Statistical Report

M20DRA

DAP Study

The Drug Access Protocol

Entrectinib and Larotrectinib for NTRK gene fusions

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

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Executive Summary

Background

From November 2021 to August 2024, larotrectinib and entrectinib were part of the DAP study following their temporary reimbursement status by Zorginstituut Nederland. While awaiting their tumor-agnostic assessment of the "Stand van Wetenschap en Praktijk" for NTRK inhibitors, patients with NTRK fusions could access NTRK inhibition in DAP, enabling additional real-world efficacy and safety data collection.

Effective July 27, 2023, Zorginstituut Nederland issued a full reimbursement of larotrectinib and entrectinib.

Methods

All patients with metastatic, locally advanced cancer harboring an NTRK gene fusion with no satisfactory treatment options were eligible for inclusion in DAP. Patients were treated with 100mg Larotrectinib BID or 600mg Entrectinib QD, until disease progression or unmanageable toxicity.

The primary endpoints of DAP were clinical benefit (CB), defined as objective tumor response (OR) (e.g. complete or partial response (CR; PR)), or stable disease (SD) ≥ 16 weeks. Additionally, treatment-related grade ≥3 adverse events were collected. Secondary endpoints included overall survival (OS), progression free survival (PFS), and duration of response (DoR).

Results

A total of 18 patients started treatment with NTRK inhibitors in DAP. At time of analysis, 11 patients were still on treatment. Therefore, the median time on treatment was not reached (95% CI: 12 months – NA). Median follow-up was 18.5 months (95% CI: 13.9 – NA).

With 14 patients showing CB, the CB rate was 77.8% (95% CI: 52.4 – 93.6). Eleven patients had an OR, of which two CR and nine PR. The resulting OR rate was 61.1% (95% CI: 35.7 – 82.7).

The median DoR was 22.3 months (95% CI: NA – NA). The median PFS was 24.4 months (95% CI: 11.6 – NA). The median OS was not reached. The 24 months OS was 71.8% (95% CI: 53.6 – 96.2).

In the current cohort, 5 patients had 6 grade ≥3 or higher adverse events.

Conclusion

Treatment with NTRK inhibition shows a marked efficacy and survival in the majority of patients with NTRK fusions across multiple tumor types, with a favorable safety profile. This DAP cohort confirms earlier promising clinical trial data and provides new real-world evidence.

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1 Introduction

1.1 Background

Larotrectinib and Entrectinib are protein kinase inhibitors (TKIs) targeting neurotrophic receptor tyrosine kinase (NTRK) 1, 2 and 3. Even though response data from previous clinical trials was promising, Zorginstituut Nederland was unable to adequately assess whether these drugs met the requirements of the "Stand van Wetenschap en Praktijk" at the time given their tumor-agnostic setting. Therefore, both drugs were only partly reimbursed by the Dutch healthcare system until an adequate assessment method was developed. To facilitate patient access and streamline data collection in the meantime, Larotrectinib and Entrectinib were included in the DRUG Access Protocol (DAP) in 2021. The DAP is a prospective, non-randomized protocol that aims to provide real-world efficacy and safety data by describing the anti-tumor activity and safety of unauthorized anti-cancer drugs awaiting FDA/EMA approval and of authorized anti-cancer drugs that are awaiting reimbursement in the Netherlands. In DAP, patients are enrolled in multiple parallel cohorts, each defined by a novel unauthorized drug and its requested label after authorization. Here, we present the efficacy and safety results both Larotrectinib and Entrectinib after 3 years of accrual in DAP.
Given the promising data from previous clinical trials, which were confirmed in the DAP cohorts described in this report, Zorginstituut Nederland has decided to completely reimburse Larotrectinib and Entrectinib effective July 27, 2023.

1.2 Methods

All patients with metastatic, locally advanced, or inoperable cancer harboring an NTRK gene fusion with no satisfactory treatment options were eligible for inclusion in DAP. For Entrectinib, no prior NTRK-inhibition therapy was allowed. Patients were treated with 100mg Larotrectinib twice daily, or 600mg Entrectinib 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 defined as date of data extraction of the eCRF, which was 2024-10-17.

2 Analysis set

The data used for this report was downloaded from the eCRF at 2024-10-17. At that time the DAP had included 321 patients of which 18 patients received one of the drugs considered in this report (Entrectinib, Larotrectinib). Of those, all 18 patients started treatment and are used in the analysis. They are listed in table 2.1.
Four patients were submitted to the study team for potential treatment but never started study treatment and were *not* included in the eCRF.

