Statistical Report

M20DRA

DAP Study

The Drug Access Protocol

Tepotinib for MET-mutated NSCLC

Vincent van der Noort building on earlier work of Karlijn Verkerk and Erik van Werkhoven

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1 Introduction

1.1 Background

With an incidence of approximately 2.5 million cases per year, lung cancer is the most common cancer worldwide, and the leading cause of cancer-related mortality. The advent of precision oncology has substantially improved the survival of patients with non-small lung cancer (NSCLC). One of the available targeted therapies in the Drug Access Protocol (DAP) is tepotinib. Tepotinib is a tyrosine kinase inhibitor (TKI) that selectively inhibits the MET protein in cancer cells. Splice site alterations of the MET protein can result in the loss of exon 14 and lead to increased signaling of the RAS-RAF and PI3K signaling pathways. These oncogenic MET exon 14 (METex14) skipping mutations are found in 3-4% of the patients with NSCLC. In the open-label phase 2 trial by Paik and colleagues, 99 patients with advanced NSCLC and a confirmed METex14 skipping mutation were treated with tepotinib and evaluated for clinical efficacy. The objective response rate was 46%, with 46 patients showing a partial response at the first response evaluation. The median duration of response was 11.1 months. Based on the results of this study, tepotinib monotherapy was approved by the EMA in December 2021 for the treatment of patients with advanced NSCLC harboring METex14 skipping mutations. Pending reimbursement decision by the health care authorities, patients in the Netherlands have had access to tepotinib in the DAP since December 2022. Here, we evaluate the clinical efficacy and safety of tepotinib for the treatment of NSCLC using real-world data from the DAP.

1.2 Methods

Adult patients with advanced non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping alterations, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy, were eligible for inclusion in DAP. Patients were treated with 450 mg tepotinib once daily, until disease progression or unmanageable toxicity.
The primary endpoints of this analysis were clinical benefit, defined as objective tumor response (e.g. complete or partial response) or stable disease for at least 16 weeks, according to the RECIST v1.1 guidelines. Additionally, treatment-related grade 3 or higher adverse events, and serious adverse events are both primary endpoints with regards to safety. Secondary endpoints include overall survival, progression free survival, and duration of response.
Data cut-off was 16-Jan-2025, the date of data extraction from the eCRF was 2025-05-12.

2 Analysis set

The data used for this report was downloaded from the eCRF at 2025-05-12. At that time the DAP had included 325 patients of which 46 in the cohort considered in this report (Tepotinib for MET exon 14 skipping mutated NSCLC). Of these patients, 46 actually started treatment. They are listed in table 2.1. For the present cohort, the data was cleaned and up to date up to 16 January 2025.
All 46 patients started treatment.

Table 2.1: Patients used in the analysis with their data as known at the time of registration

Patient	Tumor	Drug	Target	Gender	Age	WHO
DRUGA-01-01-0071	NSCLC	Tepotinib	MET	male	49	WHO 2
DRUGA-01-01-0072	NSCLC	Tepotinib	MET	male	65	WHO 0
DRUGA-01-01-0075	NSCLC	Tepotinib	MET	female	75	WHO 1
DRUGA-01-01-0076	NSCLC	Tepotinib	MET	female	63	WHO 0
DRUGA-01-01-0081	NSCLC	Tepotinib	MET	female	83	WHO 1
DRUGA-01-01-0082	NSCLC	Tepotinib	MET	female	79	WHO 0
DRUGA-01-01-0084	NSCLC	Tepotinib	MET	male	80	WHO 0
DRUGA-01-01-0086	NSCLC	Tepotinib	MET	female	69	WHO 1
DRUGA-01-01-0088	NSCLC	Tepotinib	MET	female	81	WHO 1

Table 2.1: *(continued)*

Patient	Tumor	Drug	Target	Gender	Age	WHO
DRUGA-01-01-0089	NSCLC	Tepotinib	MET	female	73	WHO 1
DRUGA-01-01-0090	NSCLC	Tepotinib	MET	female	82	WHO 1
DRUGA-01-01-0096	NSCLC	Tepotinib	MET	female	73	WHO 0
DRUGA-01-01-0097	NSCLC	Tepotinib	MET	male	76	WHO 1
DRUGA-01-01-0098	NSCLC	Tepotinib	MET	female	70	WHO 1
DRUGA-01-01-0101	NSCLC	Tepotinib	MET	female	60	WHO 2
DRUGA-01-01-0103	NSCLC	Tepotinib	MET	female	75	WHO 0
DRUGA-01-01-0105	NSCLC	Tepotinib	MET	female	70	WHO 2
DRUGA-01-02-0047	NSCLC	Tepotinib	MET	female	73	WHO 2
DRUGA-01-02-0049	NSCLC	Tepotinib	MET	male	73	WHO 2
DRUGA-01-02-0051	NSCLC	Tepotinib	MET	male	58	WHO 2
DRUGA-01-02-0053	NSCLC	Tepotinib	MET	female	58	WHO 1
DRUGA-01-02-0054	NSCLC	Tepotinib	MET	female	76	WHO 1
DRUGA-01-02-0058	NSCLC	Tepotinib	MET	male	75	WHO 1
DRUGA-01-02-0059	NSCLC	Tepotinib	MET	female	73	WHO 2
DRUGA-01-02-0063	NSCLC	Tepotinib	MET	male	72	WHO 2
DRUGA-01-02-0067	NSCLC	Tepotinib	MET	female	77	WHO 0
DRUGA-01-02-0068	NSCLC	Tepotinib	MET	male	74	WHO 1
DRUGA-01-05-0005	NSCLC	Tepotinib	MET	male	71	WHO 1
DRUGA-01-06-0024	NSCLC	Tepotinib	MET	male	68	WHO 1
DRUGA-01-06-0025	NSCLC	Tepotinib	MET	female	76	WHO 2
DRUGA-01-06-0027	NSCLC	Tepotinib	MET	female	76	WHO 1
DRUGA-01-06-0028	NSCLC	Tepotinib	MET	male	77	WHO 1
DRUGA-01-06-0029	NSCLC	Tepotinib	MET	female	77	WHO 2
DRUGA-01-06-0030	NSCLC	Tepotinib	MET	male	80	WHO 1
DRUGA-01-06-0032	NSCLC	Tepotinib	MET	male	76	WHO 1
DRUGA-01-06-0034	NSCLC	Tepotinib	MET	female	72	WHO 1
DRUGA-01-07-0039	NSCLC	Tepotinib	MET	female	76	WHO 1
DRUGA-01-07-0043	NSCLC	Tepotinib	MET	female	72	WHO 1
DRUGA-01-07-0045	NSCLC	Tepotinib	MET	female	78	WHO 2
DRUGA-01-07-0046	NSCLC	Tepotinib	MET	male	85	WHO 1
DRUGA-01-07-0047	NSCLC	Tepotinib	MET	male	73	WHO 1
DRUGA-01-07-0050	NSCLC	Tepotinib	MET	male	85	WHO 1
DRUGA-01-07-0051	NSCLC	Tepotinib	MET	female	73	WHO 1
DRUGA-01-08-0025	NSCLC	Tepotinib	MET	female	73	WHO 1
DRUGA-01-09-0007	NSCLC	Tepotinib	MET	female	67	WHO 2
DRUGA-01-09-0008	NSCLC	Tepotinib	MET	male	77	WHO 1

3 Baseline characteristics

Table 3.1 summarizes the baseline characteristics of the patients in the analysis set.

Table 3.1: Baseline characteristics

	Patients 46	
Age (approximately) at consent		
Median (range)	73.5	(49–85)
Median (IQR)	73.5	(71.25–77)
Gender		
male	18	39%
female	28	61%
WHO PS		
WHO 0	7	15%
WHO 1	27	59%
WHO 2	12	26%
Target (from cohort-assignment form)		
MET	46	100%
Tumor type (as on Baseline form)		
Lung Cancer: Non-Small Cell	46	100%
Number of previous therapy lines		
0	3	7%
1	35	76%
2	4	9%
3	2	4%
4	2	4%
Previous radiotherapy		
No	20	43%
Yes	26	57%

If WHO was not filled out on baseline, the value at the time of first treatment is used (if available). This was the case for 0 patients in the current cohort.

