RARE HEAD AND NECK TUMOURS

New approaches in systemic treatment for relapsed or metastatic disease

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OUTLINE

Salivary gland carcinoma
  - Genomic alterations and targeted therapies
  - Immunotherapy

Other rare tumours
  - Genomic alteration and targeted therapies
  - Immunotherapy
SALIVARY GLAND CARCINOMA

Genomic alterations and targeted therapies
BACKGROUND
Salivary gland carcinoma

Uncommon neoplasms accounting for up to 5% of all cancers of the head and neck
Young patients

Characterised by slow growth, multiple local recurrences, and prolonged clinical course, often with the delayed development of distant metastasis
A lot of histological subtypes (20): Heterogeneity in terms of clinical presentation, biological behaviour and sensitivity to treatment

- Mucoepidermoid carcinoma 30–35%
- Adenocarcinoma NOS 20%
- Adenoid cystic carcinoma (ACC) 10%
- Salivary duct carcinoma 5–10%

Concurrent with pathological diversity, there is remarkable genetic diversity with regard to the various genetic pathways and chromosomal rearrangements that govern each subtype
BACKGROUND

Salivary gland carcinoma

Data on systemic treatment are based on retrospective or nonrandomised Phase 2 trials.
There is no standard for cytotoxic or targeted therapy.

Chemotherapy is employed almost exclusively with a palliative aim in patients with metastatic and/or recurrent disease and has demonstrated **poor activity**.
Most common regimens are:

- Cisplatin, adriamycin, cyclophosphamide (CAP) for ACC and non ACC
- Carboplatin / paclitaxel for non ACC
- Platin / vinorelbine for ACC

Treatment should be reserved for those patients with symptoms and/or rapid disease progression.
BACKGROUND

Salivary gland carcinoma

Important advances have been made in the understanding of the molecular pathogenesis of SGCs.

Recent studies using next-generation sequencing and genomic and expression profiling methods have identified several genomic alterations of potential clinical significance. Targetable alterations are:

- Tyrosine kinase receptors
- Transcriptional coactivators
- Transcription factors

These alterations are important biomarkers for molecular diagnosis as well as for the development of new therapeutic strategies.
# GENOMIC ALTERATIONS

In 10 different salivary gland cancer histologic subtypes

<table>
<thead>
<tr>
<th>Typically low-grade salivary gland cancers (n = 264)</th>
<th>Typically higher grade salivary gland cancers (n = 359)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenoid cystic carcinoma</strong>&lt;br&gt;Patients (N) 154</td>
<td><strong>Muco-epidermoid carcinoma</strong>&lt;br&gt;57&lt;br&gt;<strong>Salivary duct carcinoma</strong>&lt;br&gt;44&lt;br&gt;<strong>Adenocarcinoma, not otherwise specified</strong>&lt;br&gt;117&lt;br&gt;<strong>Carcinoma, not otherwise specified</strong>&lt;br&gt;119&lt;br&gt;<strong>Carcinoma ex pleomorphic adenoma</strong>&lt;br&gt;22</td>
</tr>
<tr>
<td>GAs/tumor 1.6</td>
<td><strong>Myo-epithelial carcinoma</strong>&lt;br&gt;20&lt;br&gt;<strong>Adenocarcinoma, not otherwise specified</strong>&lt;br&gt;42&lt;br&gt;<strong>Carcinoma, not otherwise specified</strong>&lt;br&gt;58&lt;br&gt;<strong>Carcinoma ex pleomorphic adenoma</strong>&lt;br&gt;63</td>
</tr>
<tr>
<td>Median age in years 55</td>
<td><strong>Polymorphous low grade adenocarcinoma</strong>&lt;br&gt;3.6&lt;br&gt;<strong>Salivary duct carcinoma</strong>&lt;br&gt;3.6&lt;br&gt;<strong>Adenocarcinoma, not otherwise specified</strong>&lt;br&gt;67&lt;br&gt;<strong>Carcinoma, not otherwise specified</strong>&lt;br&gt;63&lt;br&gt;<strong>Carcinoma ex pleomorphic adenoma</strong>&lt;br&gt;65</td>
</tr>
<tr>
<td>Gender (% female/% male) 50% F / 50% M</td>
<td><strong>Mammary analog secretory carcinoma</strong>&lt;br&gt;12&lt;br&gt;<strong>Salivary duct carcinoma</strong>&lt;br&gt;28&lt;br&gt;<strong>Adenocarcinoma, not otherwise specified</strong>&lt;br&gt;61&lt;br&gt;<strong>Carcinoma, not otherwise specified</strong>&lt;br&gt;63&lt;br&gt;<strong>Carcinoma ex pleomorphic adenoma</strong>&lt;br&gt;65</td>
</tr>
<tr>
<td>Significant GAs (%) MYB-NF1B (65)</td>
<td><strong>ERBB2 (32)</strong>&lt;br&gt;46&lt;br&gt;<strong>ERBB2 (32)</strong>&lt;br&gt;46&lt;br&gt;<strong>ERBB2 (15)</strong>&lt;br&gt;48&lt;br&gt;<strong>ERBB2 (15)</strong>&lt;br&gt;48&lt;br&gt;<strong>ERBB2 (15)</strong>&lt;br&gt;48</td>
</tr>
<tr>
<td><strong>TP53 GA frequency (%)</strong>&lt;br&gt;4</td>
<td><strong>ERBB2 GA frequency (%)</strong>&lt;br&gt;0&lt;br&gt;<strong>PIK3CA GA frequency (%)</strong>&lt;br&gt;5&lt;br&gt;<strong>BRAF GA frequency (%)</strong>&lt;br&gt;0&lt;br&gt;<strong>Tumor mutational burden &gt;10 mut/Mb (%)</strong>&lt;br&gt;1</td>
</tr>
<tr>
<td><strong>TP53 GA frequency (%)</strong>&lt;br&gt;10</td>
<td><strong>ERBB2 GA frequency (%)</strong>&lt;br&gt;0&lt;br&gt;<strong>PIK3CA GA frequency (%)</strong>&lt;br&gt;3&lt;br&gt;<strong>BRAF GA frequency (%)</strong>&lt;br&gt;3&lt;br&gt;<strong>Tumor mutational burden &gt;10 mut/Mb (%)</strong>&lt;br&gt;3</td>
</tr>
<tr>
<td><strong>TP53 GA frequency (%)</strong>&lt;br&gt;0</td>
<td><strong>ERBB2 GA frequency (%)</strong>&lt;br&gt;0&lt;br&gt;<strong>PIK3CA GA frequency (%)</strong>&lt;br&gt;0&lt;br&gt;<strong>BRAF GA frequency (%)</strong>&lt;br&gt;0&lt;br&gt;<strong>Tumor mutational burden &gt;10 mut/Mb (%)</strong>&lt;br&gt;0</td>
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</tr>
</tbody>
</table>

