Langzeitüberleben bei CML 2024: Endresultat der TIGER-Studie.

Treatment Free Remission after Nilotinib Plus Peg-Interferon α Induction and Peg-Interferon a Maintenance Therapy for Newly Diagnosed CML Patients

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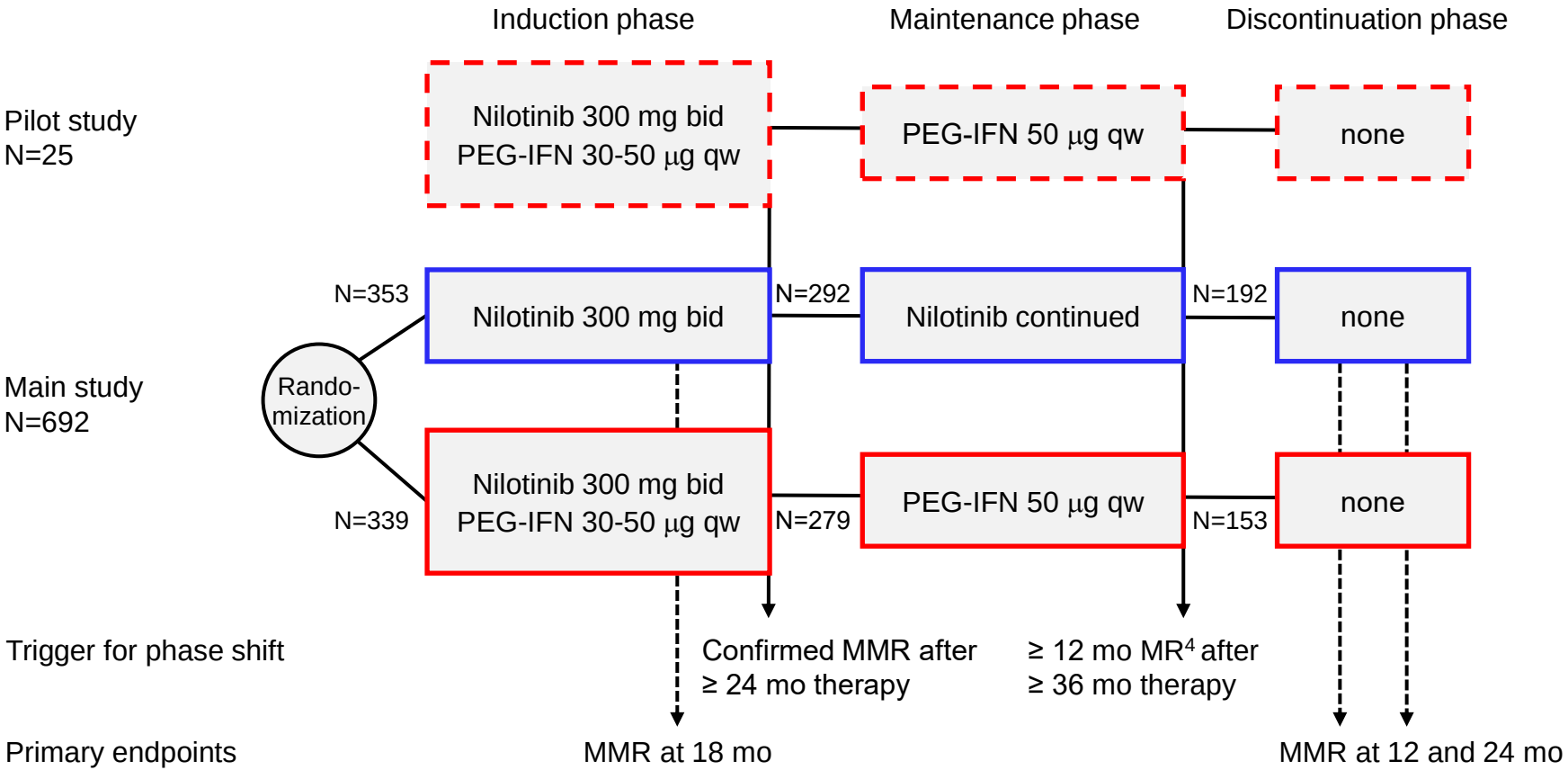
for the German CML Study Group, the SAKK and the OSHO