4 Treatment

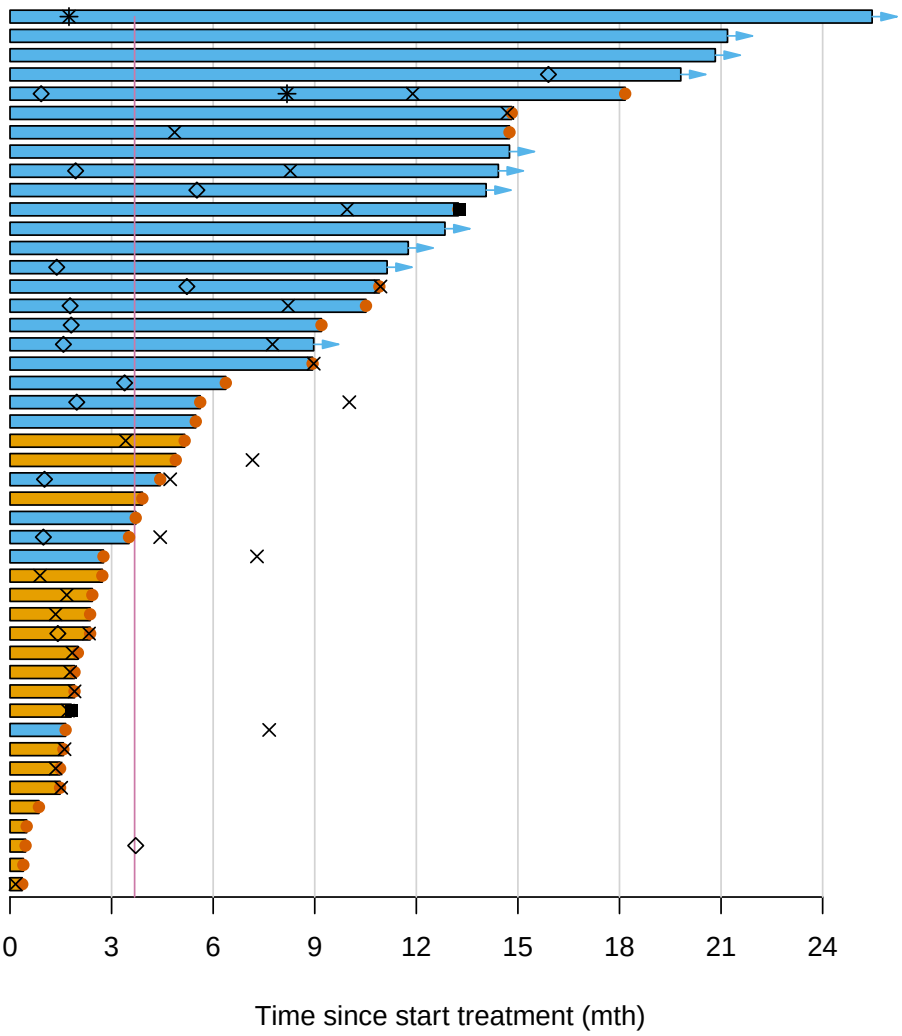
4.1 Time on treatment

There were 46 patients that started treatment, of which 11 patients were still on treatment at the time of analysis. Median time on treatment was 5.0 (95% CI:2.7 – 10.5) months. (Computed by the Kaplan-Meier method, censoring patients that are still on treatment at the last date known to be on treatment.) There were 5 patients with less than 28 days of treatment: patients DRUGA-01-01-0101, DRUGA-01-02-0047, DRUGA-01-06-0029, DRUGA-01-06-0034, DRUGA-01-07-0045 with 26, 15, 11, 12, 14 days of treatment respectively. Unlike in the DRUP-study, these patients are still evaluable.
Time on treatment is depicted graphically in the swimmer plot of figure 4.1.

4.2 Swimmerplot

The swimmer plot depicts the time on treatment for the 46 patients that started treatment. The purple line corresponds to 16 weeks. End of treatment is marked with red dot, partial response is indicated with a black diamond at the time of first appearance. Complete response is indicated by a black star at the time of first appearance. PD is indicated with a black x and death with a black square. Colors correspond to clinical benefit (see Section 5.2): blue indicates clinical benefit and orange indicates lack thereof.

Figure 4.1: Swimmmer plot of time on treatment



4.3 End of treatment

Reasons for end of treatment of the 35 patients that finished treatment are listed in table 4.1. For some patients more details are available, these are given in table 4.2.

Table 4.1: Reasons end of treatment

	Patients 35	
Reason end of treatment		
Disease progression	19	53%
Adverse event	8	22%
Symptomatic deterioration	3	8%
Patient refusal	2	6%
Death	2	6%
	1	3%
Continuation on commercial medication	1	3%

Table 4.2: Details on reasons end of treatment

DAP ID	Reason EOT	Details
DRUGA-01-01-0075	Symptomatic deterioration	progressive disease suspected on 11Sep23
DRUGA-01-01-0081	Symptomatic deterioration	ECOG 2, dyspnea G3
DRUGA-01-01-0084	Adverse event	ALAT/ASAT increased G3 + GGT increased G4
DRUGA-01-01-0086	Adverse event	edema, bilateral pleural effusion, decreased kidney function + AV block complete SAE 25Mar24
DRUGA-01-01-0101	Symptomatic deterioration	nausea, malaise, thoracic pain
DRUGA-01-02-0063	Adverse event	Edema limbs and impaired renal function, grade 3
DRUGA-01-06-0034	Adverse event	Pneumonitis grade 2, rash maculopapular grade 3
DRUGA-01-07-0039	Death	intestinal perforation
DRUGA-01-07-0043	Adverse event	diarrhea grade 2
DRUGA-01-07-0045	Adverse event	congestive heart failure grade 3
DRUGA-01-07-0050	Adverse event	Edema grade 2
DRUGA-01-07-0051	Adverse event	September dose reduction of tepotinib to 225 mg/day due to toxicity (edema, decreased appetite, GI symptoms). Edema and fatigue still ongoing.

5 Response and Clinical benefit

Response was evaluated according to RECIST for this cohort, and only in the 46 patients that started treatment.
Table 5.1 lists the best overall responses according to the measurement forms and the best overall response form.
The responses according to measurement forms distinguish between confirmed and unconfirmed PR and CR and between SD that lasted for more or less than sixteen weeks. This latter distinctions plays a role in the definition of Clinical Benefit according to the DAP definition:

> A patient has *clinical benefit* if they have disease control (i.e. CR, PR or SD) for at least sixteen weeks.

The relation between clinical benefit and responses is given in tables 5.2 and 5.3 on the group level and patient level respectively.

5.1 Objective Response

Table 5.1: Best overall response

	Patients 46	
BOR according to measurement forms		
CR (confirmed)	2	4%
CR (unconfirmed)	0	0%
PR (confirmed)	12	26%
PR (unconfirmed)	2	4%
SD $\geq$ 16 weeks	14	30%
SD $<$ 16 weeks	4	9%
PD	9	20%
NE	3	7%
BOR according to BOR-form		
CR	2	4%
PR	14	30%
SD	10	22%
non CR/non PD	4	9%
PD	13	28%
NE	3	7%

A number of things in table 5.1 look strange but are explainable (see also table 5.3):

- The patients listed as NE according to measurements are DRUGA-01-01-0075, DRUGA-01-01-0101, DRUGA-01-02-0047.
  - Patient DRUGA-01-01-0075 has a target lesion that is no longer measurable; however due to clinical deterioration we will consider this patient as not having clinical benefit. She is listed under NE in the second half of the table
  - Patient DRUGA-01-01-0101 has no post-baseline measurements and hence is unevaluable based on measurements alone. However, again due to clinical deterioration she is marked as not having CB, and in this case, marked as PD, on the BOR-form.
  - Patient DRUGA-01-02-0047 also has no post-baseline measurements, nor do we have other information about this patient. She is listed as NE in the second half of the table.
- Conversely 1 patient with NE according to the BOR form appears as 'SD $<$ 16 weeks' in the top half of the table, this is patient DRUGA-01-06-0034. This patient did have two SD measurements within the first 16 weeks, but no measurements after 16 weeks, since she had stopped treatment before then, due to AE. As a result we cannot know if she would have

reached CB if we hadn't stopped scanning her. Hence the NE on the BOR-form. The 'BOR according to measurements' just records the literal 'best observed overall response', which in this case is non-CR/Non-PD for less than 16 weeks. (Which then in turn is written as SD $<$ 16 weeks since we do not spell out the formal difference between SD for patients with measurable disease at baseline and non-CR/non-PD for patients without measurable disease at baseline in this table).

