

Original article

Efficacy of Regorafenib and Trifluridine/Tipiracil according to extended *RAS* evaluation in advanced metastatic colorectal cancer patients: a multicenter retrospective analysis.

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Short title: Efficacy of Regorafenib and Trifluridine/Tipiracil according to *RAS* analysis

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Table 1S. Flow-chart of the study

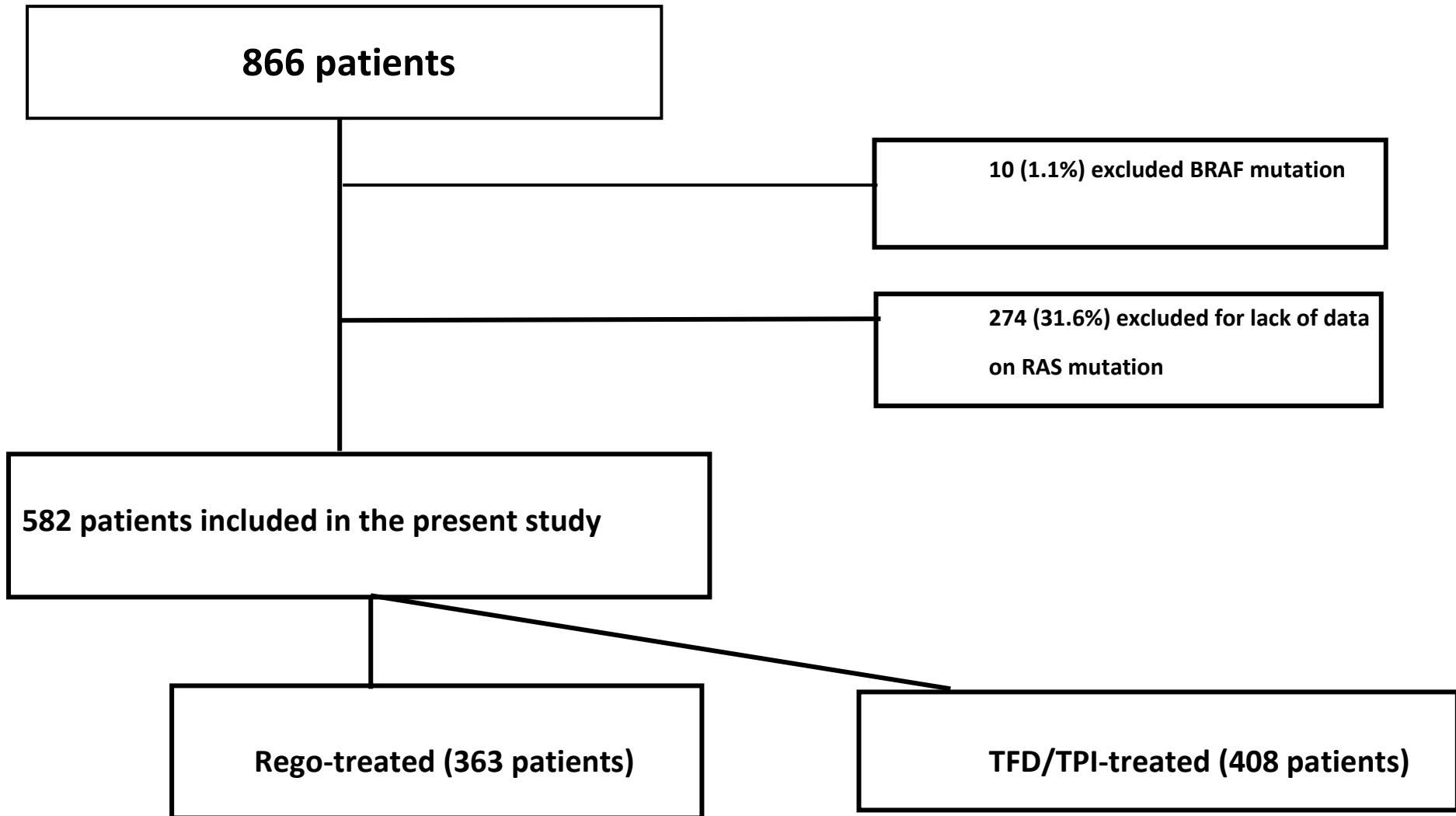


Table 2S. Comparison of patients' characteristics of rego-treated patients (n=363) and TFD/TPI-treated (408) according to each subgroup.

	<i>wt</i> (n, %)	Codon 12 (n, %)	Codon 13 (n, %)	Rare (n, %)	G12C (n, %)	G12D (n, %)
Median age (yrs)						
Rego	64.6	66.4	67.2	66.9	62.8	65.1
TFD/TPI	66.8	68.0	68.6	69.0	66.0	68.3
<i>p</i>	<i>p 0.9</i>	<i>p 0.9</i>	<i>p 1.0</i>	<i>p 0.8</i>	<i>p 0.79</i>	<i>p 0.86</i>
Gender (M/F)						
Rego	100/74	57/32	14/15	18/12	7/3	19/12
TFD/TPI	97/80	55/35	16/22	17/20	11/3	27/25
<i>p</i>	<i>p 0.69</i>	<i>p 0.8</i>	<i>p 0.7</i>	<i>p 0.36</i>	<i>p 0.86</i>	<i>p 0.54</i>
PS ECOG:						
Rego						
0	50 (28.7)	23 (25.8)	4 (13.7)	8 (26.6)	4 (40.0)	10 (32.2)
1	98 (56.3)	58 (65.1)	24 (82.7)	16 (53.3)	5 (50.0)	19 (61.2)
2	26 (14.9)	8 (8.9)	1 (3.4)	6 (20.1)	1 (10.0)	2(6.4)
TFD/TPI						
0	48 (27.1)	26 (28.8)	7 (18.4)	12 (32.4)	4 (28.5)	9 (17.3)

1	102 (57.6)	56 (62.2)	29 (76.3)	18 (48.6)	9 (64.2)	34 (65.3)
2	27 (15.2)	8 (8.8)	2 (5.2)	7 (18.9)	1 (7.1)	9 (17.3)
<i>p</i>	<i>p 0.94</i>	<i>p 0.8</i>	<i>p 0.8</i>	<i>p 0.87</i>	<i>p 0.78</i>	<i>p 0.15</i>

Primary tumor location

Rego

Right	47 (27.0)	33 (37.0)	10 (34.4)	9 (30.0)	2 (20.0)	11 (35.5)
Left	99 (57.0)	43 (48.4)	16 (55.2)	18 (60.0)	5 (50.0)	13 (41.9)
Rectum	28 (16.0)	13 (14.6)	3 (10.4)	3 (10.0)	3 (30.0)	7 (22.6)

TFD/TPI

Right	47 (26.5)	26 (28.8)	14 (36.8)	15 (40.5)	4 (28.5)	13 (25.0)
Left	90 (50.8)	41 (45.5)	16 (42.1)	14 (37.8)	8 (57.1)	27 (51.9)
Rectum	40 (22.5)	23 (25.5)	8 (21.0)	8 (21.6)	2 (14.2)	12 (23.1)
<i>p</i>	<i>p 0.28</i>	<i>p 0.16</i>	<i>p 0.40</i>	<i>p 0.16</i>	<i>p 0.63</i>	<i>p 0.56</i>

Metastatic synchronous disease:

Rego	145 (83.3)	70 (78.6)	20 (68.9)	25 (83.3)	6 (60.0)	25 (80.6)
TFD/TPI	130 (73.4)	64 (71.1)	23 (60.5)	29 (78.3)	10 (71.4)	39 (75.0)
<i>p</i>	<i>p 0.03</i>	<i>p 0.32</i>	<i>p 0.64</i>	<i>p 0.84</i>	<i>p 0.88</i>	<i>p 0.86</i>

Site of metastatic disease

Rego

Liver only	19 (10.9)	6 (6.7)	5 (17.2)	-	2 (20.0)	4 (12.9)
Liver + other	86 (49.5)	46 (51.6)	18 (62.2)	19 (63.3)	7 (70.0)	17 (54.8)
Other sites	69 (39.7)	37 (41.5)	6 (20.6)	11(36.7)	1 (10.0)	10 (32.3)