**GA, genomic alterations**
Ross JS, et al. Ann Oncol 2017;28:2539–46. © 2017 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved.
MUCOEPIDERMOID CARCINOMA (MEC)

CRTC1-MAML2 translocation

Identification of a translocation: CRTC1-MAML2
Translocation between a CREB-regulated transcription coactivator, and mastermind-like gene 2 (MAML2)

Preclinical data suggest that this translocation is oncogenic

CRTC1/MAML2 translocations are seen in 50–65% of MECs, with a higher percentage found in low- and intermediate-grade tumours

It is not clear if the translocation is associated with survival

The molecular consequences of the fusion are still unclear
Recent studies have shown that the epidermal growth factor receptor (EGFR)-ligand AREG (amphiregulin) is a downstream target of the fusion. AREG upregulation leads to EGFR-signalling activation, as an autocrine manner, increasing cell growth and survival of MEC cells
In line with this observation, CRTC1–MAML2-positive MEC cells were shown to be highly sensitive to inhibition of EGFR-signalling in a xenograft model
Few data on in vivo EGFRi activity in mucoepidermoid carcinoma

MUCOEPIDERMOID CARCINOMA

Genomic alterations

Genomic alterations in 48 mucoepidermoid carcinomas

Comparison of genes with >1 genetic alterations in mucoepidermoid carcinomas

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All N = 48 (% total GA)</th>
<th>Low grade N = 7 (%)</th>
<th>Intermediate grade N = 16 (%)</th>
<th>High grade N = 25 (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total GAs, No. (% total GA)</td>
<td>163</td>
<td>16 (8.7)</td>
<td>42 (22.9)</td>
<td>125 (68.3)</td>
<td>0.019</td>
</tr>
<tr>
<td>GAs per sample, mean ± SD</td>
<td>3.8 (±3.1)</td>
<td>2.3 (±1.4)</td>
<td>2.6 (±1.5)</td>
<td>5.0 (±3.8)</td>
<td>0.019</td>
</tr>
<tr>
<td>Base substitutions/short indels, No. (%)</td>
<td>54 (29.5)</td>
<td>8 (14.8)</td>
<td>5 (9.3)</td>
<td>41 (75.9)</td>
<td>0.028</td>
</tr>
<tr>
<td>Amplifications, No. (%)</td>
<td>22 (12.0)</td>
<td>1 (4.5)</td>
<td>2 (9.1)</td>
<td>19 (86.4)</td>
<td>0.041</td>
</tr>
<tr>
<td>Homozygous deletions, No. (%)</td>
<td>35 (19.1)</td>
<td>1 (2.9)</td>
<td>20 (57.1)</td>
<td>14 (40)</td>
<td>0.011</td>
</tr>
<tr>
<td>Gene truncations, No. (%)</td>
<td>64 (35.0)</td>
<td>4 (6.3)</td>
<td>14 (21.9)</td>
<td>46 (71.9)</td>
<td>0.055</td>
</tr>
<tr>
<td>Rearrangements/fusions, No. (%)</td>
<td>8 (4.4)</td>
<td>2 (28)</td>
<td>1 (12.5)</td>
<td>5 (62.5)</td>
<td>0.459</td>
</tr>
</tbody>
</table>
MUCOEPIDERMOID CARCINOMA