- By the same token the patients listed as 'Non-CR/non-PD' on the BOR-form should occur as 'SD $\geq$ 16 weeks' in the top half of the table.
- More generally: patients with SD $<$ 16 weeks are listed as PD on the BOR-form (to remind us that they do not meet the criteria for CB) and only patients with SD $\geq$ 16 weeks are listed as SD or non-CR/non-PD depending on the presence/absense of measurable disease at baseline.

With 14 responders in 46 evaluable patients the Objective Response Rate (ORR) is 30.4% (95% CI: $17.7 - 45.8\%$). Note: every patient is evaluable for ORR and CBR even if their BOR is NE due to all scans being unreadable. These patients are counted as non-responders since no response has been measured.
Of the patients with measurable disease at baseline ($n = 39$), who could develop both PR and CR instead of only CR, there were 14 with objective response. When only looking at these patients, the ORR was 35.9% (95% CI: $21.2 - 52.8\%$).

5.2 Clinical Benefit

There were 28 patients with clinical benefit. Table 5.2 describes their responses. With 28 benefitters in 46 evaluable patients the Clinical Benefit Rate (CBR) is 60.9% (95% CI: $45.4 - 74.9\%$). The patients with unconfirmed PR that did not have clinical benefit are patient DRUGA-01-01-0071, DRUGA-01-07-0045.

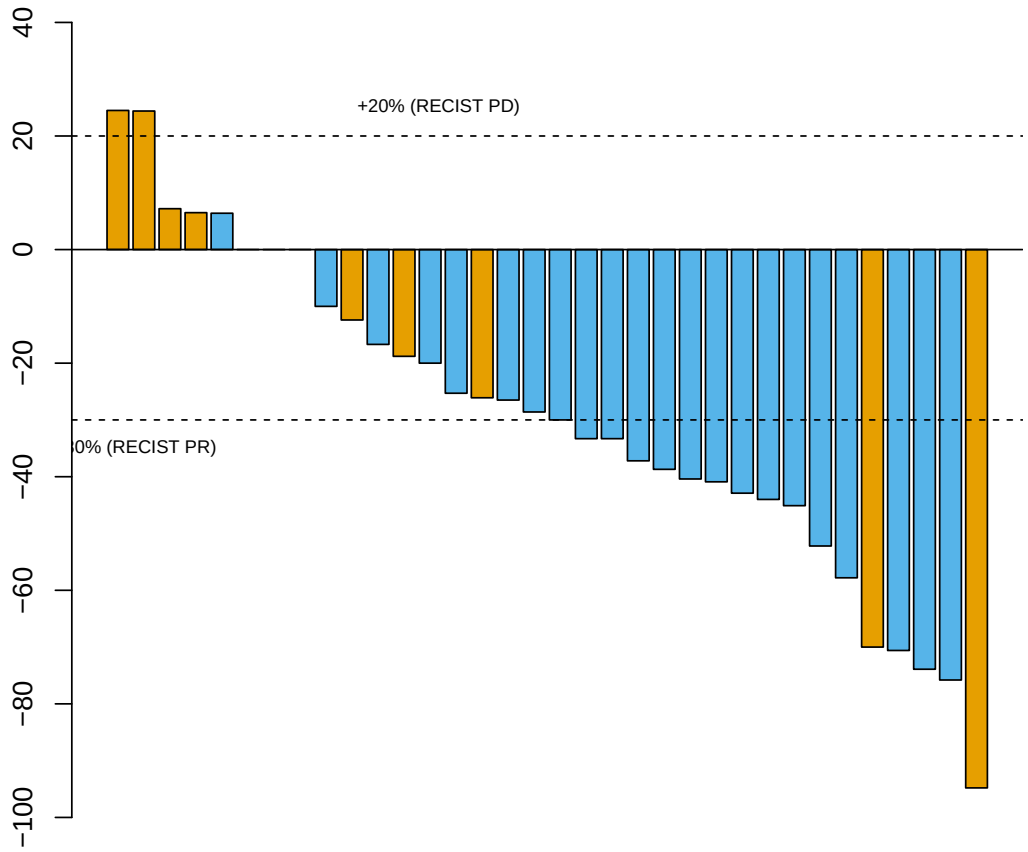
Table 5.2: Best Overall Response

	Clinical Benefit		
	CB	No CB	Total
Subjects	28	18	46
BOR according to measurement forms			
CR (confirmed)	2 (7%)	0 (0%)	2 (4%)
CR (unconfirmed)	0 (0%)	0 (0%)	0 (0%)
PR (confirmed)	12 (43%)	0 (0%)	12 (26%)
PR (unconfirmed)	0 (0%)	2 (11%)	2 (4%)
SD $\geq$ 16 weeks	14 (50%)	0 (0%)	14 (30%)
SD $<$ 16 weeks	0 (0%)	4 (22%)	4 (9%)
PD	0 (0%)	9 (50%)	9 (20%)
NE	0 (0%)	3 (17%)	3 (7%)
BOR according to BOR-form			
CR	2 (7%)	0 (0%)	2 (4%)
PR	12 (43%)	2 (11%)	14 (30%)
SD	10 (36%)	0 (0%)	10 (22%)
non CR/non PD	4 (14%)	0 (0%)	4 (9%)
PD	0 (0%)	13 (72%)	13 (28%)
NE	0 (0%)	3 (17%)	3 (7%)

5.3 Waterfall plot

For patients that are evaluable for clinical benefit that had a Recist measurement at baseline and at at least one later time point, the waterfall plot depicts the maximum decrease in tumor size. Patients with clinical benefit are depicted in blue, patients without clinical benefit in orange. Horizontal lines indicate the boundaries for partial response and progressive disease.

Figure 5.1: Waterfall plot



12 patients are not depicted in the waterfall plot: DRUGA-01-01-0075, DRUGA-01-01-0081, DRUGA-01-01-0088, DRUGA-01-01-0101, DRUGA-01-01-0105, DRUGA-01-02-0047, DRUGA-01-02-0059, DRUGA-01-06-0029, DRUGA-01-06-0030, DRUGA-01-06-0034, DRUGA-01-07-0047, DRUGA-01-07-0051. The reason is either that they do not have measurable disease at baseline, or that their target lesions are not measurable anymore during follow-up scans. The two patients with a CR, DRUGA-01-01-0072, DRUGA-01-06-0025, *are* depicted in the plot. However, since they still have measurable non-pathological lymph nodes, they do not reach 100% decline in tumor size; the RECIST rule for lymph-nodes is that they already count as CR when their diameter is below 10mm.

