Comprehensive Cancer Center
Tübingen-Stuttgart

Post ASH 2023 San Diego

Myeloproliferative Neoplasien / CML / nichtmaligne Hämatologie

Prof. Dr. R. Möhle, Med. Univ.-Klinik II, Tübingen

EBERHARD KARLS
UNIVERSITÄT
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Comprehensive
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Tübingen

Targeted Therapy bei Sichelzellkrankheit: Crizanlizumab (Adakveo®), ein Antikörper gegen P-Selektin …

Targeted Therapy bei Sichelzellkrankheit: Crizanlizumab (Adakveo®), ein Antikörper gegen P-Selektin …

… verliert 2/2023 seine Zulassung in der EU

272 Efficacy, Safety, and Biomarker Analysis of 5 Mg and 7.5 Mg Doses of Crizanlizumab in Patients with Sickle Cell Disease: Primary Analyses from the Phase III STAND Study. Miguel R Abboud, Beirut, Libanon

Unlike the previous phase II PBO-controlled SUSTAIN study, the STAND study did not demonstrate superiority of crizanlizumab (5 or 7.5 mg/kg) over PBO …

146 Primary Analysis of Spartan: A Phase 2 Trial to Assess the Efficacy and Safety of Crizanlizumab in Patients with Sickle Cell Disease Related Priapism. Modupe Idowu, Houston, USA

…patients with SCD-related priapism treated with crizanlizumab over 26 weeks experienced approximately half as many priapic events … p = 0,068 …

Deshalb „Back to the rHUts," und:

6 Hydroxyurea Dose Optimization Is Safe and Improves Outcomes for Children with Sickle Cell Anemia Living in Sub-Saharan Africa: The Reach Experience. Banu Aygun, New Hyde Park, USA

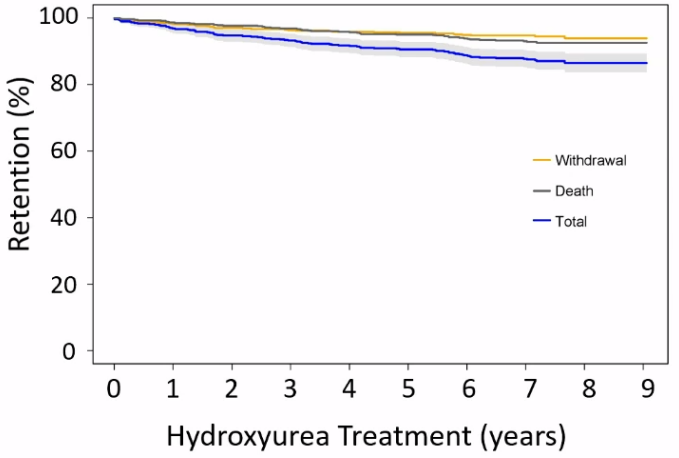
Wie dosiert man Hydroxyurea bei Sichelzellkrankheit?

Current Study Objectives

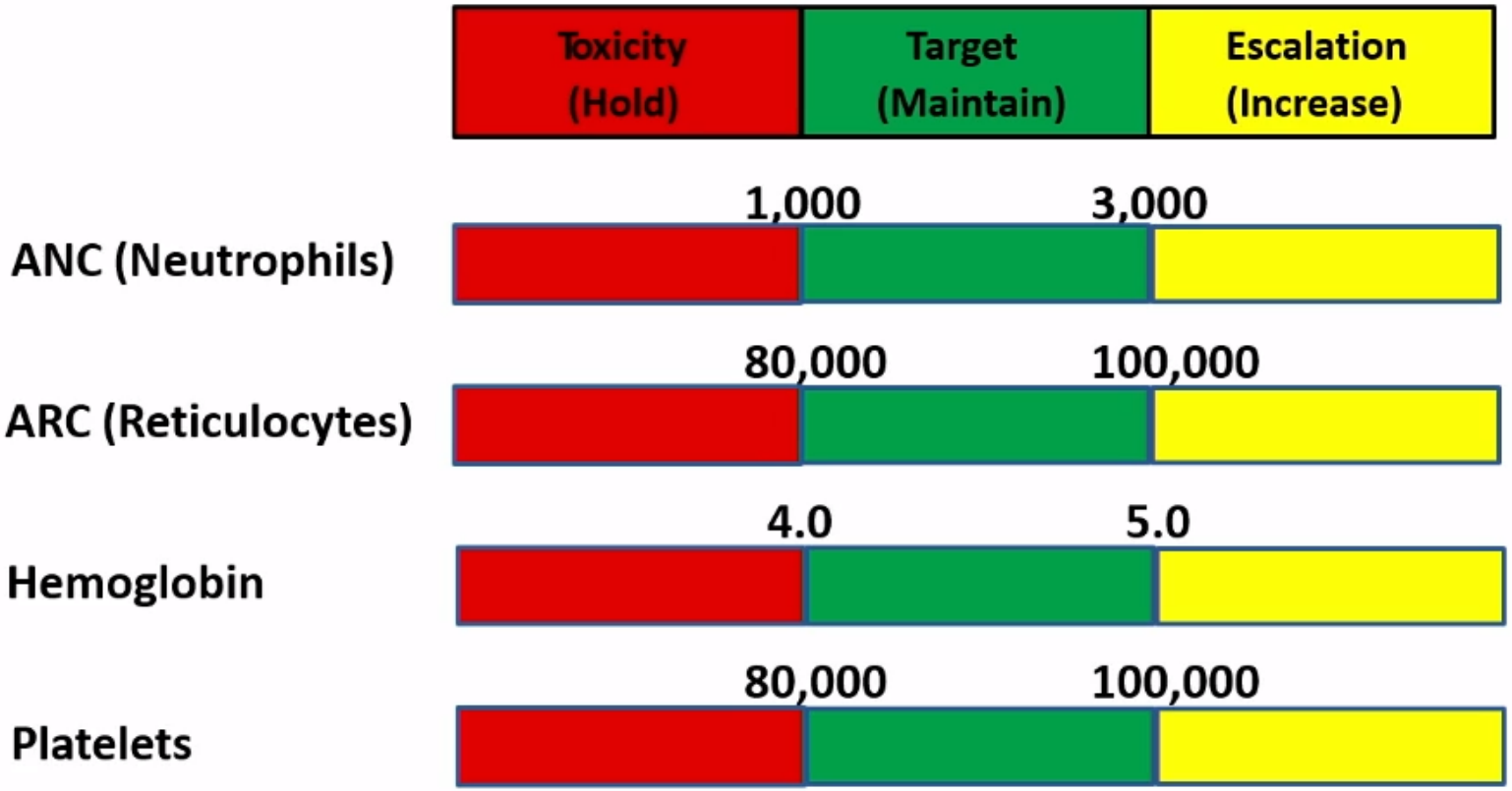
- Treatment effects over time
  - Laboratory parameters
  - Clinical outcomes
- Comparison of hydroxyurea dosing phases
  - Screening (2 months), pre-treatment
  - Fixed dose phase (0-6 months) at 15-20 mg/kg/day
  - Dose escalation phase (7-24 months), increase to MTD
  - MTD phase (>24 months), dose optimization