Genomic alterations

TP53 and cyclin family alterations are common
ERBB2 amplification relatively uncommon <10%
Greater genetic complexity in high-grade vs low-grade
PI3K pathway activation common in high-grade, less common in low-grade tumours
Frequent alterations in DNA repair genes (BAP1 GAs 20%, BRCA GAs 10%)
FGF pathways targets
One BRAF V600E mutation

- Few data available on targeted therapies in MEC
- Clinical trials are required to determine the efficacy of EGFRi, PI3Ki, PARPi, histone deacetylase… based on the genomic profile of each patient

Wang K, et al. Ann Oncol 2017;28(4):748–53. © 2017 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved.
ADENOID CYSTIC CARCINOMA
MYB/NFIB fusion

Most common tumour in the minor salivary glands and the second most common tumour in the major salivary glands

Prolonged indolent course but perineural invasion and distant metastatic spread++

Associated with a specific genetic translocation: t(6;9)(q22–23;p23–24): MYB/NFIB fusion

MYB and NFIB: 2 transcription factors

The fusion leads in loss of negative regulatory elements and to MYB overexpression

MYB is probably the major oncogenic driver

Preclinical data have shown that MYB-NFIB is regulated by AKT-dependent IGF1R signalling (key target for therapy?)

ATR is a MYB downstream target that is overexpressed in ACC and ACC PDXs. Treatment with the clinical ATR kinase inhibitor VX-970 induced apoptosis in MYB-positive ACC cells and growth inhibition in ACC PDXs

PDXs, patient-derived xenografts

ADENOID CYSTIC CARCINOMA

Other genomic alterations and potential targets

EGFR frequently overexpressed but rarely mutated

- Modest activity of EGFR inhibitors in terms of overall response rate but sometimes prolonged survival

High expression of KIT in 65–90% of ACCs, no specific driver mutations

- Lack of activity of imatinib except in a Phase 2 (Guigay J, et al.) with 2 partial response of 21 patients with high level of KIT expression

VEGF expression is an independent prognostic factor for survival

Recurrent gains of PDGF and PDGFR

- Multityrosine kinase inhibitors targeting VEGF, KIT and PDGF (sunitinib, axitinib, sorafenib, pazopanib, lenvatinib) have been evaluated with modest activity with ORR between 0% to 15%

- In the PACSA trial, pazopanib treatment resulted in an improvement in PFS but the randomised trial to confirm it could not be initiated

ADENOID CYSTIC CARCINOMA

VEGFi: Randomised Phase 2 study of axitinib versus observation in patients with recurred or metastatic adenoid cystic carcinoma

Study design
- Multicentre trial by Korea Cancer Study Group (KCSG HN16-08)
- Prospective, open-label, randomised Phase 2 trial (NCT02859012)

Key inclusion criteria
- Recurrence/metastatic/unresectable ACC
- Disease progression within 9 months of prior informed consents
- ECOG PS 0-1
- Age ≥20
- Measurable lesion
- Prior chemotherapy is allowed (any chemo line)

Response rate

<table>
<thead>
<tr>
<th></th>
<th>Axitinib (n=27)</th>
<th>Observation (n=27)</th>
<th>Observation, after crossover (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>27 (100.0)</td>
<td>14 (51.9)</td>
<td>21 (80.8)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>0 (0.0)</td>
<td>13 (48.1)</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>Overall response rate, % (95% CI)</td>
<td>0.0 (0.0–12.7)</td>
<td>0.0 (0.0–12.7)</td>
<td>11.5 (2.5–30.2)</td>
</tr>
<tr>
<td>Disease control rate, % (95% CI)</td>
<td>100.0 (87.2–100.0)</td>
<td>51.9 (31.9–71.3)</td>
<td>92.3 (74.9–99.1)</td>
</tr>
</tbody>
</table>

- First randomised study to prove efficacy of a VEGFi
- With objection: the 2 groups were imbalanced (more metastatic patients in the control group)

R 1:1
Baseline screening
Axitinib 5 mg twice daily
Until PD or unacceptable toxicity
If progression, crossover permitted

Axitinib

Observation

NGS by Foundation One CDx panel

R1:1

Axitinib

observation

6-month PFS rate, % (95% CI)
- Axitinib: 73 (52–86)
- Observation: 23 (9–41)

Median PFS, months (95% CI)
- Axitinib: 10.8 (7.1–13.6)
- Observation: 2.8 (1.7–4.2)

Hazard ratio (95% CI)
- Axitinib: 0.25 (0.14–0.48; p<0.0001)

Keam B, et al. ASCO 2020; Abstract 6503. Reproduced by permission from Prof Bhumusuk Keam.
ADENOID CYSTIC CARCINOMA

Notch pathway

NOTCH1 is upregulated in ACC tissues / normal tissues, this upregulation was even higher in ACC tissues with metastasis and recurrence compared with ACC without metastasis

NOTCH1, NOTCH2, SPEN, FBXW7 (Notch pathway genes): Commonly altered genes

NOTCH1 mutations correlate:

- with solid histology
- advanced disease stage at diagnosis
- higher incidence of liver and bone metastasis
- shorter RFS and OS

