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NANETS

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Outcomes with 5-Fluorouracil, Doxorubicin and Streptozocin (FAS) and Subsequent Therapies in Patients with Well Differentiated Pancreatic Neuroendocrine Tumors (PanNETs)

[1]Michael Lam, [2]Jane Rogers, [1]Daniel Halperin, [1]Cecile Dagohoy, [1]James Yao, [1]Arvind Dasari

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- **Background**: Targeted agents for PanNETs improve progression free survival (PFS) with little tumor regression. Recent data suggest response rates (RR) of 33% to temozolomide (tem) regimens. We aimed to evaluate outcomes of PanNET patients (pts) on FAS and its impact on subsequent everolimus or tem-based therapies.
- **Methods**: Pts with advanced PanNET with measurable disease diagnosed from 1992 to 2013 were included in this single center, retrospective study. Bolus 5-FU 400 mg/m^2, streptozocin 400 mg/m^2 (both IV days 1-5) and doxorubicin 40mg/m^2 IV (day 1) were repeated every 28 days. RR was assessed using Response Evaluation Criteria in Solid Tumors version 1.1.
- **Results**: Of 243 eligible pts, 220 were evaluable for RR and PFS with median (m) age 56. The majority (92%) had metastatic, non-functional PanNETs and 26% received prior systemic therapy (somatostatin analogues in 65%). RR to FAS was 41% [95% confidence interval (CI), 36-48%]. After a median follow up of 61 months, mPFS was 20 [95% CI, 15-23] months, median time on therapy was 5.5 months and median overall survival was 63 [95% CI, 60-71] months. The main $\geq$ grade 3 toxicities were hematologic (10%) and gastrointestinal (5.5%). Dose reductions were required in 32% of pts, 3.4% due to cardiac toxicity. The mPFS on everolimus (n=108; 68% second line) was 10 [8.0-14] months. Tem-based regimens used as salvage (n=54, 51% 4th line or beyond) resulted in a PR of 13% with mPFS of 5.2 [4.0-12] months.
- **Conclusions**: In the largest cohort of PanNets treated with chemotherapy reported, FAS demonstrated activity without significant safety concerns. FAS therapy did not appear to affect subsequent PFS with everolimus and this sequence is being evaluated prospectively in the SEQTOR study. Responses were noted with subsequent tem-based regimens although PFS was possibly limited by the line of therapy.

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Background

- Targeted agents for well differentiated neuroendocrine tumors (PanNETs) improve progression free survival (PFS)[1,2]
- Tyrosine kinase or mTOR inhibitors result in little tumor regression[1,2]
- Cytotoxic chemotherapy demonstrates anti-tumor activity in PanNETs
- Prior studies reported response rates (RR) of 39-43% to FAS chemotherapy[3,4]
- Recent data suggest a RR of 33% to temozolomide (tem) based regimens[5]

Objective

- To evaluate clinical activity through RR and PFS of FAS chemotherapy in PanNET patients (pts)
- To assess impact of FAS chemotherapy on subsequent administration of everolimus or tem-based therapies

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Methods

- This was a single center, retrospective study.
- Pts with advanced PanNET with measurable disease diagnosed from 1992 to 2013 were included.
- Bolus 5-FU 400 mg/m^2, streptozocin 400 mg/m^2 (both IV days 1-5) and doxorubicin 40mg/m^2 IV (day 1) were repeated every 28 days.
- RR was assessed using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
- Pts without serial imaging within the institution were excluded for RR and PFS evaluation
- PFS and overall survival (OS) were estimated using the Kaplan Meier method

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Results 1

- Of 243 eligible pts, 220 were evaluable for RR and PFS
- The median age was 56 years [**table 1**]
- The majority of pts (92%) had metastatic, non-functional PanNETs [**table 1**]
- 26% received prior systemic therapy (somatostatin analogues in 65%) [**table 1**]
- RR to FAS was 41% [95% confidence interval (CI), 36-48%]
- After a median follow up of 61 months, mPFS was 20 [95% CI, 15-23] months [**figure 1**]
- The median time on therapy was 5.5 months and mOS was 63 [95% CI, 60-71] months **[figure 2**]
- The main ≥ grade 3 toxicites were hematologic (neutropenia 10%) and gastrointestinal (nausea/vomiting 5.5%). Dose reductions were required in 32% of pts, 3.4% due to cardiac toxicity [**table 2**]