TFD/TPI

Liver only	22 (12.4)	11 (12.2)	6 (15.7)	3 (8.1)	3 (21.4)	6 (11.5)
Liver + other	89 (50.2)	46 (51.1)	19 (51.3)	23 (62.1)	8 (57.1)	34 (65.3)
Other sites	66 (37.2)	33 (36.6)	13(34.2)	11 (29.7)	3 (21.4)	12 (23.0)

p *p 0.80* *p 0.42* *p 0.46* *p 0.26* *p 0.73* *p 0.36*

Previous lines of therapy

Rego

2	69 (39.6)	56 (62.9)	16 (55.1)	20 (66.6)	7 (70.0)	18 (58.0)
3	63 (36.2)	14 (15.7)	6 (20.6)	3 (10.0)	2 (20.0)	10 (32.2)
4	19 (10.9)	4 (4.4)	2 (6.8)	2 (6.6)	1 (10.0)	3 (9.6)
>4	23 (13.2)	15 (16.8)	5 (17.2)	5 (16.6)	--	--

TFD/TPI

2	77 (43.5)	61 (67.7)	16 (42.1)	19 (51.3)	9 (64.2)	26 (50.0)
3	71 (40.1)	18 (20.0)	12 (31.5)	8 (21.6)	4 (28.5)	17 (32.6)
4	9 (5.0)	2 (2.2)	2 (5.2)	3 (8.1)	1 (7.1)	9 (17.3)

>4	20 (11.2)	9 (10.0)	8 (21.0)	7 (18.9)	--	--
<i>P</i>	<i>p 0.29</i>	<i>p 0.41</i>	<i>p 0.67</i>	<i>p 0.54</i>	<i>p 0.87</i>	<i>p 0.60</i>

Previous drugs administered:

Rego

Fluoropyrimidine	131 (74.0)	65 (73.0)	21 (72.4)	23 (76.6)	7 (70.0)	25 (80.6)
Oxaliplatin	127 (71.7)	58 (65.1)	22 (75.8)	22 (73.3)	7 (70.0)	23 (74.1)
Irinotecan	119 (67.2)	52 (58.4)	23 (79.3)	20 (66.6)	6 (60.0)	22 (70.9)
Bevacizumab	125 (70.6)	59 (66.2)	19 (65.5)	17 (56.6)	7 (70.0)	23 (74.1)

Anti-EGFRs	129 (72.8)	--	--	--	--	--
Immunotherapy	4 (2.2)	1 (1.1)	1 (3.4)	--	--	--
Aflibercept	12 (6.7)	7 (7.8)	2 (6.8)	6 (20.0)	2 (20.0)	4 (12.9)
Unknown	43 (24.7)	22 (24.7)	8 (27.5)	7 (23.3)	2 (20.0)	6 (19.3)

TFD/TPI

Fluoropyrimidine	173 (97.7)	86 (95.5)	36 (94.7)	36 (97.2)	14 (100.0)	52 (100.0)
Oxaliplatin	165 (93.2)	81 (90.0)	32 (84.2)	34 (91.8)	13 (92.8)	43 (82.6)
Irinotecan	166 (93.7)	82 (91.1)	35 (92.1)	34 (91.8)	14 (100.0)	45 (86.5)
Bevacizumab	95 (53.6)	75 (83.3)	28 (73.6)	28 (75.6)	9 (64.2)	42 (80.7)
Anti-EGFRs	154 (87.0)	--	--	--	--	--
Immunotherapy	2 (1.1)	2 (2.2)	2 (5.2)	--	--	--
Aflibercept	9 (5.0)	12 (13.3)	6 (15.7)	12 (32.4)	4 (28.5)	8 (15.3)

Unknown	4 (2.2)	3 (3.3)	2 (5.2)	1 (2.7)	--	--
<i>p</i>	<i>p 0.001</i>	<i>p 0.001</i>	<i>p 0.26</i>	<i>p 0.12</i>	<i>p 0.50</i>	<i>p 0.04</i>

Receiving both drugs

Rego

Receiving TFD/TPI	79 (45.4)	47 (52.8)	17 (58.6)	16 (53.3)	6 (60.0)	19 (61.2)
Before rego	46 (26.4)	26 (29.2)	8 (27.5)	10 (33.3)	4 (40.0)	9 (29.0)
After rego	33 (18.9)	21 (23.5)	9 (31.0)	6 (20.0)	2 (20.0)	10 (32.2)

TFD/TPI

Receiving Rego	80 (45.1)	49 (54.4)	17 (44.7)	16 (43.2)	7 (50.0)	19 (36.5)
Before TFD/TPI	32 (18.0)	19 (21.1)	9 (23.6)	5 (13.5)	2 (14.2)	10 (19.2)
After TFD/TPI	48 (27.1)	30 (33.3)	8 (21.0)	11 (29.7)	5 (35.7)	9 (17.3)

<i>P</i>	<i>p 0.90</i>	<i>p 0.90</i>	<i>p 0.50</i>	<i>p 0.56</i>	<i>p 0.94</i>	<i>p 0.06</i>
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Abbreviations: ecog, eastern cooperative oncology group; EGFR, epidermal growth factor receptor; f, female; m, male; n, number; ps, performance status; rego, regorafenib; TFD/TPI, trifluridine/tipiracil; yrs, years; wt, wild type

Table 3S. Objective response according to RAS subgroups

	<i>Partial response (n)</i>	<i>Stable disease (n)</i>	<i>Progressive disease (n)</i>	<i>p</i>
WT patients				
Rego-treated (174 pts)	8	26	140	0.74
TFD/TPI-treated (177 pts)	7	22	148	
Codon 12				
Rego-treated (89 pts)	2	14	73	0.76
TFD/TPI-treated (90 pts)	2	18	70	
Codon 13				
Rego-treated (29 pts)	0	5	24	0.35
TFD/TPI-treated (38 pts)	2	4	32	
Rare mutations				
Rego-treated (30 pts)	0	6	24	0.53
TFD/TPI-treated (37 pts)	1	5	31	
G12C mutation				

Rego-treated (10 pts)	0	3	7	1.0
TFD/TPI-treated (14 pts)	0	3	11	

G12D mutation

Rego-treated (31 pts)	0	4	27	0.61
TFD/TPI-treated (52 pts)	1	9	41	

Table 4S. Dose reductions according to each subgroup

	WT	Codon 12	Codon 13	Rare	G12C	G12D
Rego-treated	174 pts	89 pts	29 pts	30 pts	10 pts	31 pts
100% dose	110	56	16	12	5	20
75% dose	35	18	8	9	3	6
50% dose	29	15	5	9	2	5
TFD/TPI-treated	177 pts	90 pts	38 pts	37 pts	14 pts	52 pts
100% dose	133	69	28	26	8	37
75% dose	38	19	8	8	3	12
50% dose	6	2	2	3	3	2
	<i>p 0.002</i>	<i>p 0.003</i>	<i>p 0.2</i>	<i>p 0.02</i>	<i>p 0.8</i>	<i>p 0.15</i>

Table 5S. Comparison of patients' characteristics according to sequence in each subgroup.

	wt (81)	Codon 12 (49)	Codon 13 (17)	Rare (16)	G12C (7)	G12D (20)
Median age (yrs)						
TFD/TPI-Rego	68.2	68.7	64.0	63.9	64.2	68.6
Rego-TFD/TPI	65.2	62.0	70.7	71.8	62.0	55.0
<i>p</i>	<i>p 0.80</i>	<i>p 0.66</i>	<i>p 0.66</i>	<i>p 0.54</i>	<i>p 0.92</i>	<i>p 0.27</i>
Gender (M/F)						
TFD/TPI-Rego	24/16	18/11	4/5	5/6	4/1	7/3
Rego-TFD/TPI	25/16	13/7	3/4	2/4	1/1	8/2
<i>p</i>	<i>p 0.89</i>	<i>p 0.90</i>	<i>p 0.65</i>	<i>p 0.97</i>	<i>p 0.89</i>	<i>p 1.0</i>
PS ECOG:						
TFD/TPI-Rego						
0	10	9	1	3	1	3
1	27	18	7	5	3	7
2	3	2	1	2	1	0
Rego-TFD/TPI						
0	16	7	0	1	1	3
1	22	11	7	4	1	6

2	3	2	1	1	0	1
<i>p</i>	<i>p 0.39</i>	<i>p 0.90</i>	<i>p 0.62</i>	<i>p 0.78</i>	<i>p 0.64</i>	<i>p 0.58</i>