ADENOID CYSTIC CARCINOMA

Notch pathway

Phase 1 in 22 patients with LY30399478 (Notch inhibitor):¹
  - 1 PR, 15 (68%) SD, 5 PD
  - 4 patients with SD for at least 6 months
  - PFS 5.3 months

Phase 2 of AL101 (4 mg and 6 mg weekly) in patients with NOTCH activating mutations²
40 patients treated, 39 (treated in the 4 mg cohort) evaluable
  - PR: 6 patients 15%
  - SD: 21 patients 53%
  - PD: 12 patients 30%

1. Even C, et al. Invest New Drugs 2020;38(2):402–9. Reproduced under the terms of the Creative Commons Attribution 4.0 International License (available at: http://creativecommons.org/licenses/by/4.0/; accessed May 2021); 2. Ferrarotto R, et al. Ann Oncol 2020;31 (suppl_4):s663. © 2020 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved.
SALIVARY DUCT CARCINOMA

10% of SGCs, highly aggressive subtype, poor prognosis
Bears a pathological resemblance to ductal carcinoma of the breast
Higher mutational burden than many other salivary carcinomas, 78% of patients >1 mutation

Genomic analysis of the 50 most altered genes of SDCs:
- 3.6 GA / tumour
- TP53 mutations most frequent alteration
- PIK3CA mutations including hotspot mutation (E542K, E545K, H1047R)
- EGFR mutations, but no activating mutations
- ERBB2 amplification (30%)
SALIVARY DUCT CARCINOMA

Androgen deprivation for androgen-receptor-positive advanced SDC

Most salivary duct carcinomas express the androgen receptor (67–89%)

Table 4. Reported cases of hormone therapy for androgen positive–salivary gland carcinoma

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>N</th>
<th>Treatment</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hulst (1994) [13]</td>
<td>Case report</td>
<td>1</td>
<td>LH-RH analogue</td>
<td>CR 1</td>
</tr>
<tr>
<td>Soper (2013) [16]</td>
<td>Case report</td>
<td>1</td>
<td>CAB + IMRT</td>
<td>PR 1</td>
</tr>
<tr>
<td>Yamamoto (2014) [17]</td>
<td>Case report</td>
<td>1</td>
<td>Bicalutamide</td>
<td>SD 1</td>
</tr>
<tr>
<td>Agbarya (2014) [18]</td>
<td>Case report</td>
<td>1</td>
<td>Bicalutamide + letrozole</td>
<td>PD 1</td>
</tr>
<tr>
<td>Locati (2016) [19]</td>
<td>Retrospective</td>
<td>17</td>
<td>CAB</td>
<td>CR 3, PR 8, SD 4, PD 2</td>
</tr>
<tr>
<td>Boon (2016) [20]</td>
<td>Retrospective</td>
<td>31</td>
<td>ADT²</td>
<td>CR 4, PR 10, SD 17</td>
</tr>
<tr>
<td>Present study</td>
<td>Phase II</td>
<td>36</td>
<td>CAB</td>
<td>CR 4, PR 11, SD 16, PD 5</td>
</tr>
</tbody>
</table>

²Drug: unknown.

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; LH-RH analogue, luteinizing hormone–releasing hormone analogue; CAB, combined androgen blockade; IMRT, intensity modulated radiation therapy; ADT, androgen deprivation therapy.

Combined androgen blockade seems to be more active than androgen deprivation therapy.
SALIVARY DUCT CARCINOMA

Androgen deprivation for androgen-receptor-positive advanced SDC

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients, N = 36</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>67 (46–90)</td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>28 (78)</td>
<td></td>
</tr>
<tr>
<td>≥75</td>
<td>8 (22)</td>
<td></td>
</tr>
<tr>
<td>Median follow-up length, months (range)</td>
<td>15 (1.3–38)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (94)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30 (83)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6 (17)</td>
<td></td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parotid gland</td>
<td>27 (75)</td>
<td></td>
</tr>
<tr>
<td>Submandibular gland</td>
<td>6 (17)</td>
<td></td>
</tr>
<tr>
<td>Minor salivary gland</td>
<td>3 (8)</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivary duct carcinoma</td>
<td>34 (94)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma, NOS</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>AR positivity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>6 (17)</td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>30 (83)</td>
<td></td>
</tr>
<tr>
<td>HER2 status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>4 (11)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>32 (89)</td>
<td></td>
</tr>
</tbody>
</table>

Disease status
- Locally advanced disease$^b$ | 3 (8) |
- Recurrent/metastatic disease | 33 (92) |

Disease extent
- Loco-regional disease | 13 (36) |
- Distant metastasis | 23 (64) |
- Visceral metastasis | 15 (42) |
- Previously untreated | 8 (22) |
- Previous treated | 28 (78) |
- Surgery | 27 (75) |
- Radiation therapy | 23 (64) |
- Chemotherapy | 16 (44) |
- Prior (neo)adjuvant therapy | 5 (14) |
- Prior concomitant chemoradiotherapy | 11 (31) |
- Prior lines of chemotherapy for RM disease
  - 0 | 26 (72) |
  - ≥1 | 7 (14) |

$^b$HER2 status according to breast cancer ASCO/CAP guideline (supplementary Reference 1, available at Annals of Oncology online).

