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MEETING SUMMARY
ASCO 2019, Chicago, USA

Fransen McGinley, PA-C
University of Oklahoma Stephenson Cancer Center,
Oklahoma City, USA

UPDATES IN ADJUVANT, NEOADJUVANT AND METASTATIC CRC

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ADJUVANT CHEMOTHERAPY

3 VS 6 MONTHS ADJUVANT FOLFOX OR CAPOX FOR HIGH RISK STAGE II AND STAGE III COLON CANCER PATIENTS: EFFICACY RESULTS OF HELLENIC ONCOLOGY RESEARCH GROUP (HORG) PARTICIPATION TO THE INTERNATIONAL DURATION EVALUATION OF ADJUVANT CHEMOTHERAPY (IDEA) PROJECT

Sougklakos et al. ASCO 2019 Abstract #3500

PROSPECTIVE POOLED ANALYSIS OF 4 RANDOMIZED TRIALS INVESTIGATING DURATION OF ADJUVANT OXALIPLATIN-BASED THERAPY (3 VS 6 MONTHS) FOR PATIENTS WITH HIGH-RISK STAGE II CRC

Iveson et al. ASCO 2019 Abstract #3501

CAPOX, capecitabine + oxaliplatin; CRC, colorectal cancer; FOLFOX, folinic acid + fluorouracil + oxaliplatin

ADJUVANT CHEMOTHERAPY BACKGROUND

- Standard of care adjuvant chemotherapy for high-risk stage II and stage III colon cancer is FOLFOX for 6 months[1, 2]
- Significant neurotoxicity associated with 6 months of oxaliplatin
- Two studies aim to answer these questions:
  - Is 3 months of adjuvant chemotherapy inferior to 6 months?
  - Does 3 months of adjuvant chemotherapy improve toxicity over 6 months?

1. Casadaban L, et al. Cancer. 2016;122:3277-3287; 2. Andre T, et al. N Engl J Med. 2004;350:2343-2351

ADJUVANT CHEMOTHERAPY ANSWERING THE QUESTIONS

ABSTRACT 3500
IS 3 MONTHS OF ADJUVANT THERAPY AS GOOD AS 6 MONTHS IN STAGE II/III COLON CANCER?

- The **HORG-IDEA** study randomized patients with high-risk stage II and stage III colon cancer to 3 or 6 months of adjuvant FOLFOX or CAPOX
  - High-risk stage II disease was defined as: T4, obstruction or perforation, extramural vascular invasion, poorly-differentiated tumors
- Primary endpoint: 3-year DFS; non-inferiority study
- 1121 patients were included
  - One third of patients was > 70 years old
  - Baseline characteristics were well balanced
- There was a **limited difference in 3-years DFS** (0.7%) between the 3-month and the 6-month treatment group (hazard ratio [HR] 1.05)
- 3 months of adjuvant treatment resulted in **less peripheral sensory neuropathy** vs 6 months

CAPOX, capecitabine + oxaliplatin; DFS, disease-free survival; FOLFOX, folinic acid + fluorouracil + oxaliplatin

Sougklakos I, et al. Abstract #3500 Presented at ASCO 2019

ADJUVANT CHEMOTHERAPY ANSWERING THE QUESTIONS

ABSTRACT 3501
IS 3 MONTHS OF ADJUVANT THERAPY AS GOOD AS 6 MONTHS IN HIGH-RISK STAGE II CRC?