Primary tumor location

TFD/TPI-Rego

Right	11	11	4	6	2	1
Left	19	10	4	4	3	7
Rectum	11	8	1	1	0	2

Rego-TFD/TPI

Right	10	7	2	2	1	5
Left	26	7	4	3	1	4
Rectum	15	6	2	1	0	1
<i>p</i>	<i>p 0.73</i>	<i>p 0.97</i>	<i>p 0.62</i>	<i>p 0.69</i>	<i>p 0.54</i>	<i>p 0.14</i>

Metastatic synchronous disease:

TFD/TPI-rego	33	22	4	8	4	7
Rego-TFD/TPI	25	12	5	5	1	8
<i>p</i>	<i>p 0.05</i>	<i>p 0.38</i>	<i>p 1.0</i>	<i>p 0.91</i>	<i>p 0.89</i>	<i>p 1.0</i>

Site of metastatic disease

TFD/TPI-Rego

Liver only	6	2	3	1	2	2
Liver + other	18	14	4	9	2	5
Other sites	16	13	2	1	1	3

Rego-TFD/TPI

Liver only	6	4	1	3	0	1
Liver + other	20	6	4	2	2	5
Other sites	15	10	3	1	0	4

p *p 0.93* *p 0.25* *p 0.56* *p 0.11* *p 0.34* *p 0.78*

Previous lines of therapy

TFD/TPI-Rego

2	19	23	3	6	4	3
3	18	4	2	3	1	7
4	2	1	3	1	0	0
>4	1	1	1	1	0	0

TFD/TPI

2	16	11	7	3	2	6
3	19	3	1	2	0	4
4	4	3	1	1	0	0

>4	2	3	0	0	0	0
<i>P</i>	<i>p 0.40</i>	<i>p 0.18</i>	<i>p 0.26</i>	<i>p 0.84</i>	<i>p 0.60</i>	<i>p 0.36</i>

Previous drugs administered:

TFD/TPI-Rego

Fluoropyrimidine	39	29	9	9	4	9
Oxaliplatin	36	28	6	8	5	8
Irinotecan	33	28	8	7	4	7
Bevacizumab	16	23	8	7	3	8
Anti-EGFRs	34	0	0	0	0	0
Immunotherapy	2	1	0	1	0	0
Aflibercept	10	5	0	2	2	3
Unknown	0	0	0	0	0	0

Rego-TFD/TPI

Fluoropyrimidine	37	19	6	5	2	9
Oxaliplatin	35	17	5	4	2	8
Irinotecan	32	17	6	5	2	8
Bevacizumab	22	15	6	5	2	7
Anti-EGFRs	36	0	0	0	0	0
Immunotherapy	0	0	1	1	0	0
Aflibercept	2	4	1	0	0	2

Unknown

2

1

2

0

0

1

p

p 0.16

p 0.88

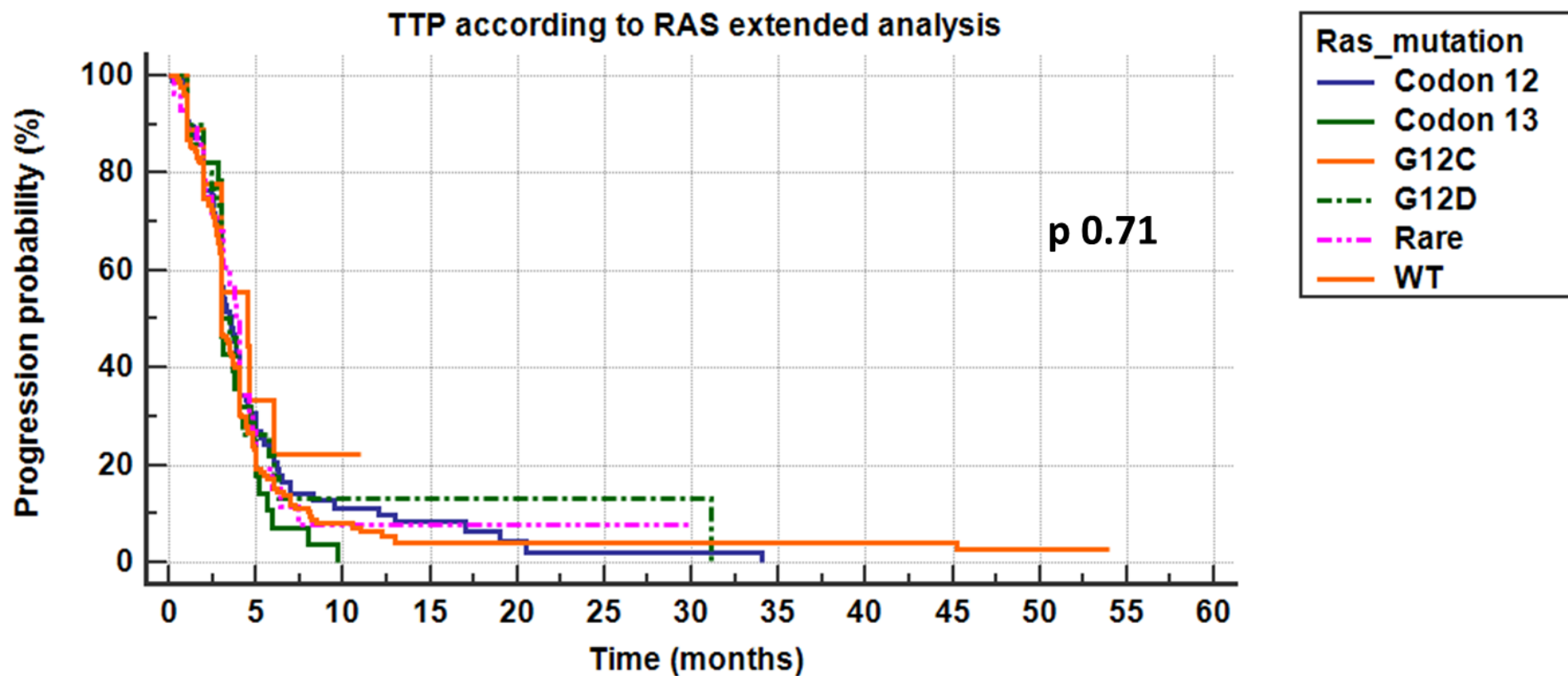
p 0.88

p 0.96

p 0.88

p 0.93

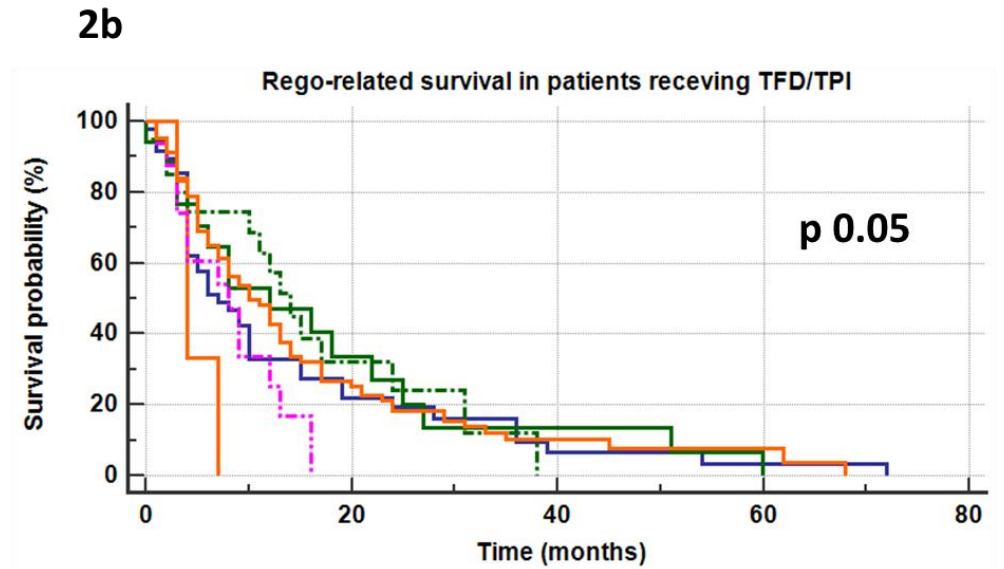
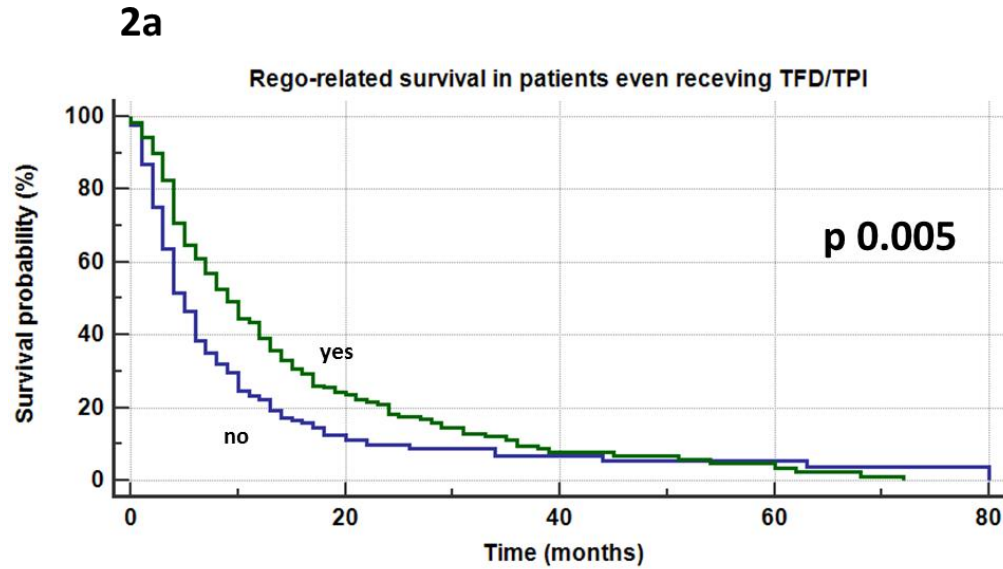
Fig 1. Time to progression of Rego-treated patients according to RAS extended analysis



Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
Codon 12	5.385	0.705	4.003 to 6.767	3.600	3.000 to 4.000
Codon 13	3.736	0.371	3.009 to 4.462	3.000	3.000 to 4.000
G12C	5.322	1.260	2.852 to 7.793	4.500	3.000 to 6.000
G12D	6.993	1.943	3.185 to 10.801	3.000	3.000 to 4.000
Rare	4.009	0.447	3.133 to 4.885	3.900	3.100 to 4.600
WT	3.928	0.214	3.509 to 4.347	3.000	3.000 to 3.700
Overall	5.714	0.558	4.620 to 6.808	3.100	3.000 to 3.700

Fig 2. Rego-related OS of patients even receiving TFD/TPI (before or after).



Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
NO	10.989	1.423	8.200 to 13.778	5.000	4.000 to 6.000
yes	14.999	1.266	12.517 to 17.480	9.000	7.000 to 12.000
Overall	12.916	0.931	11.090 to 14.741	6.000	6.000 to 8.000

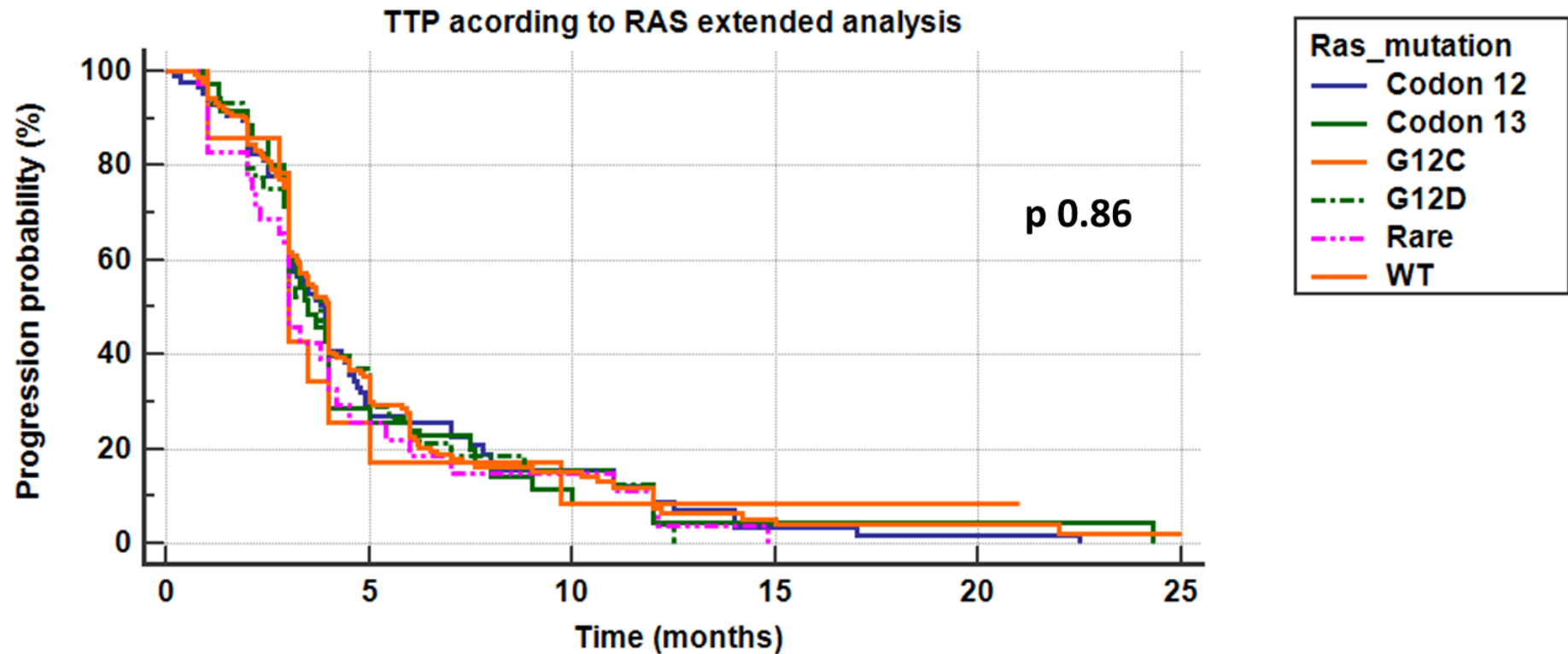
Ras_mutation

- Codon 12
- Codon 13
- G12C
- - - G12D
- ... Rare
- WT

Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
Codon 12	8.657	0.814	7.061 to 10.252	7.000	4.000 to 10.000
Codon 13	15.134	3.000	9.254 to 21.015	12.000	5.000 to 22.000
G12C	4.833	0.642	3.575 to 6.091	4.000	4.000 to 7.000
G12D	16.410	2.910	10.706 to 22.114	14.000	10.000 to 24.000
Rare	8.147	1.298	5.602 to 10.691	8.000	4.000 to 12.000
WT	5.830	0.207	5.424 to 6.237	10.000	8.000 to 13.000
Overall	14.999	1.266	12.517 to 17.480	9.000	7.000 to 12.000

Fig n 3. Time to progression of TFD/TPI-treated patients according to RAS extended analysis

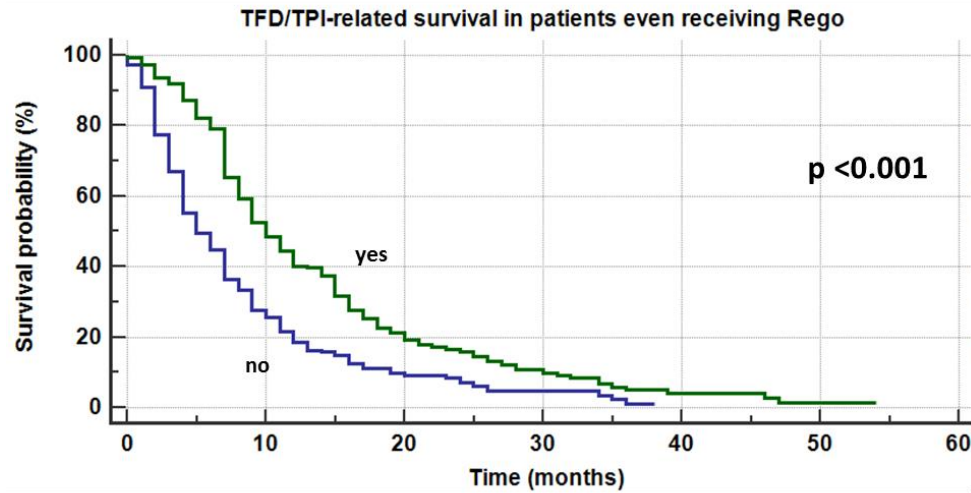


Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
Codon 12	5.090	0.429	4.248 to 5.931	3.900	3.000 to 4.400
Codon 13	4.693	0.527	3.661 to 5.726	3.500	3.000 to 4.000
G12C	5.203	1.583	2.100 to 8.306	3.000	3.000 to 4.000
G12D	4.901	0.537	3.848 to 5.953	3.800	3.000 to 5.000
Rare	4.450	0.656	3.165 to 5.735	3.000	2.800 to 4.000
WT	5.314	0.382	4.565 to 6.062	4.000	3.300 to -
Overall	5.199	0.252	4.705 to 5.692	3.700	3.300 to 4.000

Fig 4. TFD/TPI-related OS of patients even receiving Rego (before or after).

