Descriptive Characterization of *NOTCH1*-Mutated Mantle Cell Lymphoma

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INTRODUCTION

NOTCH1 mutations occur in 5-12% of mantle cell lymphoma (MCL) and are associated with aggressive histology and inferior survival[1,2]. The NOTCH1 gene encodes a transmembrane receptor; mutations in the PEST domain result in truncation, resistance to proteasomal degradation, and constitutive pathway activation[3,4].

However, not all NOTCH1 variants are functionally equivalent. Truncating mutations (frameshifts, nonsense, fusions) are definitively loss-of-function (LOF), while missense variants are of uncertain significance (VUS)[4,5]. We hypothesized that functional classification of NOTCH1 variants would identify clinically distinct subgroups.

AIM

To characterize clinical outcomes in NOTCH1-mutated MCL stratified by variant pathogenicity using CancerVar classification.

METHOD

Study Design: Retrospective analysis of 27 patients with NOTCH1-mutated MCL at Moffitt Cancer Center. NGS was performed at diagnosis (59%) or relapse (41%).

Variant Classification: NOTCH1 variants were classified into three functional categories. Truncating mutations (frameshifts, nonsense, fusions) were classified as loss-of-function (LOF) based on mutation type. Missense variants were classified as variants of uncertain significance (VUS) and further stratified using CancerVar into high-risk VUS (Tier 2-3, Score 7-8) or low-risk VUS (Tier 3, Score ≤5).

Outcomes: First-line response, BTK inhibitor response and progression free survival were compared across classification groups and treatment modalities.

CONCLUSIONS

Variant class separated first-line response, but not survival.

LOF patients were markedly more likely to be primary refractory to first-line therapy, yet the progression-free survival curves overlapped and the difference did not reach significance.

Treatment failure was the dominant feature of this cohort. 44% were primary refractory to first-line therapy, 45% progressed or died within 24 months, and 91% of patients given a BTK inhibitor progressed on it. Fewer than half ever achieved a documented complete response at any point.

Refractoriness carried forward across lines of therapy. Of the 11 patients refractory to first-line treatment, 6 went on to a BTK inhibitor and 4 progressed on that as well. No patient given a BTK inhibitor at third line or later responded.

RESULTS

KEY FINDINGS

- **27 patients:** 17 LOF, 8 high-risk VUS, 2 low-risk VUS.
- **44% were primary refractory to first-line therapy**; **45% progressed or died within 24 months** (POD24).
- Median PFS **38.0 months**; **11 of 27 (41%) have died.**
- **12 of 27 (44%) received a BTK inhibitor** — median line 2, median **5.0 months** on drug.
- **91% progressed on the BTK inhibitor**; none treated at third line or later responded.
- LOF was more often refractory than high-risk VUS (**56% vs 14%**), but PFS did not differ (P = 0.27).

Table 1. Baseline characteristics (n=27)

Characteristic	Value
Age, median (range), y	66 (49–82)
Male	21 (81%)
Bulky disease >5 cm	12 (44%)
LDH elevated (>225 U/L)	14 (61%)
Ki-67, range	<10–95%
IgHV unmutated	16 (84%)
TP53 mutated	8 (31%)

Table 2. First-line Outcomes by NOTCH1 variant class

NOTCH1 variant class	Patients	Complete response	Partial or mixed	Primary refractory	Median PFS, mo
LOF	17	5 (31%)	2 (12%)	**9 (56%)**	25.3
High-risk VUS	8	**5 (71%)**	1 (14%)	1 (14%)	51.0
Low-risk VUS	2	1 (50%)	0 (0%)	1 (50%)	1.0
All patients	**27**	**11 (44%)**	**3 (12%)**	**11 (44%)**	**38.0**

Table 3. First-line treatment received

First-line treatment	Patients	Median mo on therapy	Complete response	Partial or mixed	Primary refractory	Stopped for progression	Later BTKi
Combination chemoimmunotherapy	16	3.9	**9 (60%)**	1 (7%)	**5 (33%)**	7 (44%)	7 (44%)
Bendamustine-based	6	4.3	4 (67%)	1 (17%)	1 (17%)	2 (33%)	2 (33%)
R-CHOP-based	7	3.4	5 (83%)	0 (0%)	1 (17%)	2 (29%)	4 (57%)
Other chemotherapy	3	5.4	0 (0%)	0 (0%)	3 (100%)	3 (100%)	1 (33%)
Single-agent / non-chemotherapy	11	6.0	**2 (20%)**	2 (20%)	**6 (60%)**	6 (55%)	5 (45%)
Rituximab alone	7	1.0	1 (14%)	2 (29%)	4 (57%)	4 (57%)	2 (29%)
Other non-chemotherapy	4	21.9	1 (33%)	0 (0%)	2 (67%)	2 (50%)	3 (75%)

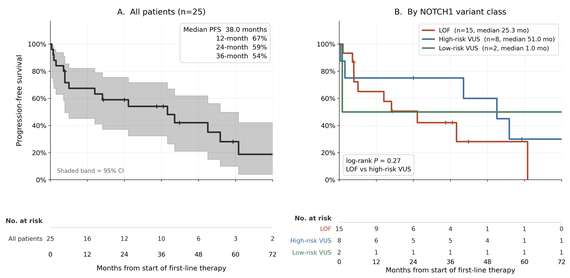

Figure 1. Progression-free survival from start of first-line therapy. (A) All patients. (B) Stratified by NOTCH1 variant class. Tick marks are censored observations; numbers at risk are shown below each panel. 25 of 27 patients had a recorded first-therapy date.

Table 4. BTK inhibitor experience

	Treated	Progressive disease	Complete response	Median mos on drug
By NOTCH1 variant class				
LOF	7	**6 (100%)**	0 (0%)	4.0
High-risk VUS	4	4 (100%)	0 (0%)	7.4
Low-risk VUS	1	0 (0%)	1 (100%)	ongoing
By line at which BTKi was given				
First line	2	2 (100%)	0 (0%)	21.9
Second line	5	3 (75%)	**1 (25%)**	2.0
Third line or later	5	**5 (100%)**	0 (0%)	4.0
By agent				
Ibrutinib	6	6 (100%)	0 (0%)	20.3
Acalabrutinib	2	1 (100%)	0 (0%)	4.0
Zanubrutinib	4	3 (75%)	1 (25%)	6.0
All treated with a BTKi	**12**	**10 (91%)**	**1 (9%)**	**5.0**

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CONTACT INFORMATION

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