Offenlegung Interessenskonflikte

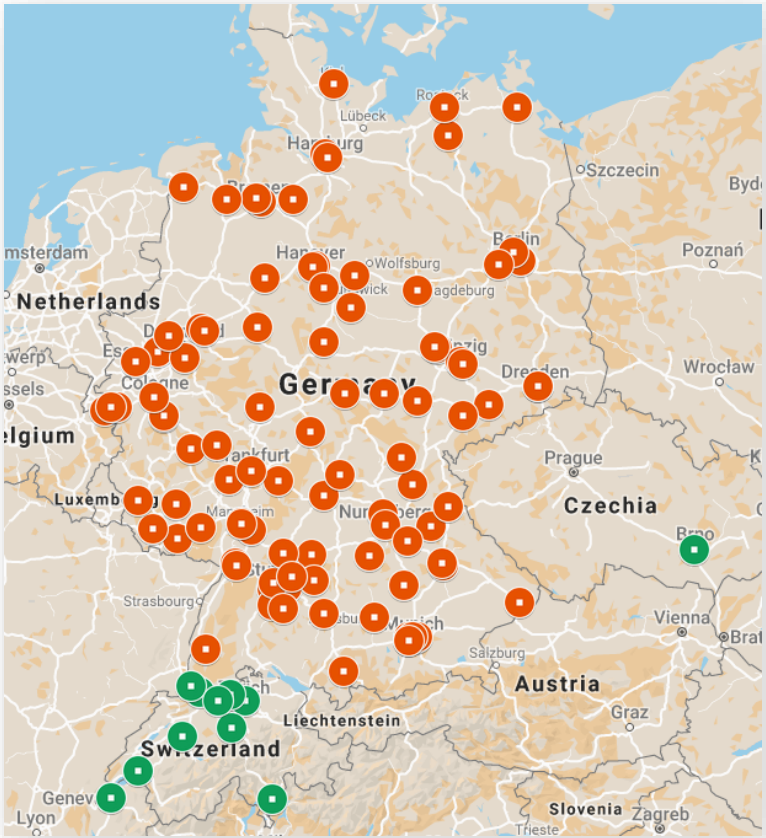
1. Anstellungsverhältnis oder Führungsposition	UK Jena
2. Beratungs- bzw. Gutachtertätigkeit	Novartis, Incyte, TERNS
3. Besitz von Geschäftsanteilen, Aktien oder Fonds	keine
4. Patent, Urheberrecht, Verkaufslizenz	BCR::ABL1 Mutationen
5. Honorare	Springer/Nature
6. Finanzierung wissenschaftlicher Untersuchungen	Novartis, BMS, MSD, Pfizer, Incyte, TERNS, Enliven
7. Andere finanzielle Beziehungen	keine
8. Immaterielle Interessenkonflikte	keine

TIGER STUDY

N=717 (Median follow up 6.4 years)



Participating sites (n=110)



TIGER = TKI + Interferon initiated in Germany

EudraCT no.	2010-024262-22
Clinicaltrials.gov	NCT01657604
Recruitment	2012-2017

German CML Study Group

East German Study Group on Hematology and Oncology, OSHO

Swiss Group for Clinical Cancer Research, SAKK

Czech Leukemia Study Group, CELL

Participating sites:

99	Germany	35	Academic departments
10	Switzerland	44	Regional hospitals
1	Czech Republic	31	Resident physicians

Baseline parameters

	Randomized total pts. (N=692)	Nilotinib-Monotherapy (N=353)	Nilotinib + Peg-IFN (N=339)
Sex n (%)			
female	281 (40.6)	148 (41.9)	133 (39.2)
male	411 (59.4)	205 (58.1)	206 (60.8)
Age (years) median (range)	51 (18 – 85)	51 (19 – 81)	51 (18 – 85)
WBC (/nl)	82.7 (2.5 – 605.0)	86.1 (2.5 – 605.0)	81.3 (2.7 – 556.0)
Blasts PB (%)	1 (0 – 15)	1 (0 – 12)	1 (0 – 15)
Basophils (%)	4 (0 – 32)	4 (0 – 27)	4 (0 – 32)
Platelets (/nl)	365 (49 – 3440)	350 (49 – 3440)	380 (86 – 3255)
Eosinophils (%)	2 (0 – 79)	2 (0 – 79)	2 (0 – 57)
Hemoglobin (g/dl)	12.1 (4.7 – 17.5)	12.1 (4.7 – 17.5)	12.0 (6.9 – 16.7)

