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MEETING SUMMARY
ASCO GI 2019, San Francisco, USA

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CANCERS OF THE LOWER GI TRACT

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This content is supported by an Independent Educational Grant from Bayer

CCTG CO.26 TRIAL: A PHASE II RANDOMIZED STUDY OF DURVALUMAB PLUS TREMELIMUMAB AND BEST SUPPORTIVE CARE (BSC) VS. BSC ALONE IN PATIENTS WITH ADVANCED REFRACTORY CRC

Chen EX, et al. ASCO GI 2019, Abst #481

CCTG CO.26
INTRODUCTION

- Immune checkpoint blockade has shown to be only active in MSI-H metastatic colorectal cancer[1-3]
- This randomised phase 2 study evaluated whether combining durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA-4) would lead to improved patient survival vs. best supportive care in patients with refractory mCRC[4]

1. Lee et al. NEJM 2015; 2. Overman JCO 2018; 3. Overman Lancet Oncol. 2017; 4. Chen EX, et al. ASCO GI 2019, Abst #481
Anti-CTLA-4, antibody to cytotoxic T-lymphocyte-associated protein; Anti-PD-L1, antibody to programmed cell death ligand-1; mCRC, metastatic colorectal carcinoma; MSI-H, microsatellite instability high; vs, versus

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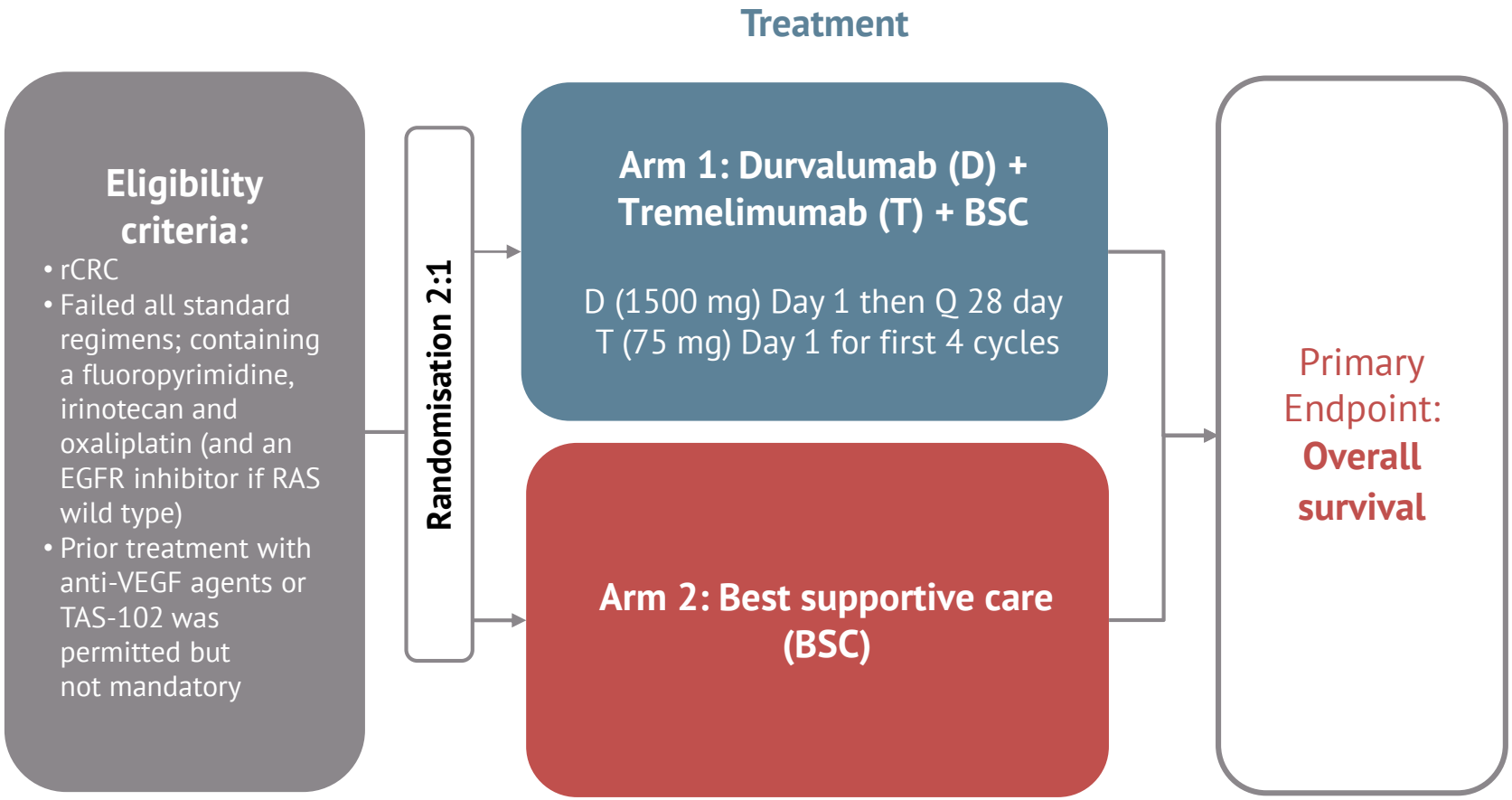
DESIGN