Variable	Level	Overall
		243
Age (years), median [IQR]		56 [47 - 63]
Gender	Female	106 (44)
	Male	137 (56)
Metastasis	M0	20 (8)
	M1	223 (92)
Prior systemic treatment	No	181 (74)
	Yes	62 (26)
Prior SSA	No	203 (84)
	Yes	40 (16)

IQR – interquartile range; M0 – no metastasis; M1 – metastasis; SSA – somatostatin analog

Table 1: Baseline characteristics

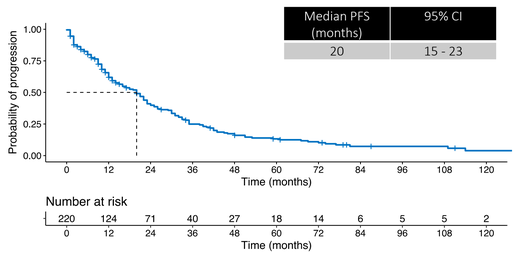

Figure 1: PFS on FAS

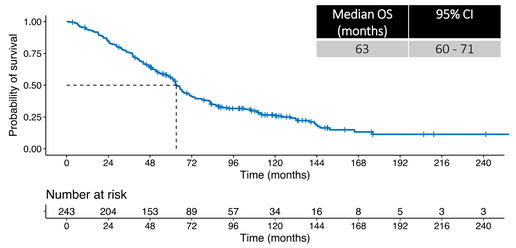

Figure 2: OS on FAS

Toxicity	N (%)
Hematologic	
- Neutropenia	22 (10)
- Thrombocytopenia	3 (1.4)
Gastrointestinal	
- Nausea/vomiting	12 (5.5)
- Diarrhea	11 (5.0)

Table 2: Grade 3 / 4 toxicity

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Results 2

- The mPFS on everolimus (n=108; 68% second line) was 10 [95% CI, 8.0-14] months [**figure 3**]
- Tem-based regimens used as salvage (n=54, 51% 4th line or beyond) [**figure** 4] resulted in a PR of 13% [**figure 5**] with mPFS of 5.2 [95% CI, 4.0-12] months [**figure 6**]

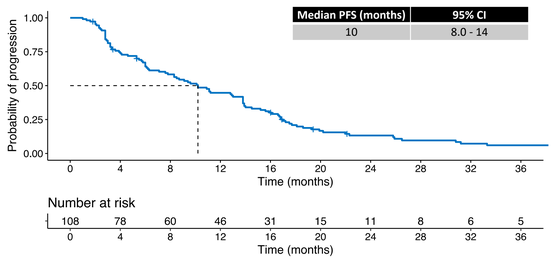

Figure 3: PFS on everolimus

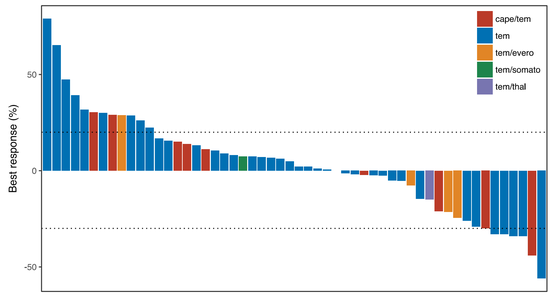

Figure 5: Waterfall plot of best response on tem

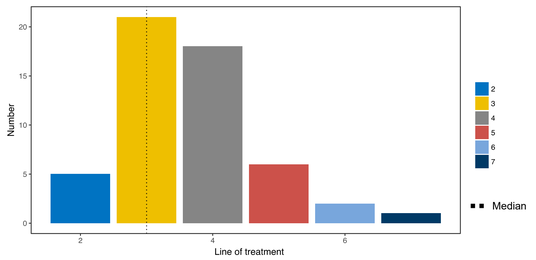

Figure 4: Line of tem-based treatment

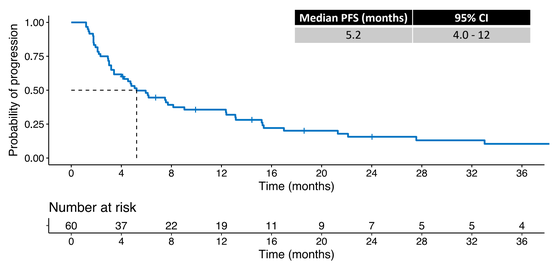

Figure 6: PFS on tem-based treatment post FAS

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Abstract
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Conclusion

