431P Neoadjuvant treatment with Regorafenib and Capecitabine combined with radio-therapy in locally advanced rectal cancer. A multicenter phase Ib trial (RECAP) SAKK 41/16

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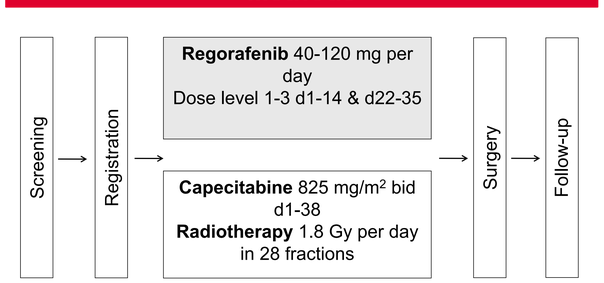
Abstract: 431P

Background

- Currently high risk locally advanced rectal cancer (LARC) patients are treated with intensified neoadjuvant chemotherapy and radiation (TNT).
- Another approach is using a multi TKI Sorafenib instead of Oxaliplatin or Irinotecan. The precedent SAKK 41/08 study with Sorafenib combined with long course chemoradiation (LcCRT) showed npCR/pCR rate of 60% (45% npCR, 15% pCR) with acceptable toxicities. (1-3)
- This potential improvement in clinical outcome by adding a multi-TKI as Regorafenib (R) to LcCRT was investigated in the SAKK 41/16 trial.

Methods



- Patients with T3-4 and/or N+ M0 rectal cancer were included. A DYPD wildtype status was mandatory.
- Neoadjuvant LcRCT was given with Capecitabine 825mg/m² d1-d38 and 28 fractions of 1.8Gy (50.4Gy).
- R was added d1-14 and d22-35. R was given in a dose escalation (DE) 3+3 design 40, 80 and 120 mg qd.
- The recommended dose (RD) of 80 mg was used for cohort expansion (CE) including 19 patients (6 patients from DE and additional 13 patients from CE).
- The primary endpoints were dose limiting toxicity (DLT) for the DE and for the CE pathological response defined as grade 3 (near complete regression npCR) or 4 (complete regression pCR) according to Dworak histopathological classification.
- Statistical considerations:19 patients were required based on a one-sided type I error 20% and a power 80% for a single-stage design assuming a npCR/pCR rate of ≥ 40% for H1 compared to npCR/pCR rate of ≤ 20% for H0.

Results I Dose Escalation

Between 03.03.2017 and 22.04.2021, 25 patients were accrued into the trial from 6 sites in Switzerland.

Tab 1 **Baseline characteristics (DE and CE)**

Variable	Total (N=25)
Sex	
Female / Male	9 (36%) / 16 (64%)
Age median (range)	62 y (46-75 y)
WHO performance status	
0	25 (100%)
mrT	
T3 / T4a / T4b	21 (84%) / 2 (8%) / 2 (8%)
mrN	
N0 / N1 / N2	4 (16%) / 12 (48%) / 9 (36%)
RAS status	
Wild-type / RAS mut / Unknown	13 (52%) / 11 (44%) / 1 (4%)

Tab 2 **Primary endpoint dose limiting toxicity (DLT)**

Dose Level (DL)	DLT
40 mg (n=3)	no
80 mg (n=3)	no
120 mg (n=3)	2 DLT G3 maculo-papular skin rash G3 dermatitis in radiation field
80 mg (n=3)	2 DLT in 1 patient G3 arterial hypertension, G3 Palmar-plantar-erythrodysesthesia syndrome

- The median delivered radiation dose was 50.4 Gy (min 43.2, max 50.4). Dose reduction was needed in 2 patients in DL 2 due to toxicity.
- Dose modifications for R were necessary in 3 patients (2 dose level (DL) 2 and 1 DL 3).
- Dose modification of at least one dose of Capecitabine was done in 16 patients. Mostly due administrative reasons and bank holidays, only 4 reductions were done due to toxicities in DL 2.
- From 25 patients 24 underwent surgery. Total meserectal excision (TME) was performed in 18 patients, abdomino-perineal excision (APR) in 5 patients.
- 1 patient was not operated due to clinical CR.
- All patients had R0 resection.

Results II Cohort Expansion

Cohort expansion (CE) n=19, 6 patients from DE were included.

Tab 3 **Primary endpoint pathological response (central review)**

Variable	Total (N=19)
Dworak tumor regression grade	
0: No regression	1 (5.3%)
1: Minimal regression	0 (0.0%)
2: Moderate regression	9 (47.4%)
3: Good regression	5 (26.3%)
4: Total regression	3 (15.8%)
Missing*	1 (5.3%)

*1 patient was not operated due clinical CR after neoadjuvant treatment and followed a watch and wait strategy

- The primary endpoint of Dworak 3 and 4 npCR/pCR was reached in 8 patients (42.1%, one-sided 80% CI (lower bound): 30.7%; 95% CI: 20.3%-66.5%).
- No relationship between RAS status and response could be found (Fisher test, p = 1).

Tab 4 **Secondary endpoints**

Variable	Operated patients (N=18)
R0 resection	18 (100%)
CRM clear	18 (100%)
Quality of mesorectal excision	
Complete	15 (83.3%)
Near complete	2 (11.1 %)
Incomplete	1 (5.6%)
Sphincter preservation	14 (77.8%)
Downstaging T and/or N	11 (61.1%) / 15 (83.3%)
Postoperative complications	6* (35.3%)⁺

*including insufficiency of anastomosis 1 (5.6%), local infection 3 (17.6%), need for local intervention (reoperation, drainage of hematoma/abscess) 3 (17.3%), bladder dysfunction 1 (5.6%) , erectile dysfunction 1 (5.6%)
⁺one operated patient did not have a postoperative assessment (N=17)

- No grade 4/5 toxicities from the trial treatment with R were observed.
- 15 (83.3%) patients showed a downstaging of T or N from initial assessment with MRI compared to the pathological assessment at surgery.
- All patients had good quality of surgery (all R0, CRM clear, 83.3% completeness of quality of mesorectal excision according to Nagtegaal).
- Postoperative complications are in line what is observed with standard CRT. (1-3)
- No local relapse occurred, 1 patient suffered distant relapse in the liver (Fig.1+2)

Fig 1: **Time to local relapse**

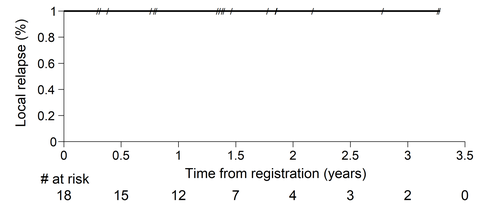
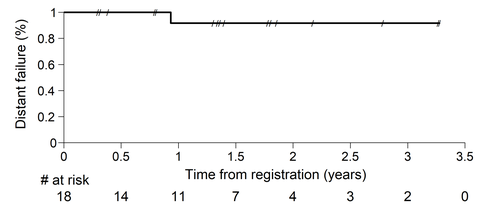


Fig 2: **Time to distant failure**



Conclusions

- Adding Regorafenib in RD 80 mg to LcCRT in LARC reached the primary endpoint for the CE and showed high activity.
- This regimen did not prolong the neoadjuvant treatment time in contrast to TNT. Toxicity was manageable, and postoperative complications were as expected.
- This regimen deserves further investigation especially in efficacy comparison to TNT regimens.

References

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