Pilot Phase

25 patients

Randomization

692 patients

<u>Total</u>

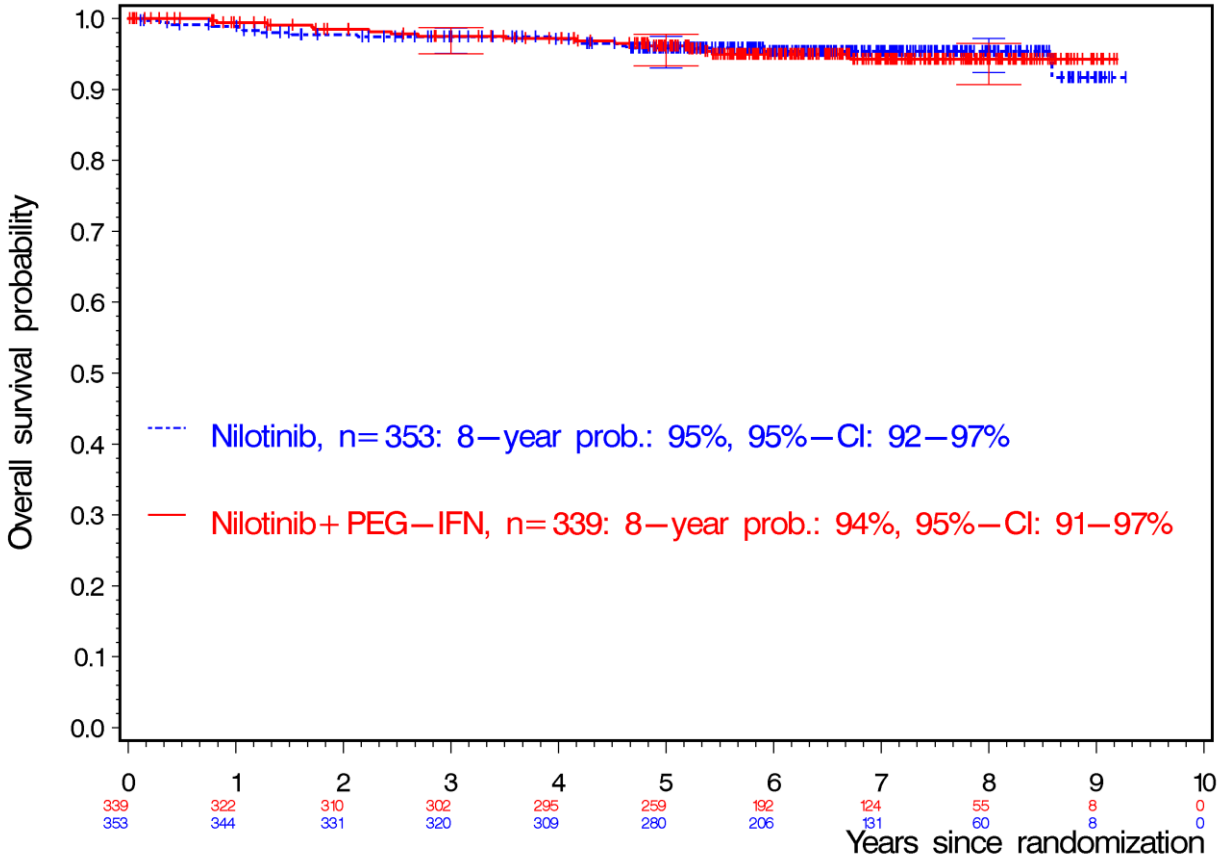
717 patients

Stratification according to EUTOS risk score

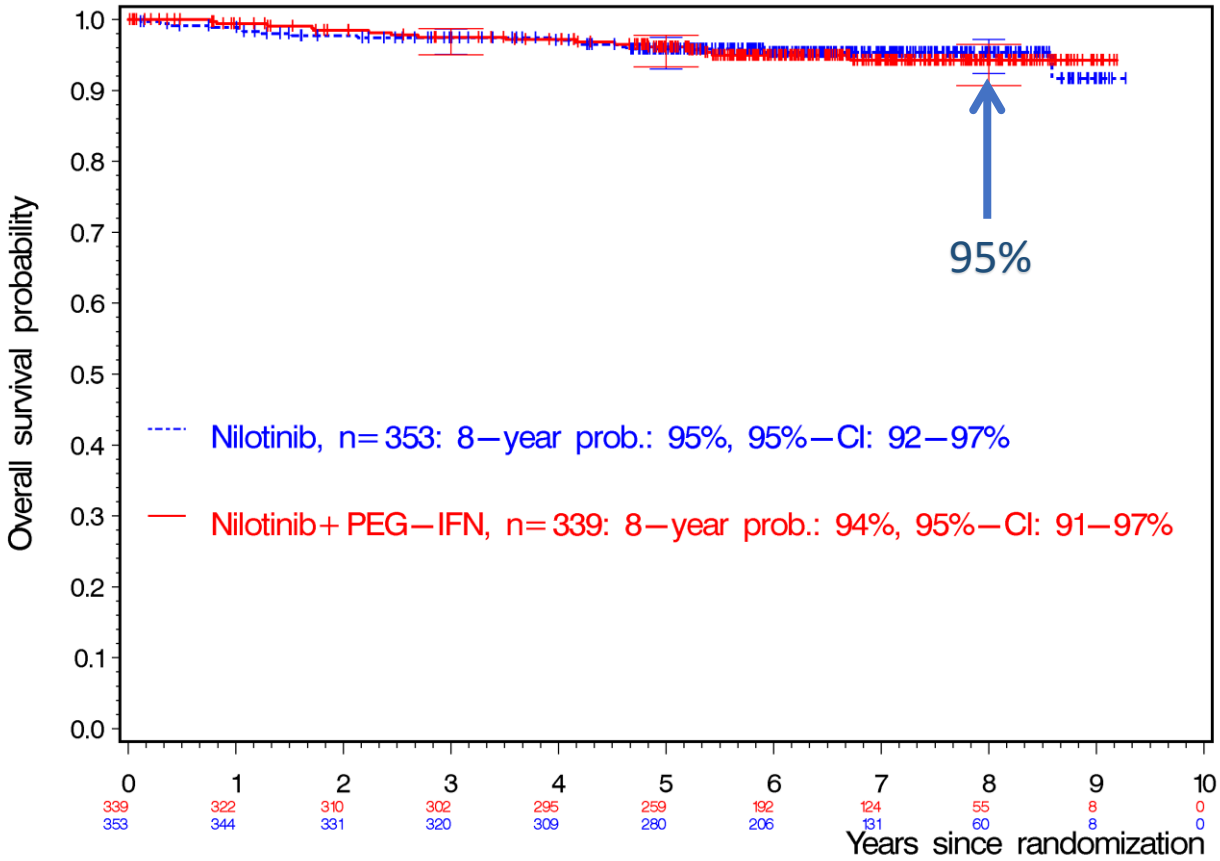
Risk scores	Total (N=692)	Nilotinib-Monotherapy (N=353)	Nilotinib + PEG-IFNα (N=339)
EUTOS-Score[1] %			
High risk	13	14	13
Low risk	87	86	87
ELTS-Score[2] %			
High risk	10	9	11
Intermediate risk	29	32	27
Low risk	60	59	62