- In the largest cohort of PanNETs treated with chemotherapy reported, FAS demonstrated activity without significant safety concerns
- FAS therapy did not appear to affect subsequent PFS with everolimus and this sequence is being evaluated prospectively in the SEQTOR study
- Responses were noted with subsequent tem-based regimens although PFS was possibly limited by the line of therapy

References

1. Raymond E. Sunitinib maleate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011; 364:501.
2. Yao JC. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011; 364:514.
3. Dilz LM. Streptozocin/5-fluorouracil chemotherapy is associated with durable response in patients with advanced pancreatic neuroendocrine tumours. Eur J Cancer 2015; 51:1253.
4. Kouvaraki MA. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 2004; 22:4762.
5. Kunz PL. A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group. J Clin Oncol 36, 2018 (suppl; abstr 4004).

Baseline characteristics

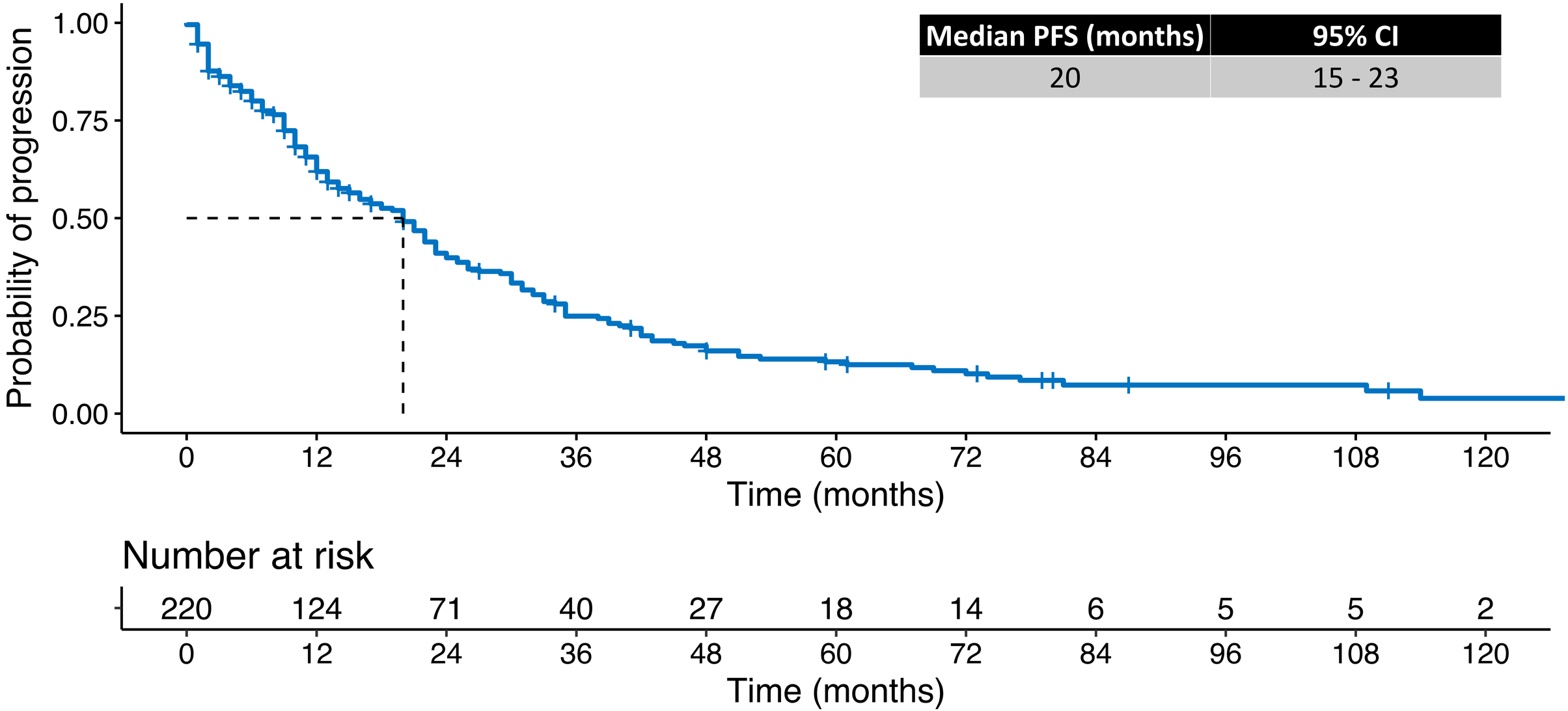
Variable	Level	Overall (%)
		243
Age (years), median [IQR]		56 [47 - 63]
Gender	Female	106 (44)
	Male	137 (56)
Metastasis	M0	20 (8)
	M1	223 (92)
Genetic syndrome	Sporadic	231 (95)
	MEN1	12 (5)
Functional status	Functional	26 (11)
	Non-functional	216 (89)
Prior primary resection	No	191 (79)
	Yes	52 (21)
FAS line of therapy	First line	208 (86)
	Second or later	33 (14)

