Identification of a FGFR3-TACC3 fusion in esophageal cancer

Aberrant activation of fibroblast growth factor (FGF) signaling due to up-regulation of FGF receptor gene (FGFR) expression, alternative splicing of FGFR transcripts, FGFR mutations or translocations, or increased availability of FGF has been found to contribute to carcinogenesis [1]. FGFR fusions have recently been detected in several epithelial cancers [2, 3], but the contribution of such fusions to cancers of the upper digestive tract, including esophageal squamous cell carcinoma (ESCC) and gastric cancer (GC), has remained largely unknown (supplementary Table S1, available at Annals of Oncology online). We have now examined clinical specimens of ESCC (n = 74, supplementary Table S2, available at Annals of Oncology online) and GC (n = 114, supplementary Table S3, available at Annals of Oncology online) for the presence of major FGFR1, FGFR2, and FGFR3 fusion transcripts, including those with breakpoints previously uninvestigated in these cancers, with the use of a next-generation sequencing panel (see supplementary Materials and Methods and supplementary Table S4, available at Annals of Oncology online). We detected a targetable fusion between exon 18 of FGFR3 and exon 11 of TACC3 in one ESCC clinical specimen (Figure 1A and B). Furthermore, split FGFR3 signals were apparent in this specimen by fluorescence in situ hybridization (FISH) with break-apart probes (Figure 1C). The patient was a 64-year-old man with unresectable T4bN3M1 poorly differentiated ESCC of stage IV. He was treated with palliative chemoradiotherapy including platinum-doublet followed by taxane chemotherapy. The patient died of cancer progression, with his overall survival time having been 9.5 months.

FGFR fusions with an intact kinase domain have been identified in various cancers including glioblastoma multiforme and bladder cancer, and these fusion genes were found to promote cell proliferation in vivo and in vitro [2]. FGFR aberrations have been suggested as a potential prognostic factor for ESCC, and a recurrent fusion between exon 18 of FGFR3 and exon 11 of TACC3 has also previously been detected at a frequency of 2.1% (1/48) in ESCC [4, 5]. We have now identified the same fusion at a frequency of 1.4% (1/74) in ESCC with the use of the most comprehensive panel for FGFR fusion transcript detection reported to date, whereas other FGFR fusions were not detected in the ESCC or GC specimens analyzed. Unfortunately, our results provide weak clinical evidence to support the notion.

Given that FGFR fusions are predictive of sensitivity to molecularly targeted inhibitors in several types of solid tumor, including lung adenocarcinoma, patients with ESCC harboring FGFR fusions such as FGFR3-TACC3 should be considered as potential candidates for clinical trials testing such agents. Our results provide sequence information that should prove useful for

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**Figure 1.** Detection of an FGFR3-TACC3 fusion in a patient with ESCC. (A) Circos plot of the sequenced FGFR fusion transcripts. Two FGFR1, eight FGFR2, and four FGFR3 fusion genes as well as five housekeeping genes (HMSB, TBP, JG678, MYC, and LMNA) were assayed with a next-generation sequencing panel for FGFR fusion transcript detection (Life Technologies). (B) Schematic representation of the fusion protein encoded by the FGFR3-TACC3 fusion gene detected in an ESCC patient. The fusion joins exon 18 of FGFR3 as the 5′ partner and exon 11 encoding the coiled-coil domain of TACC3 as the 3′ partner. Ig, TM and TK indicate the immunoglobulin, transmembrane, and tyrosine kinase domains of FGFR3, respectively. (C) FISH analysis of paraffin-depleted sections of ESCC tumors positive or negative for the FGFR3-TACC3 fusion with Texas red-labeled (red) and fluorescein-labeled (green) probes targeted to the 5′ and 3′ regions of FGFR3, respectively. Separated signals (arrowheads) indicate the presence of the FGFR3-TACC3 fusion.
A previously healthy 54-year old man was diagnosed with metastatic pancreatic ductal adenocarcinoma (PDAC) in February 2015; the primary tumor was localized in the tail of the pancreas. Histological confirmation of disease was based on a liver biopsy. The patient started chemotherapy with a FOLFIRINOX regimen in March 2015 [1], that was de-escalated to mFOLFOX-6 and finally 5-FU/FA due to toxicity (thrombocytopenia, peripheral neuropathy); maintenance 5-FU/FA was given until June 2016. During this treatment, a very good partial response occurred, with a decline in CA 19-9 levels from 8.149 U/ml (pre-treatment) to a nadir of 5 U/ml in March 2016. On sequential CT imaging studies, the liver metastases as well as the pancreatic primary decreased dramatically in size, and the radiographic finding correlated well with a rapid clinical benefit response (e.g. no further need for analgesics since May 2015).

After the first preliminary data on the role of anti-PD-1 treatment in non-colorectal gastrointestinal cancers harboring a mismatch-repair deficiency (dMMR) were presented [2], and in the light of limited chemotherapeutic options due to persistent (treatment-associated) thrombocytopenia, we decided to determine the MMR status in our patient. At our reference laboratory for molecular pathology, a PCR-based assay found a dMMR status in the microsatellite markers BAT25, DSSS536, and D17S250 of the NCI consensus set. A subsequent human genetic counseling analysis. PLoS One 2014; 9: e105524.

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