[1] Hasford et al., Blood. 2011;118:686-92
[2] Pfirrmann et al., Leukemia. 2016;30:48-56

Overall survival by randomized therapy



Overall survival by randomized therapy



<u>10 year survival rates</u>

IRIS	Imatinib	83%
CML IV	Imatinib	83%
ENESTnd	Nilotinib	90%
	Imatinib	88%

Hochhaus et al. NEJM 2017
Hehlmann et sl. Leukemia 2017
Kantarjian et al. Leukemia 2021

Progression / study termination

Disease progression n=20

Total blast phases n=17

17 progressions in induction,
2 in maintenance,
1 in TFR phase

Allo-SCT n=28 in 26 patients

After progression n=15
In chronic phase n=13

End of study (n=89)

Total death: n=35 (5.1 %)

20 patients died in induction,
9 in maintenance,
6 in discontinuation phase

9 CML related deaths
(8 blast phases)

Withdrawal of consent/
Lost to follow up: n=54 (7.8 %)

First primary endpoint: MMR at 18 mo.

Nilotinib (n=313):

81% (95%-CI: 76-85%), 253 with MMR

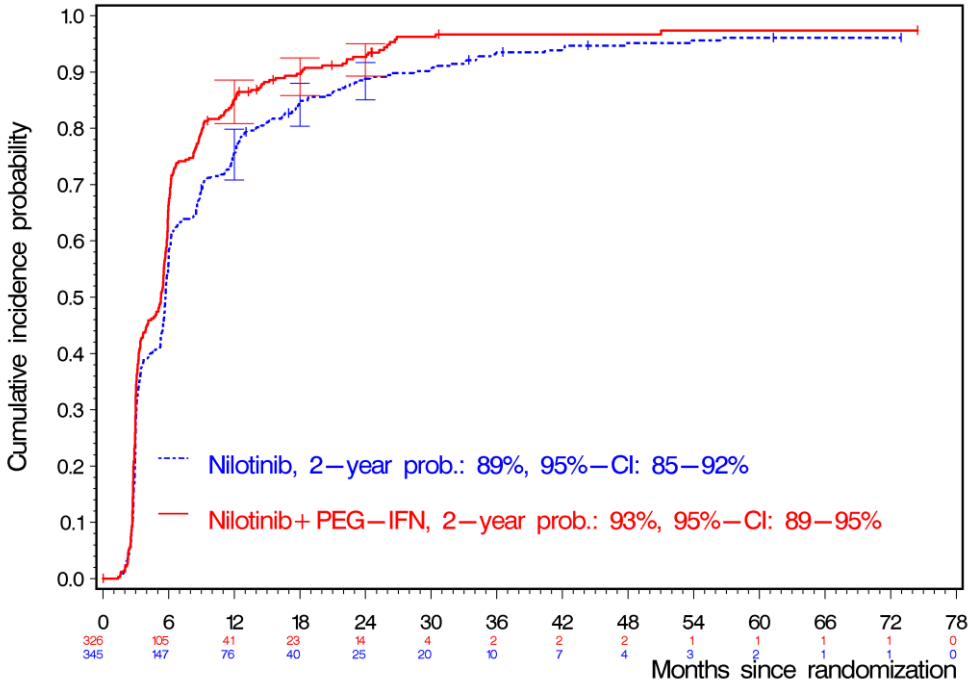
Nilotinib + IFN (n=292):