5.4 Listing of all patients with their best overall response and clinical benefit

Table 5.3: Response and clinical benefit on patient level

DRUP-ID	BOR (measurements)	BOR (BOR form)	Clinical Benefit	Days on treatment
DRUGA-01-01-0071	PR (unconfirmed)	PR	0	72
DRUGA-01-01-0072	CR (confirmed)	CR	1	775
DRUGA-01-01-0075	NE	NE	0	119
DRUGA-01-01-0076	PD	PD	0	45
DRUGA-01-01-0081	SD <16 weeks	PD	0	157
DRUGA-01-01-0082	PR (confirmed)	PR	1	603
DRUGA-01-01-0084	SD $\geq$ 16 weeks	SD	1	84
DRUGA-01-01-0086	PR (confirmed)	PR	1	171
DRUGA-01-01-0088	SD $\geq$ 16 weeks	non CR/non PD	1	449
DRUGA-01-01-0089	PR (confirmed)	PR	1	320
DRUGA-01-01-0090	PD	PD	0	58
DRUGA-01-01-0096	PR (confirmed)	PR	1	428
DRUGA-01-01-0097	SD $\geq$ 16 weeks	SD	1	50
DRUGA-01-01-0098	PR (confirmed)	PR	1	332
DRUGA-01-01-0101	NE	PD	0	26
DRUGA-01-01-0103	SD $\geq$ 16 weeks	SD	1	391
DRUGA-01-01-0105	PD	PD	0	48
DRUGA-01-02-0047	NE	NE	0	15
DRUGA-01-02-0049	SD <16 weeks	PD	0	74
DRUGA-01-02-0051	PR (confirmed)	PR	1	135
DRUGA-01-02-0053	SD $\geq$ 16 weeks	SD	1	634
DRUGA-01-02-0054	PR (confirmed)	PR	1	280
DRUGA-01-02-0058	PR (confirmed)	PR	1	107
DRUGA-01-02-0059	SD $\geq$ 16 weeks	non CR/non PD	1	272
DRUGA-01-02-0063	SD $\geq$ 16 weeks	SD	1	449
DRUGA-01-02-0067	SD $\geq$ 16 weeks	SD	1	167
DRUGA-01-02-0068	PD	PD	0	45
DRUGA-01-05-0005	PR (confirmed)	PR	1	339
DRUGA-01-06-0024	PD	PD	0	72
DRUGA-01-06-0025	CR (confirmed)	CR	1	553
DRUGA-01-06-0027	SD $\geq$ 16 weeks	SD	1	451
DRUGA-01-06-0028	SD <16 weeks	PD	0	55
DRUGA-01-06-0029	PD	PD	0	11
DRUGA-01-06-0030	SD $\geq$ 16 weeks	non CR/non PD	1	645
DRUGA-01-06-0032	PD	PD	0	83
DRUGA-01-06-0034	SD <16 weeks	NE	0	12
DRUGA-01-07-0039	SD $\geq$ 16 weeks	SD	1	403
DRUGA-01-07-0043	SD $\geq$ 16 weeks	SD	0	149
DRUGA-01-07-0045	PR (unconfirmed)	PR	0	14
DRUGA-01-07-0046	SD $\geq$ 16 weeks	SD	1	358
DRUGA-01-07-0047	PD	PD	0	58
DRUGA-01-07-0050	PR (confirmed)	PR	1	194
DRUGA-01-07-0051	SD $\geq$ 16 weeks	non CR/non PD	1	113
DRUGA-01-08-0025	PR (confirmed)	PR	1	273
DRUGA-01-09-0007	PR (confirmed)	PR	1	439
DRUGA-01-09-0008	PD	PD	0	61

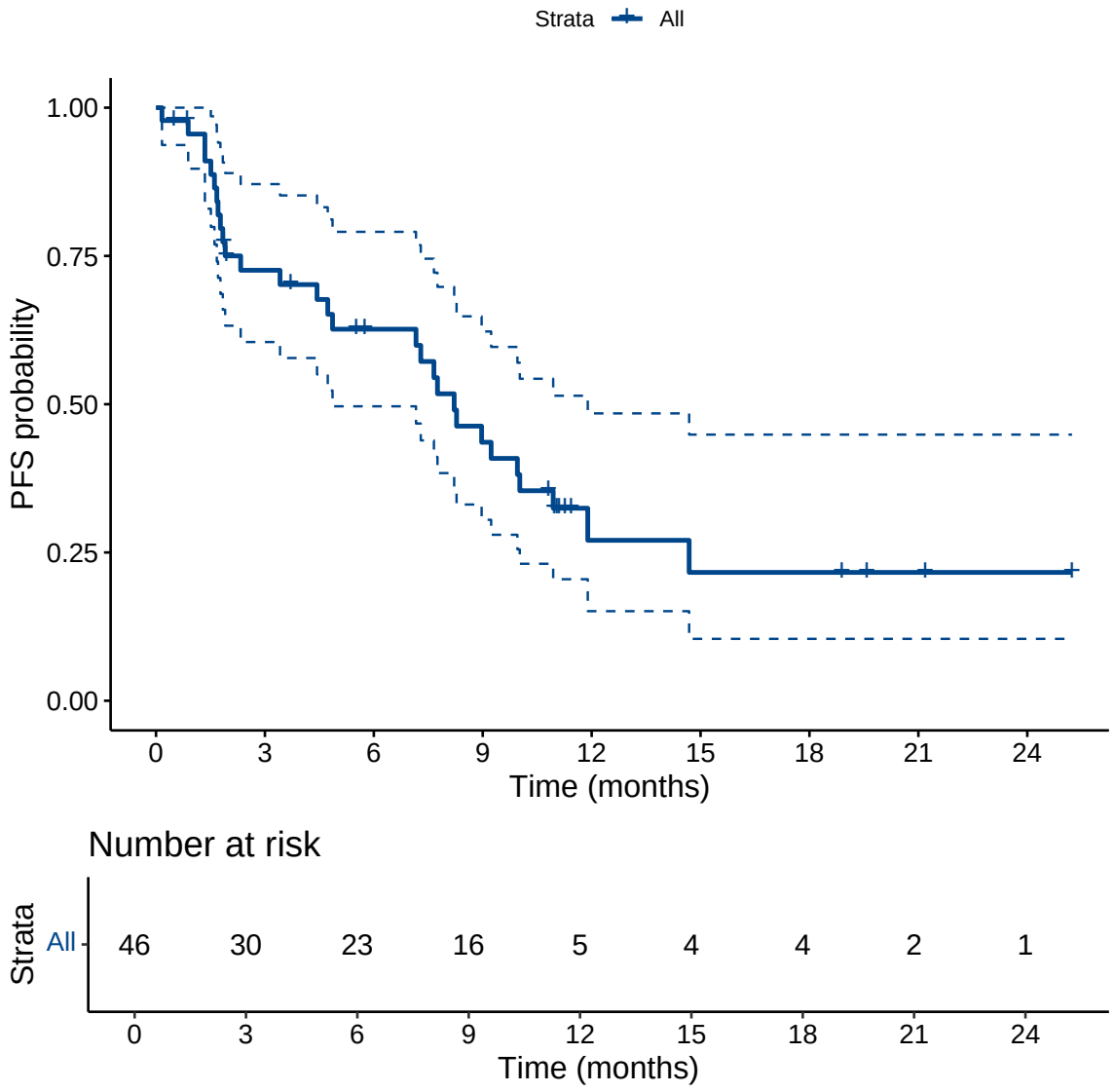
6 Progression free survival and duration of response

Progression free survival is defined as the time from start treatment to first progression or death. Patients alive without progression that are still on treatment, or discontinued treatment for reasons other than progression or death are censored at the time of their last tumor measurement. PFS is analysed in the subgroup of 46 patients that started treatment.
Duration of response is the time from first measurement of (partial or complete) response, until the first measurement of progression or death, with the same censoring rule. Obviously this is measured in the subset of patients with response. We make two separate plots: one for all responders and one for only confirmed responders. By definition the confirmed responders have all have a duration of response of at least the time between the first measurement of response and the confirmation scan, which, per protocol, will be at least four weeks and in practice in this cohort varies from 7.3 weeks to 13.4 weeks. Of course we hope that for most patients the actual duration of response will be even longer.

6.1 Progression free survival

Median PFS was 8.2 (95% CI: 4.9 – 11.9) months. The 3 months PFS was 72.6% (95% CI: 60.5% – 87.1%), the 6 months PFS was 62.6% (95% CI: 49.6% – 79.1%) and the 1 year PFS was 27% (95% CI: 15.1% – 48.5%).
The PFS curve is plotted in figure 6.1.