Study Characteristics and Retention

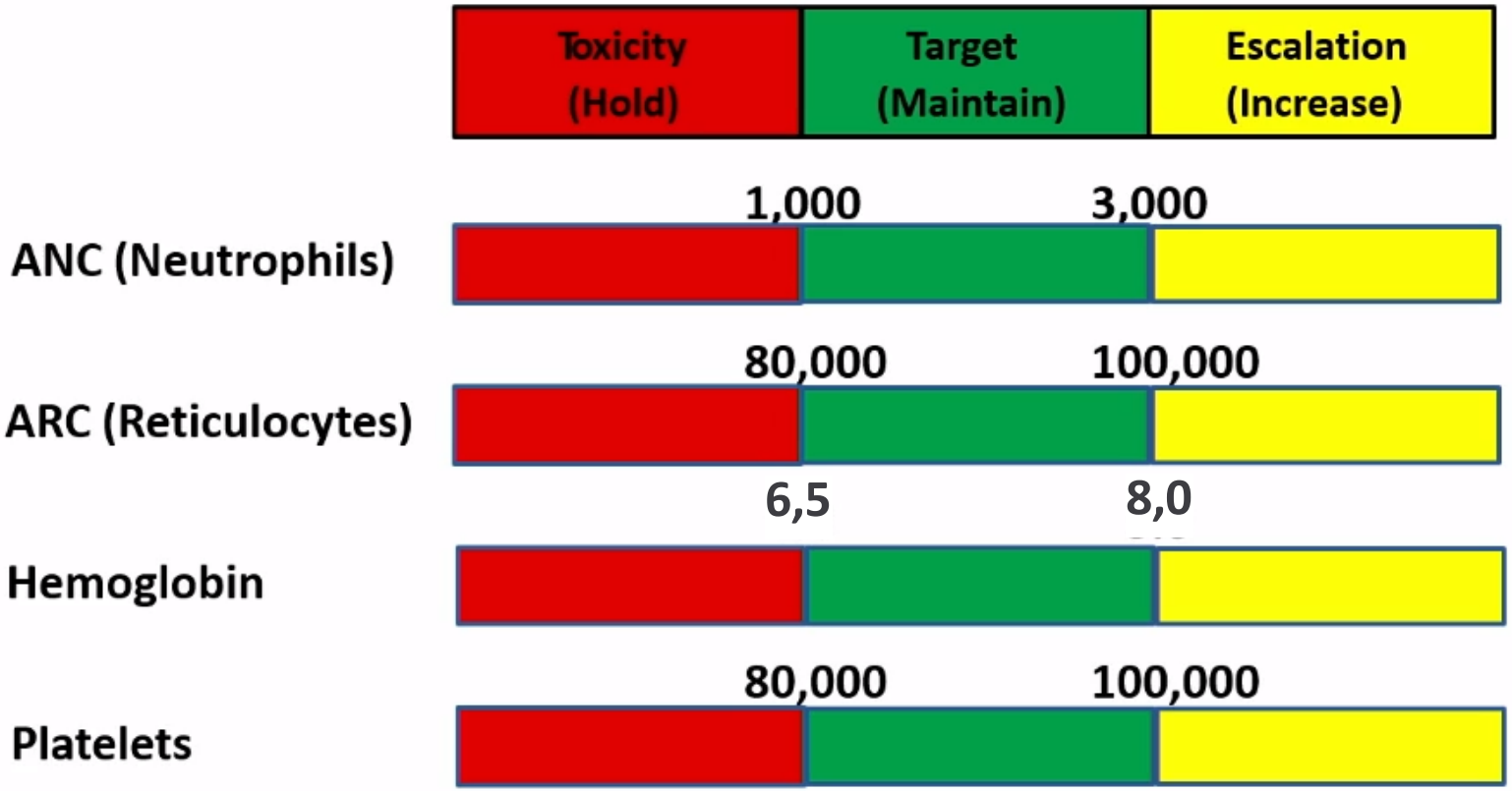
- Enrollment age: 5.4 ± 2.4 years
- 606 started treatment; currently 522 (86%) remain in the trial
- 44 deaths, 40 study exits
- Average treatment duration: 85 months (75-108 months)
- Now >4300 patient years of hydroxyurea treatment