88% (95%-CI: 83-91%), 256 with MMR

p=0.0214

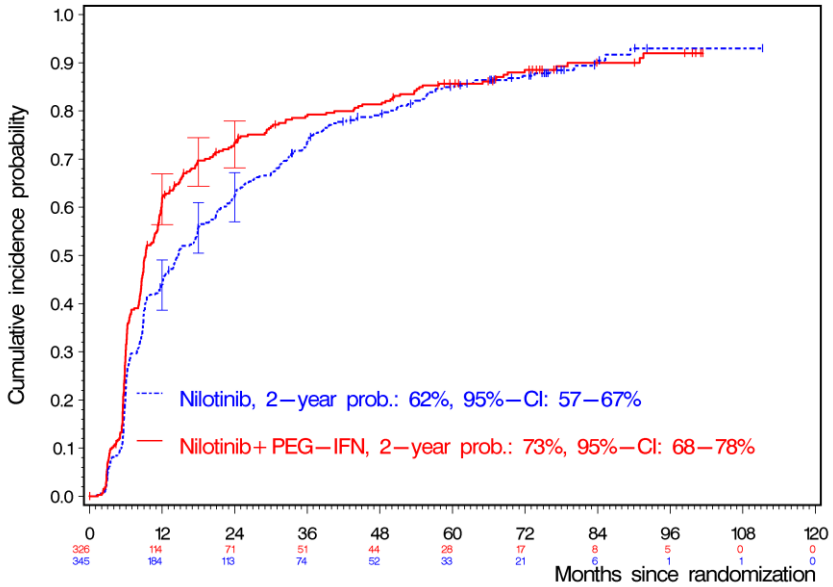
Since confirmatory testing had already been performed in 2019, hypothesis 1 could not be rejected.

Cumulative incidence of MMR

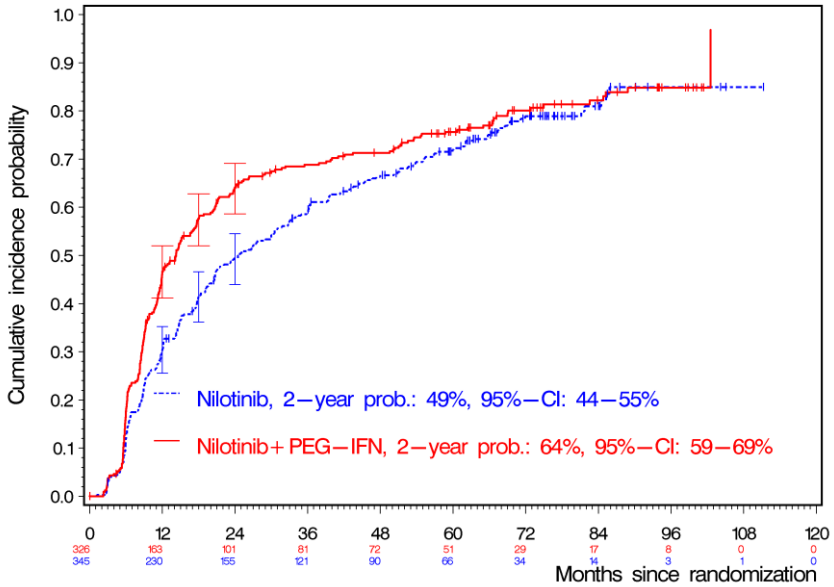


Cumulative incidences of DMR

MR^4



$MR^{4.5}$



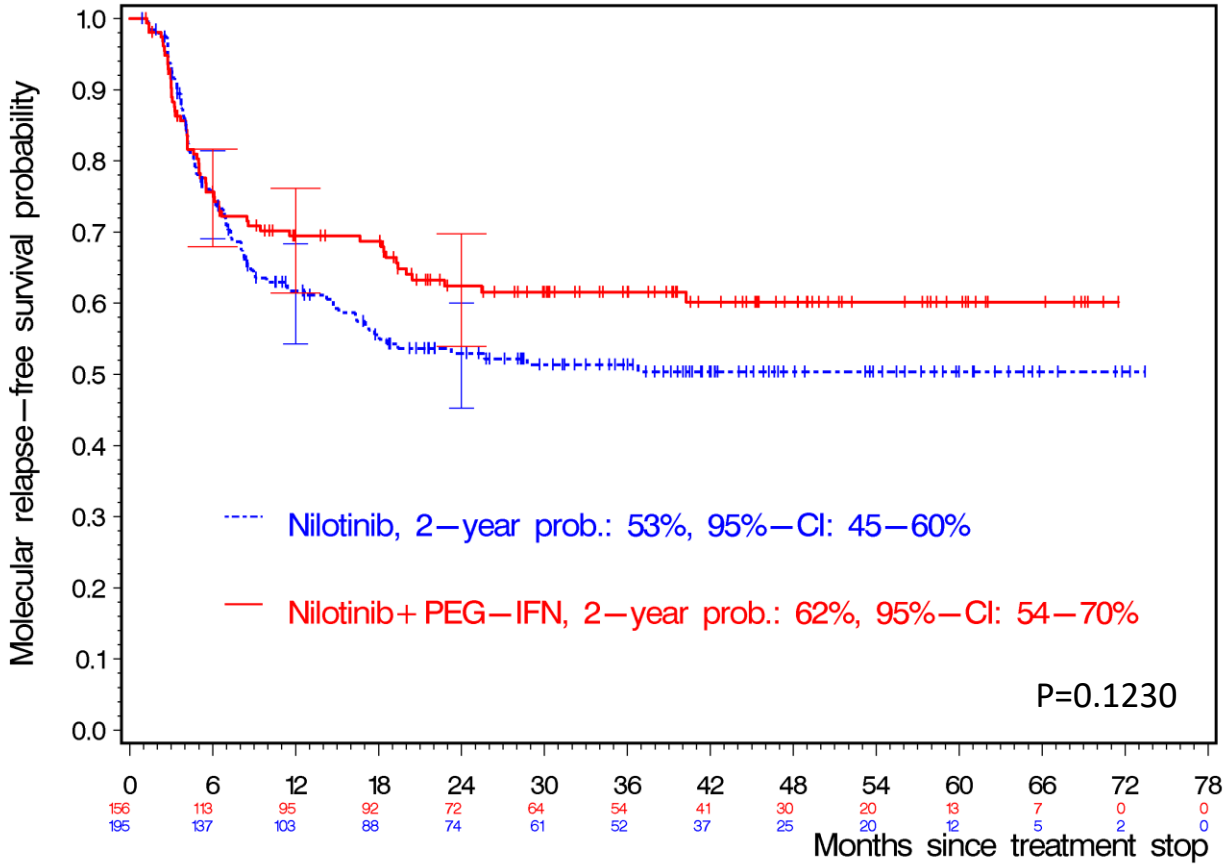
6 EUTOS IS standardized central labs; typical transcripts only