4a

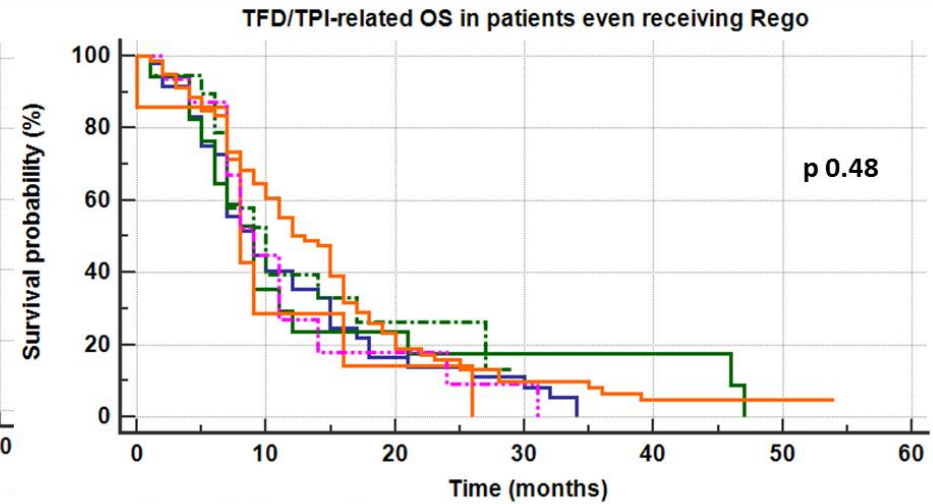


Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
NO	8.308	0.598	7.137 to 9.479	5.000	4.000 to 7.000
yes	13.518	0.751	12.046 to 14.990	10.000	9.000 to 12.000
Overall	11.018	0.551	9.937 to 12.098	7.000	7.000 to 9.000

Ras_mutation
 — Codon 12
 — Codon 13
 — G12C
 - - - G12D
 - · - · Rare
 — WT

4b



Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
Codon 12	11.906	1.302	9.354 to 14.458	9.000	7.000 to 12.000
Codon 13	11.706	2.190	7.414 to 15.997	9.000	6.000 to 12.000
G12C	10.571	2.885	4.918 to 16.225	8.000	7.000 to 16.000
G12D	13.750	2.291	9.260 to 18.240	10.000	7.000 to 17.000
Rare	11.784	2.239	7.396 to 16.173	9.000	7.000 to 14.000
WT	13.590	0.847	11.929 to 15.251	13.000	10.000 to 16.000
Overall	13.981	0.868	12.280 to 15.683	10.000	9.000 to 12.000

Fig 5. OS of all-RAS wt patients according to sequence (81 pts).

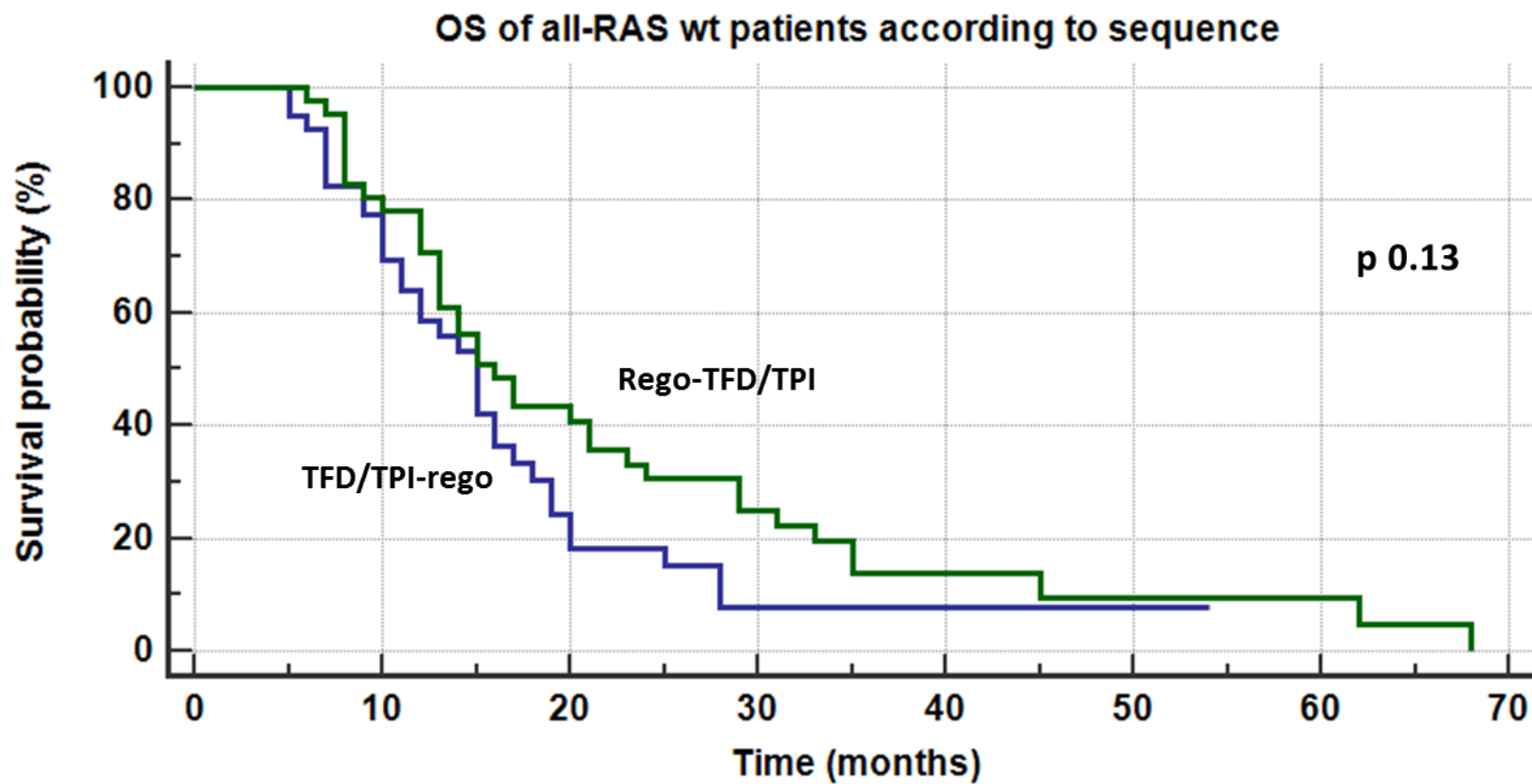
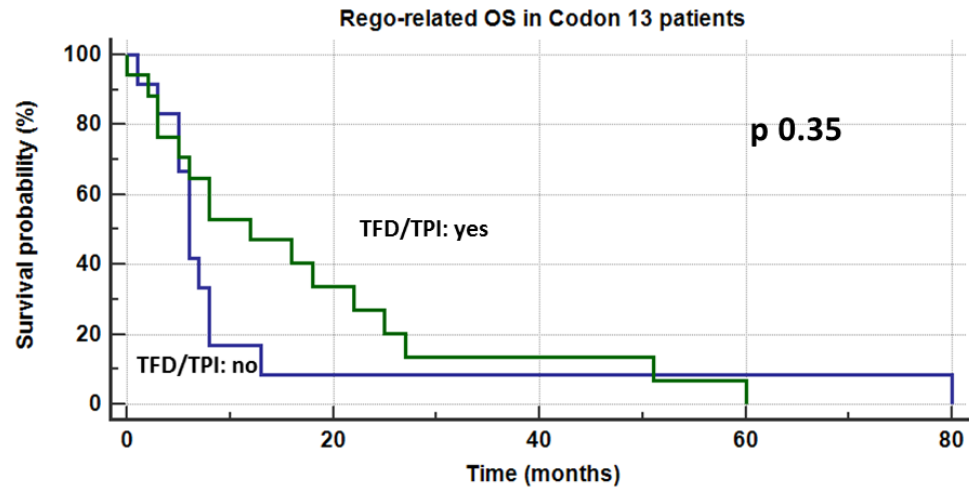