Phase II, randomised study



Chen EX, et al. ASCO GI 2019, Abst #481

Anti-VEGF, antibody to vascular endothelial growth factor; BSC, best supportive care; D, durvalumab; EGFR, epidermal growth factor; Q, every; RAS, RAS proto-oncogene GTPase; rCRC, refractory colorectal carcinoma; T, tremelimumab; TAS-102, drug code name for trifluridine and tipiracil

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RESULTS (1)

- N=180 enrolled, 179 patients randomised
- Baseline patient characteristics were well-balanced between both groups, except for more patients with KRAS mutation in the D+T group vs. BSC group (78% vs. 49%)
- 93% of patients had cfDNA analysis
- MSI was determined using cfDNA. MSI-high was 1% in D+T group and 2% in BSC group. Hence, majority was MSS colorectal cancer

Chen EX, et al. ASCO GI 2019, Abst #481

BSC, best supportive care; cfDNA, cell-free deoxyribose nucleic acid; D, durvalumab; KRAS, KRAS proto-oncogene, GTPase; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSS, microsatellite stable; N, number of patients; rCRC, refractory colorectal carcinoma; T, tremelimumab

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RESULTS (2)

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Outcomes:

	D+T (N=119)	BSC (N=61)	
Overall survival	6.6 months	4.1 months	HR=0.72 (0.54-0.97), p=0.07
Response rate	1%	0%	
DCR	22.7%	6.6%	(p = 0.006)

Toxicities:

Adverse events	D+T (N=118)	BSC (N=61)
Any, grade =/>3	64%	20%
Fatigue, grade =/>3	13%	3%
Abdominal pain, grade =/>3	23%	7%

Chen EX, et al. ASCO GI 2019, Abst #481

BSC, best supportive care; D, durvalumab; DCR, disease control rate; HR, hazard ratio; N, number of patients; p probability; T, tremelimumab

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COMMENTS

- **The study results suggest that D+T prolongs overall survival compared to BSC, in refractory MSS mCRC patients**
- **Limitations of results:**
  - Number of lines of therapy was not clearly stated
  - Patients did not receive TAS-102 as it was not available in Canada at that time
  - Use of anti-VEGF therapy or regorafenib were grouped as one
- Although the study claims no difference in QoL between both groups, the higher grade 3/4 toxicities in the D+T group is concerning especially in this heavily pre-treated patient population

