The initial molecular response predicts the deep molecular response but not treatment-free remission maintenance in a real-world chronic myeloid leukemia cohort

Sandrine Saugues,[1,2*] Céline Lambert,[3*] Elisabeth Daguenet,[4] Gabrielle Roth-Guepin,[5] Françoise Huguet,[6] Pascale Cony-Makhoul,[7] Hyacinthe Johnson Ansah,[8] Martine Escoffre-Barbe,[9] Ali Turhan,[10] Philippe Rousselot,[11] Andreï Tchirkov,[3,12] Dalil Hamroun,[13] Eric Hermet,[14] Bruno Pereira[3] and Marc G. Berger[1,2,14]

[1]Hématologie Biologique, CHU Clermont-Ferrand, Clermont Ferrand; [2]Equipe d'Accueil EA7453 CHELTER, Université Clermont Auvergne, Clermont Ferrand; [3]Unité de Biostatistiques, DRCI, CHU Clermont-Ferrand, Clermont Ferrand; [4]Hématologie, Institut de Cancérologie Lucien Neuwirth, Saint-Priest-en-Jarez; [5]Hématologie Clinique, CHRU Brabois, Vandoeuvre-les-Nancy; [6]Hématologie, Institut Universitaire du Cancer Toulouse Oncopole, CHU de Toulouse, Toulouse; [7]Hématologie, CH Annecy-Genevois, Pringy; [8]Institut d'Hématologie de Basse Normandie, CHU, Caen; [9]Hématologie, Hôpital de Pontchaillou, CHU de Rennes, Rennes; [10]INSERM U935 - Service d'Hématologie, Hôpital Bicêtre AP-HP, Le Kremlin Bicêtre; [11]Hématologie Clinique, Centre Hospitalier de Versailles and UMR1184, Le Chesnay; [12]Cytogénétique Médicale, CHU Clermont-Ferrand, Clermont Ferrand; [13]Direction de La Recherche Et de L'Innovation, CHRU de Montpellier, Montpellier and [14]Hématologie Clinique Adulte, CHU Clermont-Ferrand, Clermont Ferrand, France

SS and CL contributed equally as first authors.

Correspondence: M.G. Berger
mberger@chu-clermontferrand.fr

Received: December 19, 2023.
Accepted: April 24, 2024.
Early view: May 2, 2024.

https://doi.org/10.3324/haematol.2023.284860

Supplementary material – Saugues S. et al., 2023

Supplementary Table 1. Characteristics of the patients included and excluded from the study.

	Included (n=408)	**Excluded (n=393)**	**p**
Men, N (%)	211 (51.7)	226 (57.5)	0.10
Age at diagnosis (years)	56.2 ± 15.9	55.8 ± 16.1	0.70
Sokal score, N (%)			<0.001
Low (<0.8)	139 (34.1)	88 (22.4)	
Intermediate (0.8-1.2)	178 (43.6)	138 (35.1)	
High (>1.2)	83 (20.3)	65 (16.5)	
Unknown	8 (2.0)	102 (26.0)	
ELTS, N (%)			
Low (≤1.5680)	223 (54.7)	149 (37.9)	<0.001
Intermediate (1.5680-2.2185)	127 (31.1)	100 (25.4)	
High (>2.2185)	50 (12.2)	42 (10.7)	
Unknown	8 (2.0)	102 (26.0)	
Duration of follow-up (months)	62 [33; 98]	105 [51; 160]	<0.001
First-line TKI, N (%)			
Imatinib	274 (67.2)	310 (78.9)	<0.001
Nilotinib	101 (24.7)	46 (11.7)	
Dasatinib	17 (4.2)	24 (6.1)	
Other TKI	16 (3.9)	13 (3.3)	
TKI treatment duration (months)	70 [41; 101]	103 [65; 149]	<0.001
Time between diagnosis and TKI treatment initiation (months)	0.8 [0.5; 1.2]	0.8 [0.4; 1.4]	0.39

Data are presented as number of patients N (percentage), mean ± standard deviation, or median [25th; 75th percentiles].
ELTS: EUTOS long-term survival; Other TKI: bosutinib (n=11) or ponatinib (n=18); TKI: tyrosine kinase inhibitor.

