GASTROINTESTINAL TUMORS, NON-COLORECTAL

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DISCLOSURES

• Eli-Lilly
• Celgene
• Sanofi-Aventis
• Merck
• Roche
Treatment

HR = 0.90 (0.74 to 1.09)
Log rank test p = 0.285

Survival Probability

By treatment

Placebo - median OS = 3.60m
Gefitinib - median OS = 3.73m

By performance status

PS0 - HR = 1.00
PS1 - HR = 1.40 (1.10, 1.78)
PS2 - HR = 2.98 (2.22, 3.98)
Log rank test p < 0.0001

PS0 - median OS = 6.03m
PS1 - median OS = 3.93m
PS2 - median OS = 1.97m

COG 2012

ESMO 29th Sept 2012
Conclusions

- COG is the first RCT in the second line setting in esophageal cancer
- The primary end point of OS was not met
- The dominant effect of PS on PFS and OS has been demonstrated for the first time
- The trial demonstrated positive secondary end point of PFS with HR 0.79, P = 0.017
- Significant relief of odynophagia in the gefitinib arm (p=0.004)
- The disease control rate was 26% at 8 weeks (P = 0.014) on Gefitinib and durable responses were seen
- There were no new or worrying safety signals
- The translational research project TRANSCOG will analyse predictive biomarkers in over 300/450 patients biopsies and give guidance to identification of the patients most likely to benefit from this treatment modality

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GASTRIC CANCER

Stratification:
- Center
- Measurable lesion (RECIST)

N = 628

Primary endpoint: OS
Secondary endpoints: PFS, RR, Safety

Docetaxel 40 mg/m² on Day 1
S-1 80 mg/m² on Days 1–14
q 3 weeks

S-1 80 mg/m² on Days 1–28
q 6 weeks

Until disease progression
Overall Survival

**Log-rank p=0.0319**

**HR=0.837 (95% CI: 0.711-0.985)**
Update at ESMO 2012

• The median survival time was 12.5 months in the DS group and 10.8 months in the S-1 group (p=0.0319) (HR=0.837)

• PFS was 5.3 months in the DS group and 4.2 months in the S-1 group (p=0.001)

• RR was 38.8% in the DS group and 26.8% in the S-1 group (p=0.0048).

• Adding docetaxel to S-1 significantly improved OS, PFS and RR, nevertheless resulted in some increasing proportion of haematological toxicities. DS is a new treatment option for patients with untreated AGC...at least in Asia...
Again GASTRIC CANCER: the EXPAND trial in one slide

- Cetuximab in combination with XP (cape and CDDP)
- Large global Phase III trial (904 pts)
- Sound biological rationale
- **PFS as primary endpoint: not met** (4.4 vs 5.6 m)
- The same for the secondary endpoints
- Consistent results across subgroups
- Unfavourable risk/benefit ratio
- Biomarker analysis ongoing (97%: tissue available)
Pancreatic cancer Study TH-CR-404

Advanced Pancreatic Cancer (N=214) → Randomize 1:1:1

- Gemcitabine + TH-302 (240 mg/m²)
- Gemcitabine + TH-302 (340 mg/m²)
- Gemcitabine (1000 mg/m²)

Crossover (randomized to one of Gemcitabine plus TH-302 dose groups)

Gemcitabine + TH-302 (240 or 340 mg/m²)

Stratification: Stage (Unresectable Locally Advanced vs. Distant Metastases)

TH-302 Gem

Cycle 1
- Day 1
- Day 8
- Day 15
- Day 22

Cycle 2
- Day 29
- Day 36
- Day 42

Cycle 3...
- Day 49
- Day 56

Efficacy Assessment
Progression-Free Survival by treatment

- Gemcitabine (N= 69)
- Gemcitabine + TH-302 (240, N= 71)
- Gemcitabine + TH-302 (340, N= 74)

Gemcitabine vs Gemcitabine + TH-302 (240)
HR: 0.655 (95% CI: 0.46 – 1.02)
Log-rank test: p = 0.060

Gemcitabine vs Gemcitabine + TH-302 (340)
HR: 0.589 (95% CI: 0.40 – 0.88)
Log-rank test: p = 0.008

Med: 3.6
Gemcitabine alone

Med: 6.0
TH-302 240 + Gemcitabine
Study TH-CR-404
Gemcitabine versus Gemcitabine + TH-302 (340 mg/m²)

Consistent TH-302 Dose Effect

• Efficacy
  – PFS primary efficacy endpoint reached (median 3.6 mo to 6.0 mo)
  – Increase in response rate (10% to 26%)
  – Greater mean decrease in CA19-9 (523 U/L versus 5385 U/L)
  – Open label crossover study not designed for estimating OS treatment effect
    • Increase in median OS (6.9 mo to 9.2 mo)
  – Longer survival after crossover randomization (2.6 mo to 13.4 mo*)

*240 mg/m² crossover vs. 340 mg/m² crossover
Comment

Strenghts

• Cytotoxic drug
• New way of action
• Positive results
• Consistent results
• Favourable toxicity profile

Weaknesses

• Mixed population of LAPC and metastatic
• Another Gem vs Gem + XX without biological selection
• Hematological toxicity
HCC: the SEARCH trial

- **Objective**
  - To compare the efficacy and safety of sorafenib plus erlotinib with sorafenib plus placebo as first-line treatment in patients with advanced/unresectable HCC

- **Design**
  - Randomized, double-blind, placebo-controlled phase III trial conducted in 26 countries in Europe, North and South America, and Asia Pacific
  - Study aim: show a 33% increase in median OS compared to sorafenib + placebo using a one-sided alpha of 0.025; a total of 521 events are required to achieve 90% power

- **Inclusion criteria similar to SHARP and AP studies**
  - Advanced HCC
  - Child-Pugh A
  - PS 0, 1

- **Stratifications**
  - ECOG PS
  - Geographic region
  - Vascular invasion/
    - Extrahepatic spread
  - Smoking

- **Treatment arms**
  - Sorafenib 400 mg bid + Placebo 150 mg qd
  - Sorafenib 400 mg bid + Erlotinib 150 mg qd

- **Primary endpoint:**
  - OS

- **Secondary endpoints:**
  - TTP
  - DCR
  - Safety
Conclusions

- This trial did not meet its primary endpoint; The addition of erlotinib to sorafenib did not significantly prolong OS (HR 0.929) or TTP (HR 1.135) in the overall study population.

- The delivered daily doses of sorafenib plus erlotinib or placebo were all similar in the two study arms, however, treatment duration in the combination arm was shorter.

- ORR tended to be higher in the sorafenib plus erlotinib arm (p=0.051), whereas DCR was significantly higher in the sorafenib plus placebo arm (p=0.0104).

- The study confirmed the known safety profiles of sorafenib and erlotinib, however, increased toxicity was observed in the sorafenib + erlotinib arm.

- Further insight could come from ongoing Biomarker and PK analyses.

- Sorafenib monotherapy remains the standard of care in unresectable HCC.
GI non-colorectal at a glance

- Not so many studies
- Good quality trials (registrative but also independent)
- Difficult funding
- Mixed results (positive: gastric and pancreatic; negative: gastric again and HCC; mixed: esophageal…)
- More hypothesis generating that practice changing
- Increased role of biological characterization: personalized medicine!
- A lot of work to do