Figure 6.1: Progression free survival in evaluable patients, measured from start treatment



6.2 Duration of Response

Median duration of response in all 16 responders was 6.4 (95% CI: 5.7 – NA) months. 93.3% (95% CI: 81.5% – 100%) of responders achieved 3 months DoR; 6 months DoR was achieved by 70% (95% CI: 49.2% – 99.7%) of responders and 1 year DoR was reached by 13.1% (95% CI: 2.4% – 70.9%) of responders. The DoR curve is plotted in figure 6.2.

Restricting our attention only to the 14 *confirmed* responders, the median duration of response in was 6.4 (95% CI: 6.2 – NA) months. 100% (95% CI: 100% – 100%) of responders achieved 3 months DoR; 6 months DoR was achieved by 75% (95% CI: 54.1% – 100%) of confirmed responders and 1 year DoR was reached by 14.1% (95% CI: 2.6% – 75.6%) of confirmed responders. The DoR curve is plotted in figure 6.3.

Figure 6.2: Duration of response: time from first measurement of response to PD or death

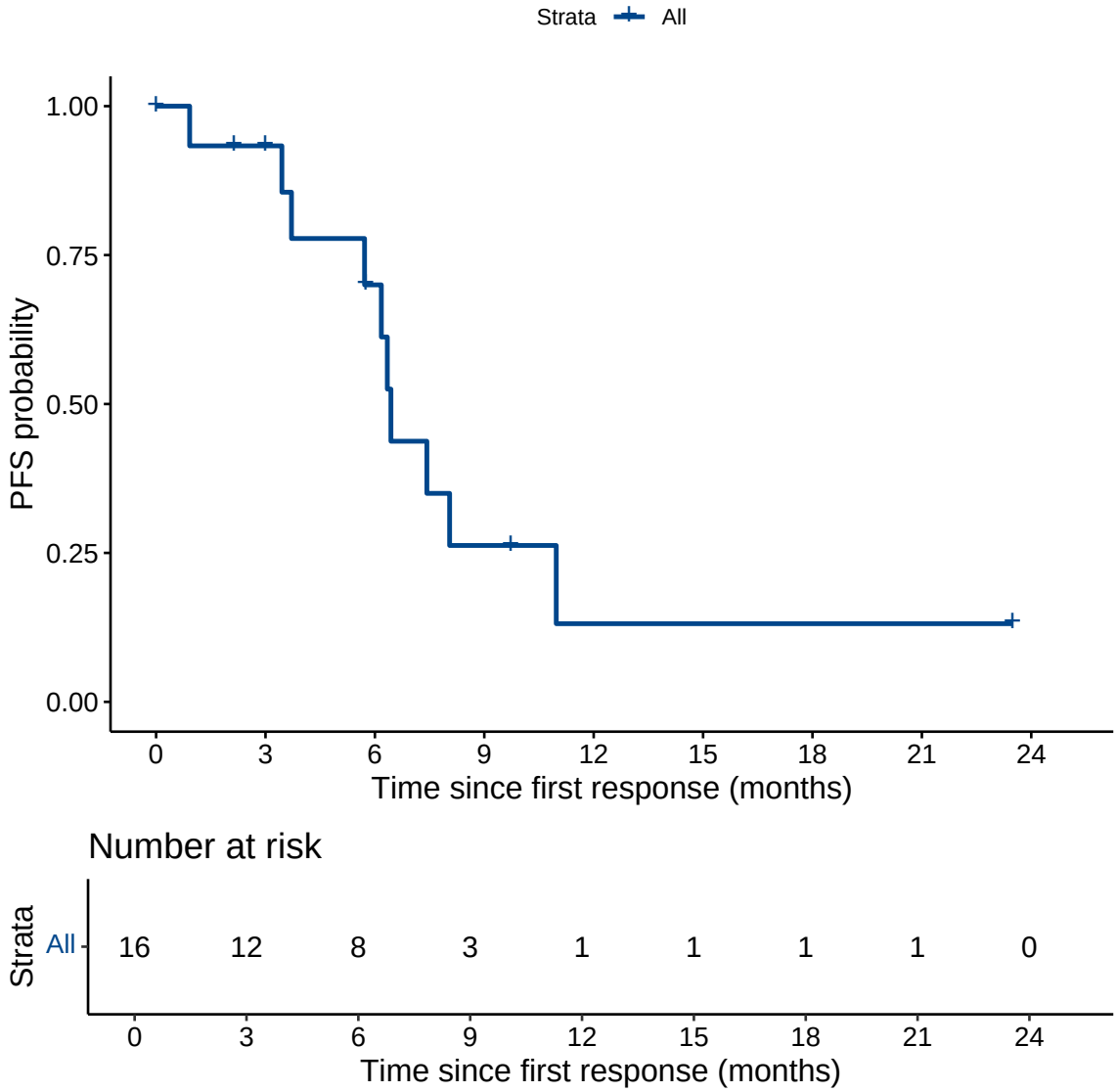
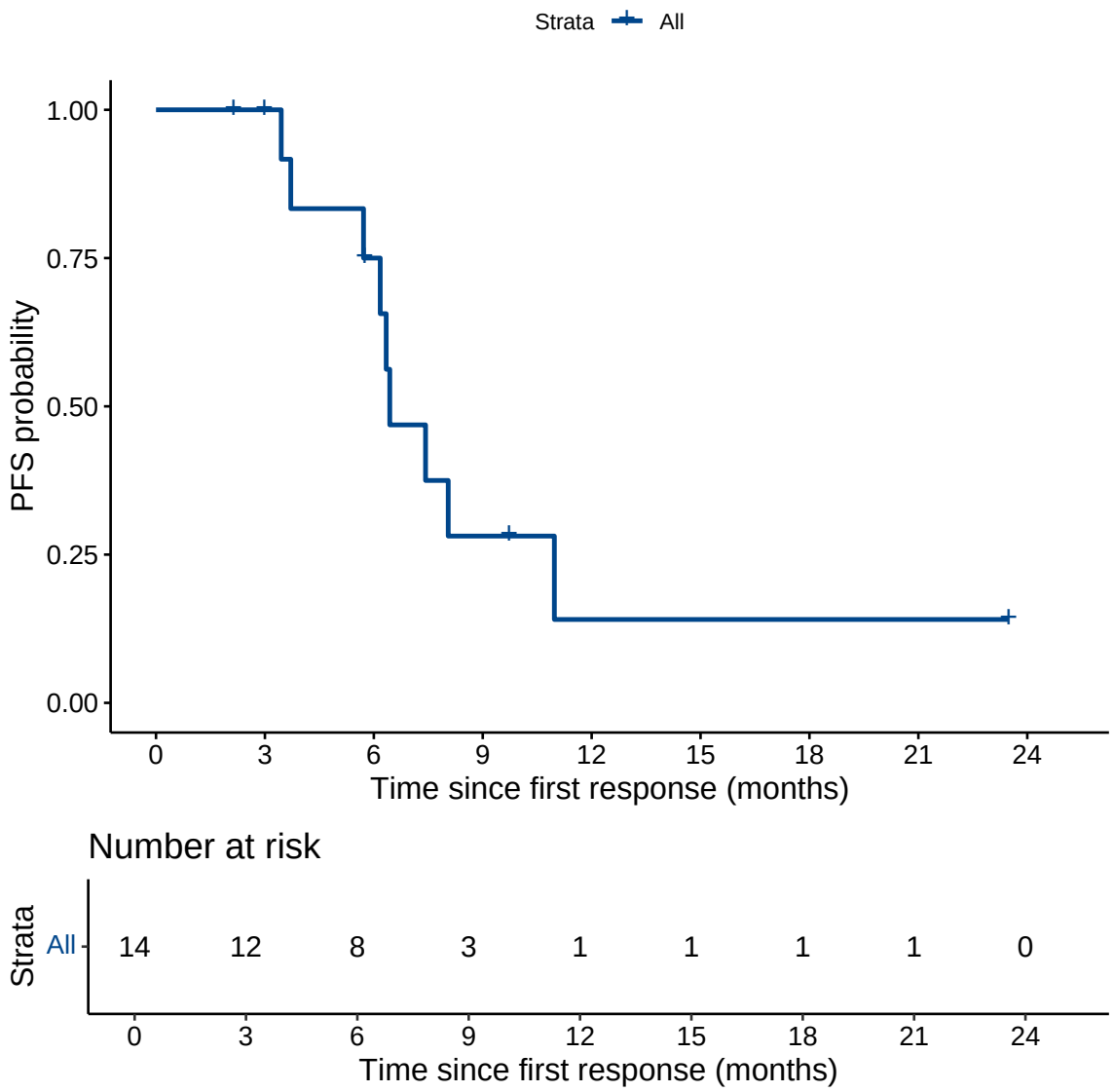