Supplementary Table 2. Halving time according to the calculation method.

	n	Halving time calculated with the first day of treatment as start of *BCR::ABL1* kinetics	Halving time calculated with the day of the diagnostic blood test as start of *BCR::ABL1* kinetics
MMR at M12	180	13 [10; 16]	16 [12; 21]
MR4 at M24	123	12 [9; 16]	15 [11; 21]
MR4.5 at M48	118	12 [9; 16]	15 [12; 20]
MR5 at M48	85	12 [9; 16]	14 [11; 20]
Patients who met the criteria for TKI discontinuation	127	14 [11; 20]	18 [13; 26]
Patients who stopped TKI for optimal therapeutic response in real life	70	12 [9; 16]	17 [11; 24]
TFR at M12 after TKI discontinuation	41	13 [10; 16]	17 [13; 23]
TFR at M18 after TKI discontinuation	37	13 [10; 16]	17 [14; 23]
TFR at M24 after TKI discontinuation	33	14 [11; 16]	17 [14; 23]
IMA subgroup	274	20 [13; 31]	25 [17; 41]
2G-TKI subgroup	118	13 [10; 18]	17 [13; 25]

Data are presented as median [25th; 75th percentiles]. MMR: major molecular response; MR4: molecular responses 4-log reduction; MR4.5: molecular responses 4.5-log reduction; MR5: molecular responses 5-log reduction; M12: month 12; M18: month 18; M24: month 24; TFR: treatment-free remission; TKI: tyrosine kinase inhibitor; IMA: imatinib; 2G-TKI: second generation TKI (nilotinib or dasatinib).

Supplementary data 1: Complementary information on the CML observatory

The French Chronic Myeloid Leukemia (CML) observatory database was created in 2013. This real-world database consists of a robust security infrastructure to support data authentication, confidentiality and integrity. It is not a registry to include all patients but rather a database to form a very large French cohort. To access the system, each user receives a personal username and password. The security of the connection is enhanced by a temporary authentication key valid for one minute, consisting of a 6-digit number generated by the software. Online data input and access are restricted to clinicians and clinical research assistants with a personal account. The administrator generates the access codes, after the user has signed a written agreement. Healthcare professionals have secure access to the data of the patients with CML they follow. Conversely, only fully anonymous data are available to researchers and for analysis. Indeed, all registered patients have a CML ID that is automatically generated at the first registration. The CML Observatory is hosted by a professional health data host (MIPIH). The CML Observatory has been authorized by CNIL (authorization no. 914456), the French data protection authority. It is promoted by Clermont-Ferrand University Hospital that is the coordinating center. The data used for the present study were collected at nine participating centers.

The clinical and laboratory data of each patient are recorded after obtaining the informed consent. The record sheet has been adapted to the follow-up of patients with CML. Data recording is retrospective and prospective. The registration of patients is done on a voluntary basis by physicians at each center. Potential biases induced by the choice of including a patient, which could be arbitrary, are mitigated by the multicenter design; moreover, the sample analyzed presented characteristics close to those of published cohorts. This suggests that patient recruitment is not affected by a major recruitment bias. At the time of the database freeze for the study, nine French expert centers were participating in the CML Observatory. The CML Observatory is currently expanded (14 centers opened, 6 in the process).

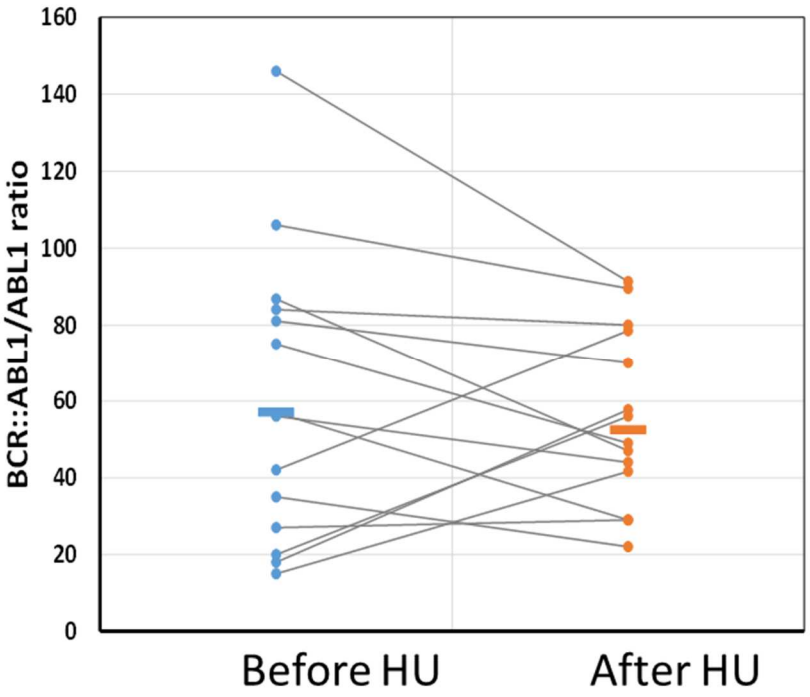
Supplementary Figure 1:
Pre-TKI hydroxyurea does not influence BCR::ABL1 level. The absence of the influence of hydroxyurea (HU) was verified. In the Chronic Myeloid Leukemia (CML) Observatory cohort where we found 14 patients who had taken hydroxyurea and had BCR::ABL1 transcript quantification data at diagnosis (before hydroxyurea) and just before tyrosine kinase inhibitor (TKI) initiation (after hydroxyurea). No significant difference was observed, confirming the literature results. NS: not significant tyrosine kinase inhibitor.