Variable	Level	Overall (%)
CgA at baseline	Elevated	124 (69)
	Normal	57 (31)
Prior systemic treatment	No	181 (74)
	Yes	62 (26)
Prior SSA	No	203 (84)
	Yes	40 (16)
Prior everolimus	No	229 (94)
	Yes	14 (6)
Prior sunitinib	No	239 (98)
	Yes	4 (2)
Prior pazopanib	No	241 (99)
	Yes	2 (1)
Prior chemotherapy	No	220 (90)
	Yes	23 (10)

Abbreviations:
M0 – no metastasis; M1 – metastasis; CgA – Chromogranin A; SSA – somatostatin analogs

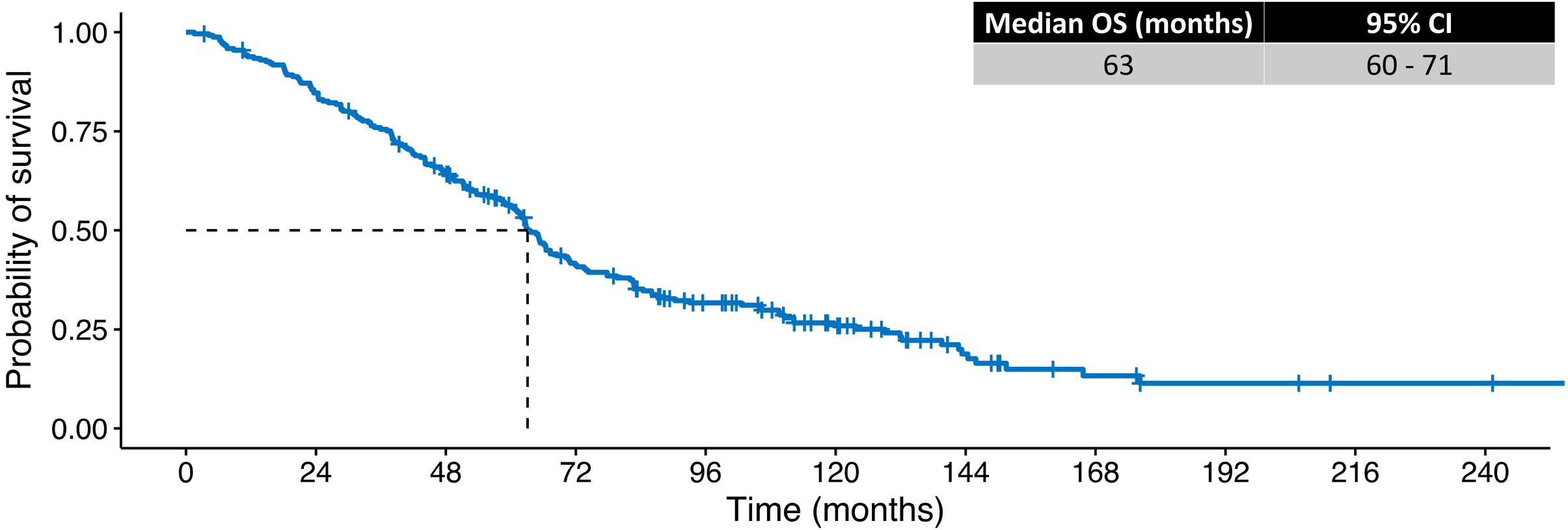
PFS on FAS chemotherapy

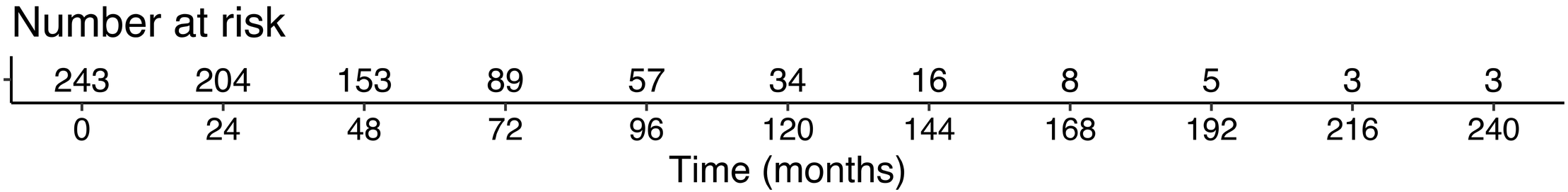
Median PFS (months)	95% CI
20	15 - 23



OS on FAS chemotherapy

Median OS (months)	95% CI
63	60 - 71



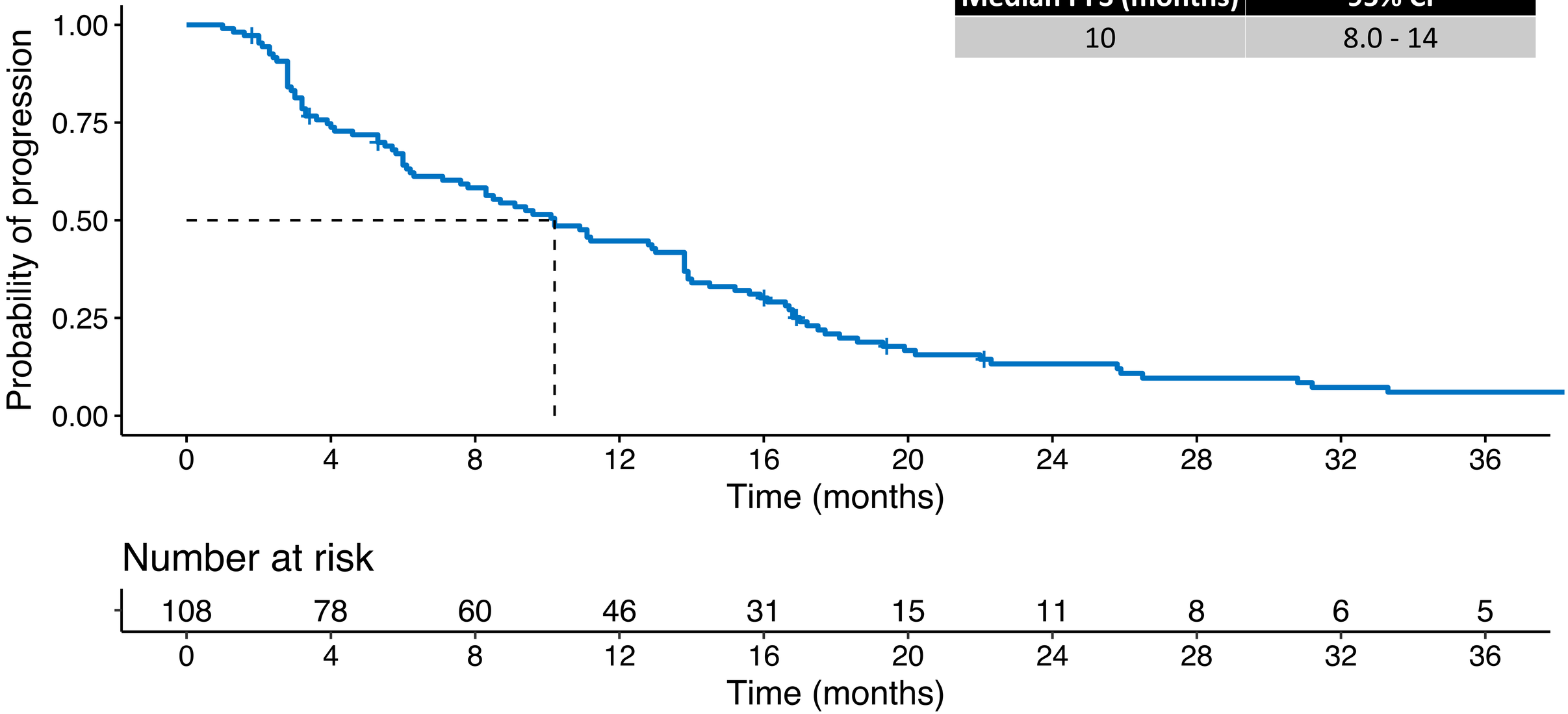


Grade 3 / 4 toxicities on FAS chemotherapy

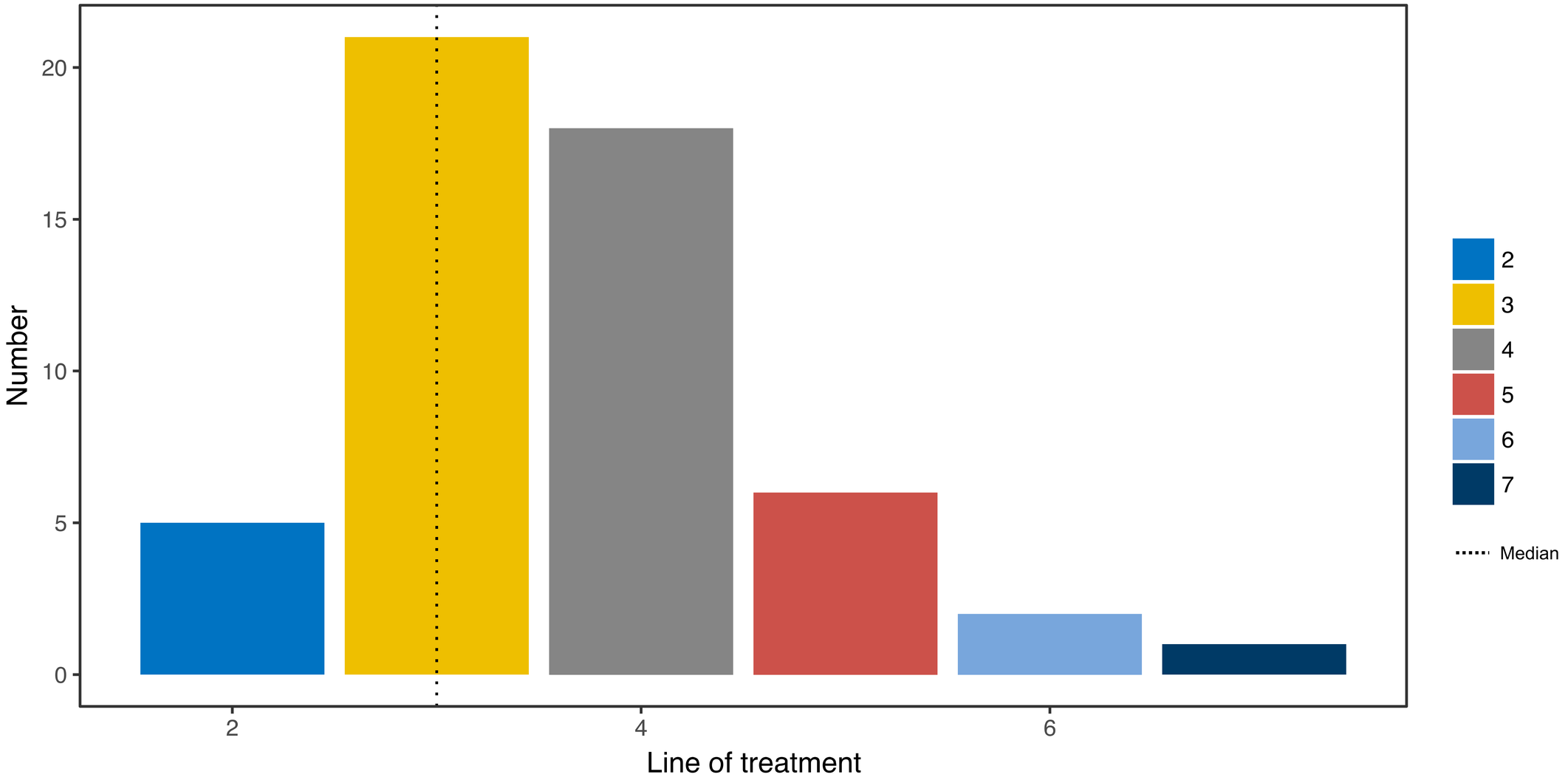
Toxicity	N (%)
Hematologic	
- Neutropenia	22 (10)
- Thrombocytopenia	3 (1.4)
- Anemia	2 (0.9)
Gastrointestinal	
- Nausea/vomiting	12 (5.5)
- Mucositis	8 (3.6)
- Diarrhea	11 (5.0)
Fatigue	6 (2.7)
Blood glucose	
- Hypoglycemia	2 (0.9)
- Hyperglycemia	5 (2.3)
Appetite loss	4 (1.8)
Cardiac	3 (1.4)
Fever	3 (1.4)
Elevated serum creatinine	2 (0.9)
Edema	2 (0.9)
Hepatic	
-Elevated LFTs	1 (0.5)
Hand-foot syndrome	1 (0.5)
Pancreatitis	1 (0.5)