- DAP-79: Larotrectinib: patient was unable to halt concomitant anti-cancer therapy and did therefore no longer meet the selection criteria for inclusion
- DAP-99: Larotrectinib: patient preferred not to be treated
- DAP- 115: Larotrectinib: IHC and RNAseq were negative for NTRK3-gene-reassortment, and patient was therefore no longer eligible for inclusion
- DAP-221: Entrectinib: patient was still eligible for standard of care

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

Patient	Tumor	Drug	Target
DRUGA-01-01-0027	Sarcoma: adult	Larotrectinib	NTRK3
DRUGA-01-01-0032	Breast Cancer	Larotrectinib	NTRK2
DRUGA-01-01-0044	Lung Cancer: Non-Small Cell	Larotrectinib	NTRK1
DRUGA-01-01-0074	Breast Cancer	Entrectinib	NTRK3
DRUGA-01-01-0077	Lung Cancer: Non-Small Cell	Larotrectinib	NTRK3
DRUGA-01-01-0078	Lung Cancer: Non-Small Cell	Larotrectinib	NTRK3
DRUGA-01-01-0080	Ovarian Cancer	Larotrectinib	NTRK3
DRUGA-01-03-0001	Pancreatic Cancer	Larotrectinib	NTRK1
DRUGA-01-03-0006	Pancreatic Cancer	Larotrectinib	NTRK1
DRUGA-01-03-0008	Thyroid Cancer	Larotrectinib	NTRK3
DRUGA-01-05-0001	Salivary Gland Cancer	Larotrectinib	NTRK3
DRUGA-01-05-0006	Thyroid Cancer	Larotrectinib	NTRK3
DRUGA-01-06-0033	Spindle cell neoplasm Right upper lung lobe	Larotrectinib	NTRK1
DRUGA-01-07-0020	Secretory carcinoma skin cheek	Larotrectinib	NTRK3
DRUGA-01-07-0030	Thyroid Cancer	Larotrectinib	NTRK3
DRUGA-01-09-0004	Sarcoma: adult	Larotrectinib	NTRK3
DRUGA-01-09-0005	Melanoma	Larotrectinib	NTRK3
DRUGA-01-48-0001	Sarcoma: infantile	Larotrectinib	NTRK3

3 Baseline characteristics

Tables 3.1 and 3.2 summarize the baseline characteristics of the patients in the analysis set. Table 3.2 is based on the Excelfile made by Floor rather than the data in the eCRF.

Table 3.1: Baseline characteristics

	Patients 18	
Age (approximately) at consent		
Median (range)	58	(0–75)
Median (IQR)	58	(38.5–72.75)
Gender		
male	9	50%
female	9	50%
WHO PS		
WHO 0	8	44%
WHO 1	8	44%
WHO 2	2	11%
Target		
NTRK1	4	22%
NTRK2	1	6%
NTRK3	13	72%
Tumor type (as on Baseline form)		
Breast Cancer	2	11%
Lung Cancer: Non-Small Cell	3	17%
Melanoma	1	6%
Ovarian Cancer	1	6%
Pancreatic Cancer	2	11%
Salivary Gland Cancer	1	6%
Sarcoma: adult	2	11%
Sarcoma: infantile	1	6%
Secretory carcinoma skin cheek	1	6%
Spindle cell neoplasm Right upper lung lobe	1	6%
Thyroid Cancer	3	17%

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.

Table 3.2: Previous treatments

	Patients 18	
Previous systemic lines		
0	5	28%
1	7	39%
2	3	17%
4	1	6%
5	1	6%
7	1	6%
Previous Hormonal Lines		
No	16	89%
Yes	2	11%
Previous Chemotherapy Lines		
No	10	56%
Yes	8	44%
Previous Targeted Lines		
No	11	61%
Yes	7	39%
Previous Immunonotherapy Lines		
No	15	83%
Yes	3	17%
Previous radiotherapy cycles		
No	10	56%
Yes	8	44%