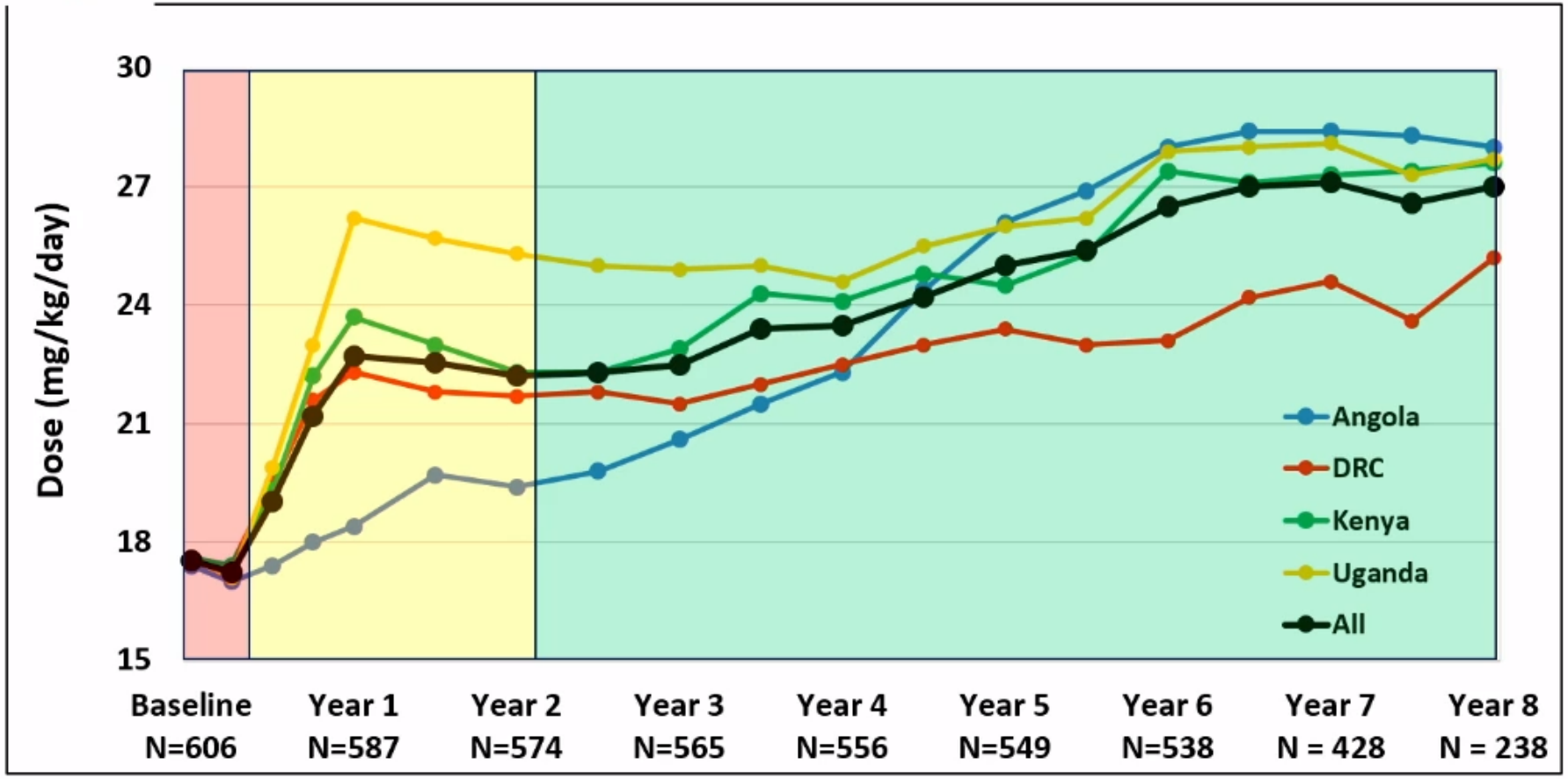
Hydroxyurea Dose Optimization



Hydroxyurea Dose Optimization



Hydroxyurea Dose Over Time



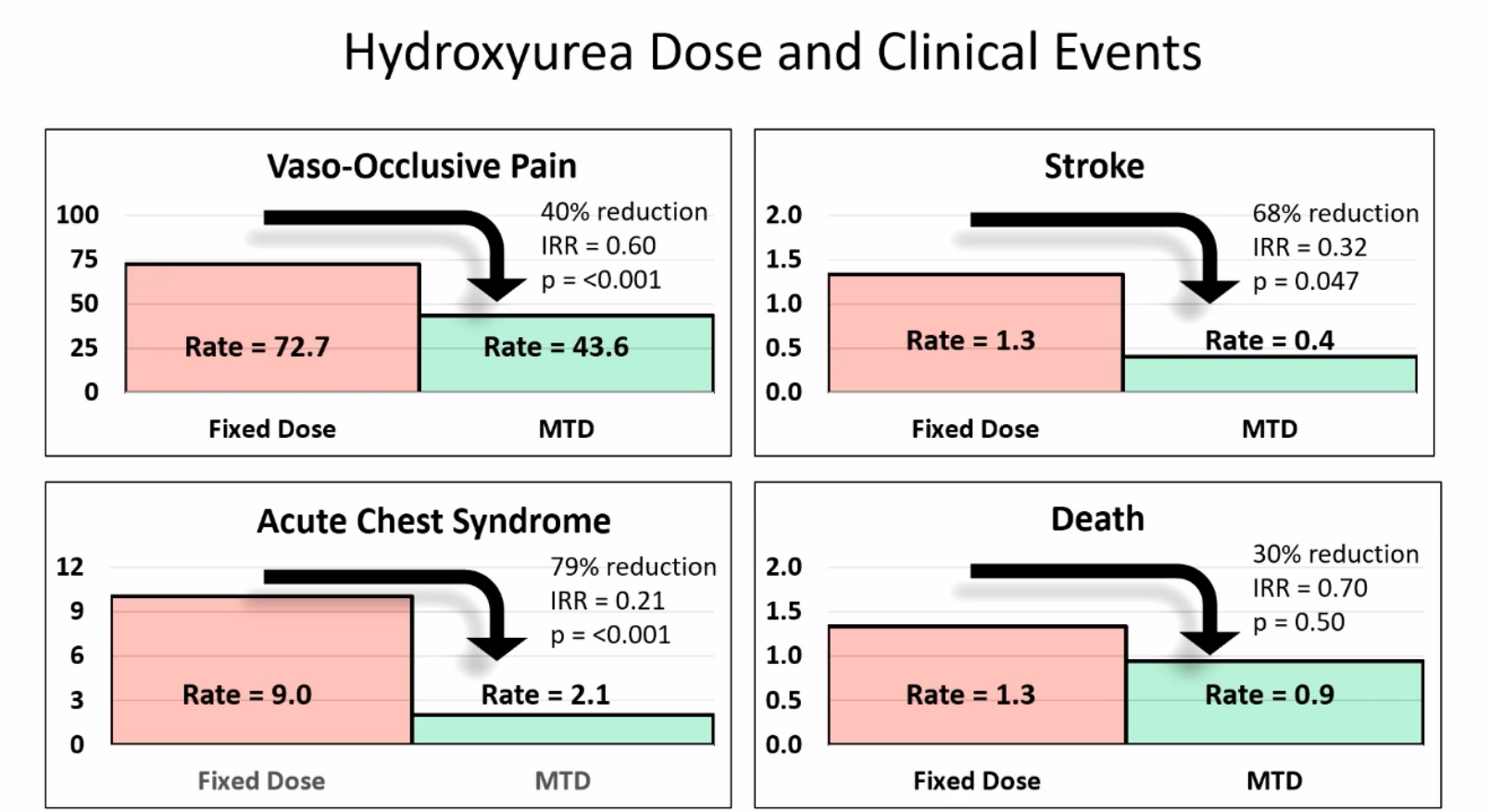
Ergebnisse und Schlussfolgerungen:

Vergleich: Phase mit der HU Startdosis vs. Phase der max. tolerierten Dosis

Entsprechend beim Erwachsenen: ca. 1 g / Tag vs. 2 g / Tag

Reduktion von Krisen bei gut steuerbarer Therapie, nur 2-3 Laborkontr. / Jahr reichen!