PFS on everolimus therapy

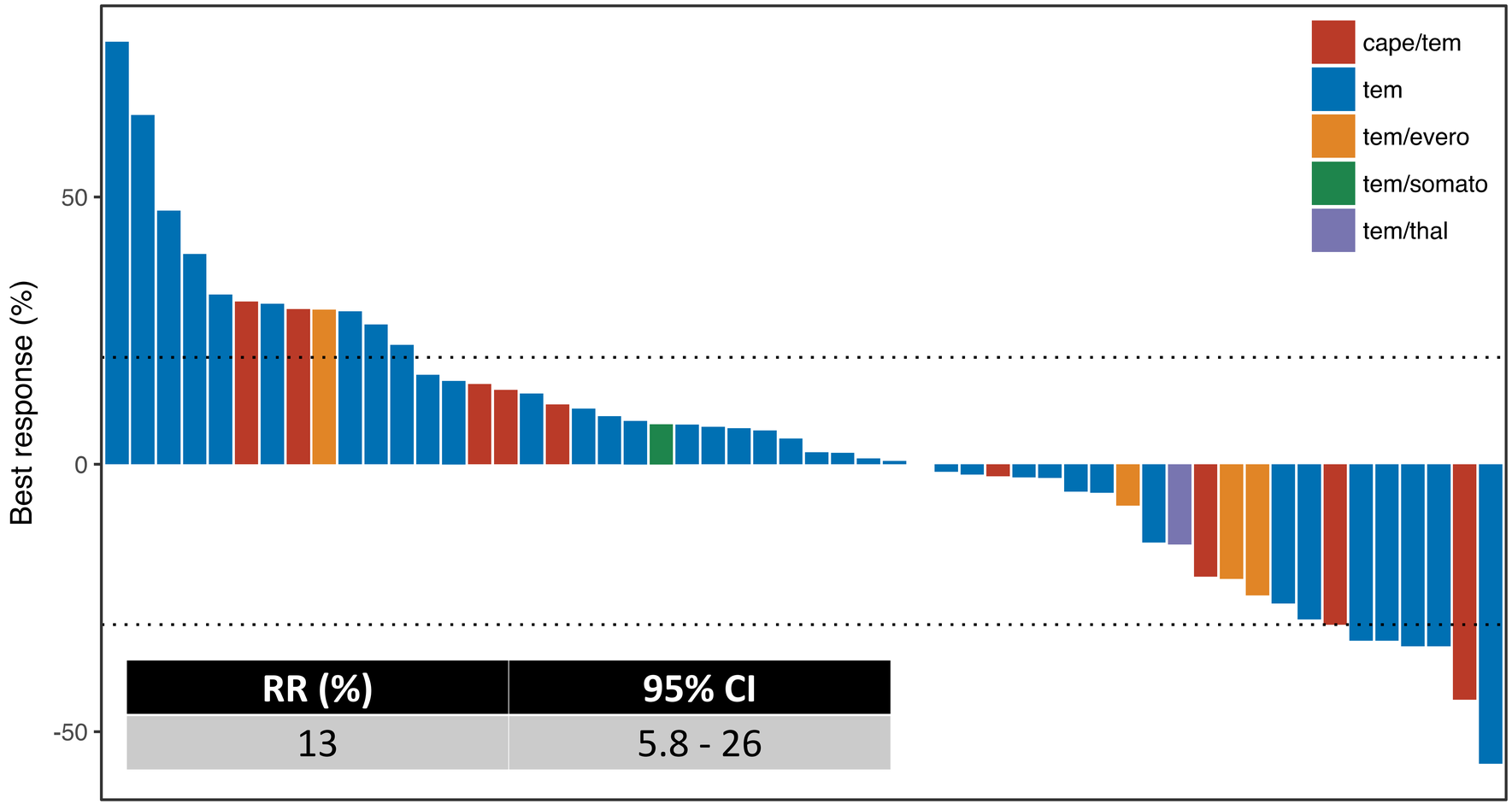
Median PFS (months)	95% CI
10	8.0 - 14



Line of tem-based treatment

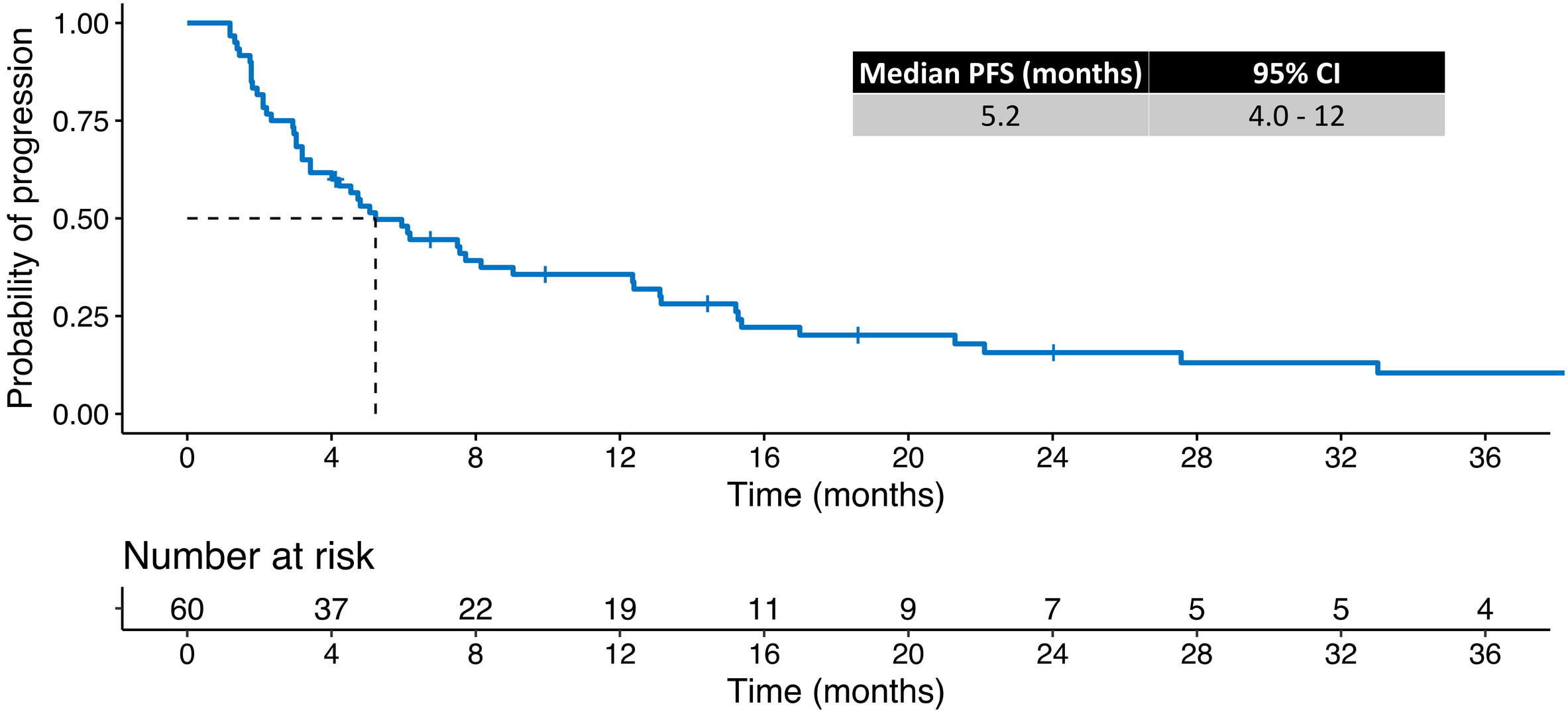


Waterfall plot of best response on tem therapy post FAS chemotherapy



Abbreviations:
Cape/tem – capecitabine/temozolimide; tem – temozolomide; tem/evero – temozolomide/everolimus; tem/somato – temozolomide/somatostatin; tem/thal – temozolomide/thalidomide

PFS on tem-based treatment post FAS



Median PFS (months)	95% CI
5.2	4.0 - 12