Loss of MGMT Protein Expression by Immunohistochemistry is Associated with Response to Capecitabine/Temozolomide in Neuroendocrine Neoplasms (NENs)

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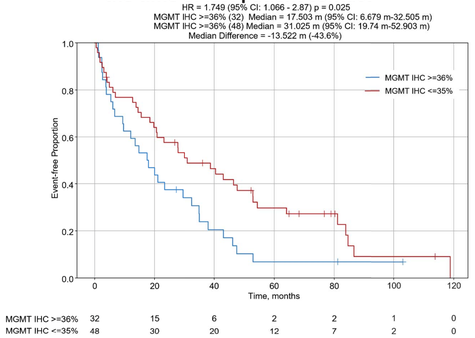
Introduction

- A recent prospective phase II study (ECOG-ACRIN E2211) demonstrated that O6-methylguanine-DNA methyltransferase (MGMT) deficiency was associated with a significant response to capecitabine and temozolomide (CAPTEM) in pancreatic neuroendocrine neoplasms (NENs), however, routine MGMT analysis in NENs was not recommended.
- Our study sought to demonstrate whether loss of MGMT protein expression is associated with improved overall survival (OS) in patients receiving CAPTEM for NENs from various tumor sites.

Materials and Methods

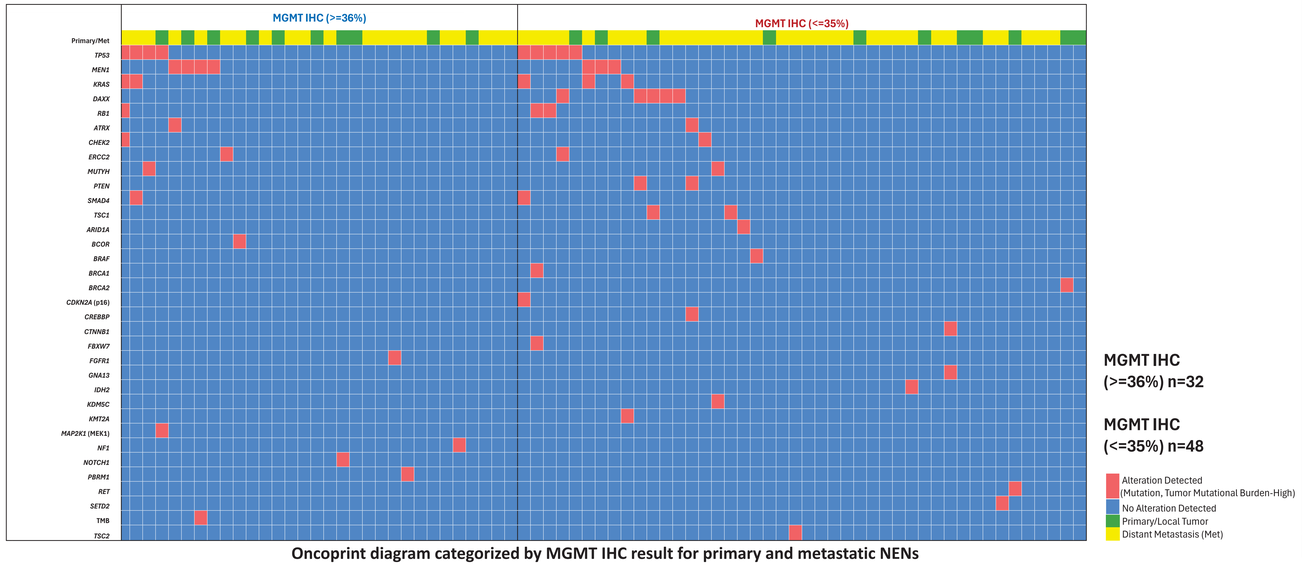
- Paraffin-embedded tumor samples were evaluated by immunohisto-chemistry (IHC) using an MGMT monoclonal antibody. Intact MGMT protein expression (IHC positivity) was defined as any staining intensity (>1+) in ≥36% of neoplastic cells.
- IHC and pyrosequencing for MGMT promotor methylation was studied in an independent cohort of 58 NENs.
- Real-world overall survival (OS) was extrapolated from insurance claims data with Kaplan-Meier estimates from the date of first CAPTEM administration to the last date of contact.

OS from the time of first CAPTEM administration to the time of last patient contact



57% Concordance of IHC & Pyrosequencing

		Pyrosequencing n (%)		n (% within total)
		Methylated	Unmethylated	Total
IHC	IHC ≤ 35% (negative expression)	4 (80)	24 (45.3)	28 (48.3)
	IHC ≥ 36% (positive expression)	1 (20)	29(54.7)	30 (51.7)



Oncoprint diagram categorized by MGMT IHC result for primary and metastatic NENs

Results

The study cohort included 80 patients (42 men, 38 women) with a median age of 57 years [range: 19-89]). They had various NENs (33 pancreatic, 17 intestinal, 7 pulmonary, 8 other, and 15 of unknown origin) treated with CAPTEM. The median OS for the 48 patients with MGMT negative tumors was 31 months compared to 17.5 months for the 32 patients whose tumors were MGMT positive by IHC (HR: 1.75 [95% CI: 1.066-2.87], p=0.025). IHC results from the independent cohort of 58 NENs showed only 57% concordance with pyrosequencing results.

Conclusions

MGMT promotor status by IHC may be a clinically useful indicator that predicts improved OS for NENs treated with CAPTEM but does not reliably correlate with the findings of MGMT promoter methylation by pyrosequencing.

References

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