxaliplatin is Neurotoxicity
- Oxaliplatin alters voltage-gated Na(+) channel kinetics on sensory neurons[3]
- It is Suggested that neurotoxicity could be antagonised by Na(+) channel blocker carbamazepine [4]
- Randomized phase II study of carbamazepine was performed, but it could not prove the definite efficacy and safety of CABR for prevention of OHP-associated neurotoxicity because of the small number of patients[5]


1 de Gramont A, et al. J Clin Oncol 2000,18, 2938-2947
2 Gracchetti S, et al. J Clin Oncol 2000,18, 136-147
3 Grolleau F, et al. Jneurophysiol 2001, 85, 2293-2297
4 Adelsberger H, et al. Eur J Pharmacol 2000, 406, 25-32
5 Delius, et al. Invest New Drugs 2007,25,173-180

# Oxaliplatin-associated neurotoxicity

- Acute neurotoxicity :
  - Transient oro-facial-laryngeal or peripheral neuropathy
  - Neuromuscular manifestations (# myotonia, channellopathies)
  - Triggered or exacerbated by cold
- Chronic neurotoxicity :
  - Sensory peripheral neuropathy
  - Cumulative, dose-related
  - Generally resolves slowly when treatment is discontinued

# Objective and endpoints

- **Objective**

  **To evaluate the safety and efficacy of the of the carbamazepine for the neurotoxicity caused by FOLFOX**

- **Endpoint**

  **Primary:**

  **Neurotoxicity frequency of accumulation dose 500mg/m$^2$ of L-OHP**

  **Secondary:**

  1. **TTF：time to treatment failure**
  2. **Neurotoxicity incidence**
  3. **The median of the L-OHP total dose**
  4. **Tumor response rate based on application of RECIST**
  5. **Others**

# Statistical considerations

- Neurotoxicity of the accumulation dose of Oxaliplatin=75-85%
- The incidence of the neurotoxicity is expected with 40-50% by carbamazepine
- Two-sided $\alpha$=0.05, statistical power=80%

  25 evaluable patients needed

  – *Calculated by the method of Fischer exact

Continuation rate of 6 cycles of mFOLFOX6 to be 80%.

Then the number of the necessary cases becomes

<u>35 patients.</u>

# Eligibility criteria

1. Histologically and/or cytologically proven colorectalum cancer
2. Previous treatment or not does not matter（except for Oxaliplatin）
3. Ability to take oral medication.
4. Age: 20- 75.
5. PS (ECOG scale): 0, 1, 2.
6. No other serious concomitant disease.
7. Adequate organ function (bone marrow, heart, lung, liver, kidney, etc.).

| | | | |
|---|---|---|---|
| ✓Leukocyte(WBC) | 3,000-12,000/$mm^3$ | ✓AST | 2.5 UNL or less |
| ✓Neutrophil(Neu) | 1,500/$mm^3$ or more | ✓ALT | 2.5 UNL or less |
| ✓Platelet(Plt) | 100,000/$mm^3$ or more | ✓Total bilirubin(T-Bil) | 1.5 UNL or less |
| ✓ALP | 2.5 UNL or less | ✓Serum creatinine(Ccr) | UNL or less |

