Notch1 mutations to define a subgroup of adenoid cystic carcinoma (ACC): Tumor stage, propensity to bone and liver metastasis, risk of relapse, and overall survival. (Abstract #6081)

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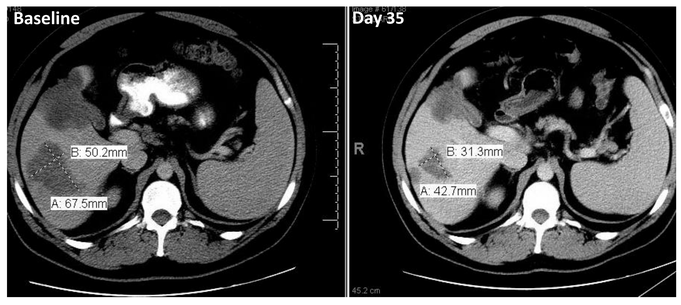
Background:

- ACC corresponds to ~ 25% of salivary gland cancers
- It is chemotherapy refractory and there is no standard of care treatment for patients with metastatic disease
- ACC genotyping revealed alterations in the Notch (N) pathway in 13-29% of cases [1,2]
- One ACC patient identified in our institution with an activating Notch1 (N1) mutation achieved a partial response after 2 cycles of a N1 inhibitor in a phase I trial (*Fig. 1*)[3]

In this study, we investigate the clinical and pathologic characteristics of N1 mutant ACC.

***Fig 1*. N1 mutant ACC patient achieved a partial response upon treatment with the Notch1 inhibitor OMP-52M51, under the clinical trial NCT01778439.**
(Image provided as courtesy by Oncomed)



38% reduction of target lesions

- 28 yo gentleman, progressed through 4 lines of systemic therapy
- N1 activating mutations in the tumor (S2467fs* and L1600Q),
- cell-free DNA identified a 3rd mutation (V1721G)

Methods:

- N1 sequencing was performed in 102 pts (71 using WES and 31 using a 50 gene panel including N1 exons 26, 27, 34)
- IHC for N1 intracellular domain (NICD) was performed in 71 samples to evaluate its value as a surrogate for N1 activating mutations.
- Comparisons between tumor characteristics and clinical outcomes in patients with or without activating N1 mutations (PEST or HD domain) were performed.

Results:

***Fig 2*. N1 mutations identified in ACC**

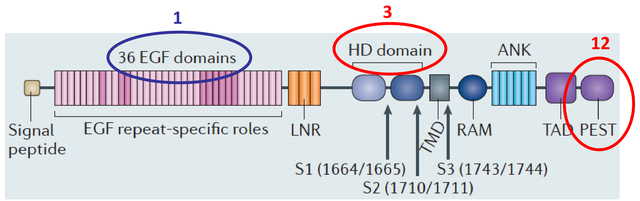


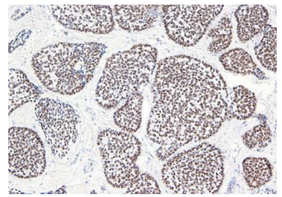
Image adapted from Reference 4

- N1 activating mutations in 14 pts (13.7%)
- Only 1 patient with a mutation in the EGF domain (non-activating)

***Table 1*. Patient's characteristics**

Overall population characteristics	N or Median	% or Range
AGE	52	19-75
SEX		
Male	63	62 %
Female	39	38 %
DISEASE SITE		
Maxillary sinus	20	20 %
Base of tongue	17	17 %
Parotid	12	12 %
Palate	12	12 %
Trachea	11	11 %
Submandibular and sublingual	18	18 %
Unknowns and others sites	12	12 %
HISTOLOGICAL SUBTYPE		
Tubular	7	7 %
Cribriform	34	33 %
Solid	37	36 %
Unknown	24	24 %
T STAGE		
T1/T2	17	17 %
T3	34	33 %
T4	40	39 %
Unknown	11	11 %
DISEASE STAGE AT DIAGNOSIS		
I/II/III	42	41 %
IVA/B	36	35 %
IVC	16	16 %
Unknown	8	8 %
TREATMENT MODALITY TO THE PRIMARY TUMOR		
Surgery	94	92 %
Concurrent chemoradiation	6	6 %
No treatment	2	2 %
ADJUVANT RADIATION THERAPY (+/- CT)	80	78 %
SYSTEMIC THERAPY	45	44 %

***Fig 3*. N1 pathway activation demonstrated by IHC for NICD**



- 71 samples tested for IHC: Sensitivity = 100%; Specificity = 51.6%

***Table 2*. Frequency of tumor recurrence and overall patients outcomes**

	N or Median	% or moths
TUMOR RECURRENCE		
Yes	81	79 %
No	21	21 %
RECURRENCE SITE		
Local	25	25 %
Lung	53	52 %
Pleura	16	16 %
Bone	35	34 %
Liver	13	13 %
Others	24	24 %
RECURRENCE FREE SURVIVAL	30.8	months
OVERAL SURVIVAL	108.4	months

***Table 3*. Correlations between clinico-pathologic characteristics and N1 mutational status**

	N1 mut	N1 wt	OR	p value
Stage at diagnosis				
I/II/III	2/14 (14%)	40 /88 (45%)		
IVA/B	8/14 (57%)	28/88 (32%)		**0.03**
IVC	4/14 (29%)	12/88 (14%)		
Unknown	0 (0%)	8/88 (9%)		
Histological subtype				
Tubular/cribriform	1/14 (7%)	40/88 (45%)		**0.003**
Solid	11/14 (79%)	26/88 (30%)		
Unknown	2/14 (14%)	22/88 (25%)		
Disease recurrence				
Local	7/14 (50%)	18/88 (20%)	**3.8**	**0.038**
Lung	5/14 (36%)	48/88 (55%)	0.5	0.25
Pleura	1/14 (7%)	15/88 (17%)	0.4	0.69
Bone	9/14 (64%)	26/88 (30%)	**4.2**	**0.01**
Liver	5/14 (36%)	8/88 (9%)	**5.4**	**0.01**
Others	7/14 (50%)	17/88 (19%)	**4.1**	**0.02**

***Fig 4*. Recurrence free survival according to N1 mut status**

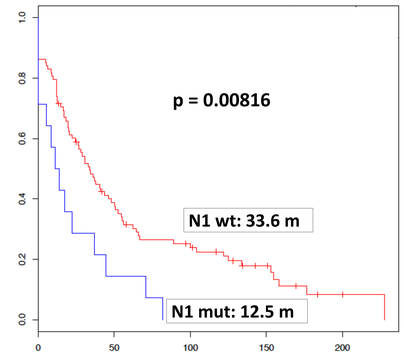


***Fig 5*. Overall survival according to N1 mut status**

Conclusions:

- N1 activating mutations occurs in 13.7% (14/102) of ACC pts
- N1 mutation defines a more aggressive phenotype, with a distinct pattern of metastatic spread, higher risk of relapse, and shorter overall survival
- The identification of genetic events that activate N1 and the encouraging response observed in an index case suggest an opportunity to further explore N1 as a therapeutic target in ACC.

References:

1. Stephens, P.J., et al., J Clin Invest, 2013.
2. Ho, A.S., et al., Nat Genet, 2013.
3. Patnaik, A., et al., Eur J Cancer, 2014.
4. Anderson ER, et al., Nat Rev Drug Discov, 2014.