LOCALLY ADVANCED OESOPHAGO-GASTRIC JUNCTION CANCER

Radka Obermannova, MD, PhD
Grant/Research Support: Czech Health Research Council, Merck

Consultant: Servier, Sotio, Merck

Speaker’s Bureau: Eli Lilly, BMS, Merck, Roche
43 years old male patient
No family history
No medical history, only bipolar disorder currently asymptomatic
PS1
No smoking, no alcohol,
Lawyer, marathon runner, married, 2 children
Difficulties of swallowing

Weight loss 6kg/4months

Tiredness

Anorexia

At the time of diagnosis: height 176cm, weight 66 kg, BMI 21.3
Q1: Diagnostics in gastric/OGJ cancer

Endoscopy: Siewert II tumour, adenocarcinoma G3, HER 2 negative

Standard investigations?
- Endoscopic ultrasound (EUS)
- CT or PET/CT
- All of above
- Exploratory laparoscopy
- No additional investigations

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SIEWERT CLASSIFICATION

Schneider PM et al. *Springer Cham* 2017
DIAGNOSIS NOVEMBER 2016

Endoscopy: Siewert II tumour
Histology: adenocarcinoma G3
HER2 negative
Endoscopic ultrasound: cT3N2M0
PET/CT scan: no metastases

Operable OGJ cancer
cT3N2(PET/CT)M0, stage IIIB
Q2: NEXT STEPS?

- Perioperative chemotherapy
- Neoadjuvant chemoradiotherapy
- Upfront surgery, adjuvant chemotherapy
- Upfront surgery/adjuvant chemoradiotherapy

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Q3: NEXT STEPS- PERIOPERATIVE TREATMENT

3 cycles of ECF 2-6/2016
Side effects: vomitus G1, neuropathy G2, weight loss
Effect:
Clinically: weight loss, symptoms withdrawal
CT: SD according to RECIST
Surgery July 2016:
Perioperative Therapy

**UK MAGIC 2006**
- Stomach Cancer 74%
- EGJ +DE Cancer 26%
- 5-y-OS: 36% vs 23%
- ECF

**French FNCLCC 2011**
- Stomach Cancer 25%
- EGJ+DE Cancer 75%
- 5-y-OS: 38% vs 24%
- 5-FU

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PERIOPERATIVE TREATMENT /REGIMENS/

- Doublets: 5-FU/cisplatin or FOLFOX
- Triplets ECF was substituted by FLOT or modifications with docetaxel in fit patients or non-elderly

French FNCLCC 2011

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**PERIOPERATIVE TREATMENT /REGIMENS/**

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<table>
<thead>
<tr>
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<th>ECF/ECX</th>
<th>FLOT</th>
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<tbody>
<tr>
<td>mOS</td>
<td>35 months</td>
<td>50 months</td>
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<td>[27-46]</td>
<td>[38-na]</td>
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<td>p</td>
<td>0.012 (log rank)</td>
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Al-Batran et al. *ASCO* 2017; abstract 4006

- OS rate* ECF/ECX FLOT
- 2y 59% 68%
- 3y 48% 57%
- 5y 36% 45%
Q3: Next steps- postoperative treatment?

**Transthoracal Oesophagectomy**
**Adenocarcinoma G3, ypT3N2(6/15LN)M0, Mandard TRG 4, HER2negative**

*Radka Obermannova, MMCI*

**Treatment standard – postoperative chemotherapy**
Q3: NEXT STEPS- POSTOPERATIVE TREATMENT?

Treatment standard – postoperative chemotherapy
Q3: NEXT STEPS- POSTOPERATIVE TREATMENT?

CRITICS
(NL, Sweden)
Stage Ib-IVa

CTx (ECX) → Resection → Radio-CTx
CTx (ECX) → Resection → CTx (ECX)

Q3: Next steps- postoperative treatment

VESTIGE STUDY

EORTC 1707 (start 2019)

DESIGN

Resectable OG cancer

CHEMO

SURGERY

N+/R1 or both

Standard chemotherapy

Adjuvant ipilimumab + nivolumab

1:1 randomisation

Lordick F et al, EORTC GI Group 2017
POSTOPERATIVE TREATMENT

- 3 cycles of ECF by June 2017
- ....according to treatment standard
- Side effects: vomitus G1, neuropathy G2,
- After chemotherapy patient clinical conditions were PS 1, weight loss 16 kg, no symptoms
DISEASE RELAPSE …… OCTOBER 2017
(3 MONTHS AFTER COMPLETION OF POSTOPERATIVE CHEMOTHERAPY ECF)

- PS1, weight 61kg, asymptomatic
- PET/CT: 2 lung lesions 8-10mm in diameter, mets suspected
- Referred to our center for trial treatment with PD-L1

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Q3: NEXT STEPS: OPERABLE 2 NEW LUNG LESIONS IN BOTH LUNGS

- Palliative chemotherapy
- Surgery because of operable lesions and unclear etiology
- WW strategy and CT in 2 or 3 months
- Other options?