8. Written informed consent.

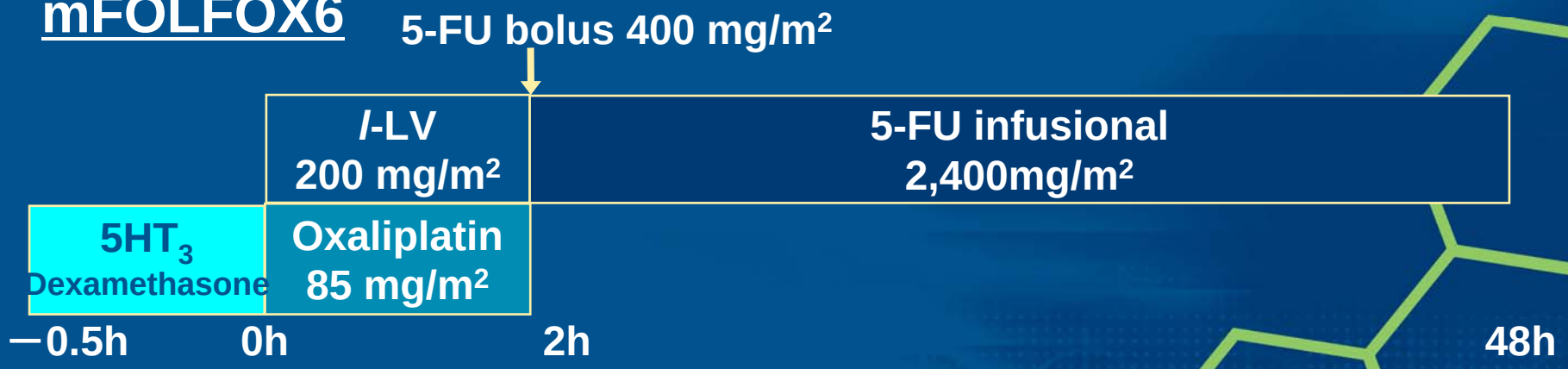
# Schedule for Treatment

**Carbamazepine :**

**100mg was orally administrated twice a day for 7 days from day 1 every 2 weeks.**

**By a symptom, increase a dose in quantity to 800mg a day.**

**mFOLFOX6**



# Evaluation of the toxicity

- **Neurotoxicity :**

  **Divided it into Acute and Chronic, and judged the neurotoxicity according to DEB-NTC.**

  **DEB-NTC**

  **Grade 1: within 7 days**

  **Grade 2: more than 7 days**

  **Grade 3: persistent functional impairment**

- **Others: CTCAE ver3.0**

# Patient Characteristics

| | |
|---|---|
| Sex： Male/Female | 26/9 |
| Age： Median［Range］ | 65［38 – 74］ |
| PS(ECOG)： 0 / 1 | 30 / 5 |
| Measurable disease： Yes / No | 18 / 17 |
| Histology： wel / mod / por / muc | 7 / 25 / 2 / 1 |
| Metastatic： Yes / No | 31/4 |
| Site ： Liver / Lung / Lymph node / Others | 17 / 9 / 7 / 8 |
| Prior Chemotherapy： | |
| 0/1～ | 12/23 |