Figure 6.3: Duration of response: time from first measurement of response to PD or death for confirmed responders



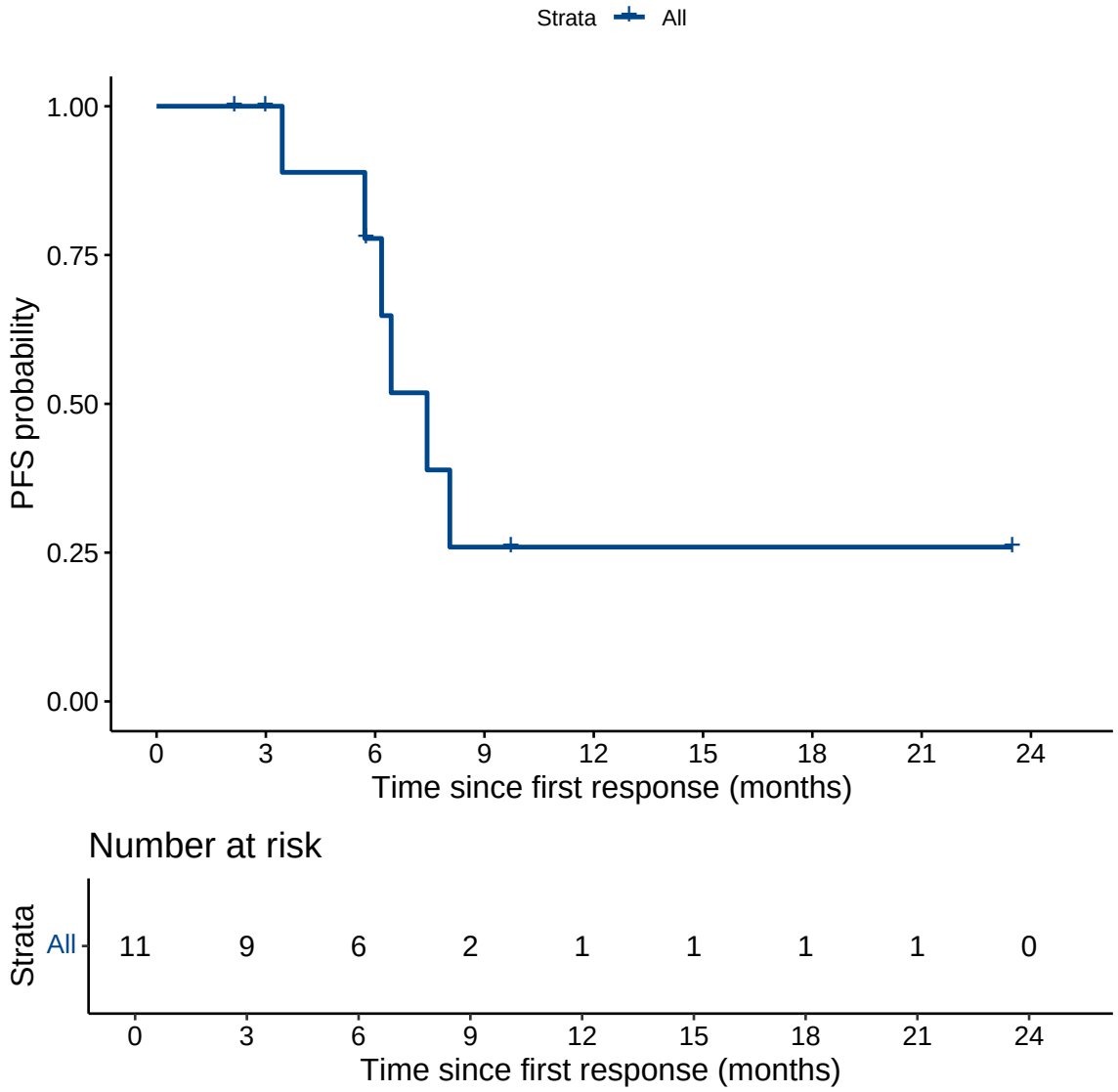
6.3 Duration of response by WHO-status

We calculate DoR separately for patients with WHO 0-1 (as in the registration study) and WHO 2.
With 11 confirmed responders, the response rate in the 34 patients with WHO status 0 or 1 was 32.4% (95% CI: $17.4 - 50.5\%$). With 3 confirmed responders, the response rate in the 12 patients with WHO status 2 was 25% (95% CI: $5.5 - 57.2\%$). Both unconfirmed PR's took place in the WHO-2-group.
Of the two patients with a complete responses one had WHO 0 and one had WHO 2. Both had measurable disease, which means that all responders had measurable disease at baseline. Since in total 28 patients in the WHO-0-1-group and 11 patients in the WHO 2 group had measurable disease, the ORR in only patients with measurable disease and WHO 0 or 1 is 39.3% (95% CI: $21.5 - 59.4\%$) and the ORR in only patients with measurable disease and WHO 2 is 27.3% (95% CI: $6 - 61\%$).

Duration of response in patients with WHO 0 or 1

Median duration of response in the 11 responders with WHO 0 or 1 was 7.4 (95% CI: 6.2 – NA) months. 100% (95% CI: 100% – 100%) of responders achieved 3 months DoR; 6 months DoR was achieved by 77.8% (95% CI: 54.9% – 100%) of responders and 1 year DoR was reached by 25.9% (95% CI: 7.9% – 84.7%) of responders. The DoR curve is plotted in figure 6.4.
As stated before all responses in this group were confirmed.

Figure 6.4: Duration of response: time from first measurement of response to PD or death, WHO 0-1 patients only



Duration of response for patients with WHO 2

Median duration of response in the 5 responders with WHO 2 was 5 (95% CI: 0.9 – NA) months. 75% (95% CI: 42.6% – 100%) of responders achieved 3 months DoR; 6 months DoR was achieved by 50% (95% CI: 18.8% – 100%) of responders. No responders in this group reached 1 year DoR. The DoR curve is plotted in figure 6.4.

Restricting our attention only to the 3 *confirmed* responders, the median duration of response in was 6.3 (95% CI: 3.7 – NA) months. 100% (95% CI: 100% – 100%) of responders achieved 3 months DoR; 6 months DoR was achieved by 66.7% (95% CI: 30% – 100%) of confirmed responders. The DoR curve is plotted in figure 6.6.