Supplementary Figure 2:
Cumulative incidence of the molecular response milestones. Panels show the cumulative incidence of MMR, MR4, MR4.5 and MR5 in the whole cohort throughout the entire follow-up period (A) and in the first 2 years (B), and then MMR (C, D), MR4 (E, F), MR4.5 (G, H), and MR5 (I, J) in function of the first-line treatment subgroup (imatinib, 2G-TKI or other TKI). For each subgroup, the step-function curves of cumulative incidence increased with each event, according to the actual proportion of patients who achieved that response at each time point until the last known response. MMR: major molecular response; MR4: molecular responses 4-log reduction; MR4.5: molecular responses 4.5-log reduction; MR5: molecular responses 5-log reduction; Other TKI: first-line treatment with bosutinib or ponatinib; 2G-TKI: first-line treatment with nilotinib or dasatinib.

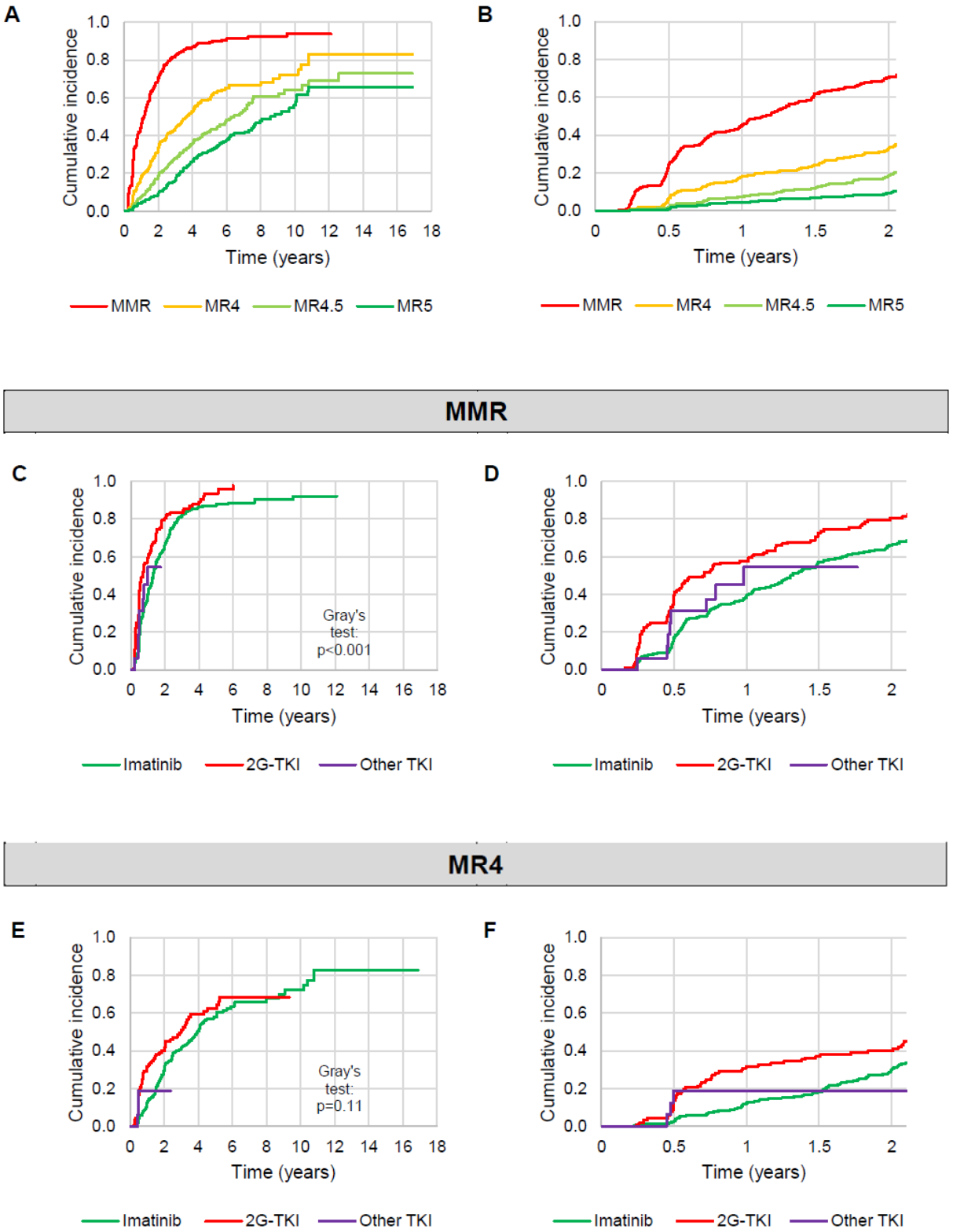
Supplementary Figure 3:
Boxplots showing the halving time values in the whole cohort (A) and in the two first-line treatment subgroups, imatinib (B) and 2G-TKI (C). In each subgroup, patients are divided in two groups: patients who achieved or not that molecular response milestone. The central line is the median, the edges of the box are the 25th and 75th percentiles, the upper whisker is calculated as the maximum of (75th percentile + 1.5 × (75th percentile – 25th percentile)), and the lower whisker is calculated as the minimum of (25th percentile – 1.5 × (75th percentile – 25th percentile)). MMR: major molecular response; MR4: molecular responses 4-log reduction; MR4.5: molecular responses 4.5-log reduction; MR5: molecular responses 5-log reduction; 2G-TKI: second-generation tyrosine kinase inhibitor (nilotinib or dasatinib). *: $p<0.001$.