$^b$Locally advanced disease was defined as that which met at least one of the following conditions in newly diagnosed patients: (i) primary lesion of T4b, (ii) cervical lymph node metastasis of N2c or N3 according to UICC/TNM, 7th edition, and (iii) cervical lymph node metastasis invading the carotid artery.

ECOG, Eastern Cooperative Oncology Group; AR, androgen receptor; HER2, human epidermal growth factor receptor 2.
SALIVARY DUCT CARCINOMA
Androgen deprivation for androgen-receptor-positive advanced SDC

Table 2. Treatment efficacy \((N = 36)\)

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Best overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N)</td>
</tr>
<tr>
<td>CR</td>
<td>4</td>
</tr>
<tr>
<td>PR</td>
<td>11</td>
</tr>
<tr>
<td>SD</td>
<td>16</td>
</tr>
<tr>
<td>PD</td>
<td>5</td>
</tr>
<tr>
<td>Confirmed objective response (CR + PR)</td>
<td>15</td>
</tr>
<tr>
<td>Clinical benefit (CR + PR + SD (\geq) 24 weeks)</td>
<td>27</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>8.8</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>30.5</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival; CI, confidence interval; NR, not reached.

Best reduction from baseline in target lesions. Of the 36 patients, 27 patients (75%) showed tumour shrinkage relative to baseline.

- High efficacy of combined androgen blockade
- EORTC1206 trial: Randomised trial comparing CAB vs chemotherapy in non pretreated patients with the objective to define the place of CAB in R/M SDC
ADENOCARCINOMA OF THE SALIVARY GLANDS
ERBB2 amplification in SGCs, HER2 expression according to the subtype

ERBB2 amplification frequency: All tumours excluding breast and gastric/gastroesophageal junction tumours

<table>
<thead>
<tr>
<th>Intercalated duct subtypes</th>
<th>No. 2+</th>
<th>No. 3+</th>
<th>No. screened</th>
<th>% positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoid cystic</td>
<td>2</td>
<td>1</td>
<td>70</td>
<td>4</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0</td>
<td>3</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Acinic cell</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Carcinoma expleomorphic adenoma</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Myoepithelial</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Excretory duct subtypes</th>
<th>No. 2+</th>
<th>No. 3+</th>
<th>No. screened</th>
<th>% positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucoepidermoid</td>
<td>1</td>
<td>2</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Salivary duct</td>
<td>1</td>
<td>9</td>
<td>12</td>
<td>83</td>
</tr>
<tr>
<td>Squamous</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>1</td>
<td>1364</td>
<td>17</td>
</tr>
</tbody>
</table>

*One poorly-differentiated cancer was 3+.

This plot includes solid tumours (467/28 106 samples and 442/25 637 patients) with a minimum of 50 sequenced tumours and ERBB2 amplification >0% using MSK-IMPACT assay. The numbers in the brackets are the total number of sequenced tumours (cBioPortal.org).

After breast cancers and gastric/gastroesophageal junction tumours, SGCs: First tumour type with HER amplification (8%)
Mainly: Adenocarcinoma NOS and SDCs

ADENOCARCINOMA OF THE SALIVARY GLANDS

Targeting HER2

Table 1
Literature review on HER2-targeted therapies in metastatic salivary duct carcinoma.a

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Number of patients</th>
<th>Therapy</th>
<th>Clinical benefit</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agulnik et al. [12]</td>
<td>Phase II trial</td>
<td>4</td>
<td>Lapatinib</td>
<td>No CR or PR</td>
<td>Unknown</td>
</tr>
<tr>
<td>Limaye et al. [13]</td>
<td>Case series</td>
<td>5</td>
<td>Trastuzumab, paclitaxel and carboplatin</td>
<td>1 × CR</td>
<td>18 months</td>
</tr>
<tr>
<td>Perissinotti et al.</td>
<td>Case series</td>
<td>11</td>
<td>3 patients: Trastuzumab only</td>
<td>2 × PR</td>
<td>Unknown</td>
</tr>
<tr>
<td>Falchook et al., [15]</td>
<td>Phase I trial</td>
<td>3</td>
<td>8 patients: Trastuzumab and chemotherapyb</td>
<td>2 × PD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 × SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 × PD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 × non-evaluable</td>
<td></td>
</tr>
<tr>
<td>De Block et al. [16]</td>
<td>Case series</td>
<td>3</td>
<td>Trastuzumab, lapatinib and bevacizumab</td>
<td>1 × PR</td>
<td>3 months</td>
</tr>
<tr>
<td>Takahashi et al. [9]</td>
<td>Phase II trial</td>
<td>45</td>
<td>Trastuzumab and chemotherapyb</td>
<td>1 × SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 × PD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 × PR</td>
<td>11 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31 × CR/PR → Response rate 69%</td>
<td>11.3 months</td>
</tr>
</tbody>
</table>


a Case-reports were excluded.

b Different combinations of chemotherapy were used.

