mTOR signaling pathway by previous studies. Furthermore, the knockdown of SNRPE re-sensitized tumor cells to the mTOR inhibitor everolimus which was proved invalid in TNBCs.

Conclusions: Our study reveals that SNRPE was highly amplified in TNBCs and promoted the progression of tumor cells via DP103-mediated mTOR signaling activation. Thus, our study provides a promising therapeutic target for TNBC.

No conflict of interest.

122 Poster

Targeting BRAF WT metastatic melanomas: Identifying ERBB4 mutant alleles as biomarkers for novel combinatorial treatment strategies

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Background: The treatment of metastatic melanoma (MM) has been dramatically improved through the use of BRAF and MEK inhibitors in patients whose tumors harbor activating mutations in *BRAF*. However, these mutations occur in only ~50% of MMs and a targeted therapy(ies) has yet to be identified for those MMs that contain wild-type (WT) *BRAF*. Using The Cancer Genome Atlas melanoma (TCGA-SKCM) dataset, we discovered that 20% of *BRAF* WT melanomas harbor a missense mutation in *ERBB4*, which encodes a member of the epidermal growth factor receptor (EGFR/ErbB1) family of receptor tyrosine kinases. Hence, our goal is to evaluate whether *ERBB4* mutant alleles function as biomarkers and targets for therapeutic intervention in *BRAF* WT MMs.

Materials, Methods, and Results: Of the 469 genomes in the TCGA-SKCM dataset, 70 harbor at least one missense mutation in *ERBB4*, resulting in a total of 76 unique *ERBB4* missense mutations. These mutations do not appear to be random occurrences, but instead appear to be the result of selection. For example, the incidence of *ERBB4* mutant alleles is greatly reduced in melanomas that possess *BRAF* driver mutations and/or driver events in PI3K pathway genes. In contrast, the incidence of *ERBB4* mutant alleles is markedly elevated in melanomas that possess genetic alterations that result in elevated RAS signaling. Indeed, melanomas that possess an *ERBB4* mutant allele AND a genetic alteration that results in elevated RAS signaling are associated with a marked decrease in survival. Taken together, these data indicate that *ERBB4* mutant alleles cause elevated PI3K signaling, which cooperates with elevated RAS signaling to drive the genesis and/or progression of BRAF WT MMs.

The existence of 76 unique *ERBB4* mutations in the TCGA-SKCM dataset highlights one of the challenges in identifying the *ERBB4* mutant alleles that function as *bona fide BRAF* WT MM drivers. The other challenge is that *ERBB4* functions as a context-dependent oncogene and tumor suppressor gene. Hence, we will describe the ongoing development and validation of innovative, positive-selection screens for gain-of-function *ERBB4* mutant alleles and for loss-of-function *ERBB4* mutant alleles from the library of *ERBB4* mutant alleles found in the TCGA-SKCM dataset. The gain-of-function *ERBB4* mutant alleles would enhance ERBB4 signaling in contexts in which *ERBB4* functions as an MM oncogene, whereas the loss-of-function *ERBB4* mutant alleles would disrupt ERBB4 signaling in contexts in which *ERBB4* functions as an MM tumor suppressor gene.

Conclusions: *In silico* analyses of the TCGA-SKCM dataset indicate that *ERBB4* mutant alleles function as drivers of *BRAF* WT MM. We will present our progress in developing and validating *in vitro* positive selection strategies to identify which of the 76 *ERBB4* mutant alleles found in the TCGA-SKCM dataset function as *bona fide* drivers of *BRAF* WT MMs.

No conflict of interest.

123 Poster

Arcagen: Molecular profiling of rare cancer patients – analysis of the pilot study (87 patients)

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Rare cancers, defined as histological diagnoses with an incidence of <6/100,000/year, include more than 300 histological subtypes and may affect all organs. Even though they represent 20% of all adult cancers, they account for more than 30% of cancer mortality. They are clearly under-represented in clinical research programs, especially in research programs exploring genomic alterations of cancer. In order to fill this gap, the EORTC-EURACAN developed a collaborative clinical research project called "Arcagen." This project aims to recruit 1,000 patients with rare cancer and perform a molecular profiling, using the Foundation Medicine tests.

Here, we present the results of the pilot study (feasibility) including 87 patients from three French sites. In total, 98 samples were analysed (55 using the FoundationOne and 43 using the FoundationOne Heme test). We had a global failure rate of 14.3% (only 4.6% for FoundationOne Heme), mainly due to sample quality issues or limited tumor tissue.

Seventy-seven patients (85 samples) had available molecular and clinical data and were included in the analysis. Forty-one patients (53.2%) were diagnosed with sarcoma, 9 (11.6%) with ovarian Yolk Sac Tumor (YST), 14 (18.2%) with rare head and neck cancers and 13 (17%) with thymic cancer. Male to female ratio was almost 1:1 (38 male and 35 female) and the median age at diagnosis was 48 years (range 28–85).

Most patients had reportable genomic alterations (89%). The most common alterations were linked to the cell cycle regulation, in particular in sarcoma and rare head and neck tumors (TP53, RB1 as well as CDKN2A/B deletions or MDM2 amplification). Multiple single-nucleotide variants (SNVs) were detected in the RAS/RAF family, and could be of notable interest in the YST and thymic tumors. The TMB status was globally low across all samples with a median of 3 Muts/MB (range). Only 5.1% of tumors had mutations that were directly targetable with approved agents: NTRK fusion (n = 1; sarcoma), EGFR 20 insertion (n = 1; head and neck tumor) and FGFR fusion/amplification (n = 2; sarcoma). However, regarding global actionability (independently of disease type), we could recommend a targeted treatment for 39% of the patient population (n = 30). The respective targeted therapies comprised CDK4/6 inhibitors, RTKI, PARPi, mTOR inhibitors, and immune checkpoint inhibitors.

Prospective recruitment is ongoing for this project. Liquid biopsy possibility was added in case of screening failure on FFPE material, to optimize the success rate for molecular analysis for all patients. The pilot study highlights a need for specific research on rare cancers to find driver alterations and develop adequate therapies.

Conflict of interest:
Corporate-sponsored Research: This research is done with a grant from Roche.

124 Poster

Mutations and copy number alterations in diffuse gliomas are shaped by different mechanisms

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Background: Mutational mechanisms that shape the genome in gliomas remain largely unknown. Uncovering these mechanisms can help improve current treatments and guide further treatments, which are desperately needed for gliomas. Various mutational processes leave their individual marks in the form of single nucleotide variations (SNV), indels, copy number variations (CNV) or their combinations. We hypothesized that different molecular subsets of gliomas may be caused by different mechanisms, which would be reflected by differences in the burden of different forms of these genetic alterations. In this work we quantified the burden of SNV, indels and CNV using exome sequencing and compared them in diffuse gliomas.

Materials and methods: Whole exome sequencing was performed in 37 primary diffuse glioma patients (tumor and matched blood). 8 further exomes