Fig 6. Rego-related and TFD/TPI-related OS of Codon 13 patients

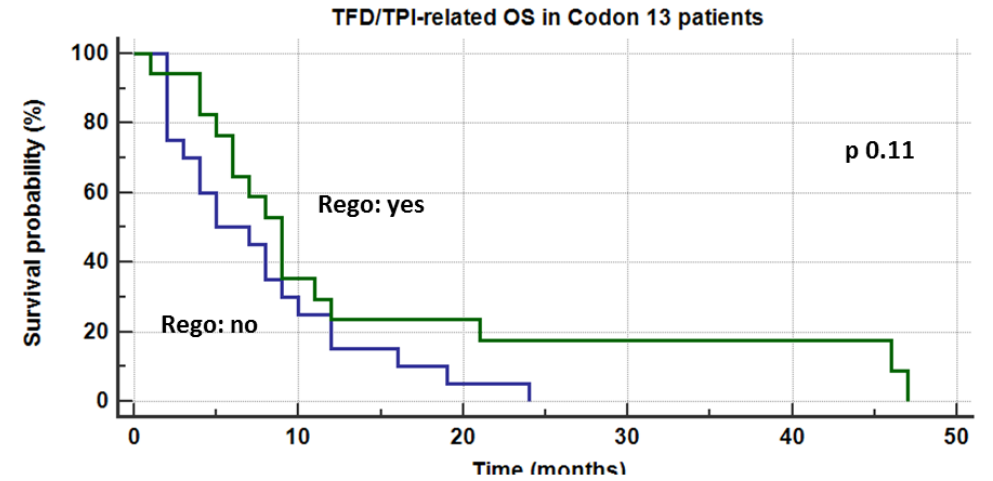
6a



Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
NO	12.333	6.209	0.164 to 24.503	6.000	5.000 to 8.000
yes	17.487	4.421	8.823 to 26.152	12.000	5.000 to 22.000
Overall	15.565	3.730	8.255 to 22.875	8.000	6.000 to 13.000

6b



Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
NO	7.800	1.389	5.077 to 10.523	5.000	3.000 to 10.000
yes	14.794	3.823	7.302 to 22.287	9.000	6.000 to 12.000
Overall	11.014	1.966	7.161 to 14.866	8.000	5.000 to 9.000

Fig 7. OS of Codon 13 patients according to sequence (17 pts).

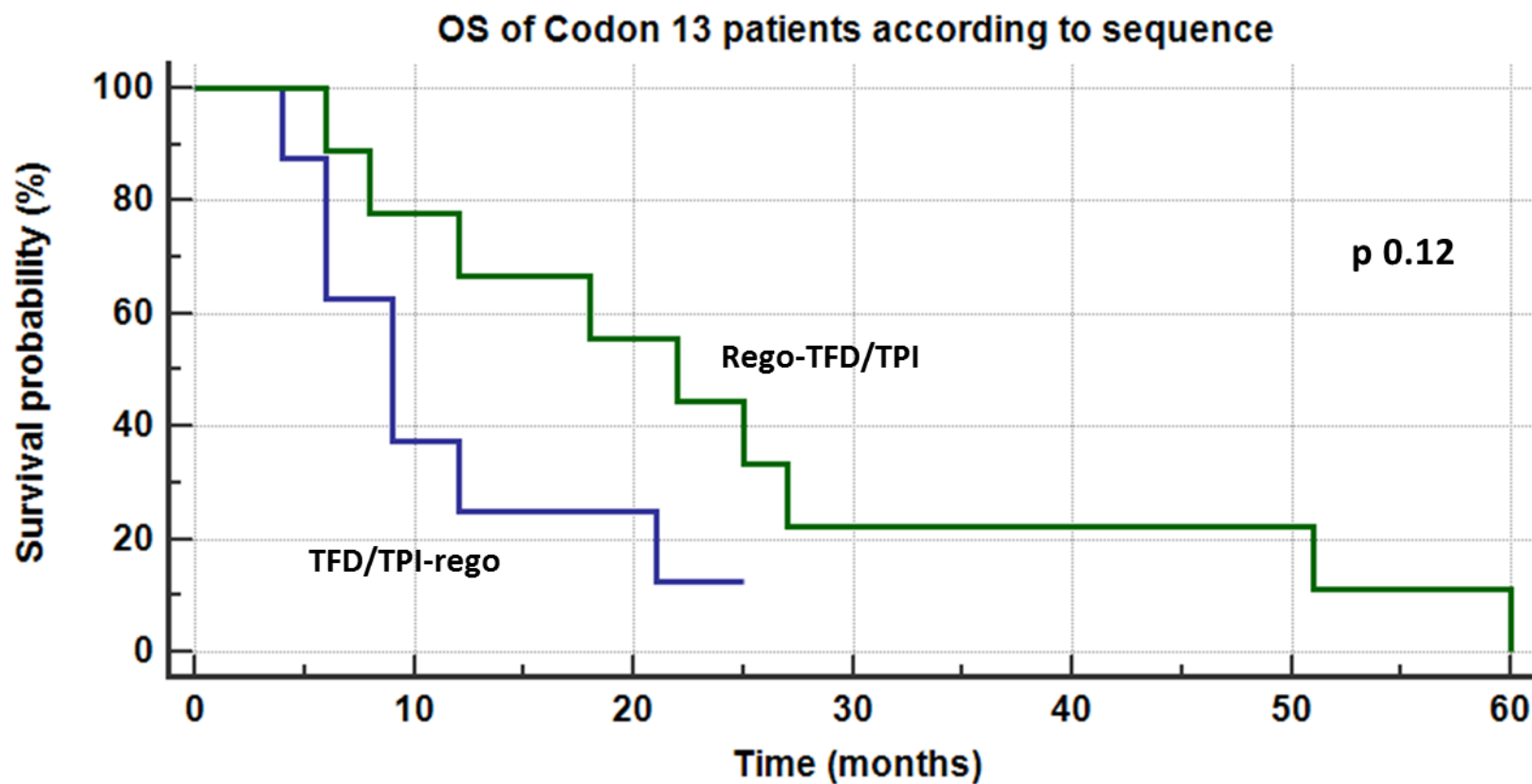
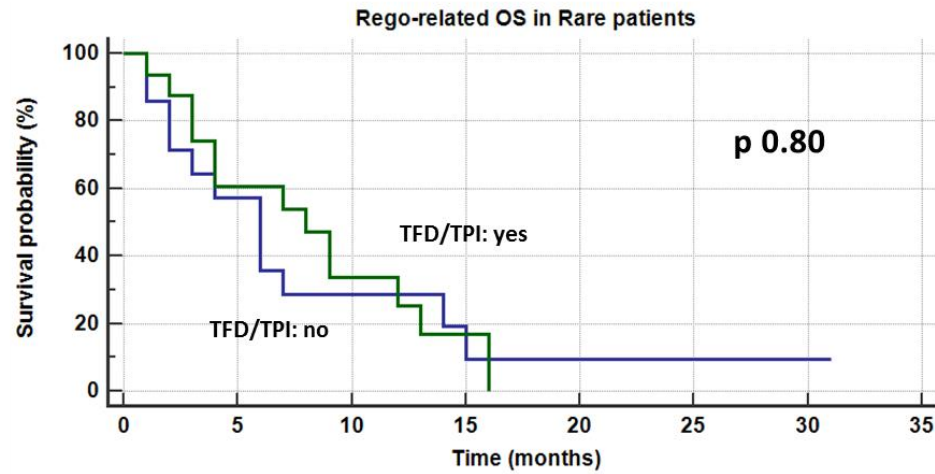


