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Tyrosine kinase inhibitor discontinuation in non-allografted Philadelphia-positive acute lymphoblastic leukemia patients: a Campus ALL real-life study

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DISCLOSURES

The authors have no conflicts of interest to disclose.

AUTHORS' CONTRIBUTION

MD and MA analyzed data and wrote the manuscript, CP, NF, VC, MC, FG, SP, PS, ET, provided clinical and followed patients, RF and SC designed research, analyzed data, wrote and critically revised the manuscript.

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DATA-SHARING STATEMENT

Datasets are maintained in an electronic database at the Department of Translational and Precision Medicine, Sapienza University of Rome. Data are available from the corresponding author upon request.

To the Editor,

Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) patients are currently treated with tyrosine kinase inhibitors (TKI) in combination with either steroids, chemotherapy or, more recently, immunotherapy. In the past, allogeneic transplant (SCT) was considered the only potential curative option. With the introduction of more potent TKIs, as well as immunotherapy, particularly blinatumomab, the role of SCT is nowadays debated, particularly for patients who achieve an early molecular response[1-3].

Patients not undergoing SCT will receive TKIs indefinitely even though long-term TKI administration may be associated with serious side effects (including off-target toxicities such as vascular events, cytopenias, and hepatotoxicity), have a high economic burden, and can, in some cases, negatively impact on patients' quality of life.

TKI discontinuation has proven feasible in chronic myeloid leukemia (CML) and is now a reality in the clinical management of CML patients with well-defined biological features[4,5].

In view of the efficacy of the novel approaches combining a TKI with immunotherapy with long-term survival rates approaching 80%[2], it is becoming of primary interest to investigate if TKI discontinuation may become a reality also for Ph+ ALL and, should this the case, for which patients. To this end, we collected and hereby report the outcome of a series of adult Ph+ ALL patients in complete hematologic response who did not undergo a SCT and discontinued TKI treatment for any reason different from relapse/progression. The study was approved by local ethic committee (CE 5629, 21/11/2019).

Retrospective clinical data on 18 patients treated at 8 hematology centers participating in the Campus ALL network in Italy were collected. Their frontline treatment included a TKI with or without mild chemotherapy according to the center policy and/or to the ongoing national clinical trial. For the purpose of this study, only patients who were treated with a chemo-free approach or with the addition of low intensity chemotherapy were considered.

Major molecular response (MMR) was defined as a level of *BCR::ABL1/ABL1* of <0.01%. Molecular relapse was defined as the loss of MMR in two consecutive samples. Overall survival (OS) was calculated from the time of TKI discontinuation to the last follow-up. Treatment-free remission (TFR) was defined as the time interval between the date of therapy discontinuation and the date of TKI resumption due to molecular/hematologic relapse or, if this did not occur, the date of the last follow-up. Relapse-free survival (RFS) was calculated from the time of TKI discontinuation to the last follow-up or to the date of

molecular/hematologic relapse. Median follow-up was estimated using the reverse Kaplan-Meier method.

The median age of our cohort was 65 years (range 22-84); 8 patients (44.4%) were females, 11 harbored a p190 transcript and 7 a p210 transcript. Conventional karyotyping at diagnosis showed the t(9;22) translocation as the only cytogenetical abnormality in 9 patients. In 2, the t(9;22) translocation was found in the context of a complex karyotype. One additional patient had a del(11) in addition to the t(9;22) translocation and another one had a normal karyotype. Karyotyping failed in 5 patients.

The first TKI administered in this cohort was imatinib in 9 patients (50%), dasatinib in 4 (22%), sequential nilotinib/imatinib (GIMEMA LAL1408[6]) in 1 (6%) and ponatinib in 4 (22%). During the follow-up, 6 patients were maintained on the same TKI since the start of treatment. The median number of TKIs used was 2 (range 1-3). The median time of TKI exposure prior to discontinuation was 84.5 months (range 4-205). At the time of discontinuation, 17/18 patients were in complete molecular response. The median time to molecular response achievement was 5 months (range 1-69). This information was not available for 1 patient. The characteristics of patients are summarized in Table 1.

The reason for not undergoing a SCT was a clinical decision (mainly due to age/unfitness and sustained molecular response) in 12 patients, donor unavailability in 3 and patient's refusal in the remaining 3.

