Enhanced efficacy of anti-VEGFR2/taxane therapy after progression on immune checkpoint inhibition (ICI) in patients with metastatic gastroesophageal adenocarcinoma (mGEA).

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Abstract

Background:
Most pts with mGEA do not respond to ICI or anti-VEGFR2 (ramucirumab/paclitaxel [RAM/TAX])[1,2]. We unexpectedly observed durable responses in 2 patients on RAM/TAX after progression on an ICI trial (KN-059)[3]. We performed a pilot to examine if ICI impacts efficacy of subsequent RAM/TAX in a larger cohort and explored alterations in the tumor microenvironment.

Methods:
All patients with mGEA at Mayo Clinic who received RAM/TAX (2014-19) were included (N = 87). Outcomes were best objective response rate (ORR), progression-free survival (PFS), duration of response (DOR), and overall survival (OS). Chi-square and multivariate (MV) logistic and Cox regression were used.

Results:
15 consecutive patients with measurable mGEA received ICI immediately followed by RAM/TAX after irRECIST progression. Most patients (95%) did not respond to ICI. Yet on RAM/TAX, ORR was 73%. In these patients (who received ICI followed by RAM/TAX), PFS on RAM/TAX was longer than on last chemotherapy before ICI (12.3 vs 3.0 m, P < .001). Outcomes on RAM/TAX in these patients were significantly better than in patients who received RAM/TAX alone (see Table). Associations were strengthened after adjusting for total lines of therapy, line of therapy of RAM/TAX, age, and ECOG PS. Exploratory analysis of paired tumor biopsies collected pre-ICI and on RAM/TAX revealed that the frequency of intratumoral immunosuppressive FOXP3+ Tregs decreased on RAM/TAX, whereas the frequency of antitumor CD8+ T cells was preserved.

Conclusions:
RAM/TAX immediately preceded by ICI was associated with significantly higher OS, PFS, ORR, and DOR than RAM/TAX alone, suggesting ICI may enhance efficacy of subsequent anti-VEGFR/taxane therapy. This novel sequence of therapy will be tested prospectively in a new randomized phase 2 trial (NCT04069273).

Patients & Methods

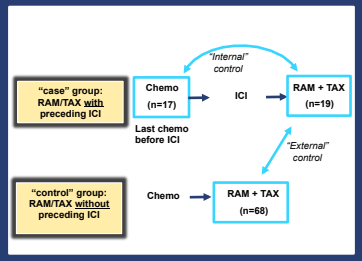


Figure 1 – Analytic Approach: 4 regimen and 2 key comparisons.

	RAM/TAX … With preceding ICI (n=19)*	Without preceding ICI (n=68)	P
Age, y (median)	58.2	62.2	.638
Male	15 (79%)	53 (78%)	.925
ECOG PS 0-1 before RAMTAX	16 (84%)	60 (89%)	.284
RAMTAX 3L+	17 (89%)	24 (35%)	<.0001
Total lines of therapy (median)	3	3	.142
Tumor diff, poor	11 (58%)	44 (67%)	.571
HER2 positive	4 (21%)	11 (16%)	.363

PD-L1 and MMR status not available for majority of patients who received RAM/TAX without preceding PD-1.

* In patients who received RAM/TAX with preceding PD-1, 95% (18/19) of patients were pMMR, and 5% (1/19) were dMMR.

Table 1 – Patient baseline characteristics (n=87).

RAM/TAX …	With preceding ICI	Without preceding ICI	p
	n = 19 [a]	n = 68	
ORR	58%	18%	< .001
DOR	10.5 m	4.3 m	.021
OS	15.0 m	7.6 m	.003

[a]*Includes 4 pts with non-measurable disease*

Summary

- Patients with mGEA had significantly improved RR, DOR PFS, and OS on RAM/TAX with (*vs.* without) preceding ICI.
- In the same group of patients, RR and PFS were higher on RAM/TAX (with preceding ICI) *vs.* on last chemo before ICI.
- This better-than-expected outcome on RAM/TAX with preceding ICI was observed in patients whose tumors never regressed on ICI alone.

Conclusions

- Predefined serial immunotherapy combination of PD-1 blockade followed by anti-VEGFR2/taxane therapy could benefit mGEA patients with primary resistance to anti-PD-1 therapy.
- This serial immunotherapy combination may be a novel option for patients with primary resistance to ICI and will be tested prospectively in a new randomized phase 2 trial (NCT04069273).

Results

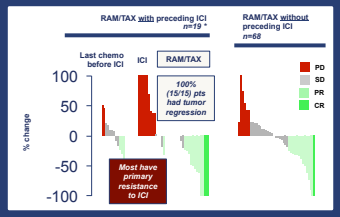


Figure 2 – Best response assessment of target lesions.

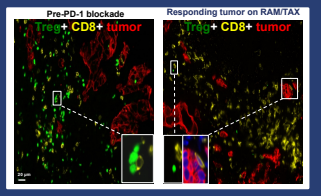


Figure 3 – Immunofluorescent analysis from a responder: substantial reduction (post vs. pre-Treatment) in intratumoral density of immunosuppressive FOXP3+ Tregs, with preserved density of antitumor CD8+ T cells.

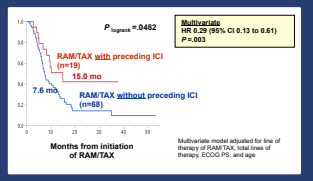


Figure 4 – Overall survival (OS): RAM/TAX with *vs.* without preceding ICI.

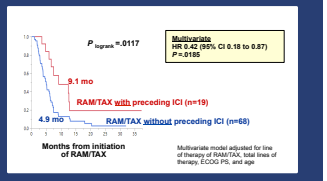


Figure 5 – Progression-free survival (PFS): RAM/TAX with *vs.* without preceding ICI.

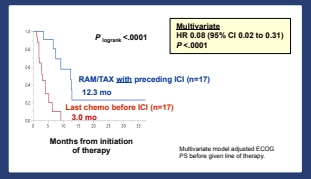
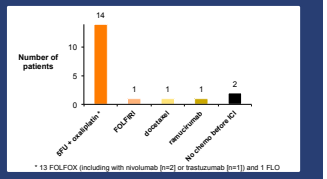


Figure 6 – Progression-free survival (PFS): RAM/TAX with preceding ICI *vs.* Last chemo before ICI.



* 13 FOLFOX (including with nivolumab [n=2] or trastuzumab [n=1]) and 1 FLO

Figure 7 – Last chemotherapy regimen received before ICI.

References

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2. Fuchs CS, Doi T, Jang RWJ et al. J Clin Oncol 2017;35(suppl 15):4004A.
3. Chakrabarti, S., Dong, H. M., Parijadi, H., Ross, H. J., Yoon, H. H. Oncologist, 23(7), 840-843.

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