Fig 8. Rego-related and TFD/TPI-related OS of Rare patients

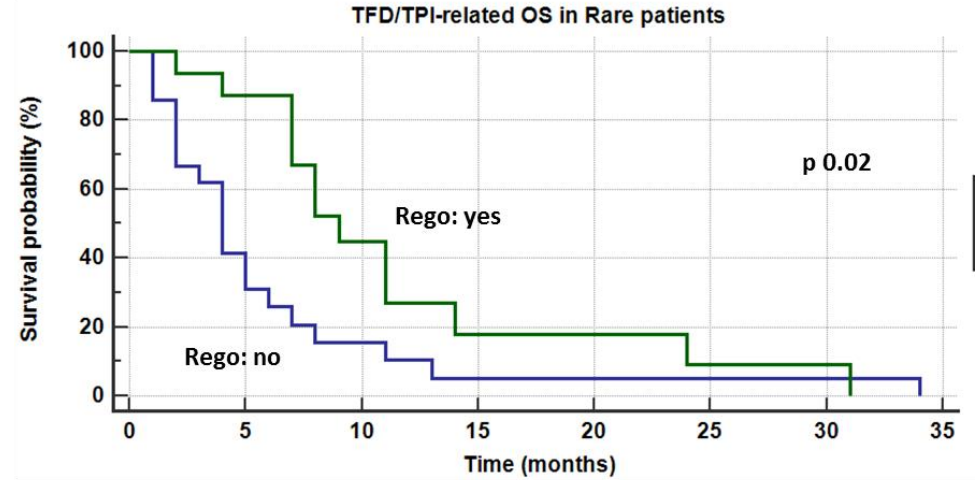
8a



Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
NO	7.000	1.446	4.167 to 9.833	6.000	2.000 to 14.000
yes	8.147	1.298	5.602 to 10.691	8.000	4.000 to 12.000
Overall	8.565	1.503	5.619 to 11.511	6.000	4.000 to 9.000

8b



Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
NO	5.929	1.497	2.994 to 8.863	4.000	2.000 to 6.000
yes	11.784	2.239	7.396 to 16.173	9.000	7.000 to 14.000
Overall	8.584	1.464	5.715 to 11.453	7.000	4.000 to 8.000

Fig 9. OS of Rare patients according to sequence (16 pts).

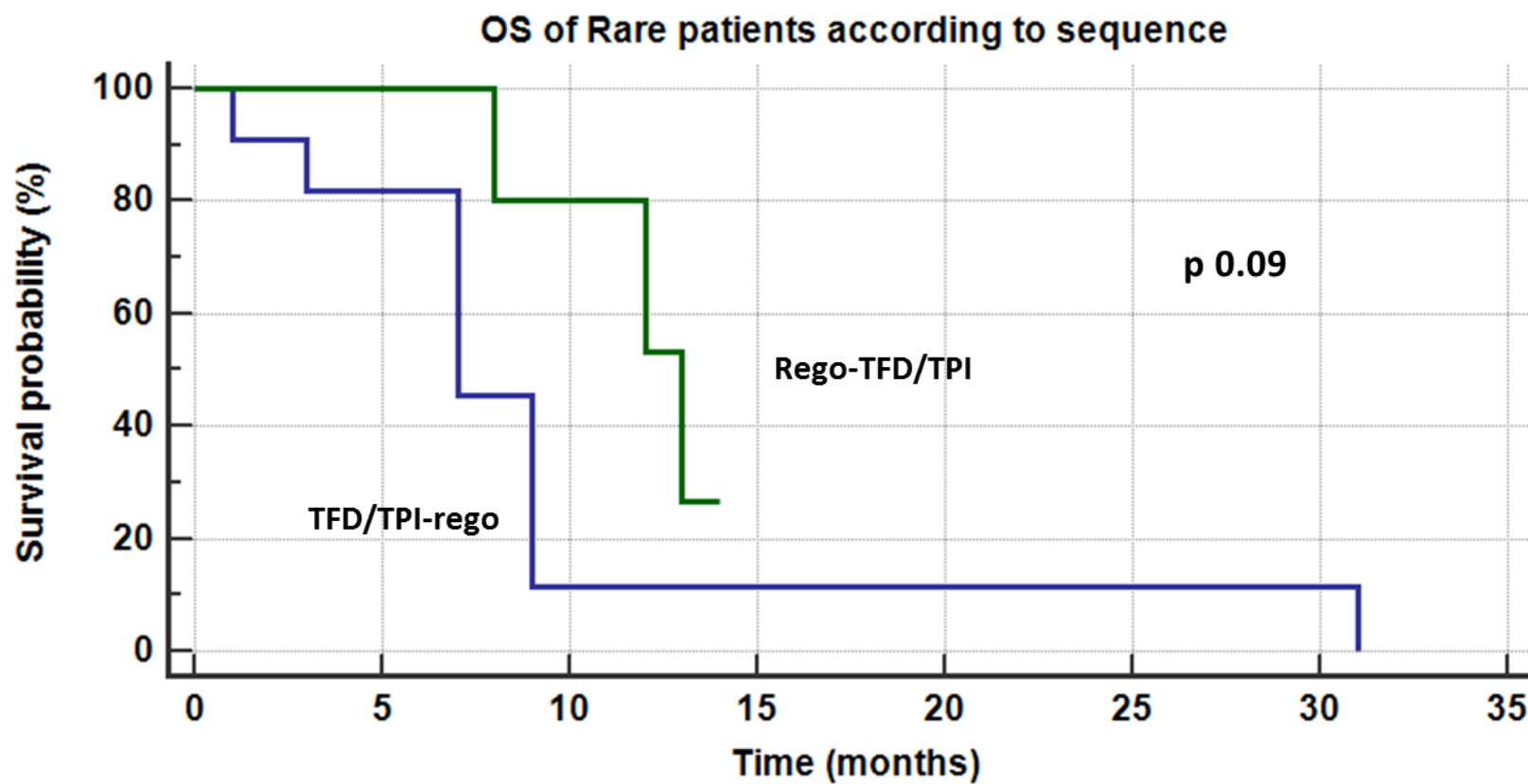
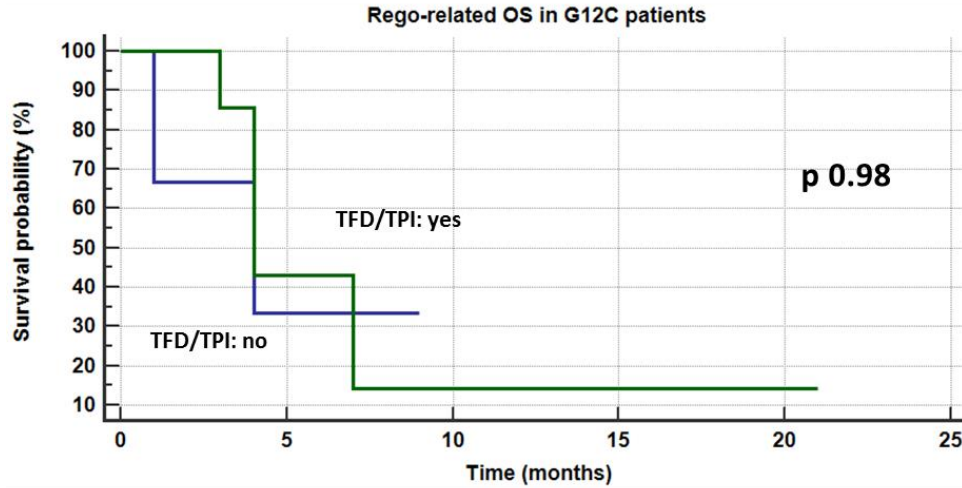


Fig 10. Rego-related and TFD/TPI-related OS of G12C patients

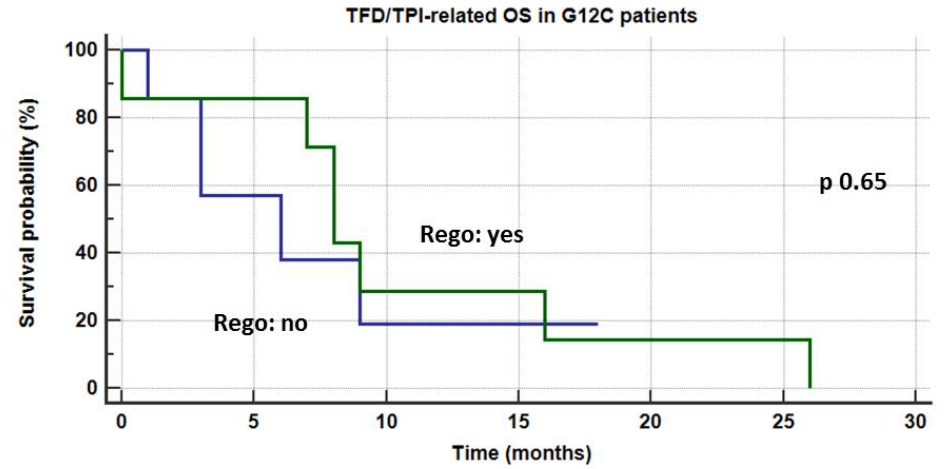
10a



Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
NO	8.667	5.084	-1.299 to 18.632	4.000	1.000 to 4.000
yes	5.429	0.779	3.902 to 6.955	4.000	4.000 to 7.000
Overall	7.600	2.183	3.322 to 11.878	4.000	4.000 to 7.000

10b



Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
NO	8.810	3.604	1.745 to 15.874	6.000	3.000 to 9.000
yes	9.429	2.098	5.316 to 13.541	8.000	7.000 to 16.000
Overall	9.627	2.345	5.030 to 14.224	8.000	3.000 to 9.000

Fig 11. OS of G12C patients according to sequence (7 pts).