The main reason leading to TKI discontinuation was toxicity in 12 patients and clinical or patient's decision in the other 6 patients. Reported toxicities were vascular or cardiac events (n=7), recurrent pleural effusion (n=2), severe skin ulcerations (n=1), severe diffuse muscle cramps and severe gastrointestinal symptoms (n=1).

The median time of TFR after discontinuation was 14 months (range 1-96). At the last follow-up, 5 of the 18 patients (28%) experienced a molecular relapse after a median time of 4 months from TKI discontinuation. Four of the 5 patients restarted treatment with the last TKI administered and regained a molecular remission; 3/5 are alive and well at the last follow-up after 5, 48, and 136 months, respectively. One patient ultimately died from a metastatic gastric cancer after 39 months from TKI restart (Table 1, Figure 2). The last patient refused to restart treatment and is being closely monitored by molecular analysis. At the last follow-up (March 2024) *BCR::ABL1/ABL1* was 0.83%, with a persistent hematologic remission. Overall, 3 patients died while in remission, 1 due to a gastric cancer, 1 of senectus (at the age of 92) and the last 1 for an unspecified cause.

The median follow-up of the 18 patients is 10 years (range 0.8-26), with a median OS not reached at the last follow-up, a 5-years OS estimated at 79%, a median RFS not reached and a 5-year RFS estimated at 63% (Figure 1A and B).

To our knowledge, this is the largest series so far reported of Ph+ ALL patients who did not undergo a SCT and discontinued TKI during the follow-up. The positive selection of cases, with a long-term observation period and no relapse during the observation period, is an intrinsic potential bias of this retrospective report. The only other report on the same topic is from the MD Anderson Cancer Center (MDACC) that published a monocentric retrospective series of 9 patients[7]. In line with what observed in the present series, 3 patients (33%) had a molecular relapse at a median of 6 months. All 3 resumed TKI treatment, and 2 regained a molecular response. After a median follow-up of 49 months, the median TFR was not reached, and the 4-year TFR rate was 65%. It must be underlined that the present cohort and the one reported from MDACC are different mostly in terms of treatment received, since the MDACC cases received a Hyper-CVAD polychemotherapy backbone plus imatinib in 4 patients, dasatinib in 4 and ponatinib in 1, whereas in our cohort all patients underwent an induction with a TKI plus steroids alone or with mild chemotherapy (such as vincristine and anthracycline).

The possibility of offering a TFR in non-transplanted Ph+ ALL patients is attractive for various reasons, including the possibility of reducing exposure to TKIs and to off-target toxicities. Notably, in our cohort no morphologic relapse occurred, making the TFR attempt a feasible option. In patients in molecular relapse, TKI rechallenge was effective with all re-treated patients regaining a molecular remission. Although the number of patients in this cohort is relatively limited and retrospective, thus not allowing to draw definitive conclusions, it suggests that a prolonged exposure to TKI treatment and an early achievement of molecular remission prior to discontinuation may be beneficial in terms of a longer TFR, mirroring a well-established concept in CML. Like in CML, it seems that Ph+ ALL patients have a higher risk of TFR failure during the first period of discontinuation. Indeed, in our series most relapses occurred during the first 12 months.

Due to the retrospective nature of this report, the molecular monitoring of these patients after discontinuation was not homogeneous but most patients were evaluated at least every 3 months during the first year. It was performed according to the local clinical practice mostly relying on peripheral blood *BCR::ABL1/ABL1* levels without centralization, as carried out in national clinical trials. A MRD analysis by immunoglobulin/T-cell receptor (Ig/TCR) gene rearrangement and by droplet digital (PCR) ddPCR on *BCR::ABL1/ABL1*

could not be performed on retrospective samples due to the lack of available biologic material. In fact, oOur group previously reported that ddPCR allows to refine the quantifiability of MRD in a considerable proportion of patients with Ph+ ALL[8]. Recent reports have also suggested that MRD evaluation by PCR or NGS-based assays for IG/TR rearrangements may provide a more accurate measure of clinically significant MRD than PCR for *BCR::ABL1* alone[9-12]. It could thus be pivotal in the setting of a TKI discontinuation program to identify patients who are more likely not to relapse upon discontinuation and to refine MRD monitoring thereafter to identify earlier patients who should restart TKI with the aim of preventing a hematologic relapse and of regaining a CMR status promptly.