Molecular relapse free survival after treatment discontinuation, ITT

Probability of MMR **at** 12 months after discontinuation:

Nilotinib (n=195):
62% (95%-CI: 54-68%)

Nilotinib + IFN (n=156):
69% (95%-CI: 61-76%)

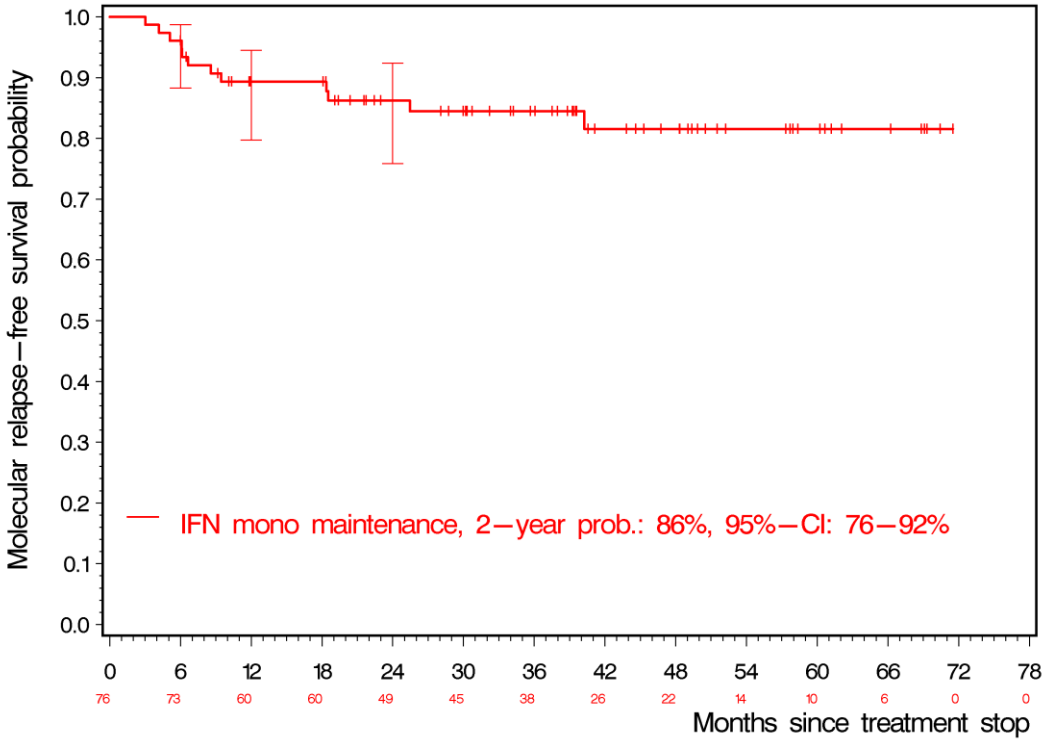


Molecular relapse free survival after IFN discontinuation

79 patients started TFR phase, median observation time: 39 months

Of these 79 patients

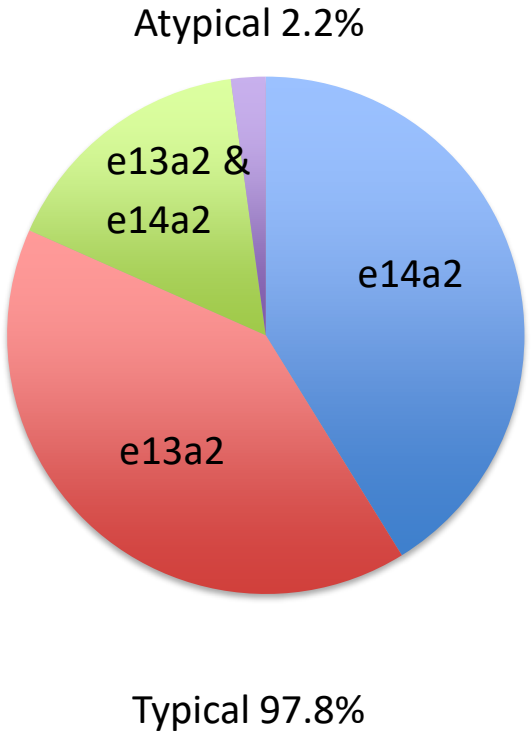
a) 3 had no follow-up
b) 11 lost MMR (1 of 11 with blast crisis)
c) 1 died before loss of MMR
d) 1 restarted TKI before loss of MMR