- Better activity of monoclonal antibody vs TKI
- Better activity of combination of anti-HER2 and chemotherapy vs anti-HER2 monotherapy

ADENOCARCINOMA OF THE SALIVARY GLANDS

Targeting HER2 with antibody drug conjugate

A Phase 2 trial of ado-trastuzumab emtansine for patients with HER2 amplified or mutant cancers (NCT02675829)

Patient characteristics

| N | Total patients treated | 10 |
| N | Age, median (range)    | 65 (36–90) |
| N | Sex, male              | 90% |
| N | Disease histology        |
|   | Adenocarcinoma          | 1 |
|   | Poorly differentiated carcinoma with apocrine features | 3 |
|   | Carcinoma NOS           | 6 |
| N | Lines of prior systemic therapy, median (range) | 2 (0–3) |
| N | Anti-androgen therapy   | 50% |
| N | HER2-targeted therapy   | 20% |

Correlating NGS with FISH and IHC

<table>
<thead>
<tr>
<th>Patients</th>
<th>NGS (HER2 amplification by adjusted fold change)</th>
<th>HER2 FISH (HER2/CEP17 ≥2)</th>
<th>HER2 IHC (3+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10 of 10</td>
<td>8 of 8</td>
<td>10 of 10</td>
</tr>
<tr>
<td>(range)</td>
<td>(2.8–22.8)</td>
<td>(2.5–9.7)</td>
<td></td>
</tr>
</tbody>
</table>
ADENOCARCINOMA OF THE SALIVARY GLANDS
Targeting HER2 with antibody drug conjugate

Best overall response

Ado-trastuzumab emtansine is highly efficacious in patients with ERBB2-amplified SGCs
The study has met its primary endpoint; a cohort expansion is warranted to confirm these results

The best anti-HER2 strategy (chemo + trastuzumab, ado-trastuzumab, pertuzumab+ trastuzumab…) needs to be determined
MAMMARY ANALOGUE SECRETORY CARCINOMA

- A recently described distinctive salivary gland tumour
- Characterised by histological and immunohistochemical resemblance to secretory carcinoma of the breast
- Harbours a recurrent balanced chromosomal translocation t(12;15)(p13;q25), which leads to a fusion gene between the ETS Variant 6 (ETV6) gene on chromosome 12 and the neurotrophic receptor tyrosine kinase (NTRK)3 gene on chromosome
- Some cases harbour rearrangements involving ETV6 and a non-NTRK3 partner
- Fusion results in dysregulated activation of several biochemical-signalling pathways that promote oncogenic initiation and growth

Durable partial response with entrectinib in a MASC

Clinical entrectinib resistance mediated by the appearance of a novel NTRK3 G623R mutation
MAMMARY ANALOGUE SECRETORY CARCINOMA

pan-Trk inhibitor

Analysis of Phase 1 and Phase 2 evaluating larotrectinib in TRK fusion-positive cancers (identified by NGS n=50, FISH n=5):

- N=55 patients including 12 patients with salivary gland carcinoma
- ORR=75%
- Median DOR not reached after 8.3 months of FU
- Median PFS not reached after a median of FU of 9.9 months
- Salivary gland carcinoma with PD as best response was pretreated with TRK inhibitor and had a NTRK3 G623R mutation

Overall response rate, according to investigator and central assessment*:

<table>
<thead>
<tr>
<th>Response (%)</th>
<th>Investigator assessment (n=55)</th>
<th>Central assessment (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (95% CI)†</td>
<td>80 (67–90)</td>
<td>75 (61–85)</td>
</tr>
<tr>
<td>Best response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>64‡</td>
<td>62</td>
</tr>
<tr>
<td>Complete response</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Could not be evaluated</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

*Percentages may not total 100 because of rounding; †Best overall response derived from responses as assessed at specified time points according to Response Evaluation Criteria in Solid Tumors, version 1.1; ‡Data include 1 patient who had a partial response that was pending confirmation at time of database lock, response was subsequently confirmed, and patient’s treatment and response are ongoing.

HRAS mutations: Up to 20% of high grade subtypes of SGCs (mucoepidermoid carcinoma, adenocarcinoma NOS, SDC)

13 patients (with PD within 6 months before treatment initiation) treated with TIPIFARNIB

Best ORR: 8% (1 durable PR [14 months]), 7 patients with a SD with a median duration of 9 months

Median PFS: 7 months

Median OS: 18 months (58.6 % alive at 12 m, 19.5 alive at 24 m)

Benefit not correlated with:
- the HRAS-mutant single nucleotide variant detected
- the co-occurrence of PI3K mutation

Promising clinical activity

SALIVARY GLAND CARCINOMA

Immunotherapy
Overall, low expression of PD1-PDL1

In an analysis of 217 surgically resected SGC specimens, high-programmed death ligand-1 expression was reported in high-grade SGC subtypes previously shown to be associated with aggressive behaviour (e.g., SDC and squamous cell carcinoma)

Programmed death ligand-1 positivity in tumour cell membrane and tumour-infiltrating mononuclear cells is associated with shorter OS and poor disease-free survival in SGC

TMB was lower (5% of tumours featuring 10 mut/Mb) in the more indolent subtypes of SGCs: Compared with the more aggressive subtypes (no tumour exceeded 21% frequency for 10 mut/Mb), TMB is significantly lower than other tumour types

IMMUNOTHERAPY

NISCAHN: Phase 2 with nivolumab in SGCs

KEYNOTE 028:¹
On the 142 screened patients, only 33 were PDL-1+; 26 patients enrolled. Disease progression was not required for inclusion. Modest activity of pembrolizumab with ORR of 12%, median PFS of 3.8 months, PFS rate at 6 months: 20.7%, median OS 13 months.

