Additional markers of response to anti-EGFR therapy in metastatic colon cancer: Morphological context matters

Eva Budinská[1], Valeriia Vasylieva[1], Martina Hrivňáková[1], Rudolf Nenutil[2], Ondrej Slabý[3,4], Beatrix Bencsíková[2], Vlad Popovici[1]

1 RECETOX, Faculty of Science, Masarykova Univerzita, Brno, Czech Republic; 2 Masaryk Memorial Cancer Institute, Brno, Czech Republic;
3 CEITEC, Masarykova Univerzita, Brno, Czech Republic; 4 Faculty of Medicine, Masarykova Univerzita, Brno, Czech Republic

EACR 2023 12 - 15 June 2023 Torino, Italy

Poster no.: P-0079

INTRODUCTION

Our previous research shows that **tumour morphology is associated with specific transcriptomic profiles**. We were interested to see whether the same applies for mutational profiles in order to develop **more sensitive patient stratification strategies.**
In metastatic setting, colon cancer patients with KRAS and NRAS wild type tumours receive anti-EGFR agents as first line treatment. The question is whether low incidence genomic aberrations that would become apparent under multiple-region tumour sampling could be used as predictors of shorter time-to-progression and, hypothetically, selection of additional (or subsequent) treatment targets. For this, we performed multiple-region deep targeted sequencing of a selected set of primary tumours and compared it to whole-tumour sections for the purpose of predicting patients with short progression-free survival.

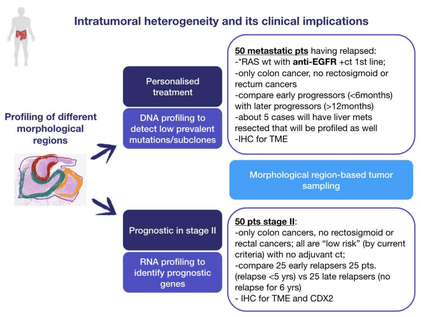

Figure 1. Conceptual study design.

METHODS

We extracted DNA of whole tumour, invasion front and multiple morphologically homogenous regions from consecutive FFPE slides of primary tumours from 41 *RAS wt colon cancer patients with anti-EGFR+ct therapy in the 1st line treatment (20 early progressors <6months after treatment + 21 late progressors >12 month after treatment). Targeted sequencing was performed using QIAGEN Human Comprehensive Cancer QIASeq DNA Panel and150bp paired-end reads at Illumina NextSeq 500. Variants were called using Mutect2 and annotated to the ClinVar db (1.69). We used Fishers exact test to test the frequency of variants between early and late progressors as well as their association with morphologies.

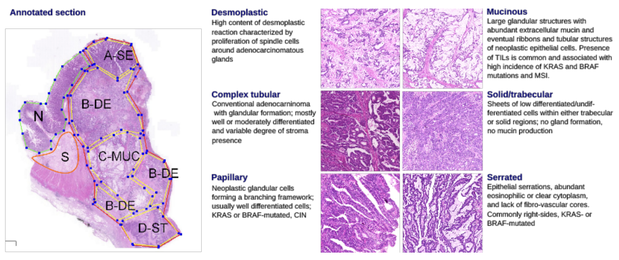

Figure 2. Schematic representation of tumour sections based on 6 morphologies.

RESULTS

We found specific variants associated with early progression in subgroups of patients, such as PDGFRA c.1507T>C, PTCH1 c4325G>A, or BRAF c.1919T>A (p.Val640Glu). Interestingly, the BRAF variant was more frequently present in mucinous and serrated regions – morphologies, that were also significantly associated with early progression. Regardless of the progression status we found several morphology specific variants, such as MLH1 gene c.1624C>T (p.Gln542Ter) in desmoplastic and solid/trabecular regions RAD50 c.2165del (p.Lys722fs) found in mucinous and complex tubular regions.