4 Treatment

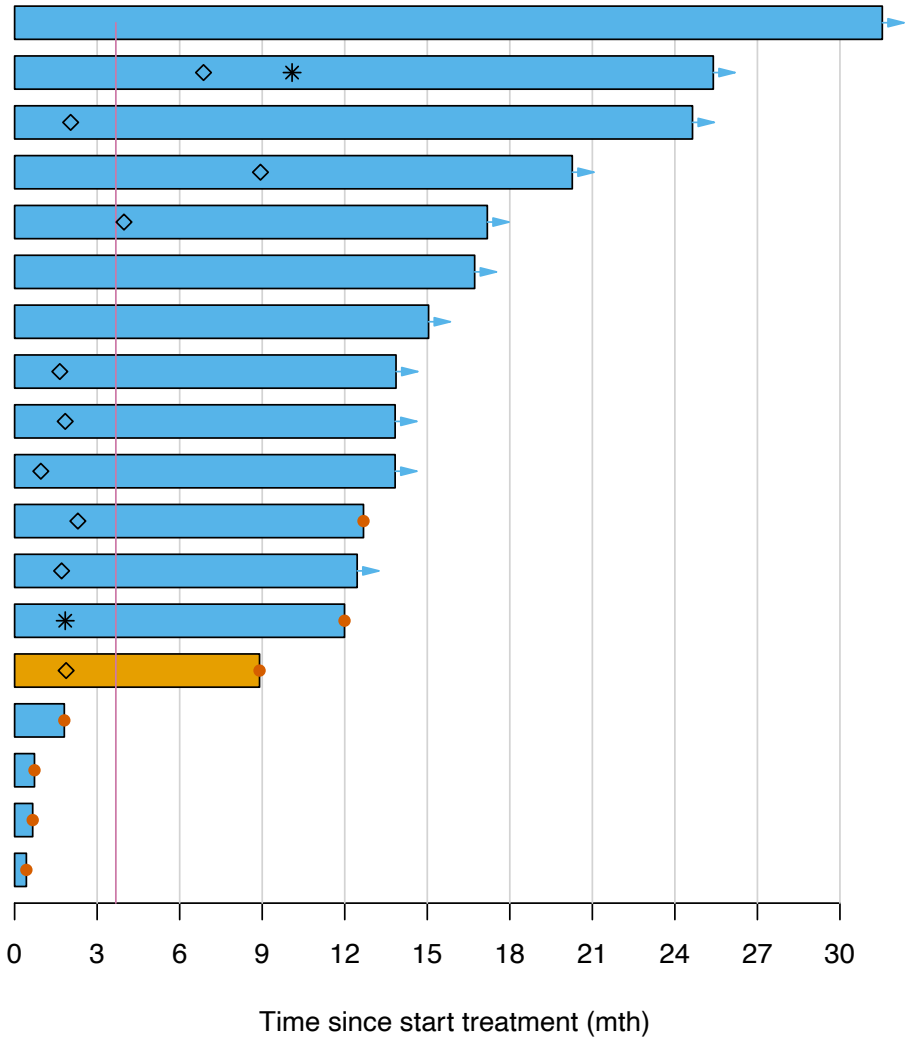
4.1 Time on treatment

There were 18 patients that started treatment, of which 11 patients were still on treatment at the time of analysis. Median time on treatment was NA (95% CI:12.0 – NA) months. There were 3 patients with less than 28 days of treatment: patients DRUGA-01-01-0027, DRUGA-01-01-0032, DRUGA-01-05-0006 with 20, 13, 22 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 18 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. CR is indicated by a black star at the time of first appearance. Colors of the bars indicate treatment: blue for larotrectinib and orange for entrectinib.

Figure 4.1: Swimmmer plot of time on treatment



4.3 End of treatment

Reasons for end of treatment of the 7 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 7	
Reason end of treatment		
Disease progression	3	43%
Adverse event	1	14%
Patient refusal	1	14%
Symptomatic deterioration	1	14%
Other	1	14%

Table 4.2: Details on reasons end of treatment

DAP ID	Reason EOT	Details
DRUGA-01-01-0032	Adverse event	fever G3 (SAE) + pain and dyspnea (not related, non SAEs)
DRUGA-01-05-0006	Symptomatic deterioration	Treatment was initially stopped because of clinical progression, due to symptoms it was not possible to take medication orally.
DRUGA-01-48-0001	Other	It was decided to do a trial stop after a year (stable scans). There was no progression or unacceptable toxicity.