Unklar: Evtl. irreversible Schädigung der Fertilität bei Männern



Resumption of Spermatogenesis and Fertility Post Withdrawal of Hydroxyurea Treatment. Virgous C, et al. Int J Mol Sci. 2023 May 27;24(11):9374

- In vivo (Maus) komplette Normalisierung der Fertilität nach Ende HU
- „ … therefore, **qualifying HU as a potential candidate for male contraception …”**

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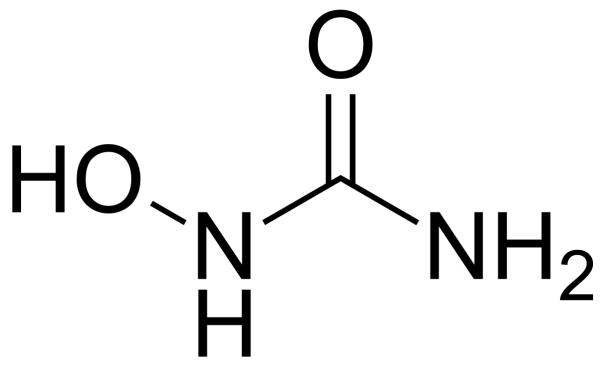

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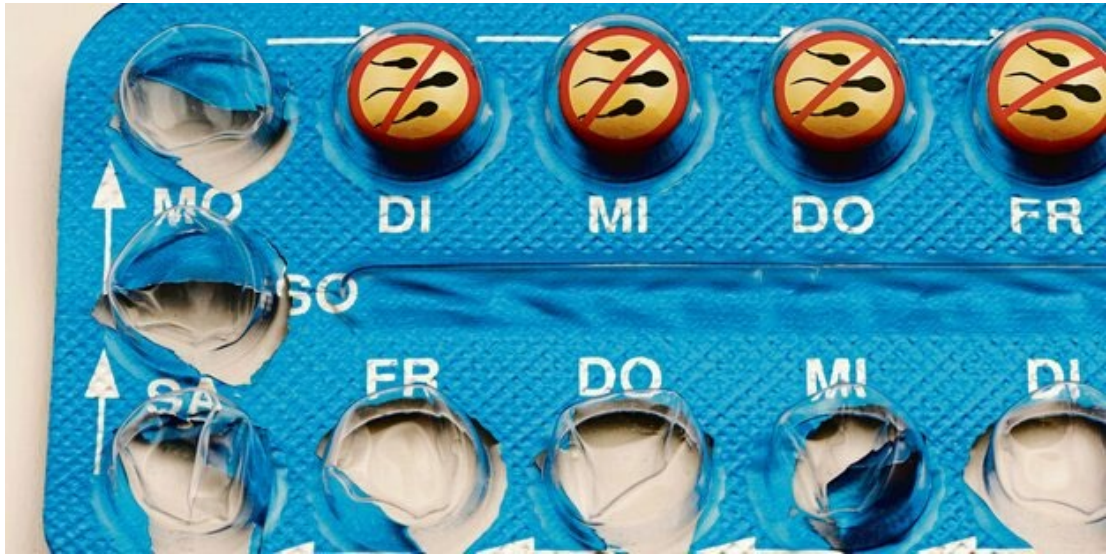

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Bild: TAZ

145 Puberty Onset and Preservation of Fertility in Male Patients with Sickle Cell Disease Treated with Hydroxyurea: Data from the European Sickle Cell Disease Cohort –Hydroxyurea Extension (ESCORT-HU Extension) Study. Mariane De Montalembert, Paris, Frankreich

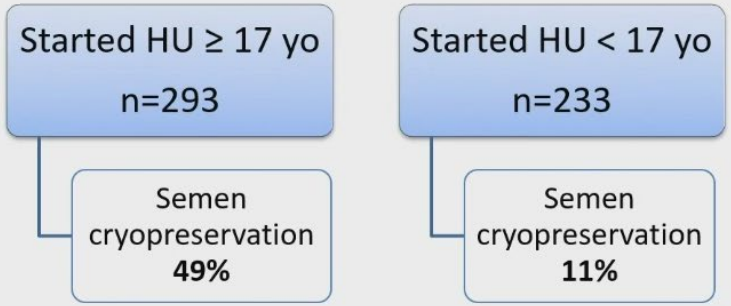
- Multicentric, prospective, non-interventional study aiming to better document the safety profile of HU
- 1860 patients were included in June 2023 in France (92% of patients), Germany, Greece and Italy.
  - Median age at inclusion : 24 [IQR: 14-40] years
  - 44.4% males
  - 87% HbSS genotype
  - Median duration of HU exposure : 8.5 [IQR: 6.4-11.6] years
- Pubescent males : 455 (56.5%) at enrolment and 72 transitioned during the study
- Our aims here were to observe in male patients:
  - Age at puberty onset
  - Fertility data
  - The use of fertility preservation strategies

Age at puberty onset in males

- The mean age at Tanner V stage did not significantly differ between males who reached puberty before starting HU and those who reached puberty after starting HU

	HU start before puberty (n=112)	HU start after puberty (n=31)
Age at puberty (Tanner V stage) (Years, mean [IQR])	15.0 [IQR: 14.0-16.0]	15.2 [IQR: 14.0-16.0]

Semen cryopreservation



- Median age at cryopreservation : 26.0 [IQR: 21.0-33.0] years
- Semen cryopreservation is free in France

Cost in France
- Freezing: 91€
- Semen analysis: 28.60€
- Annual storage cost: 39€

Semen analyses performed before HU treatment (n=66)

Semen analysis result	Number of patients (n=66)
Normal	26/40 (65%)
With qualitative abnormalities	5/40 (13%)
With qualitative and quantitative abnormalities (2 oligospermia, 2 azoospermia)	4/40 (10%)
With quantitative abnormalities (2 oligospermia, 3 azoospermia)	5/40 (13%)
Unknown	26