TIGER: Patients with atypical *BCR::ABL1* transcripts

Fifteen of 717 recruited patients (2.2%) expressed atypical *BCR::ABL1* transcripts:

e1a2, n=7
e19a2, n=4
e8a2, n=2
e13a3, n=1
e14a3, n=1



7 male, median age 64 years, range 28-80, all EUTOS low risk

Patients were randomized to receive nilotinib (n=7)
or nilotinib/PEG-IFN α2b combination (n=8).

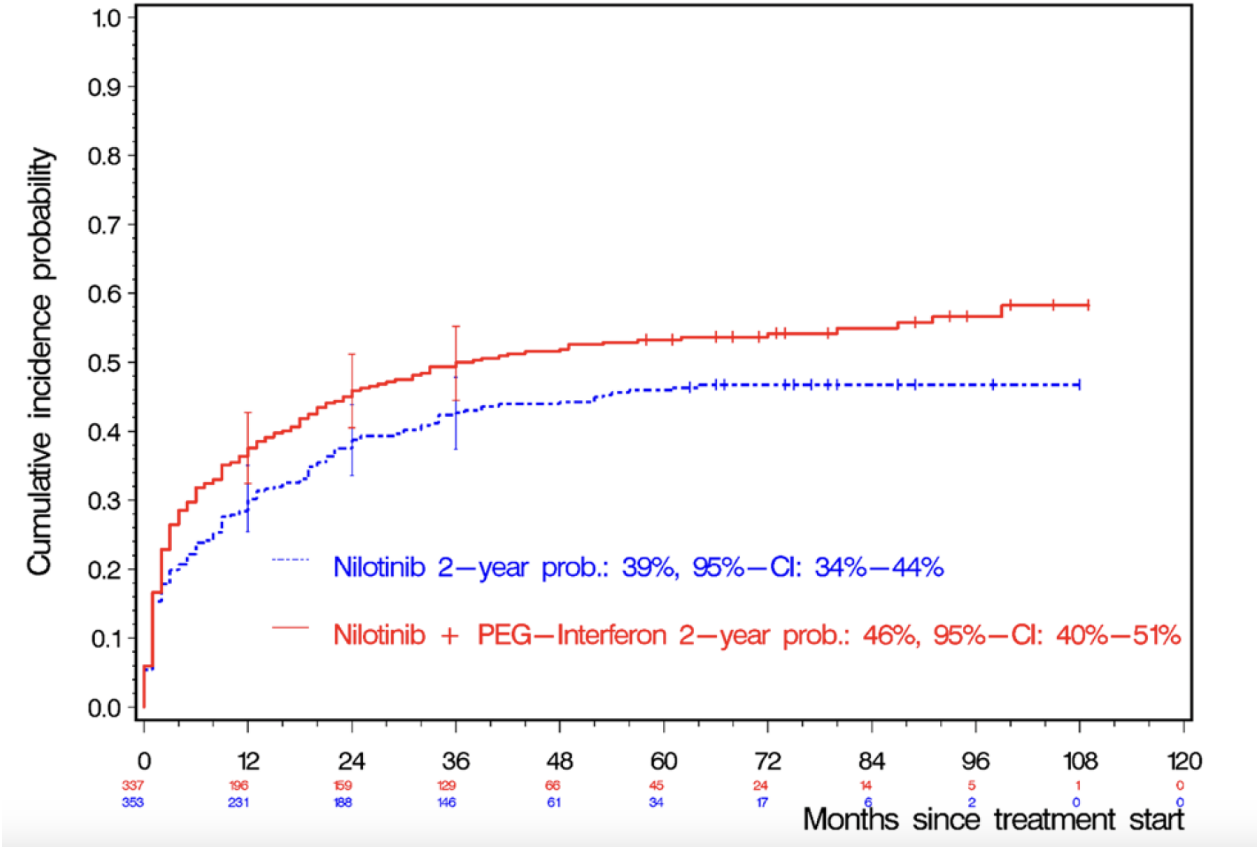
Median observation time was 72 (range, 4-121) months.

DMR in patients with atypical *BCR::ABL1* transcripts (n=15)

- Calculation of „Individual molecular response“ IMR, compared to baseline value (ratio *BCR::ABL1*/*GUSB*), or, in case of undetectable *BCR::ABL1*, sensitivity estimated by *ABL1* or *GUSB* levels (e.g., $MR^{4.5}$ 32,000 ABL1 or 77,000 GUS)*.
- 9 of 15 patients achieved and maintained a *BCR::ABL1* transcript reduction by at least 4 logs after a median treatment period of 37 mo (36-39).
  e1a2, n=4; e8a2, n=1; e14a3, n=1; e19a2, n=3
- TFR was commenced in 7 of 9 patients in DMR.
- One patient relapsed five months after treatment withdrawal.
- Median relapse free survival was 32 (range, 20-84) months.
- 6 patients failed to achieve a transcript decline by at least 3 logs.