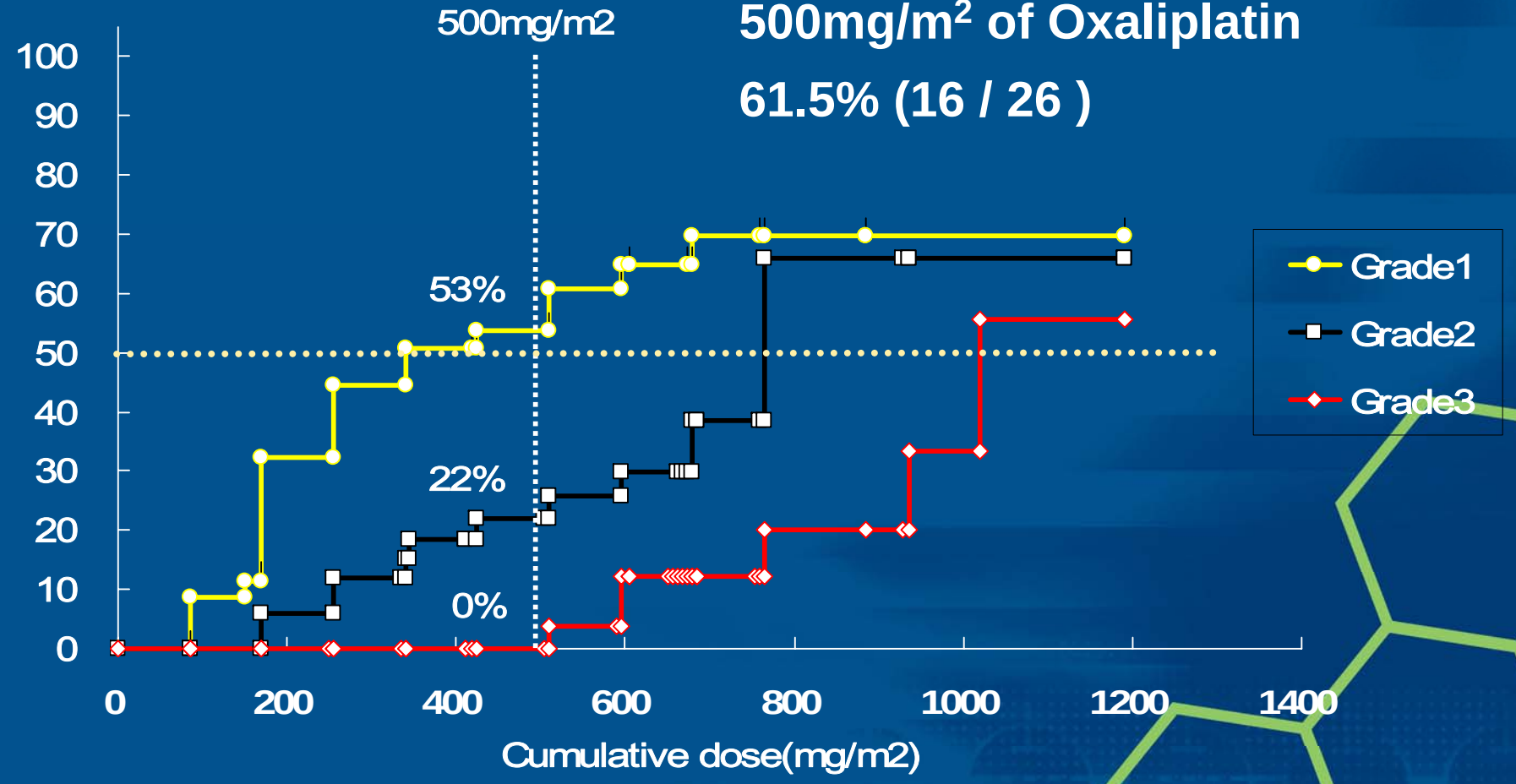
# Dosage situation

| | |
|---|---|
| **Number of Cycle** | |
| **—Overall** | **271** |
| **—Median[Range]** | **8[1～14+]** |
| **Accumulation dose of Oxaliplatin** | |
| **—Median[Range](mg/m$^2$)** | **680[85～1190+]** |
| **More than 500mg/m$^2$ (pts.)** | **26/35 (74.3%)** |
| **Dosage postponement** | |
| **—Cycles** | **57/271 (21.0%)** |
| **Dosage reduction(L-OHP)** | |
| **—Cycles** | **4/35 (11.4%)** |