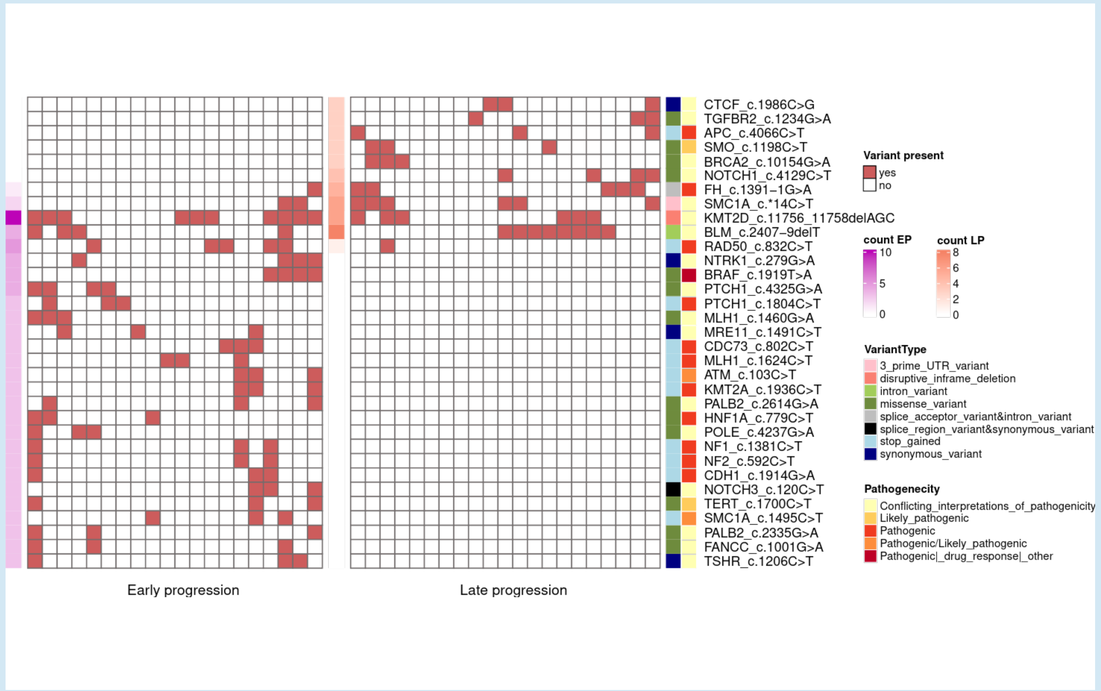

Figure 3. Map of variants specific for tumours of patients from early and late responder groups, present in at least one sampled region of the tumour.

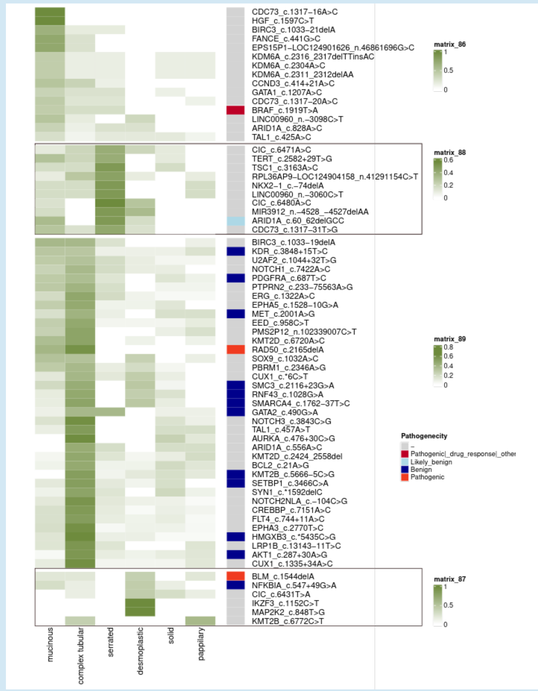

Figure 4. Heatmap of variant prevalence within the 6 morphological regions. Only variants with significantly different prevalence are shown.

CONCLUSION

1. We found **additional potentially druggable targets** in colon tumours of patients with early progression after anti-EGFR therapy in metastatic disease.
2. The presence of **certain morphologies** (mucinous, serrated) in colon tumours is indicative of **specific mutations** associated with the anti-EGFR treatment outcome.
3. Assessment of tumour morphological heterogeneity would be a reasonable tumour sampling strategy that could maximise the utility-to-costs ratio of personalized treatment.

References

Budinska et al., J Path 2013, doi: 10.1002/path.4212
Budinska et al. bioRxiv, doi: 10.1101/2023.01.24.525310

Acknowledgments

This project was supported and funded by Agentura pro Zdravotnický Výzkum Ceské Republiky (AZV) -- Grant Agency of the Czech Ministry of Health -- under grant no. NV19-03-00298.
Part of the work was carried out with the support of core facilities of RECETOX Research Infrastructure, project number LM2023069, funded by the Ministry of Education, Youth and Sports of the Czech Republic under the activity „Projects of major infrastructures for research, development and innovations".