- Normal: Etwas weniger 2/3
- Azoospermie: 5/66 (knapp 10%)

Semen analyses performed after HU treatment, with HU interruption before analysis (n=11)

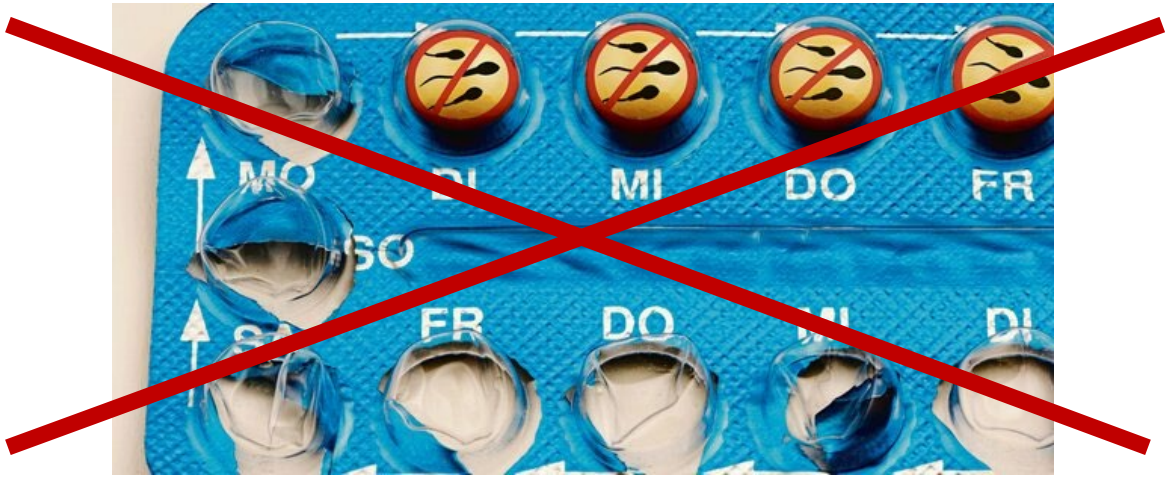
Semen analysis result	Duration of HU interruption	Other information
Normal (n=4)	3 months 3,5 months 13 months 12 months	 Transfusion during HU interruption Transfusion during HU interruption
Qualitative abnormalities (not detailed) (n=1)	1.5 year	
Quantitative abnormalities (oligospermia) (n=1)	5 months	No transfusion during HU stopping Pregnancy in partner with use of cryopreserved semen
Quantitative abnormalities (azoospermia) (n=1)	14 months	
Qualitative and quantitative abnormalities (n=4) (oligospermia)	Several years 7 months Unspecified (n=2)	

- Normal: Etwas mehr als 1/3
- Azoospermie: 1/11 (knapp 10%)

Semen analyses performed after HU treatment, without HU interruption before analysis (n=12)

Semen analysis result	Number of patients (n=12)
Normal	2
Qualitative and quantitative abnormalities (oligospermia)	2
Quantitative abnormalities (oligospermia)	1
Quantitative abnormalities (azoospermia)	4
Quantitative abnormalities (not detailed)	1
Qualitative abnormalities	1
Unknown	1