- In this prospective, pre-planned pooled analysis of four concurrent randomized phase III trials, the investigator was given choice of chemotherapy, either **FOLFOX or CAPOX**
- Patients were then randomized to either 3 or 6 months of chemotherapy
- Primary endpoint: 3-year DFS; non-inferiority study
- 3273 patients included
  - 62% received CAPOX

- Overall, non-inferiority was not shown for 3 months adjuvant treatment
- However, data strongly suggest **non-inferiority for CAPOX** and **inferiority for FOLFOX**
- 3 months of adjuvant treatment resulted in **significantly less toxicity** vs 6 months

CRC, colorectal cancer; CAPOX, capecitabine + oxaliplatin; DFS, disease-free survival; FOLFOX, folinic acid + fluorouracil + oxaliplatin
Iveson T, et al. Abstract #3501 Presented at ASCO 2019

ADJUVANT CHEMOTHERAPY TAKE-HOME MESSAGES

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- 3 months of adjuvant chemotherapy is **better tolerated** with decreased neurotoxicity
- Data strongly suggest that **3 months of CAPOX** rather than 6 months of CAPOX may be **reasonable** in patients with high-risk stage II CRC
- **3 months of FOLFOX** is **inferior** to 6 months of FOLFOX
- The choice of adjuvant chemotherapy regimen should be personalized based on the patients' disease features, social factors, performance status and financial implications

CRC, colorectal cancer; CAPOX, capecitabine + oxaliplatin; FOLFOX, folinic acid + fluorouracil + oxaliplatin

1. Sougklakos I, et al. Abstract #3500 Presented at ASCO 2019; 2. Iveson T, et al. Abstract #3501 Presented at ASCO 2019

NEOADJUVANT CHEMOTHERAPY

FOxTROT: AN INTERNATIONAL RANDOMIZED CONTROLLED TRIAL IN 1052 PATIENTS EVALUATING NEOADJUVANT CHEMOTHERAPY FOR COLON CANCER

Seymour et al. ASCO 2019 Abstract #3504

NRG-GI002: A PHASE II CLINICAL TRIAL PLATFORM USING TOTAL NEOADJUVANT THERAPY IN LOCALLY ADVANCED RECTAL CANCER – FIRST EXPERIMENTAL ARM INITIAL RESULTS

George et al. ASCO 2019 Abstract #3505

NEOADJUVANT CHEMOTHERAPY WHAT WE LEARN FROM FOxTROT

- The **FOxTROT** trial evaluated neoadjuvant chemotherapy in patients with operable, non-obstructed colon cancer
  - CT-predicted stage T3-4, N0-2, M0
  - Fit for FOLFOX and surgery
- 1052 patients were randomized 2:1
  - 6 weeks FOLFOX followed by surgery and then 18 weeks FOLFOX OR
  - Surgery followed by 24 weeks FOLFOX
  - *RAS* wild-type patients in the investigation arm could also be randomized to +/- panitumumab in the neoadjuvant phase
- **Primary endpoint**: no recurrent or persistent disease at 2 years
- Median age: 65 years