5 Response and Clinical benefit

Response was evaluated according to RECIST for this cohort, and only in the 18 patients that had at least 28 days of treatment. The 3 patients with less than 28 days of treatment (patients DRUGA-01-01-0027, DRUGA-01-01-0032, DRUGA-01-05-0006) have been discussed in section 4.1. Table 5.1 lists the best overall responses according to the measurement forms and the best overall response form. The best overall response form is available only for the 7 patients that have finished treatment. Restricted to the 18 patients with at least 28 days of treatment this means that we have BOR-forms of only 4 patients.
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 18	
BOR according to measurement forms		
CR (confirmed)	2	11%
NE	1	6%
PD	2	11%
PR (confirmed)	9	50%
SD $\geq$ 16 weeks	3	17%
SD $<$ 16 weeks	1	6%
BOR according to BOR-form		
CR (confirmed)	2	11%
NE	2	11%
non CR/non PD	1	6%
PD	2	11%
PR (confirmed)	9	50%
SD	2	11%

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

- One patient with 'SD $<$ 16 weeks' according to measurement is marked 'NE' on the BOR-form, this is patient DRUGA-01-01-0027. The patient refused further treatment after three weeks. It is unclear if this is the reason for being listed as NE.
- The patient listed as "Non-CR/Non-PD" on the BOR-form and as 'SD $\geq$ 16 weeks' in the top-half of the table is patient DRUGA-01-03-0008. This patient had no meausurable disease at baseline, so their tumor evaluation is based on non-target lesions only. Strictly speaking their response according to RECIST in case of no CR and no PD is 'Non-CR/Non-PD'. However in our classifcation this was grouped with SD, and indeed for this patient this state lasted for more than 16 weeks.

With 11 responders in 18 evaluable patients the Objective Response Rate (ORR) is 61.1% (95% CI: $35.7 - 82.7\%$). 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 has response has been measured.

5.2 Clinical Benefit

There were 14 patients with clinical benefit. Table 5.2 describes their responses. With 14 benefitters in 18 evaluable patients the Clinical Benefit Rate (CBR) is 77.8% (95% CI: $52.4 - 93.6\%$). The one patient without clinical benefit was patient DRUGA-01-03-0006.

