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Treatment Sequence in Advanced Small Bowel Neuroendocrine Neoplasms: A Simulation Study

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BACKGROUND

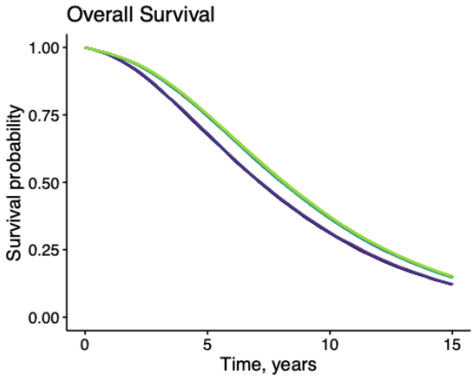
Patients with small bowel neuroendocrine neoplasms (SBNENs) typically receive somatostatin analogues as first-line therapy. Upon progression, options include Peptide Receptor Radionuclide Therapy (PRRT) followed by Everolimus (Eve) or the reverse sequence. However, PRRT increases the risk of life-limiting acute myeloid dysplasia/myelodysplastic syndrome AML/MDS. In May 2025, the FDA approved Cabozantinib (Cabo) for previously treated SBNENs. The optimal sequencing of these therapies remains a subject of clinical debate.

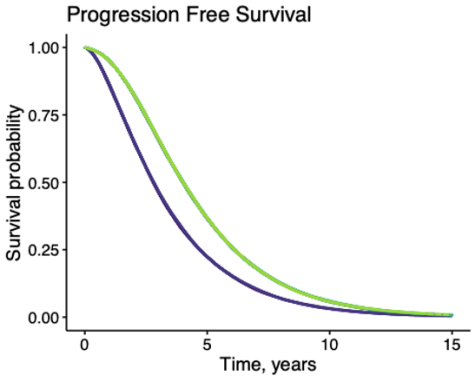
METHODS

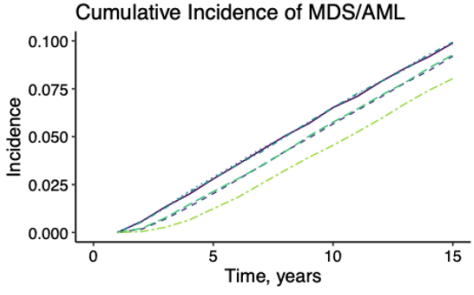
We conducted a clinical decision analysis comparing six strategies in patients with SBNENs who progress after first-line treatment: i) no access to Cabozantinib (PRRT→Eve and Eve→PRRT); ii) Cabozantinib at the third line (PRRT→Cabo→Eve and Ev→Cabo→RRT); ii) Cabozantinib at the fourth line (PRRT→Eve→Cabo and Eve→PRRT→Cabo). We compared the treatment strategies using a discrete event simulation model designed to reflect real-world patient demographics (50% female; mean age of 63 years, standard deviation of 9 years). Patients who experience progression on all lines of therapy are assumed to receive salvage treatment and may ultimately die from disease progression. In any strategy, patients initiating PRRT are at risk of developing and dying from AML/MDS. All patients have sex- and age-specific risks of mortality from other causes. Incidence functions were derived from published literature and supplemented by expert opinion.

RESULTS

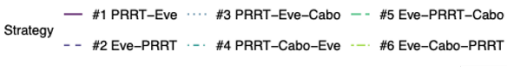
Figure 1 presents overall survival (OS), progression-free survival (PFS), and 5-year cumulative incidence of MDS/AML for the six treatment strategies. Incorporating cabozantinib increases PFS by approximately 1.2 years and OS by about 0.9 years on average. Delaying PRRT lowers the risk of MDS/AML, with the Eve→Cabo→PRRT strategy showing the lowest incidence (0.018). However, MDS/AML risk has minimal influence on overall survival. Among strategies including cabozantinib, the difference in PFS and OS between early (second-line) and delayed (fourth-line) PRRT use is less than two months







Strategy	MDS/AML IR, 5y	Median PFS	Median OS
#1 PRRT–Eve	0.035 (0.034–0.037)	2.80 (2.77–2.82)	7.13 (7.07–7.19)
#2 Eve–PRRT	0.027 (0.026–0.029)	2.81 (2.79–2.84)	7.17 (7.11–7.23)
#3 PRRT–Eve–Cabo	0.036 (0.034–0.038)	4.00 (3.97–4.03)	8.04 (7.98–8.11)
#4 PRRT–Cabo–Eve	0.035 (0.034–0.037)	4.01 (3.98–4.04)	8.07 (8.02–8.13)
#5 Eve–PRRT–Cabo	0.028 (0.026–0.029)	4.03 (4.00–4.06)	8.07 (8.01–8.13)
#6 Eve–Cabo–PRRT	0.018 (0.017–0.019)	4.01 (3.98–4.04)	8.15 (8.09–8.22)



CONCLUSIONS

Adding cabozantinib improved survival outcomes, increasing PFS and OS by over a year. Sequencing PRRT earlier or later had minimal survival impact. Delaying PRRT reduced MDS/AML risk, with the Eve→Cabo→PRRT strategy offering the best overall balance of efficacy and safety.

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