FOLFOX, folinic acid + fluorouracil + oxaliplatin

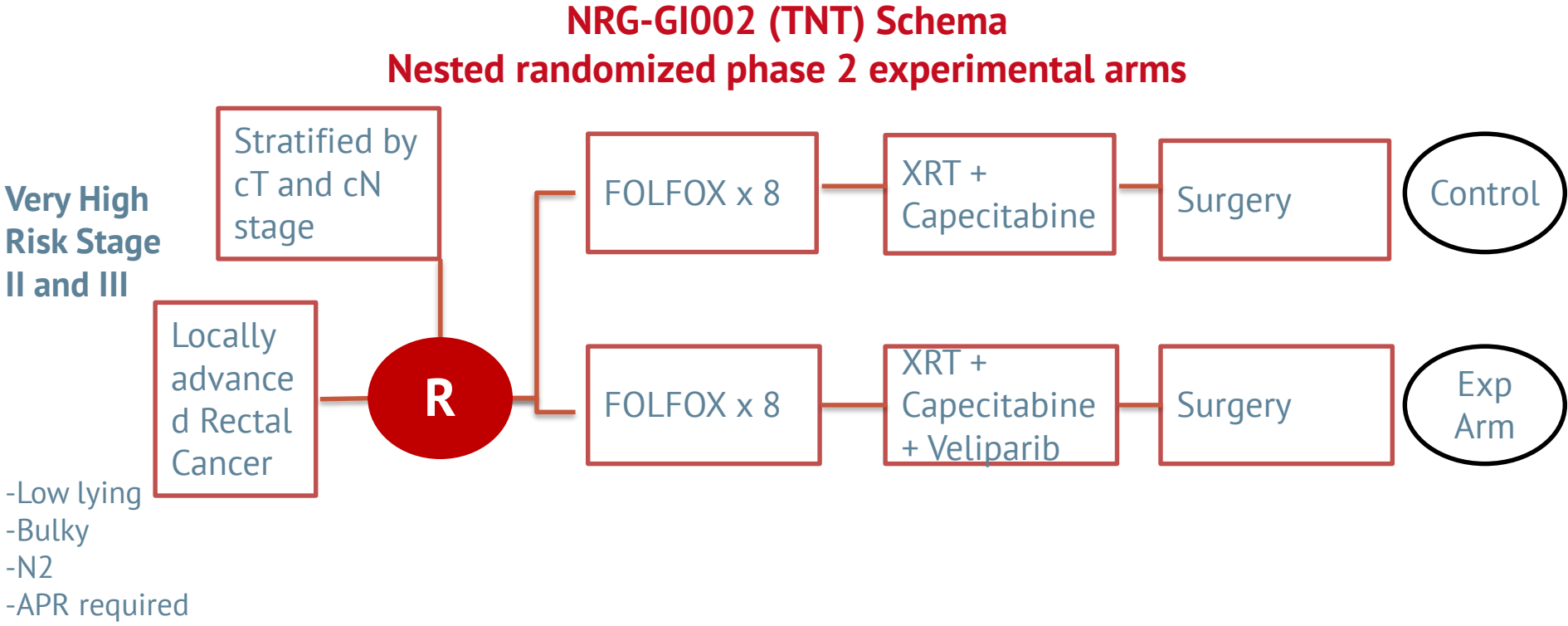
Seymour M, et al. Abstract #3504 Presented at ASCO 2019

NEOADJUVANT CHEMOTHERAPY WHAT WE LEARN FROM FOxTROT

- The study **did not meet the primary endpoint**
  - There was a trend towards improved 2-year relapse rate (HR 0.78; p = 0.08)
  - Not anticipated to change practice at this time
- Neoadjuvant chemotherapy in colon cancer was found:
  - to have **no new safety signals**
  - to have **fewer surgical complications**
  - to **downstage tumors and reduce incomplete resections**
- One **concern:** may lead to over-treating some patients
- Patients with mismatch repair deficiencies seem not to benefit

FOLFOX, folinic acid + fluorouracil + oxaliplatin; HR, hazard ratio
Seymour M, et al. Abstract #3504 Presented at ASCO 2019

NEOADJUVANT CHEMOTHERAPY
WHAT WE LEARN FROM NRG-GI002



APR, abdominoperineal resection; cT, cN: Clinical T, Clinical N category; R, randomization; XRT, radiotherapy

NEOADJUVANT CHEMOTHERAPY WHAT WE LEARN FROM NRG-GI002

- The phase II **NRG-GI002** trial evaluated total neoadjuvant therapy in locally advanced rectal cancer
  - 178 patients were randomized to 4 months of FOLFOX followed by chemoradiation with or without veliparib followed by surgery
  - One third of patients were < 50 years of age
- Patients on the **veliparib** arm had **more grade 3/4** gastrointestinal and hematologic **toxicities**
- Perioperative **surgical complications** were higher in the veliparib arm (but did not reach statistical significance)
- **Not ready to move to total neoadjuvant chemotherapy** in locally advanced rectal cancer unless part of a clinical trial

George T, et al. Abstract #3505 Presented at ASCO 2019

METASTATIC SETTING

RANDOMIZED PHASE III STUDY COMPARING FOLFOX + BEVACIZUMAB VS FOLFOXIRI + BEVACIZUMAB AS 1ST-LINE TREATMENT IN PATIENTS WITH mCRC WITH ⩾ 3 BASELINE CIRCULATING TUMOR CELLS