NISCAHN: Phase II with Nivolumab in SGCs²

<table>
<thead>
<tr>
<th>Gender</th>
<th>ACC (N = 46)</th>
<th>Non-ACC (N = 52)</th>
<th>ACC</th>
<th>Non-ACC</th>
<th>Primary Endpoint</th>
<th>Non-ACC</th>
</tr>
</thead>
<tbody>
<tr>
<td>M (%)</td>
<td>26 (56.5%)</td>
<td>29 (55.8%)</td>
<td>33.3% [90%CI: 21.8-46.6]</td>
<td>NPRtum</td>
<td>14% [90%CI: 6.8-24.7]</td>
<td></td>
</tr>
<tr>
<td>F (%)</td>
<td>20 (43.5%)</td>
<td>23 (44.2%)</td>
<td>N = 15 / 45</td>
<td>Pts alive without progression at 6 months</td>
<td>N = 7 / 50</td>
<td></td>
</tr>
<tr>
<td>Age median (range)</td>
<td>59 (36-80)</td>
<td>63 (29-81)</td>
<td>N = 46</td>
<td>Secondary Endpoints</td>
<td>N = 52</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>Yes</td>
<td>42 (91.3%)</td>
<td>49 (94.2%)</td>
<td>3 (5.8%)</td>
<td>11 (23.9%)</td>
<td>16 (30.8%)</td>
</tr>
<tr>
<td>Disease at inclusion</td>
<td>No</td>
<td>4 (8.7%)</td>
<td>3 (5.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locoregional relapse</td>
<td>Yes</td>
<td>35 (76.1%)</td>
<td>36 (69.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at inclusion</td>
<td>No</td>
<td>11 (23.9%)</td>
<td>16 (30.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Treatments</td>
<td>Surgery</td>
<td>46(100%)</td>
<td>52 (100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>39 (84.8%)</td>
<td>47 (90.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metastatic Chemotherapy</td>
<td>42 (91.3%)</td>
<td>47 (90.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histology for non-ACC (as per local review)</td>
<td>23 (50%)</td>
<td>34 (65.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mucoepidermoid carcinoma</td>
<td>6 (13.5%)</td>
<td>2 (3.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma</td>
<td>28 (53.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salivary duct carcinoma</td>
<td>2 (3.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>16 (30.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Primary endpoint not met for non-ACC
• Primary endpoint met for ACC but with limited activity with ORR <10%
• PD-L1 expression not available

Active systemic treatment for advanced and/or metastatic SGCs still represents an important unmet need.

Several genomic alterations of potential clinical significance have been identified.

The discovery of translocation generated gene fusions has allowed the improvement of the SGC classification.

Most targeted therapies have shown lack of efficacy, probably related to the fact that there was no biomarker selection.

More recent studies have been conducted on the basis of molecular-driven selection and demonstrated more efficacy: Androgen deprivation in AR-positive SDC, trastuzumab and ado-trastuzumab emtansine in HER2-positive SDC, NTRK-inhibitors in MASC (larotrectinib approved for solid tumours with NTRK fusions).

Limited clinical activity of immune checkpoint inhibitors, predictive biomarkers are required.

Combinatorial strategies should be considered to turn these cold tumours into hot tumours.

Multinational cooperation is required to conduct well designed clinical trials (homogeneity of subtypes, disease stage, progressive disease at inclusion, mandatory QoL analysis and PROs...).
OTHER TUMOUR TYPES

Genomic alterations and targeted therapies
Tremendously diverse group of neoplasms ranging from carcinomas to lymphomas and sarcomas of various types. The 2005 WHO classification included no fewer than 68 separate tumour entities in the sinonasal tract. Nevertheless, some sinonasal neoplasms did not fit neatly into any of those diagnostic categories. New distinct tumour entities have been described in the 2017 WHO classification. Interestingly, most of these newly described diagnostic entities are defined in part on their underlying viral or genetic mechanisms, supporting their separate classification and in some cases, offering potential therapeutic targets for the future.