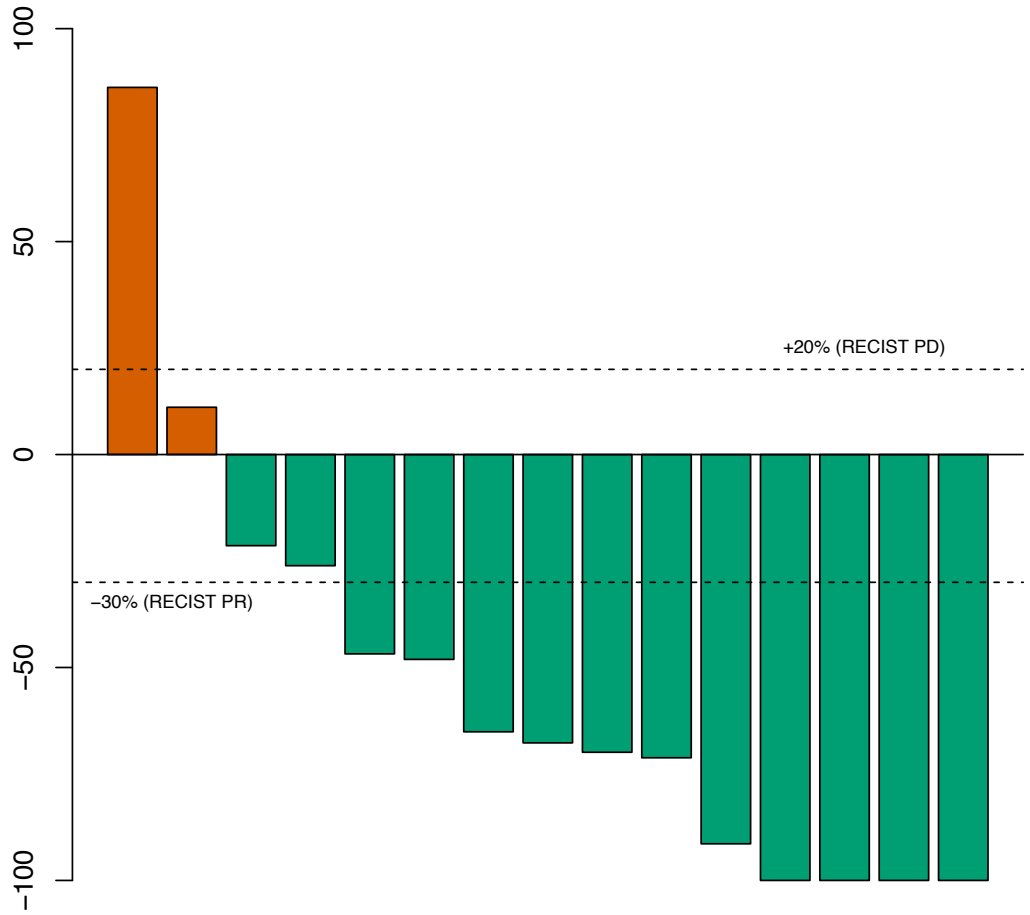
Table 5.2: Best Overall Response

	Clinical Benefit		
	CB	No CB	Total
Subjects	14	4	18
BOR according to measurement forms			
CR (confirmed)	2 (14%)	0 (0%)	2 (11%)
NE	0 (0%)	1 (25%)	1 (6%)
PD	0 (0%)	2 (50%)	2 (11%)
PR (confirmed)	9 (64%)	0 (0%)	9 (50%)
SD $\geq$ 16 weeks	3 (21%)	0 (0%)	3 (17%)
SD $<$ 16 weeks	0 (0%)	1 (25%)	1 (6%)
BOR according to BOR-form			
CR (confirmed)	2 (14%)	0 (0%)	2 (11%)
NE	0 (0%)	2 (50%)	2 (11%)
non CR/non PD	1 (7%)	0 (0%)	1 (6%)
PD	0 (0%)	2 (50%)	2 (11%)
PR (confirmed)	9 (64%)	0 (0%)	9 (50%)
SD	2 (14%)	0 (0%)	2 (11%)

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



3 patients are not depicted in the waterfall plot: DRUGA-01-01-0032, DRUGA-01-03-0008, DRUGA-01-05-0006, who were discussed before. In the picture there seem to be four patients with CR. However in reality, two of those, DRUGA-01-01-0080 and DRUGA-01-05-0001 had complete response of their target lesions but not an overall complete response due to remaining non-target lesions. Therefore, their overall response was PR.

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 according to measurements	BOR according to BOR form	Clinical Benefit
DRUGA-01-01-0027	SD <16 weeks	NE	0
DRUGA-01-01-0032	NE	NE	0
DRUGA-01-01-0044	PR (confirmed)	PR (confirmed)	1
DRUGA-01-01-0074	PR (confirmed)	PR (confirmed)	1
DRUGA-01-01-0077	SD $\geq$ 16 weeks	SD	1
DRUGA-01-01-0078	PR (confirmed)	PR (confirmed)	1
DRUGA-01-01-0080	PR (confirmed)	PR (confirmed)	1
DRUGA-01-03-0001	SD $\geq$ 16 weeks	SD	1
DRUGA-01-03-0006	PD	PD	0
DRUGA-01-03-0008	SD $\geq$ 16 weeks	non CR/non PD	1
DRUGA-01-05-0001	PR (confirmed)	PR (confirmed)	1
DRUGA-01-05-0006	PD	PD	0
DRUGA-01-06-0033	PR (confirmed)	PR (confirmed)	1
DRUGA-01-07-0020	CR (confirmed)	CR (confirmed)	1
DRUGA-01-07-0030	PR (confirmed)	PR (confirmed)	1
DRUGA-01-09-0004	PR (confirmed)	PR (confirmed)	1
DRUGA-01-09-0005	PR (confirmed)	PR (confirmed)	1
DRUGA-01-48-0001	CR (confirmed)	CR (confirmed)	1