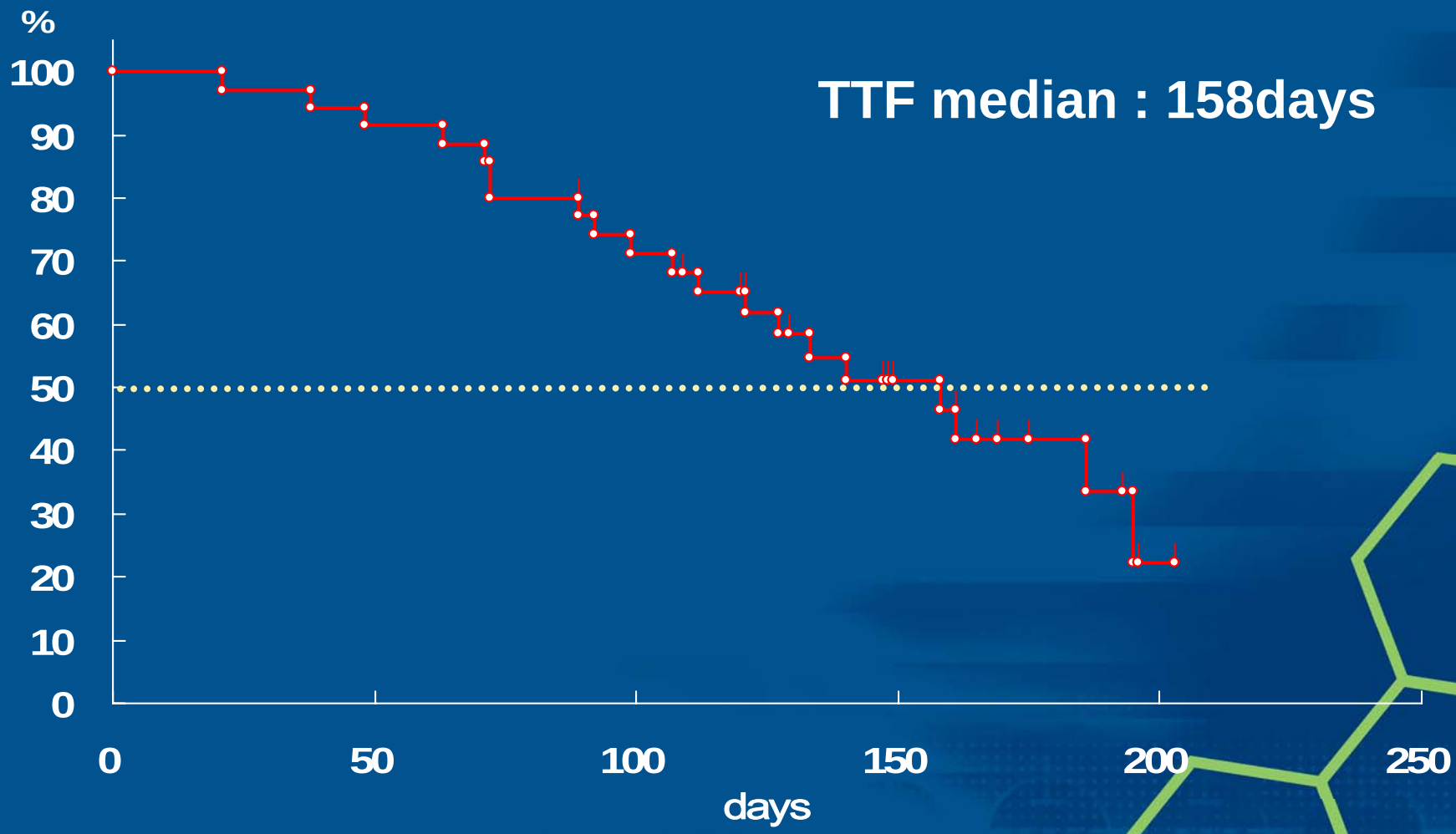
# Chronic Neurotoxicity

**Frequency of accumulation dose 500mg/m$^2$ of Oxaliplatin**

**61.5% (16 / 26 )**



# Time to Treatment Failure



# Response rate

| | CR | PR | SD | PD | Total | Response rate |
|---|---|---|---|---|---|---|
| Overall | 0 | 7 | 9 | 2 | 18 | 38.8% |
| 1st line | 0 | 5 | 2 | 0 | 7 | 71.4% |
| 2nd line~ | 0 | 2 | 7 | 2 | 11 | 18.2% |

（Except for 17 pts.without measurable disease）

**Overall response rate 7/18 = 38.8%**

# Frequency of common Toxcities

| | Grade | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | ≧G3 |
| Hemoglobin | 54.3% | 5.7% | 0% | 0% | 0% |
| Leukocytes | 42.9% | 25.7% | 8.6% | 2.9% | 11.5% |
| Neutrophils | 37.1% | 20.0% | 17.1% | 11.4% | 28.5% |
| Platelets | 51.4% | 17.1% | 0% | 0% | 0% |
| Febrile neutropenia | - | - | 2.9% | 0% | 2.9% |
| Chronic neurotoxicity | 28.6% | 28.6% | 17.1% | - | 17.1% |
| Acute neurotoxicity | 51.4% | 11.4% | - | - | - |
| Nausea | 37.1% | 25.7% | 2.9% | 0% | 2.9% |
| Vomiting | 8.6% | 14.3% | 0% | 0% | 0% |
| Anorexia | 37.1% | 34.3% | 2.9% | 0% | 2.9% |
| Fatigue | 8.6% | 8.6% | 0% | 0% | 0% |
| Diarrhea | 8.6% | 0% | 2.9% | 0% | 2.9% |
| Hypersensitivity | 5.7% | 0% | 0% | 0% | 0% |
| Dizziness | 5.7% | 0% | 0% | 0% | 0% |

Maximum toxcity per patient.