Figure 6.5: Duration of response: time from first measurement of response to PD or death, patients with WHO 2 only

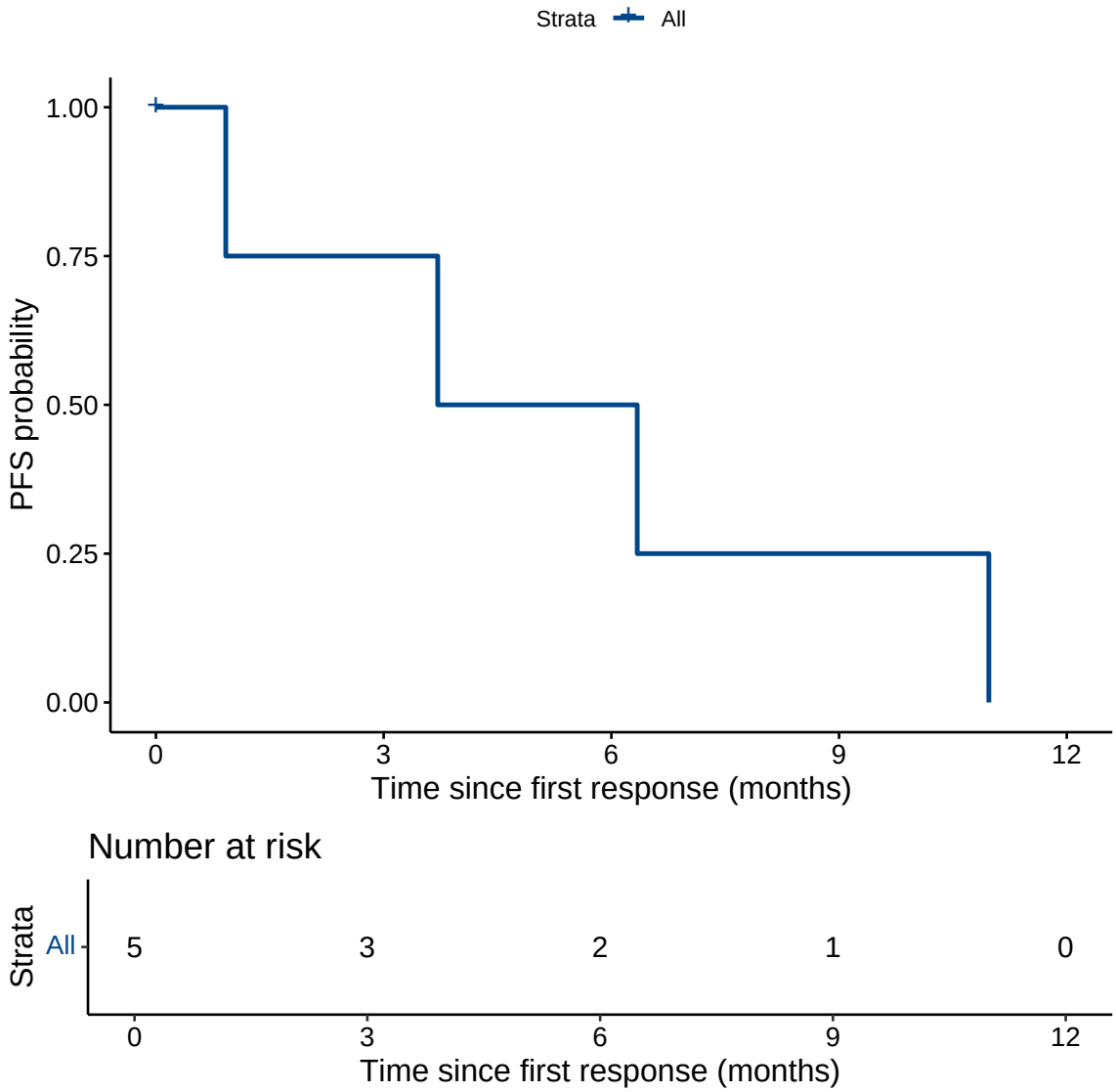
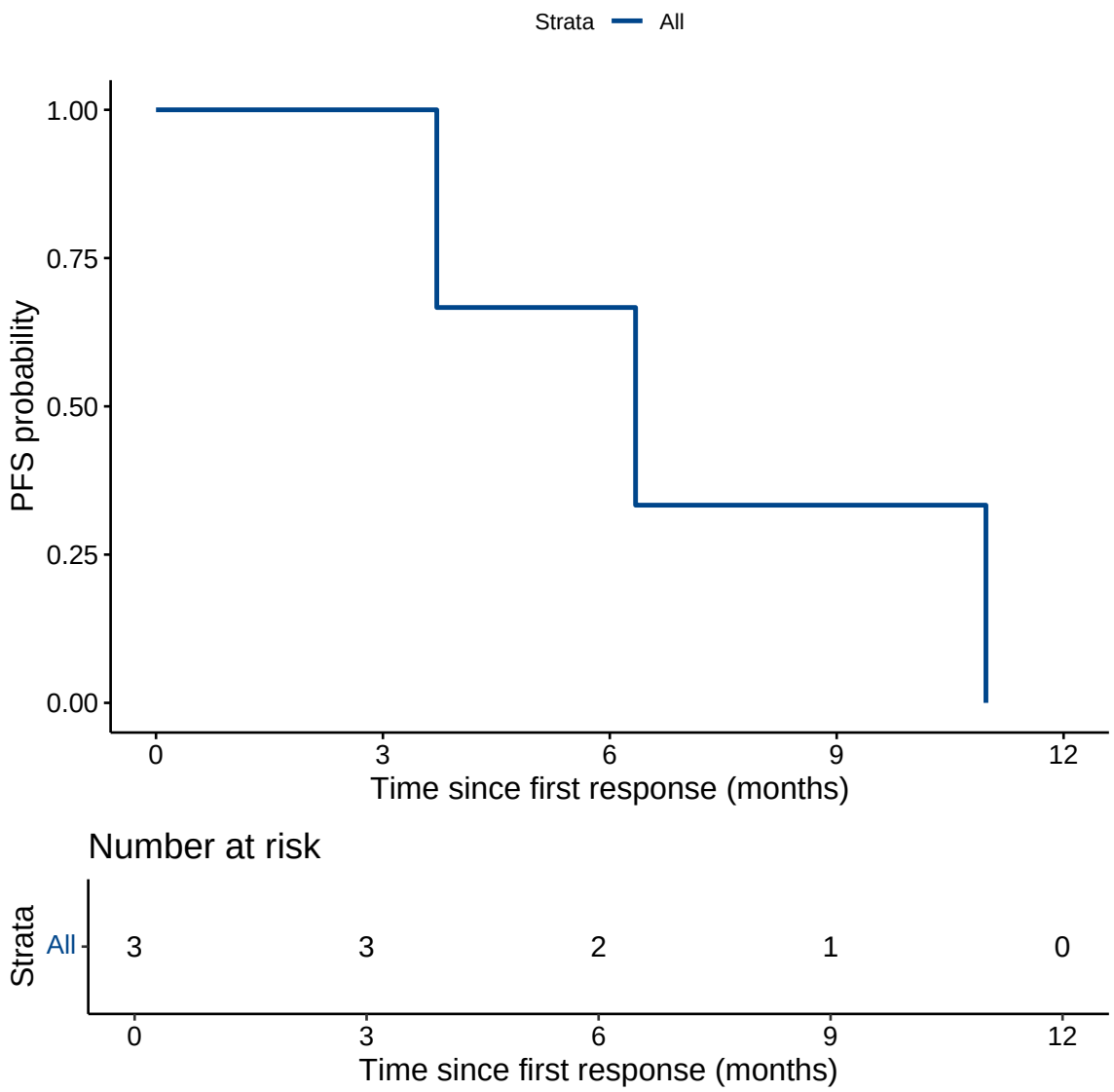