- **Normal: 1/6**
- **Azoospermie: 4/12 (d.h. 33%)**



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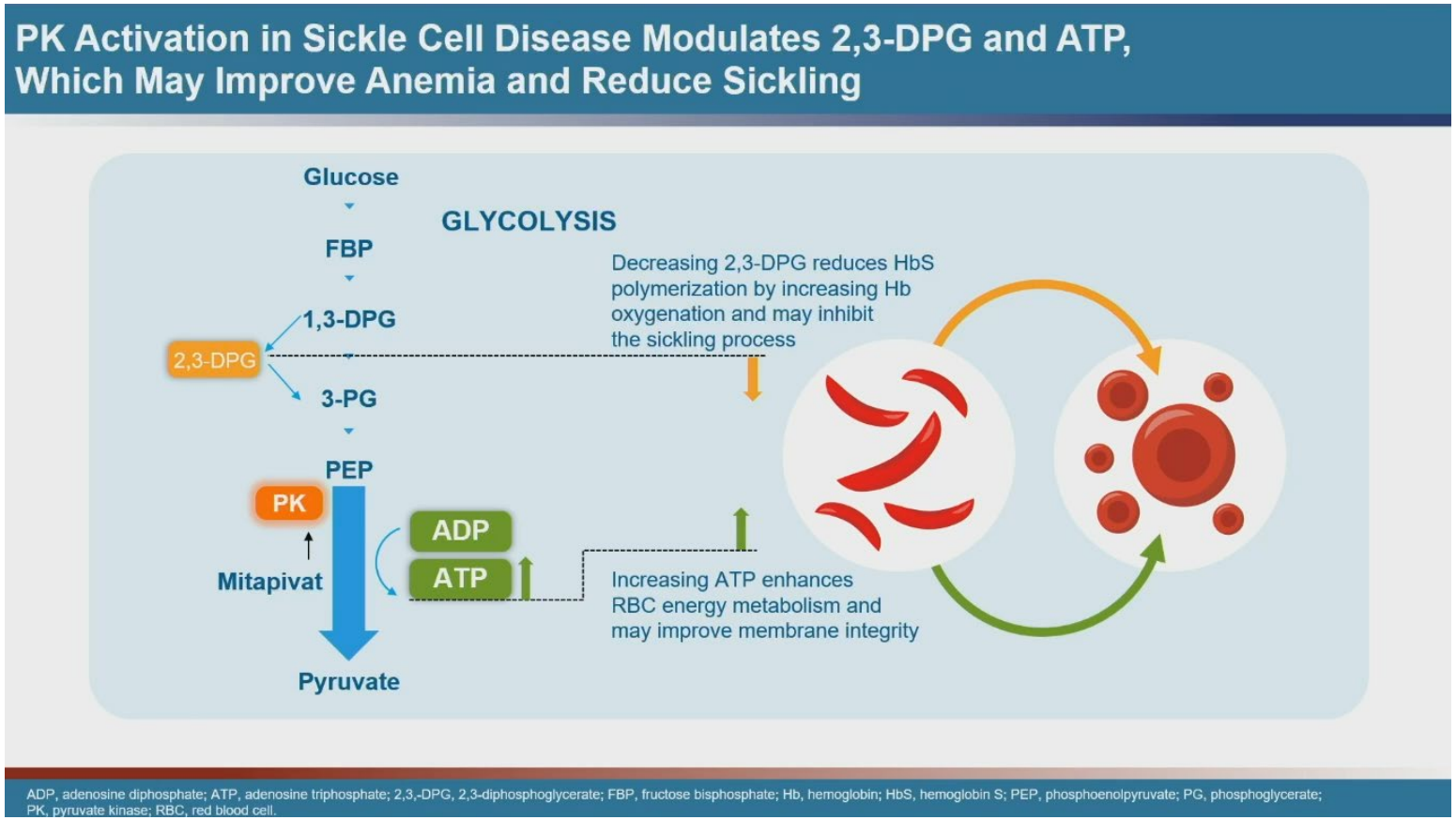
Schlussfolgerungen:

- Hydroxyurea bewirkt bei Jungen keine Änderung der Entwicklung (Erreichen der Pubertät)
- Unter Hydroxyurea ist die Fertilität bei Männern eingeschränkt (aber nicht zwangsläufig)
- Es ist immer noch unklar, wie gut sich die Spermatogenese nach Unterbrechen von HU regeneriert
- **Sperma-Kryokonservierung ist weiterhin sinnvoll, auch da man die HU-Therapie möglicherweise nicht pausieren möchte (sowohl bei Sichelzellkrankheit als auch bei MPN)**
- Falls keine Kryokonservierung erfolgte: Da eine Azoospermie nach Unterbrechen von HU nicht sehr häufig ist, könnte bei erfolglosem Kinderwunsch in den meisten Fällen wahrscheinlich eine in vitro-Fertilisation bzw. intrazytoplasmatische Spermieninjektion (ICS) angewendet werden

271 A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study of Mitapivat in Patients with Sickle Cell Disease: RISE UP Phase 2 Results. Modupe Idowu, Houston, USA

Studiendetails: Mitapivat (Pyrukynd®) aktiviert die Pyruvatkinase, zugelassen bei PK-Mangel

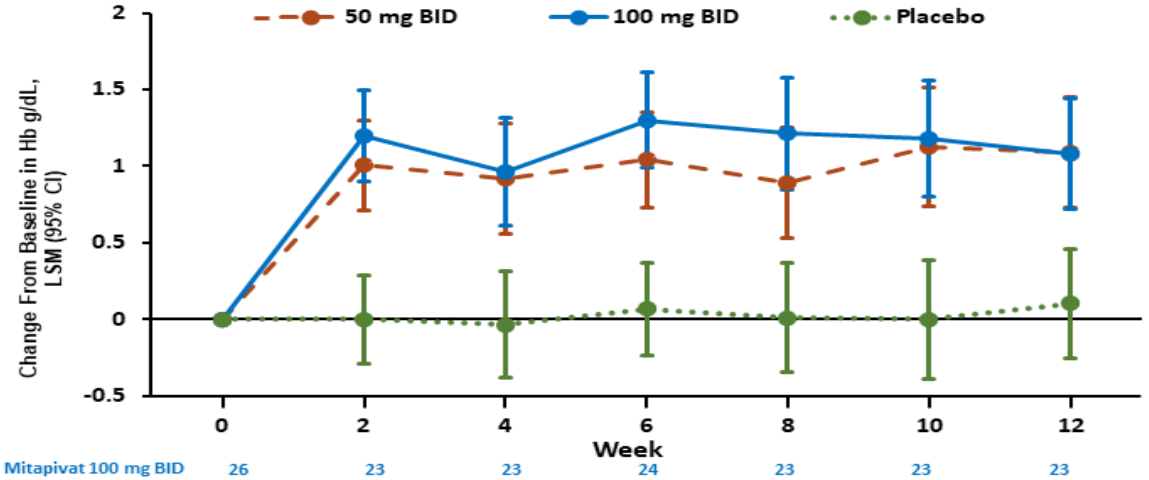


271 A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study of Mitapivat in Patients with Sickle Cell Disease: RISE UP Phase 2 Results. Modupe Idowu, Houston, USA