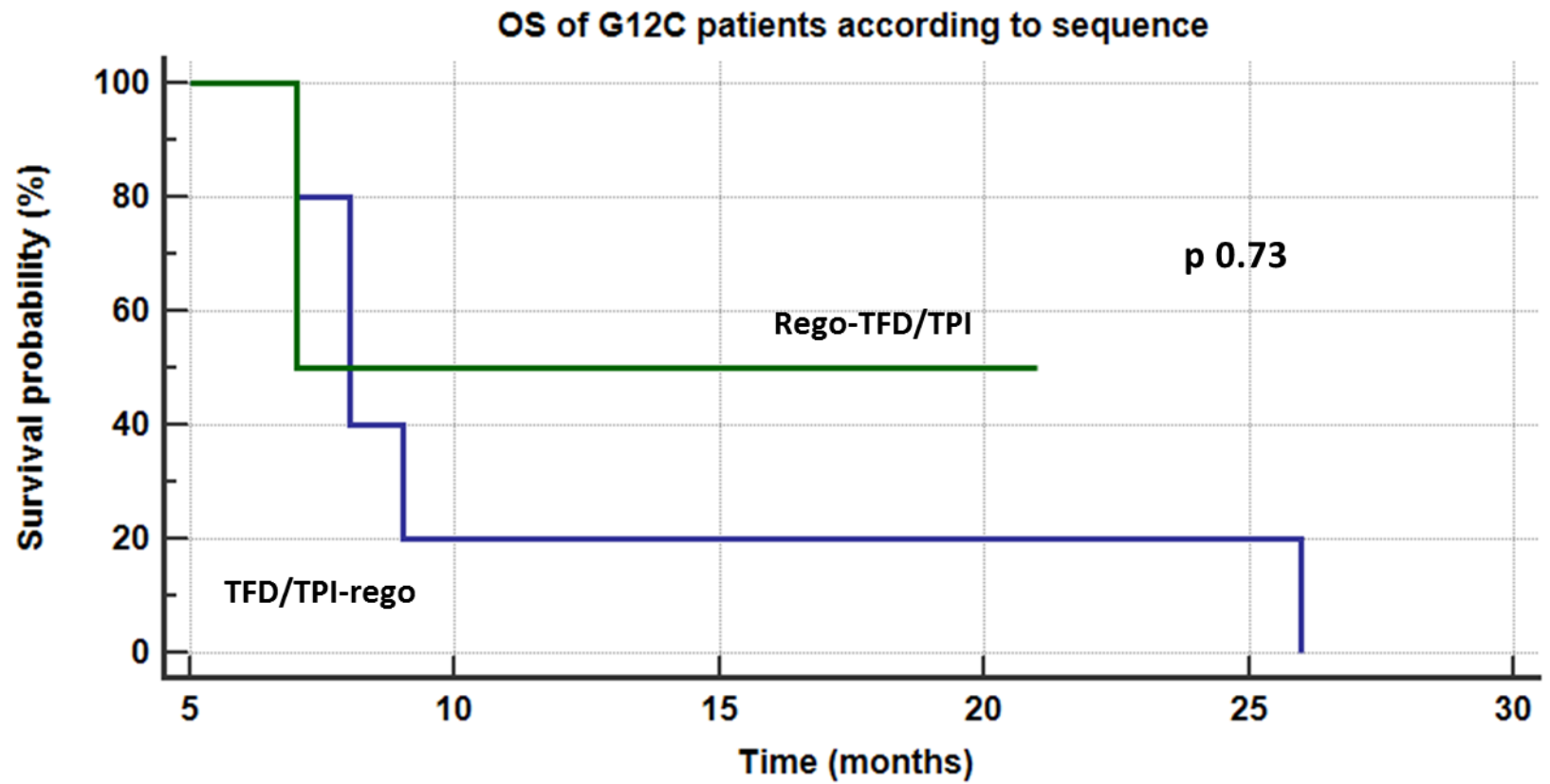
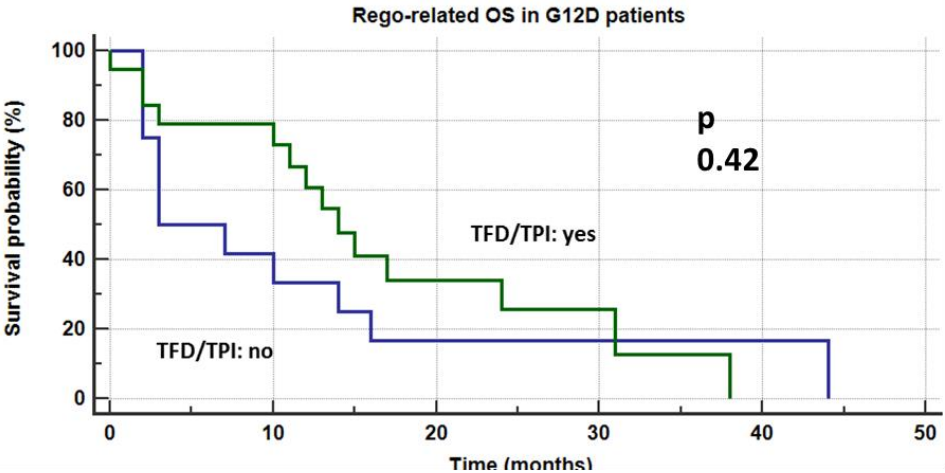


Fig 12. Rego-related and TFD/TPI-related OS of G12D patients

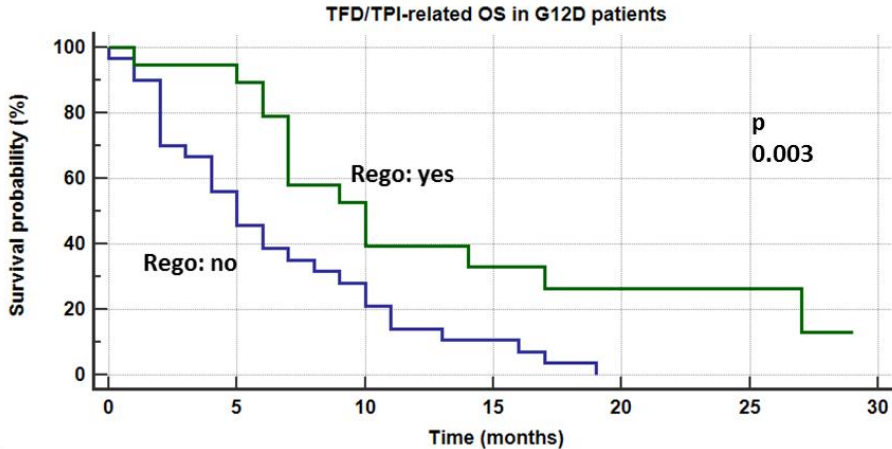
12
a



Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
NO	11.500	3.671	4.304 to 18.696	3.000	3.000 to 14.000
yes	17.193	2.975	11.362 to 23.024	14.000	11.000 to 24.000
Overall	15.460	2.648	10.270 to 20.649	12.000	7.000 to 16.000

12
b



Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
NO	6.532	0.933	4.704 to 8.360	5.000	3.000 to 8.000
yes	11.250	1.359	8.586 to 13.914	10.000	7.000 to 17.000
Overall	9.133	1.114	6.951 to 11.316	7.000	5.000 to 10.000

Fig 13. OS of G12D patients according to sequence (20 pts).