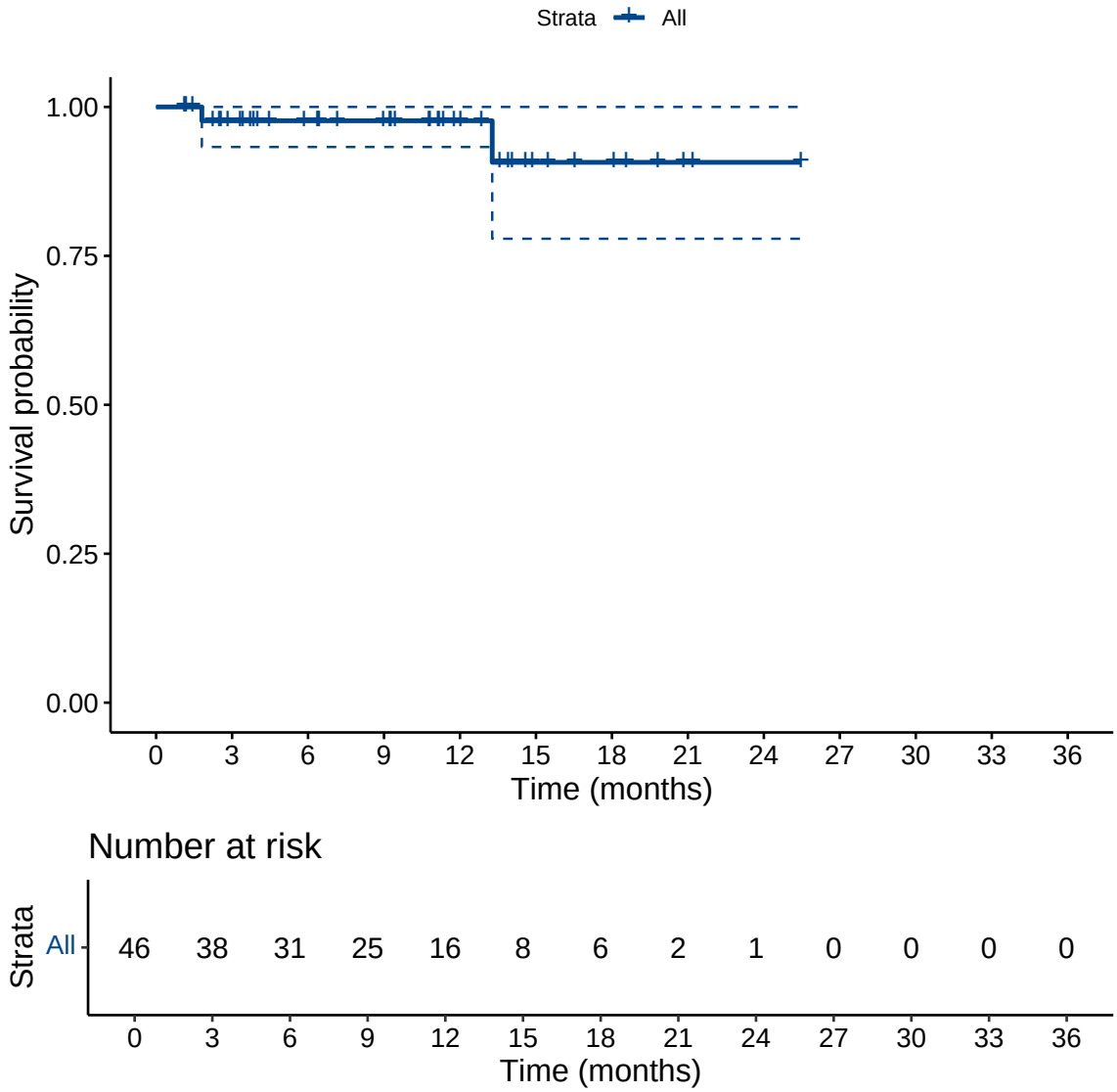
Figure 6.6: Duration of response: time from first measurement of response to PD or death for confirmed responders with WHO 2



7 Overall survival

Overall survival (OS) is defined as the time from start treatment to death of any cause. Patients alive at their last followup are censored at that time. Again it is analysed only in the 46 patients evaluable for CB according to the DAP definition.
At the time of analysis, 44 patients were still alive, median follow-up (reverse KM method) was 9.4 (95% CI: 6.4 – 12.8) months. Minimum follow-up of the patients alive at the time of analysis was 1.1 months.
Median OS was not yet reached at the time of analysis, as can be seen in the plot. The 3 months OS was 97.7% (95% CI: 93.3% – 100%), the 6 months OS was 97.7% (95% CI: 93.3% – 100%), the 1 year OS was 97.7% (95% CI: 93.3% – 100%), the 18 months OS was 90.7% (95% CI: 77.9% – 100%) and the 24 months OS was 90.7% (95% CI: 77.9% – 100%).
The OS curve is plotted in figure 7.1.

Figure 7.1: Overall survival in evaluable patients, measured from start treatment



8 Safety

There were a total of 41 Adverse Events in 21 patients, where we need to keep in mind that only adverse events of grade $\geq$ 3 and serious adverse events needed to be reported. The number of grade ≥ 3 events was 39 in 21 patients. Of these, 29 were classified as related to study treatment.

The number of serious adverse events was 16 in 12 patients. Of these 5 were related to treatment.

Due to the small number of adverse events, we just list them in Table 8.1. The number of occurrences of *related* adverse events per event type is given in table 8.2.

Table 8.1: Adverse events per patient

	DAP-ID	AE	Grade	SAE	Rel. to treatment
1	DRUGA-01-02-0053	Rash	3	No	Yes
2	DRUGA-01-07-0045	Heart failure	3	Yes	Yes
3	DRUGA-01-01-0075	Lung infection	3	Yes	No
4	DRUGA-01-01-0075	GGT increased	3	No	Yes
5	DRUGA-01-01-0075	Alkaline phosphatase increased	3	No	Yes
6	DRUGA-01-01-0075	Hyponatremia	3	No	Yes
7	DRUGA-01-02-0058	Edema	3	No	Yes
8	DRUGA-01-02-0059	Renal function decrease	3	No	Yes
9	DRUGA-01-05-0005	Chest pain	3	Yes	No
10	DRUGA-01-06-0024	Hepatitis	4	No	Yes
11	DRUGA-01-02-0051	Alat increased	3	No	Yes
12	DRUGA-01-02-0051	Edema	3	No	Yes
13	DRUGA-01-07-0043	Dyspnea	3	No	Yes
14	DRUGA-01-01-0076	Pneumonitis	3	Yes	Yes
15	DRUGA-01-01-0076	Hypoxia	3	No	Yes
16	DRUGA-01-01-0076	Chronic kidney disease	3	No	Yes
17	DRUGA-01-01-0086	Mobitz (type) II atrioventricular block	3	Yes	No
18	DRUGA-01-01-0096	Rash acneiform	3	No	Yes
19	DRUGA-01-01-0103	Hyponatremia	4	Yes	No
20	DRUGA-01-02-0063	Impaired renal function	3	No	Yes
21	DRUGA-01-02-0063	Edema limbs	3	No	Yes
22	DRUGA-01-02-0063	Impaired renal function	3	No	Yes
23	DRUGA-01-08-0025	Edema arms and legs	3	No	Yes
24	DRUGA-01-07-0039	Erythema	3	No	Yes
25	DRUGA-01-07-0039	Intestinal perforation	5	Yes	No
26	DRUGA-01-07-0039	Hypoalbuminemia	3	No	Yes
27	DRUGA-01-01-0097	Immune Related Myositis	1	Yes	Yes
28	DRUGA-01-01-0097	Chronic kidney disease	3	No	Yes
29	DRUGA-01-01-0081	Thromboembolic event	3	No	Yes
30	DRUGA-01-01-0081	Dyspnea	3	Yes	Yes
31	DRUGA-01-01-0084	Liver chemistry disorder	3	No	Yes
32	DRUGA-01-01-0084	Hypomagnesemia	4	Yes	No
33	DRUGA-01-01-0084	Aspartate aminotransferase increased	3	No	Yes
34	DRUGA-01-01-0084	GGT increased	4	No	Yes
35	DRUGA-01-01-0084	Hyperglycemia	3	Yes	No
36	DRUGA-01-06-0034	Rash maculo-papular	3	Yes	Yes
37	DRUGA-01-01-0088	Chronic kidney disease	3	No	Yes
38	DRUGA-01-01-0088	Pleural infection	3	Yes	No
39	DRUGA-01-01-0088	Pneumonitis	2	Yes	No
40	DRUGA-01-01-0088	Empyema	3	Yes	No
41	DRUGA-01-01-0088	Hyponatremia	3	Yes	No

Table 8.2: Number of AEs related to study treatment per type

Event	Frequency
Alat increased	1
Alkaline phosphatase increased	1
Aspartate aminotransferase increased	1
Chronic kidney disease	3
Dyspnea	2
Edema	2
Edema arms and legs	1
Edema limbs	1
Erythema	1
GGT increased	2
Heart failure	1
Hepatitis	1
Hypoalbuminemia	1
Hyponatremia	1
Hypoxia	1
Immune Related Myositis	1
Impaired renal function	2
Liver chemistry disorder	1
Pneumonitis	1
Rash	1
Rash acneiform	1
Rash maculo-papular	1
Renal function decrease	1
Thromboembolic event	1