It should be underlined that blinatumomab in association with a TKI (dasatinib and ponatinib) has been associated with increased rates of CMR[1,2,13,14]. This will eventually lead to a greater number of patients who could attempt TKI discontinuation. In the D-ALBA study, we documented that the combination of dasatinib and blinatumomab in the absence of systemic chemotherapy exerted a marked host immunomodulatory effect with a significant increase in NK, T-NK cells and a reduction of T regulatory cells[15], which may ultimately lead to a better control of the disease. This immune modulation could potentially lower the rates of TFR failure.

A validation of these findings in a prospective clinical trial with frequent centralized molecular monitoring is highly needed to accurately identify the optimal subset of patients with Ph+ ALL who could benefit most from TKI discontinuation. In addition, refined molecular analyses (i.e. bulk RNA sequencing, single cell RNA sequencing) may also help to identify molecular signatures of patients who may (or may not) be more likely to successfully stop treatment.

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Table 1. Patients' characteristics.

	Sex	Transcript	1° TKI used	Last TKI	Reason for discontinuation	MRD at TKI stop	Time on treatment (mo)	Time to CMR (mo)	Time from stop TKI (mo)	TFR status	Status at last FU	Time from TKI restart (mo)
P1	M	p190	Ponatinib	Ponatinib	Toxicity	Molecular response	98	5	8	Remission	Alive in CR	-
P2	M	p210	Ponatinib	Ponatinib	Toxicity	NA	93	39	3	Molecular relapse	Alive in CR	-
P3	F	p190	Dasatinib	Ponatinib	Toxicity	Molecular response	66	18	10	Remission	Alive in CR	-
P4	F	p190	Ponatinib	Ponatinib	Toxicity	Molecular response	39	1	46	Remission	Alive in CR	-
P5	M	p210	Imatinib	Ponatinib	Pt decision	Molecular response	94	20	7	Remission	Alive in CR	-
P6	F	p190	Dasatinib	Imatinib	Toxicity	Molecular response	76	5	50	Remission	Alive in CR	-
P7	F	p190	Ponatinib	Ponatinib	Toxicity	Molecular response	35	1	50	Remission	Dead (for other cause)	-
P8	M	p190	Dasatinib	Dasatinib	Pt decision	Molecular response	113	52	10	Remission	Alive in CR	-
P9	F	p190	Imatinib	Imatinib	Pt decision	Molecular response	205	73	2	Molecular relapse	Alive in CR	5
P10	M	p190	Imatinib	Imatinib	Toxicity	Molecular response	73	1	5	Remission	Alive in CR	-
P11	M	p210	Imatinib	Nilotinib	Pt decision	Molecular response	115	8	31	Remission	Alive in CR	-
P12	F	P210	Imatinib	Imatinib	Pt decision	Molecular response	145	3	96	Remission	Alive in CR	-
P13	M	p190	Imatinib	Imatinib	Toxicity	Molecular response	160	1	38	Remission	Alive in CR	-
P14	F	p210	Nilotinib/ Imatinib	Nilotinib/ Imatinib	Toxicity	Molecular response	38	5	31	Molecular relapse	Dead (for other cause)	39
P15	M	p210	Imatinib	Imatinib	Toxicity	Molecular response	134	4	14	Molecular relapse	Alive in CR	48
P16	M	p190	Imatinib	Dasatinib	Toxicity	Molecular response	4	5	1	Remission	Dead (for unknown cause)	-
P17	M	p190	Dasatinib	Dasatinib	Toxicity	Molecular response	56	37	14	Remission	Alive in CR	-
P18	M	p190	Imatinib	Dasatinib	Pt decision	Molecular response	31	16	4	Molecular relapse	Alive in CR	136

Abbreviations: TKI, tyrosine kinase inhibitors; MRD, minimal residual disease; CMR, complete molecular response; CMR, complete molecular response; TFR, treatment free remission; FU, follow-up.