  Local methods- STX? Radiofrequency ablation?

Disease recurrence 3 months after completion of primary treatment

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CT scan January 2018
Complete remission of described 2 lesions but new 3 lesions in both lungs

CT scan May 2018
2 lesions mets? in progression– accessible for histological verification

VATS June 2018- adenocarcinoma G2, HER2 amplification, PD-L1 negative, pMMR
CENTRAL VALIDATION OF HER2 IN GASTRIC CANCER: HIGH HETEROGENEITY IN HER2 EXPRESSION AND ITS IMPACT ON SURVIVAL

VARIANZ-Study
548 pts with advanced gastric cancer enrolled
Target: 50 HER2-positive gastric cancer pts treated with chemoTx + trastuzumab

Patient recruitment

Visit 1
Start 1st line treatment

Visit 2-5
every 12 months

Central HER2 evaluation

HER2 immunohistochemistry
(IHC/ DCS, CB11, HI608C0I)

HER2 amplification
(CISH/ Zytomed Syst., C-3022-40)

Haffner I, IGCC 2019
Courtesy Florian Lordick
514 patients have been tested for HER2 by central pathology

- **green**: 90 HER2 positive tested by central pathology
- **blue**: 424 HER2 negative tested by central pathology

79 of 369 reports deviate to local pathology (21.4%)

- HER2 positive concordant to local report
- HER2 positive without information to local report
- HER2 positive deviating to local report
- HER2 negative deviating to local report
- HER2 negative without information to local report
- HER2 negative concordant to local report
pts. central HER2 positive trastuzumab treated vs. central HER2 negative trastuzumab treated

confirmed trastuzumab indication

unconfirmed trastuzumab indication
SINCE AUGUST 2018 SYSTEMIC TREATMENT- FIRST LINE
RESTAGING- CT SCANS

January 2019 partial remission
April 2019 complete remission
June 2019 Treatment stop because of toxicity- neurotoxicity, relaps of bipolar symptoms (brain MRI without pathology), PS2

First line: August 2018- June 2019
Trastuzumab/5-fluorouracil/folinic acid/cisplatin……trastuzumab/5-FU/folinic acid
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First line: August 2018- June 2019
Trastuzumab/5-fluorouracil/folinic acid/cisplatin……trastuzumab/5-FU/folinic acid, August 2019 clinically stable, next CT planned in September 2019
DISEASE PROGRESSION?

- Back to first line with trastuzumab
- Ramucirumab/paclitaxel
- Ramucirumab
- Chemotherapy
  - (irinotecan, docetaxel, paclitaxel, FOLFIRI)
Inoperable or metastatic gastric cancer

Psilatieve chemotherapy

HER2-negative
- Platinum + fluoropyrimidine-based doublet or triplet regimen

HER2-positive
- Trastuzumab + CF/CX

Consider clinical trials of novel agents

Second-line chemotherapy at progression

ECOG PS 0–1
- Paclitaxel + ramucirumab

ECOG PS 2
- MSI-High: Pembrolizumab or Nivolumab
- Ramucirumab monotherapy or irinotecan or taxane monotherapy

ECOG PS 3–4 or patient preference
- MSI-High: Pembrolizumab or Nivolumab (preferred)

Symptom control

Second line:?

THANK YOU FOR YOUR ATTENTION.
Neoadjuvant Therapy

Esopec

N=438
Stadium II
Stadium III

Neoadjuvant Radio-CTX – CROSS Regimen RESECTION

Primary Endpoint: OS
3-years-OS-Rate
55% CROSS vs. 68% FLOT

Neoadjuvant Chemo-Tx: FLOT Regimen RESECTION

**Perioperative Therapy**

**UK MAGIC 2006**

- Stomach Cancer: 74%
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**5-y-OS**

- Surgery alone: 36%
- ECF: 23%


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**5-y-OS**

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- 5-FU: 24%


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![Graph showing overall survival rates for surgery alone and chemotherapy in UK MAGIC 2006 and French FNCLCC 2011 studies.](image)
Perioperative Treatment for Localized Gastric Cancer AIO-FLOT

Overall Survival

**Overall Survival**

- **mOS**: 35 months vs. 50 months
  - ECF/ECX: 35 months [27-46]
  - FLOT: 50 months [38-na]

- **HR**: 0.77 [0.63 - 0.94]
  - Log rank: p=0.012

- **2y OS rate**: ECF/ECX: 59% vs. FLOT: 68%
- **3y OS rate**: ECF/ECX: 48% vs. FLOT: 57%
- **5y OS rate**: ECF/ECX: 36% vs. FLOT: 45%

*projected OS rates

**Al-Batran et al. ASCO 2017; abstract 4006**
MSI-H Gastric Cancer – Postoperative Chemotherapy

Kim SY et al. *Int. J. Cancer* 2015; 137: 819–825