*Schäfer et al. J Cancer Res Clin Oncol. 2021;147:3081-9.

Cumulative incidence of adverse events, Grade 3-5



Incidence of adverse events, Grade 3-5

	Nilotinib monotherapy, N=353		Nilotinib-PEG-IFN combination, N=337	
	n	%	n	%
Vascular disorders	24	**6.8**	16	**4.7**
Cardiac disorders	19	5.4	19	5.6
Psychiatric disorders	3	**0.8**	12	**3.6**
Infections	17	4.8	19	5.6
Dermatological disorders	9	2.5	16	4.7
Gastrointestinal disorders	11	3.1	19	5.6
Endokrine disorders	2	0.1	3	0.1
Renal disorders	2	0.1	1	0.0
Median duration Nilotinib	32 mo.		27.5 mo.	
Median duration IFN	-		32.6 mo.	

EORTC QLQ-C30 longitudinal differences functional subscales

Nilotinib	longitudinal differences					
EORTC QLQ-C30	Scre	EM3	EM6	EM12	EM18	EM24
Physical functioning (PF2)	0,0	0,9	-0,2	-1,4	-1,0	-2,8
Role functioning (RF2)	0,0	1,3	2,5	1,4	-0,5	0,5
Emotional functioning (EF)	0,0	6,1	4,1	3,4	3,4	4,7
Cognitive functioning (CF)	0,0	1,0	-1,8	-3,1	-3,6	-6,3
Social funcitoning (SF)	0,0	2,0	1,2	1,9	1,7	1,2
Fatigue (FA)	0,0	-3,5	-1,9	-1,3	-2,2	-1,0
Nausea/Vomiting (NV)	0,0	-0,7	-2,2	-1,5	-2,2	-2,6
Pain (PA)	0,0	-2,8	-1,7	1,6	-0,8	0,7
Dyspnea (DY)	0,0	-1,5	-1,8	-0,6	1,8	3,8
Insomnia (SL)	0,0	-1,3	-3,0	-2,4	-0,3	-1,0
Appetite loss (AP)	0,0	-5,8	-8,1	-5,6	-7,3	-7,1
Constipation (CO)	0,0	1,3	2,9	7,2	5,5	5,3
Diarrhea (DI)	0,0	-2,0	-1,5	-1,9	-1,5	-1,2
Financial difficulties (FI)	0,0	4,9	1,0	2,1	0,0	1,3
Quality of life (QL2)	0,0	4,5	4,8	4,9	3,7	4,0
N	231	219	204	208	183	178

worse HRQoL compared to Screening — improved HRQoL compared to Screening

small | medium differences | small differences

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EORTC QLQ-C30 longitudinal differences functional subscales

Nilotinib + interferon	longitudinal differences					
EORTC QLQ-C30	Scre	EM3	EM6	EM12	EM18	EM24
Physical functioning (PF2)	0,0	-2,9	-3,2	-2,3	-2,2	-3,7
Role functioning (RF2)	0,0	-9,4	-10,0	-9,0	-7,9	-5,8
Emotional functioning (EF)	0,0	4,6	5,3	4,7	3,1	3,7
Cognitive functioning (CF)	0,0	-5,6	-6,4	-7,0	-9,1	-7,9
Social funcitoning (SF)	0,0	-2,0	-2,6	-1,0	0,8	1,2
Fatigue (FA)	0,0	0,8	2,7	3,4	3,4	4,5
Nausea/Vomiting (NV)	0,0	1,2	0,4	1,9	0,9	0,6
Pain (PA)	0,0	1,0	1,8	3,1	0,1	1,5
Dyspnea (DY)	0,0	-0,9	4,1	4,9	4,6	5,1
Insomnia (SL)	0,0	-1,9	-1,9	-1,9	-1,5	1,0
Appetite loss (AP)	0,0	-2,4	-4,1	-1,1	-1,5	5,1
Constipation (CO)	0,0	1,7	2,7	3,4	4,0	-1,1
Diarrhea (DI)	0,0	0,3	-0,9	-1,2	-0,4	-0,8
Financial difficulties (FI)	0,0	3,4	3,1	1,5	1,1	0,9
Quality of life (QL2)	0,0	2,7	4,1	6,2	4,5	3,4
N	235	222	173	149	112	105

worse HRQoL compared to Screening — improved HRQoL compared to Screening

small | medium differences | small differences

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Conclusions

- In the context of a well-controlled trial, survival of CML pts has reached probabilities close to normal.
- The combination of Nilotinib with Interferon alpha is associated with a higher rate of molecular responses but also impaired tolerability.
- Interferon maintenance is feasible and may abbreviate the TKI treatment time, but did not result in a significantly improved chance of long-term TFR.
- Deep molecular responses and TFR attempts are feasible also in patients with atypical BCR::ABL1 transcripts using individual response data.

Acknowledgements

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