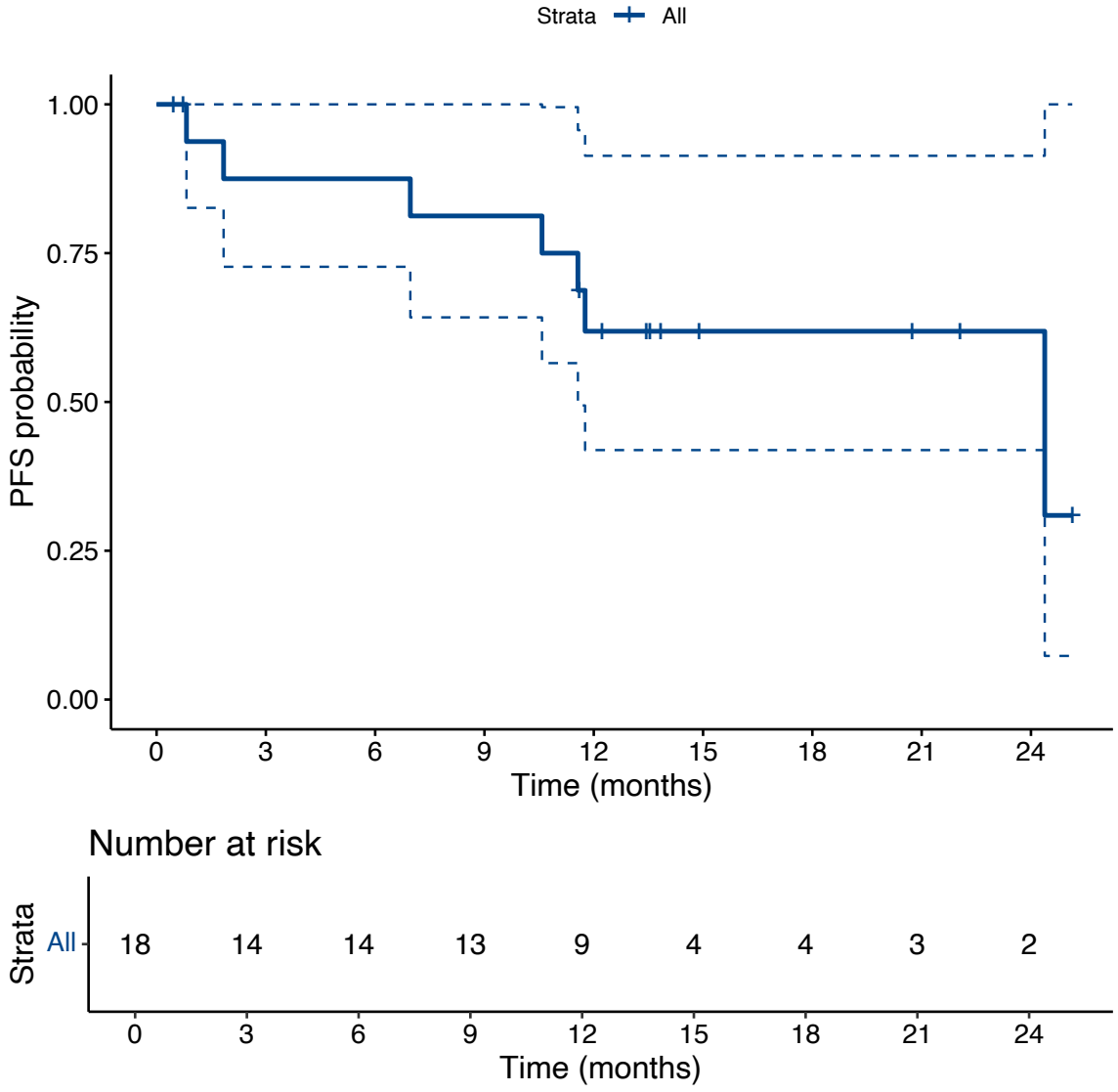
6 Progression free survival and duration of response

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 18 patients that are evaluable for clinical benefit according to the DAP definition, what, in this cohort, means that they had at least 28 days of 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.

6.1 Progression free survival

Median PFS was 24.4 (95% CI: 11.6 – NA) months. The 3 months PFS was 87.5% (95% CI: 72.7% – 100%), the 6 months PFS was 87.5% (95% CI: 72.7% – 100%) and the 1 year PFS was 61.9% (95% CI: 41.9% – 91.4%).
The PFS curve is plotted in figure 6.1.