Figure 1. Kaplan-Meier curves. A) Overall Survival B) Relapse-free survival

Figure 2. Swimmer plot of 18 Ph+ ALL patients who attempted discontinuation

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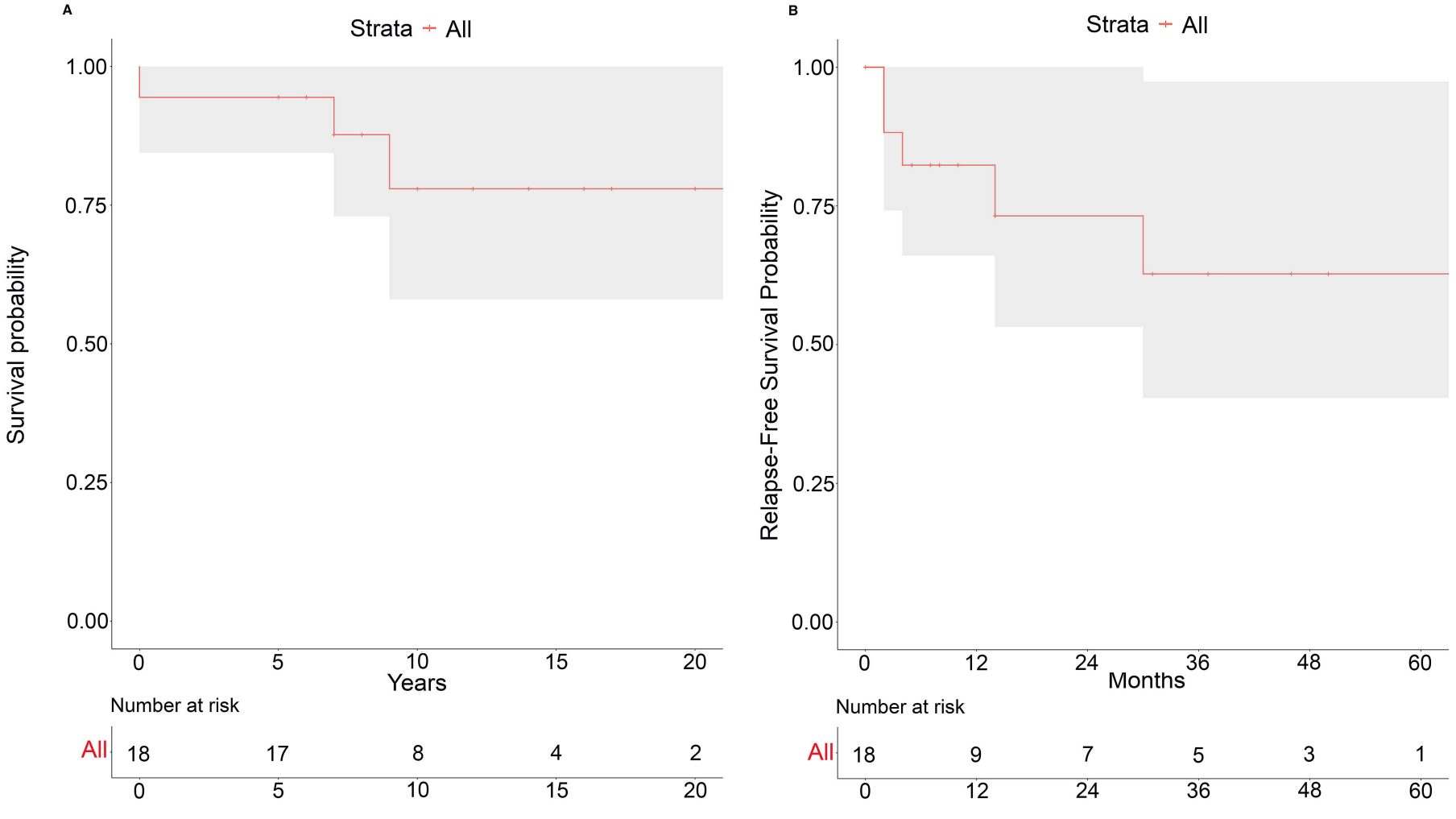
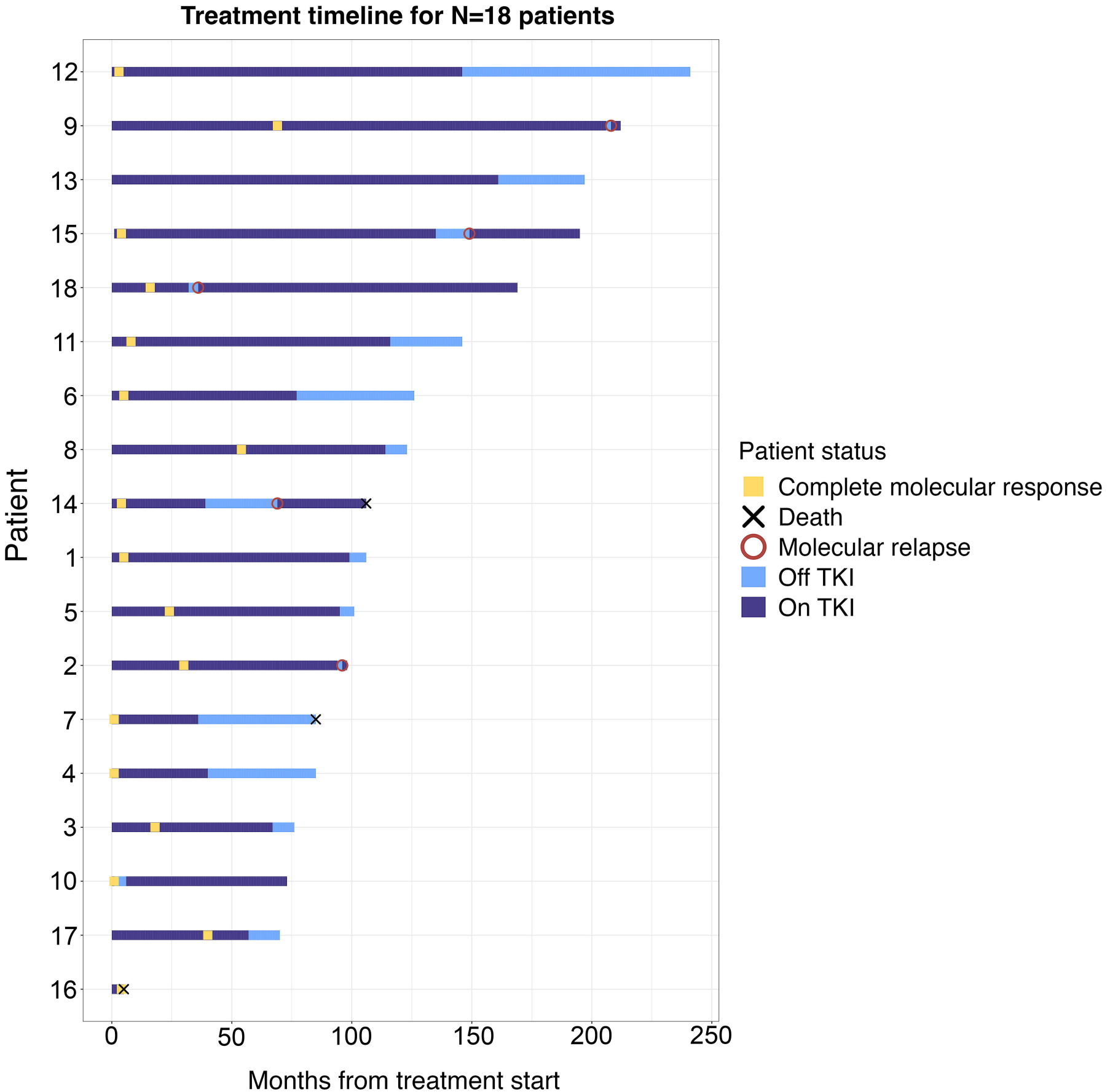


Figure 1: Kaplan-Meier curves. A) Overall Survival, B) Relapse-Free Survival


Treatment timeline for N=18 patients
Patient
12
9
13
15
18
11
6
8
14
1
5
2
7
4
3
10
17
16
0
50
100
150
200
250
Months from treatment start
Patient status
Complete molecular response
Death
Molecular relapse
Off TKI
On TKI