Chen EX, et al. ASCO GI 2019, Abst #481

Anti-VEGF, antibody to vascular endothelial growth factor; BSC, best supportive care; D, durvalumab; mCRC, metastatic colorectal carcinoma; MSS, microsatellite stable; QoL, quality of life; T, tremelimumab; TAS-102, drug code name for trifluridine and tipiracil

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CONCLUSIONS

- **The results should be validated in larger studies** before the combination treatment of durvalumab plus tremelimumab is applied in clinical practice
- **Future studies should also factor in cost effectiveness** of immunotherapy in later lines of treatment in refractory mCRC

Chen EX, et al. ASCO GI 2019, Abst #481
mCRC, metastatic colorectal carcinoma

TOTAL NEOADJUVANT THERAPY WITH SHORT COURSE RADIATION COMPARED TO CONCURRENT CHEMORADIATION IN RECTAL CANCER

Chapman W, et al. ASCO GI 2019, Abst #486

SC-TNT IN RECTAL CANCER
INTRODUCTION

- Total Neoadjuvant Therapy (TNT) is the delivery of all radiation and chemotherapy prior to surgery
- TNT has improved complete response and downstaging rates compared to adjuvant therapy in patients with rectal cancer
- This retrospective cohort study is looking at the role of short-course radiation in TNT

Chapman W, et al. ASCO GI 2019, Abst #486
SC-TNT, short-course radiation therapy in the setting of total neoadjuvant therapy; TNT, total neoadjuvant therapy

SC-TNT IN RECTAL CANCER
METHOD

Primary outcome: pCR

Secondary outcomes: neoadjuvant rectal score and recurrence rate

Patient selection:

- Patients who underwent neoadjuvant therapy followed by total mesorectal excision for Stage II or III rectal cancer from 2009 to 2018
- **SC-TNT recipients:** (25-35Gy/5 fx followed by CAPOX or FOLFOX chemotherapy) followed by surgery
- **Control group, chemoradiation therapy:** Neoadjuvant chemoradiation recipients (50-55Gy/25-28 fx with concurrent 5-FU or capecitabine) followed by surgery

Chapman W, et al. ASCO GI 2019, Abst #486

5-FU, fluorouracil; CAPOX, capecitabine and oxaliplatin; FOLFOX, leucovorin, 5-fluorouracil and oxaliplatin; fx, fractions; Gy, Gray The international system unit of radiation dose; pCR, pathologic complete response; SC-TNT, short-course radiation therapy in the setting of total neoadjuvant therapy

SC-TNT IN RECTAL CANCER
RESULTS

	CRT	SC-TNT	statistics
N	236 (60.8%)	152 (39.2%)	
Stage 3 disease	67%	77%	p=0.04
pCR	19.1%	25.0%	p=0.16
NAR score <8	28%	36%	p=0.07
Recurrence	14.3%	14.9%	p=0.87

* DFS was also no different between both groups (data in poster)

Chapman W, et al. ASCO GI 2019, Abst #486

CRT, chemoradiation therapy; DFS, disease free survival; N, patient numbers; NAR, neoadjuvant rectal; p, probability; pCR, pathologic complete response; SC-TNT, short-course radiation therapy in the setting of total neoadjuvant therapy

SC-TNT IN RECTAL CANCER
COMMENTS

- The study suggests that **SC-TNT is at least as effective as conventional long-course chemoradiation therapy**
- **Results should be interpreted with caution** as this was a retrospective, cohort study. Unanswered questions include:
  - Toxicity data
  - Neoadjuvant chemotherapy dose intensity and compliance
  - Adjuvant chemotherapy data
  - Data on R0/R1 resection
  - Feasibility of surgery in SC-TNT group
- The sample size is large for a retrospective study and provides emerging evidence that treatment outcomes may be preserved or possibly better with a change in treatment paradigm
- Prospective studies are ongoing looking into TNT in rectal cancer and we are awaiting results