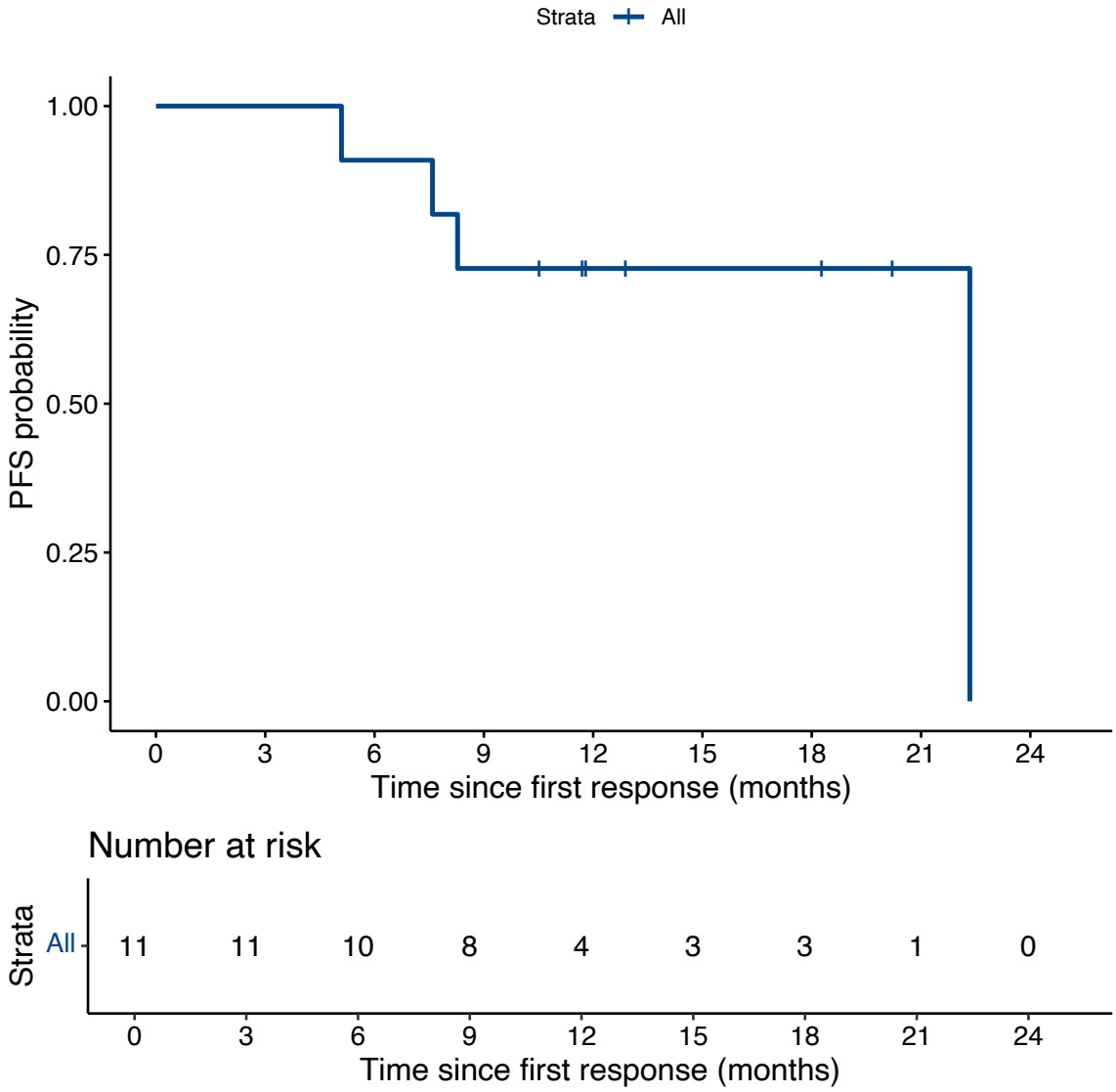
Figure 6.1: Progression free survival in evaluable patients, measured from start treatment



6.2 Duration of Response

Median duration of response was 22.3 (95% CI: NA – NA) months. 100% (95% CI: 100% – 100%) of responders achieved 3 months DoR; 6 months DoR was achieved by 90.9% (95% CI: 75.4% – 100%) of responders and 1 year DoR was reached by 72.7% (95% CI: 50.6% – 100%) of responders. The DoR curve is plotted in figure 6.2.