New entities:
- NUT carcinoma
- Biphenotypic sinonasal sarcoma

Emerging entities (provisional entities mentioned in the differential diagnosis of other tumours):
- SMARCB1-deficient carcinoma
- HPV-related carcinoma with adenoid cystic features
- Renal cell-like adenocarcinoma
SINONASAL CARCINOMA

2005 WHO CLASSIFICATION

WHO histological classification of tumours of the nasal cavity and paranasal sinuses

---

2017 WHO CLASSIFICATION

WHO classification of tumours of the nasal cavity, paranasal sinuses and skull base

---

NUT CARCINOMA

Aggressive subtype of squamous carcinoma

Patients of all ages with a predilection for young adults, median age 21 years (0–78)

Poor prognosis with a median survival <1 year

In 50% of cases, nodes involvement or metastasis at diagnosis

NUT rearrangement: in 2/3 of cases with BRD4, and in 1/3 of cases with BRD3 or NSD3

39% of the NMC arise from the HN region

NMC considered as the prototype **BET driven carcinoma** (BRD4: BET protein family)

NUT by IHC: Diffuse nuclear staining; sensitivity 87%, specificity 100%, diagnosis of NMC if >50% of tumour nuclei

NUT CARCINOMA

NUT-BRD4 fusion is associated with decreased histone acetylation

**BETi:** Birabresib – Phase 1: Of 9 patients, 3 PR, 3 SD, 3 PD; retrospective data: of 4 patients, 2 PR and 2 SD, 2 patients with OS of 18 and 19 months

**HDACi:** Vorinostat: dramatic response reported

CUDC-907, a dual HDACi/PI3K inhibitor: a case with prolonged SD (32 months)

All patients treated with BETi or HDACi will develop resistance and relapse during treatment: Combination? With anti-PD1?

SMARCB1 (INI-1) is a tumour suppressor gene located on chromosome 22q11.2
Inactivation implicated in the pathogenesis of a family of malignant neoplasms including paediatric atypical teratoid/rhabdoid tumour, rhabdoid tumours of the kidney and soft tissue, epithelioid sarcoma, myoepithelial carcinoma of soft tissue, extraskeletal myxoid chondrosarcoma …

In 2014, description of a form of SMARCB1 (INI-1) deficient sinonasal carcinoma resembling to sinonasal undifferentiated carcinoma or non-keratinizing squamous cell carcinoma, and rarely to myoepithelial carcinoma

Morphology of small round cell tumour
In IHC: Pancytokeratin+, loss of nuclear expression of INI-1 / SMARCB1, NUT–, HPV–, various expression of squamous and neuroendocrine markers
Differential diagnosis of non-keratinizing squamous cell carcinoma, sinonasal undifferentiated carcinoma, NUT carcinoma, and melanoma

Aggressive tumour, frequent local invasion into the brain and/or skull base.
Median age 52 years [19–89]
Risk of relapse +++ (local regional recurrence or distant metastasis)

SMARCB1 DEFICIENT CARCINOMA

SMARCB1/INI-1 is a core subunit of the SWI/SNF complex

- **epigenetic pathways and chromatin remodelling** through activation of PRC
- **cell cycle inhibition** via cyclin D1 suppression, activation of RB tumour suppressor gene, induction of tumour suppressor protein P16
- and inhibition of **WNT/β-catenin**

Loss of INI-1 disrupts the SWI/SNF complex function and thereby leads to increased activity in EZH2

Tazemetostat (EPZ-6438), a potent small molecule that selectively inhibits EZH2, has demonstrated activity in INI-1 deficient tumours in Phase 1 (64 patients, ORR 38%)

Phase 2 is ongoing

Accessible through an established, company-planned Expanded Access Program


OTHER TUMOUR TYPES

Immunotherapy
No data on efficacy of immune checkpoint inhibitors in sinonasal carcinoma

Nivolumab / pembrolizumab approved for squamous cell carcinoma of HN, so they can be used for SCC of sinonasal cavities

ACSE NIVOLUMAB (NCT 03012581)

- 50 rare head and neck tumours including 30 sinonasal carcinoma (intestinal type adenocarcinoma: 9; SNUC: 7; squamous cell carcinoma: 5; esthesioneuroblastoma: 3; others: 6)
- Nivolumab: 240 mg / 2 weeks
OTHER TUMOURS TYPES

Conclusions

New described entities with underlying molecular alterations and potential targeted treatment

No data on immunotherapy efficacy
CONCLUSIONS

Determination of the histologic type / subtype of tumour is pivotal (clinical evolution [ACC ≠ SDC], targetable molecular alteration depending on the subtype…)

- Expert pathologist +++
- For salivary gland carcinoma, determination of (as it will guide to a specific treatment with demonstrated efficacy):
  - HER2 status (IHC / FISH) / ERBB2 (NGS)
  - Androgen Receptor (IHC)
  - NTRK fusion (FISH, NGS…)
- For sinonasal cavities carcinoma, if the proposed diagnosis is SNUC (sinonasal undifferentiated carcinoma), ensure that these markers have been determined :
  - NUT (IHC, FISH, …)
  - INI1 (IHC)
CONCLUSIONS

Systemic treatments (and particularly cytotoxics) have limited efficacy

- No standard treatment
- VEGFi (axitinib) more efficient than observation in ACC
- Favour inclusion into clinical trials
- Perform a molecular profile +++ (HRASmut, SMARCB1−, NUT, DNA repair alteration, PI3K mut….) to guide into clinical trials, or expanded access program...

No indication for immunotherapy outside of clinical trials except for SCC of sinonasal cavities
Tumour mutational burden >10 : Consider anti-PD1 (clinical trial or approval depending on the country)
THANK YOU FOR YOUR ATTENTION

Questions

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