# Reasons for treatment discontinuation of non-PD

| Reasons | pts. | |
|---|---|---|
| Neurotoxicity | 3 | 12.5 % |
| Myelosuppression | 4 | 16.7 % |
| Resection | 5 | 20.8 % |
| Hypersensitivity | 2 | 8.3 % |
| Pts. refusal | 5 | 20.8 % |
| Others* | 5 | 20.8 % |

# Consideration: Neurotoxicity frequency of accumulation dose 500mg/m$^2$ of Oxaliplatin

| | OGSG 0603 | Nagase*1 | Gamelin*2 | |
|---|---|---|---|---|
| Regimen | mFOLFOX6 | mFOLFOX6<br>FOLFOX4 | FOLFOX4<br>FOLFOX6<br>FUFOX | |
| Pts. | 26 | 39 | 96 | 65 |
| Treatment of the support | carbamazepine | Ca/Mg | Ca/Mg | non |
| All Grade（%） | 61.5 | 48.7 | 51 | 86 |
| Grade2（%） | 15.4 | 10.3 | — | — |
| Grade3（%） | 3.8 | 0 | 0 | 20 |

*1 Annual Meeting of the Japan Society of Clinical Oncology PD5-4, 2007
*2 Clin Cancer Res. 10, 4055-4061, 2004

# Consideration: Total Oxaliplatin doses when 50% of patients had neurotoxicity

| | Treatment of the support | Grade1 | Grade2 |
|---|---|---|---|
| Trial in japan*1 | None | 255 | 765 |
| N9741*2 | | 250 | 750 |
| OGSG 0603 | Carbamazepine | 340 | 765 |

Total Oxaliplatin doses ($mg/m^2$)

*1 Yakult Honsha
*2 J Clin Oncol 22, 23-30, 2004

# Consideration: Comparison of the efficacy

| | OGSG 0603 | N9741*[1] | Nagase*[2] |
|---|---|---|---|
| Regimen | mFOLFOX6 | FOLFOX4 | mFOLFOX6 |
| Chemo. line | 1st or 2nd | 1st | 1st |
| n | 35 | 267 | 39 |
| Treatment of the support | Carbamazepine | None | Ca/Mg |
| TTF median | 5.6mo. | 5.8mo. | 5.8mo. |
| Response rate | 38.8%<br>71.4%(1st) | 45% | 48% |

*1 J Clin Oncol 22, 23-30, 2004
*2 Annual Meeting of the Japan Society of Clinical Oncology PD5-4, 2007

# Consideration: Reasons for treatment discontinuation of non-PD

| Reasons | OGSG 0603 | N9741 |
|---|---|---|
| Neurotoxicity | 12.5 % | 23% |
| Myelosuppression | 16.7 % | 23% |
| Resection | 20.8 % | 9% |
| Hypersensitivity | 8.3 % | 7% |
| Pts. refusal | 20.8 % | 29% |
| Others | 20.8 % | 9% |

*2005 Gastrointestinal Cancers Symposium, Abstract - No. 182

# Summary

- With carbamazepine,neurotoxicity frequency of accumulation dose 500mg/m2 of Oxaliplatin was 61.5%.
- TTF was 5.6 months and the overall response rate was 38.8%.
- Median cumulative oxaliplatin doses was 680mg/m2 and median treatment courses was 8.

# Summary

- Total oxaliplatin doses when 50% of patients experienced grade 1 neurotoxicities was 340mg/m$^2$.
- Neurotoxicity accounted for 12.5% of the reason for discontinuation of non-PD,that was lower than N9741 study.

# Conclusions

- It was suggested that carbamazepine might delay the incidence of cumulative neurotoxicities.
- It was suggested that carbamazepine might reduce the reason for discontinuation of neurotoxicity.