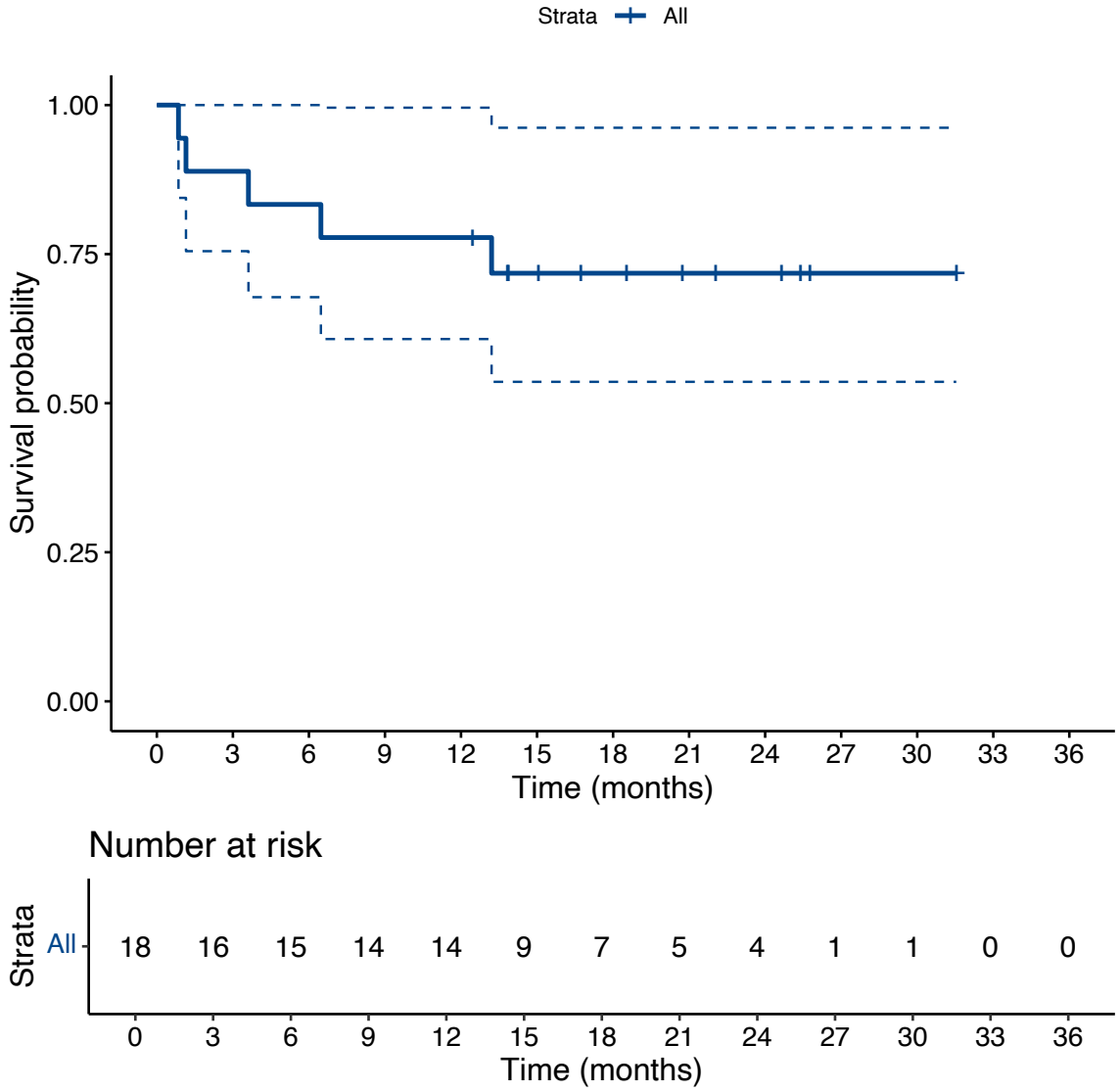
Figure 6.2: Duration of response: time from first measurement of response to PD or death



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 18 patients evaluable for CB according to the DAP definition.
At the time of analysis, 13 patients were still alive, median follow-up (reverse KM method) was 18.5 (95% CI: 13.9 – NA) months. Minimum follow-up of the patients alive at the time of analysis was 12.5 months.
Median OS was NA (95% CI: NA – NA) months. The 3 months OS was 88.9% (95% CI: 75.5% – 100%), the 6 months OS was 83.3% (95% CI: 67.8% – 100%), the 1 year OS was 77.8% (95% CI: 60.8% – 99.6%), the 18 months OS was 71.8% (95% CI: 53.6% – 96.2%) and the 24 months OS was 71.8% (95% CI: 53.6% – 96.2%).
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 6 Adverse Events in 5 patients, where we need to keep in mind that only adverse events of grade ≥ 3 and serious adverse events needed to be reported. The number of grade ≥ 3 events was 6 in 5 patients as well. The number of serious adverse events was 1 in 1 patient. Due to the small number of events, we just list them in Table 8.1. The number of occurrences 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-01-09-0005	Liver chemistry disorder	3	No	Yes
2	DRUGA-01-01-0074	Neutrophil count decreased	3	No	Yes
3	DRUGA-01-01-0077	Liver chemistry disorder	3	No	Yes
4	DRUGA-01-01-0032	Fever	3	Yes	Yes
5	DRUGA-01-03-0001	Liver chemistry disorder	3	No	No
6	DRUGA-01-03-0001	Liver chemistry disorder	3	No	No

Table 8.2: Number of AEs per type

Event	Frequency
Fever	1
Liver chemistry disorder	4
Neutrophil count decreased	1