Adenoid Cystic Carcinoma (ACC) is a neoplasm
of the secretory glands and represents the second
most common malignancy of the salivary gland. The
majority of patients present with localized disease,
however, approximately half will recur distantly in spite
of aggressive curative intent treatment. While ACC
typically recurs in the lungs and has an indolent disease
course, approximately 15% of patients exhibit a more
aggressive disease phenotype [1]. MYB or MYBL1-NFIB
translocation is present in the vast majority of ACCs and
it leads to myb protein overexpression, however, targeting
transcription factors is clinically challenging [1]. Exome-
sequencing of ACC samples revealed common alterations
in Notch-pathway genes, particularly NOTCH1 mutations
in patients with metastatic disease [2]. NOTCH1 is
involved in a well-conserved developmental pathway and
can function as either an oncogene or a tumor suppressor,
depending on the cellular context. Pathway dysregulation
can lead to many cancer-relevant cellular functions such as
proliferation, stemness, epithelial-mesenchymal transition,
genomic instability, and angiogenesis [3]. Notch signaling
is usually initiated by receptor-ligand interaction, which
ultimately leads to receptor cleavage by the gamma-
secretase complex that frees the Notch intracellular
domain to enter the nucleus and form a transcriptional
activation complex [3]. In ACC, most mutations in
NOTCH1 are activating and result in loss of the C-terminal
PEST degron domain, resulting in reduced degradation of
the NOTCH1 protein. Less frequently, point substitutions
and in-frame insertions/deletions disrupting the negative
regulatory region (NRR) are identified, which leads
to ligand-independent receptor proteolysis [2]. In our
analyses, while NOTCH1 activating mutations were seen
in 14% of ACC patients, pathway activation was detected in
56% by immunohistochemistry using a validated,
specific antibody against the cleaved notch1 intracellular
domain (NICD1), suggesting there are mechanisms other
than NOTCH1 mutation that lead to pathway activation.
Indeed, other mutations predicted to activate the Notch
pathway, such as loss-of-function mutations in SPEN, a
negative transcriptional regulator of Notch, were identified
in ACC and tend to co-occur with NOTCH1 activating
mutations [2]. There is also evidence that NOTCH1 is
a putative myb target in ACC and therefore MYB-NFIB
translocations could lead to Notch pathway activation
[4]. Using detailed histologic and clinical annotation,
we demonstrated that NOTCH1 mutations significantly
correlate with solid histology, advanced disease stage at
diagnosis, higher incidence of liver and bone metastasis,
and shorter relapse-free and overall survival [2]. This
association between Notch pathway activation and pro-
metastatic phenotype is not exclusively in ACC and has
been reported in other tumors such as breast cancer and
chronic lymphocytic leukemia (CLL) [2].

To test the hypothesis that Notch1 is a therapeutic
target in a subset of ACC, we and others have screened
genotyped ACC patient-derived xenograft (PDX) models
with Notch inhibitors and observed significant tumor
growth inhibition exclusively in the ACCX9 NOTCH1
mutant model [2, 5]. We then identified an index ACC
patient with aggressive disease that harbored at least two
NOTCH1 activating mutations (in the NRR and PEST
domains), who achieved a partial response when treated
with brontictuzumab, a specific monoclonal antibody
targeting Notch1 [2]. Clinical response to gamma-
secretase inhibitors was also reported in another NOTCH1
mutant ACC patient, supporting the oncogenic role of
NOTCH1 and its inhibition as an attractive therapeutic
strategy in ACC [5, 6]. While these responses are
encouraging, the clinical development of Notch inhibitors
has been challenging. This class of agents can cause
significant on-target toxicity, mainly diarrhea, which may
limit the achievement of therapeutically relevant doses or
continuous Notch inhibition. Moreover, the mechanism of
action of the currently available drugs might not be able to
successfully inhibit the pathway depending on its mode of
activation. Thus far, most ACC patients that participated
in phase I trials of Notch inhibitors experienced disease
stabilization rather than objective response, with the
caveat that these studies did not select patients based
on their NOTCH1 mutation status, highlighting the
importance of patient selection [6, 7]. Additionally, at
least in the reported index case [2], resistance developed
early on upon Notch inhibition suggesting activation of
alternative signaling pathways upon Notch inhibition that
lead to tumor growth and/or immune evasion, or that other
genetic events, such as myb translocations, cooperates
with NOTCH1 mutations to promote oncogenesis.

While many questions remain, transcriptomic and
proteomic characterization of NOTCH1 mutant ACCs is
ongoing and will shed light into the biology of this
aggressive patient subgroup and guide future studies
utilizing rational drug combinations. Furthermore, new
in class pan-NOTCH inhibitors that directly target the
Notch transcriptional activation complex have shown encouraging activity in gamma-secretase inhibitor refractory Notch activated triple negative breast cancer mouse models and will soon be tested in a first-in-human trial [8]. Clinical studies testing gamma-secretase inhibitors combined with targeted therapies or chemotherapy are currently ongoing (NCT02784795). These trials represents an attractive therapeutic opportunity for a subgroup of patients with this rare, aggressive, and chemo-refractory disease, for which no systemic therapy is currently available.

Renata Ferrarotto: Thoracic and Head and Neck Medical Oncology Department, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Correspondence to: Renata Ferrarotto, email RFerrarotto@mdanderson.org

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