Sastre et al. ASCO 2019 Abstract #3507

UPDATED RESULTS OF TRIBE2, A PHASE III, RANDOMIZED STRATEGY STUDY BY GONO IN THE 1ST- AND 2ND-LINE TREATMENT OF UNRESECTABLE mCRC

Cremolini et al. ASCO 2019 Abstract #3508

CRC, colorectal cancer; FOLFOX, folinic acid + fluorouracil + oxaliplatin; FOLFOXIRI, folinic acid + fluorouracil + oxaliplatin + irinotecan

METASTATIC COLORECTAL CANCER ARE 3 DRUGS BETTER THAN 2?

- In the phase III study **VISNU1** patients with metastatic CRC with ⩾ 3 baseline circulating tumor cells were randomized to first-line treatment with:
  - FOLFOX + bevacizumab OR
  - FOLFOXIRI + bevacizumab
- 349 patients included
  - 70 years or younger
  - ECOG-PS score 0-1
- **More grade 3/4 adverse events** with FOLFOXIRI + bevacizumab
  - Specifically grade 3/4 febrile neutropenia, asthenia and diarrhea
- **Improved progression free survival** with FOLFOXIRI + bevacizumab versus FOLFOX + bevacizumab (HR 0.64)

CRC, colorectal cancer; ECOG-PS, Eastern Cooperative Oncology Group performance status; FOLFOX, folinic acid + fluorouracil + oxaliplatin; FOLFOXIRI, folinic acid + fluorouracil + oxaliplatin + irinotecan; HR, hazard ratio

Sastre J, et al. Abstract #3507 Presented at ASCO 2019

METASTATIC COLORECTAL CANCER ARE 3 DRUGS BETTER THAN 2?

- The phase III **TRIBE2** study randomized patients with unresectable metastatic CRC to
  - FOLFOX + bevacizumab followed by FOLFIRI + bevacizumab after progression OR
  - FOLFOXIRI + bevacizumab followed by reintroduction after progression
- 679 patients included
  - Including patients aged 71-75 if ECOG-PS score was 0
- **Increased grade 3/4 neutropenia, febrile neutropenia and diarrhea** in the FOLFOXIRI + bevacizumab arm
- **Improved** time to second disease progression (**PFS2**) with FOLFOXIRI + bevacizumab
  - 19.1 vs 17.5 (HR 0.74)
- **Improved overall survival** in the FOLFOXIRI + bevacizumab arm
  - 27. 6 vs 22.6 months (HR 0.81)
- These data support **FOLFOXIRI + bevacizumab** as the **preferred first-line option** in **fit** patients with **right-sided colon cancer** and/or who are ***KRAS*** or ***BRAF* mutant**

CRC, colorectal cancer; ECOG-PS, Eastern Cooperative Oncology Group performance status; FOLFOX, folinic acid + fluorouracil + oxaliplatin; FOLFOXIRI, folinic acid + fluorouracil + oxaliplatin + irinotecan; HR, hazard ratio

Cremolini C, et al.. Abstract #3508 Presented at ASCO 2019

CONCLUSIONS

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Adjuvant setting:

- 3 months of CAPOX is not inferior to 6 months in CAPOX in stage II high-risk colon cancer
- 3 months of FOLFOX is inferior to 6 months FOLFOX in high-risk stage II and stage III colon cancer

Neoadjuvant setting:

- No defined role for neoadjuvant chemotherapy in colorectal cancer
- However it was found to be safe and there was tumor down-staging leading to fewer incomplete resections

Metastatic setting:

- Fit patients with right-sided, KRAS mutant colon cancer had improved overall survival with FOLFIRINOX + bevacizumab versus comparator arms

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Email
antoine.lacombe@cor2ed.com

NURSES connect
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NURSES CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com