Chapman W, et al. ASCO GI 2019, Abst #486

R0, no detectable presence of residual tumor after treatment; R1, presence of microscopic residual tumor after treatment; SC-TNT, short-course radiation therapy in the setting of total neoadjuvant therapy

SC-TNT IN RECTAL CANCER
CONCLUSION

- **Neoadjuvant short-course radiation followed by multi-agent chemotherapy is possibly as effective as long-course chemoradiation**

Chapman W, et al. ASCO GI 2019, Abst #486

CRT, chemoradiation therapy; SC-TNT, short-course radiation therapy in the setting of total neoadjuvant therapy

OUTCOMES BY TUMOR LOCATION IN PATIENTS WITH METASTATIC COLORECTAL CANCER (mCRC) TREATED WITH REGORAFENIB: FINAL ANALYSIS FROM THE PROSPECTIVE OBSERVATIONAL CORRELATE STUDY

Ducreux M, et al. ASCO GI 2019, poster #539

CORRELATE
INTRODUCTION

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- In phase 3 trials regorafenib significantly improved overall survival versus placebo in patients with mCRC who progressed on standard therapies [1,2]
- CORRELATE[3] (NCT02042144) was a prospective, observational study designed to characterize the safety and effectiveness of regorafenib in mCRC patients in clinical practice
- This abstract examined the prognostic role of **tumor sidedness** based on the final results of the CORRELATE study

1.Grothey A, et al. Lancet 2013;381:303–12; 2. Li J, et al. Lancet Oncol 2015;16:619–29; 3. Ducreux M, et al. ASCO GI 2019, poster #539
mCRC, metastatic colorectal cancer;

CORRELATE STUDY
METHODS

- Metastatic colorectal cancer patients previously treated with approved therapies were included
- Patients whose tumors were not assessable (n=64) or who had tumors in both regions (n=6) were excluded
- Primary outcome of CORRELATE: Safety (TEAE)
- **OS and PFS** were analysed in this subgroup analysis

Ducreux M, et al. ASCO GI 2019, poster #539
mCRC, metastatic colorectal cancer; n number of patients; OS, overall survival; PFS, progression free survival; TEAE, treatment emergent adverse event

CORRELATE RESULTS

- Overall, 967 patients were included in the analysis, 761 (79%) had left-sided tumors and 206 (21%) had right-sided tumors
- KRAS and BRAF mutation status and treatment modification were similar in both groups

	Left-sided mCRC	Right-sided mCRC
Median no. of prior regimens	3	3
Median duration of regorafenib (range) months	2.6 (<0.1-20.6)	2.3 (<0.1-17.8)
Median overall survival, months (95% CI)	7.5 (6.8, 8.1)	8.2 (6.6, 9.4)
Median PFS (95% CI)	2.9 months (2.8, 3.1)	2.8 months (2.6, 3.3)

Ducreux M, et al. ASCO GI 2019, poster #539

BRAF, B-Raf proto-oncogene, serine/threonine kinase; CI, confidence intervals; KRAS, KRAS proto-oncogene, GTPase; mCRC, metastatic colorectal cancer;No, number; PFS, progression free survival; RAS, RAS proto-oncogene, GTPase

CORRELATE
CONCLUSION

Survival was similar in L-sided vs. R-sided tumors in patients treated with regorafenib

Limitations of results:

- Observational study
- Sample size was imbalanced (L:79% vs. R:21%)
- L-sided group included rectal cancer.
  - Proportion of rectal cancer patients were not reported and is important to know as in the CORRECT study[1], subgroup analysis showed that regorafenib did not affect survival of patients with rectal cancer

Conclusion:

- The study does not change the current practice of regorafenib which remains as an option for mCRC patients from 3rd line and beyond, regardless of sidedness

1. Grothey A, et al. Lancet 2013;381:303–12; 2. Ducreux M, et al. ASCO GI 2019, poster #539
L, left; mCRC, metastatic colorectal cancer; R, right

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