Supplementary Figure 4:
Sensitivity analysis using data from the subgroup of patients who did not change treatment (n=258). Receiver operating characteristic curves to evaluate the four early parameters (i.e. ELTS score, Halving time, BCR::ABL1/ABL1^{IS} ratio at months 3 and 6) as predictive markers of the achievement of major molecular response (MMR) at month 12 (A, n=253 patients), molecular responses 4-log reduction (MR4) at month 24 (B, n=201), 4.5-log reduction (MR4.5) (C, n=158) and 5-log reduction (MR5) (D, n=156) at month 48 of tyrosine kinase inhibitor (TKI) treatment. AUC: area under the curve; ELTS: EUTOS long-term survival score; M3: month 3; M6: month 6; M12: month 12; M24: month 24; M48: month 48. The pairwise comparisons are shown below each figure (only if p-value <0.05, omnibus test). Black lines indicate significant differences and gray dashed lines non-significant differences.

Supplementary figure 1:

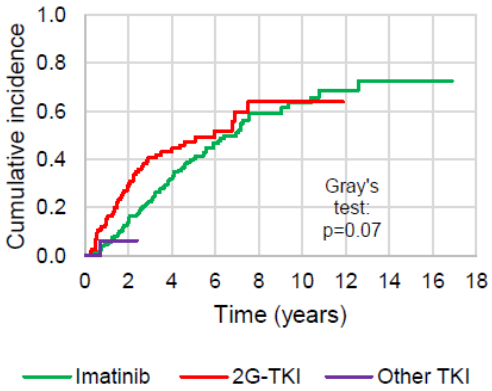


Supplementary figure 2

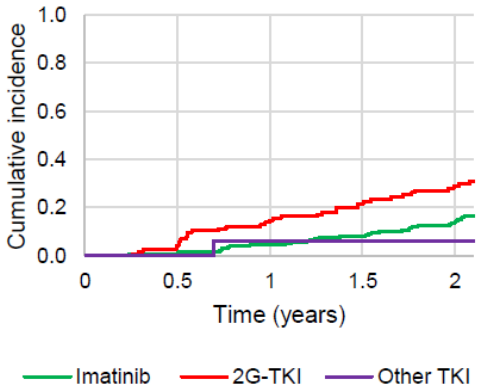


MR4.5

G

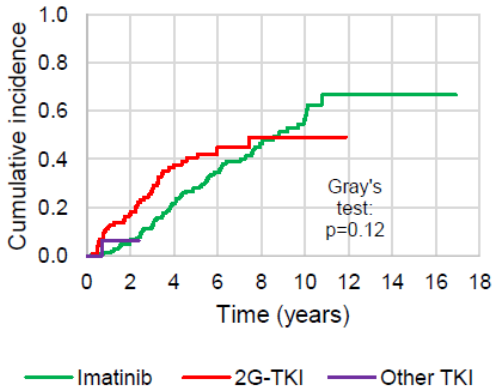


H

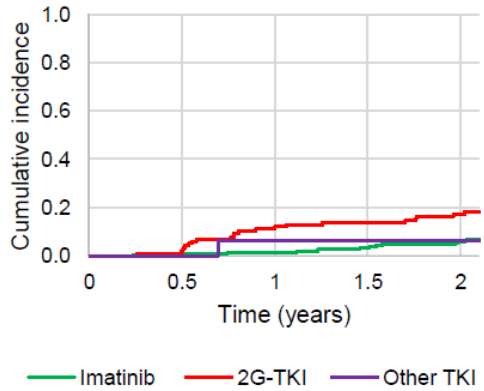


MR5

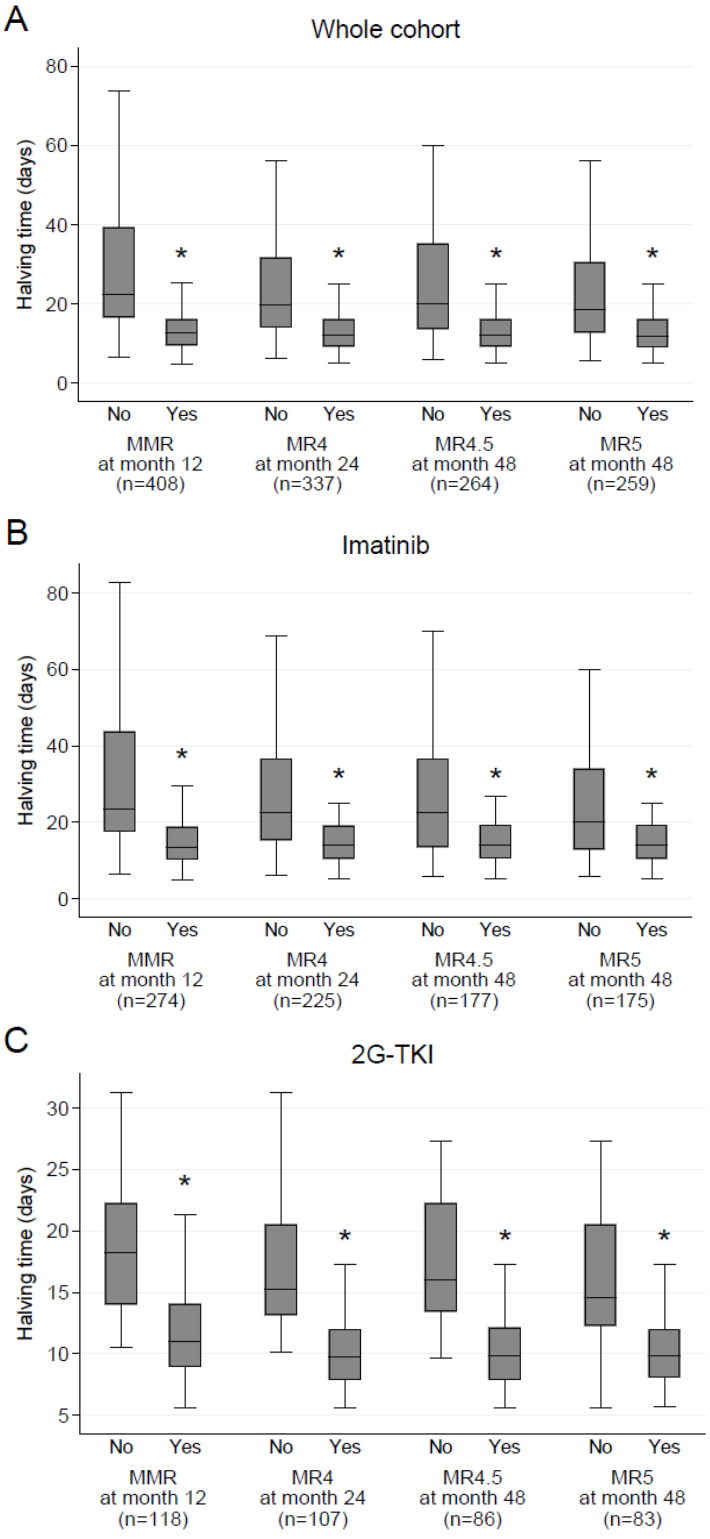
I



J



Supplementary figure 3:



Supplementary figure 4