26 Pat. erhielten Mitapivat 2x50 mg, 26 Pat. 2x100 mg, 27 Pat. Placebo, Endpunkt: Hb-Anstieg

Ergebnis: Dauerhafter Hb-Anstieg um ca. 1 g/dl, Abnahme der Hämolyseparameter

Figure 1. Longitudinal Summary of Change From Baseline in Hemoglobin Concentrations



Mitapivat 100 mg BID	26	23	23	24	23	23	23
Mitapivat 50 mg BID	26	23	19	22	24	22	22
Placebo	27	24	22	25	24	21	22

BID = twice a day; Hb = hemoglobin; LSM = least squares mean.

271 A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study of Mitapivat in Patients with Sickle Cell Disease: RISE UP Phase 2 Results. Modupe Idowu, Houston, USA

Reductions in SCPCs Were Observed at Both Doses Compared With Placebo

	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
Sickle cell pain crises			
Annualized rate (95% CI)	0.83 (0.34, 1.99)	0.51 (0.16, 1.59)	1.71 (0.95, 3.08)
Mitapivat/placebo rate ratio (95% CI)	0.48 (0.17, 1.39)	0.30 (0.08, 1.07)	
Rate reduction (mitapivat vs placebo), % (95% CI)*	51.6 (−39.4, 83.2)	70.0 (−7.4, 91.6)	

*Rate reduction is defined as 100% x 1−rate ratio).

Systemische Mastozytise: Optimierung der Behandlung möglich?

Aktuelle Behandlungsmöglichkeiten:

Midostaurin (Rydapt®)

Avapritinib (Ayvakyt®)

76 Elenestinib, an Investigational, Next Generation KIT D816V Inhibitor, Reduces Mast Cell Burden, Improves Symptoms, and Has a Favorable Safety Profile in Patients with Indolent Systemic Mastocytosis: Analysis of the Harbor Trial. Tsewang Tashi, Salt Lake City, USA

77 Initial Results from Summit: An Ongoing, 3-Part, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Study of Bezuclastinib in Adult Patients with Nonadvanced Systemic Mastocytosis (NonAdvSM), Prithviraj Bose, Houston, USA

Elenestinib und Bezuclastinib, neue 2nd Gen KIT D816V Inhibitoren, senken die Erkrankungslast und Symptome bei syst. Mastozytose.

Da nicht ZNS-gängig, deutlich weniger ZNS-NW als Avapritinib (Ayvakyt®)

CML: Optimierung der Behandlung möglich?

Vielleicht haben Sie sich schon einmal gefragt:

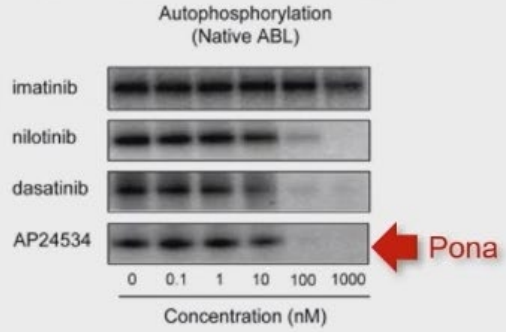
Warum nicht einen „starken“ 2nd oder 3rd Gen. TKI als Induktion am Anfang, und später dann Wechsel auf Imatinib (um Langzeit-NW zu vermeiden)?

Hat Interferon (mit TKIs) nun etwas gebracht oder nicht?

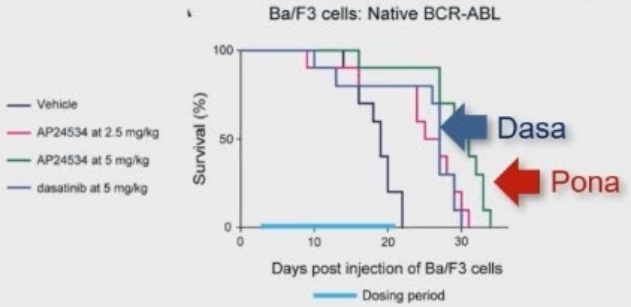
445 Trial of Imatinib after Ponatinib Induction (TIPI) in the Front-Line Treatment of Chronic Phase (CP) Chronic Myeloid Leukemia (CML) Setting. Report of the First Therapeutic Sequence. Franck E. Nicolini, Lyon, Frankreich

Ponatinib is the most potent ABL1 ATP-competitive inhibitor

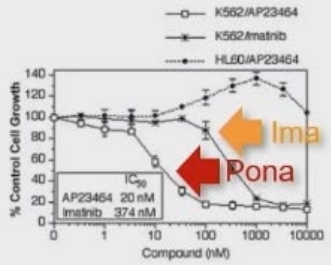
In vitro, in chemical assays*



In vivo, in SCID mice transplanted*



In vitro, in human Ph+ cell lines$

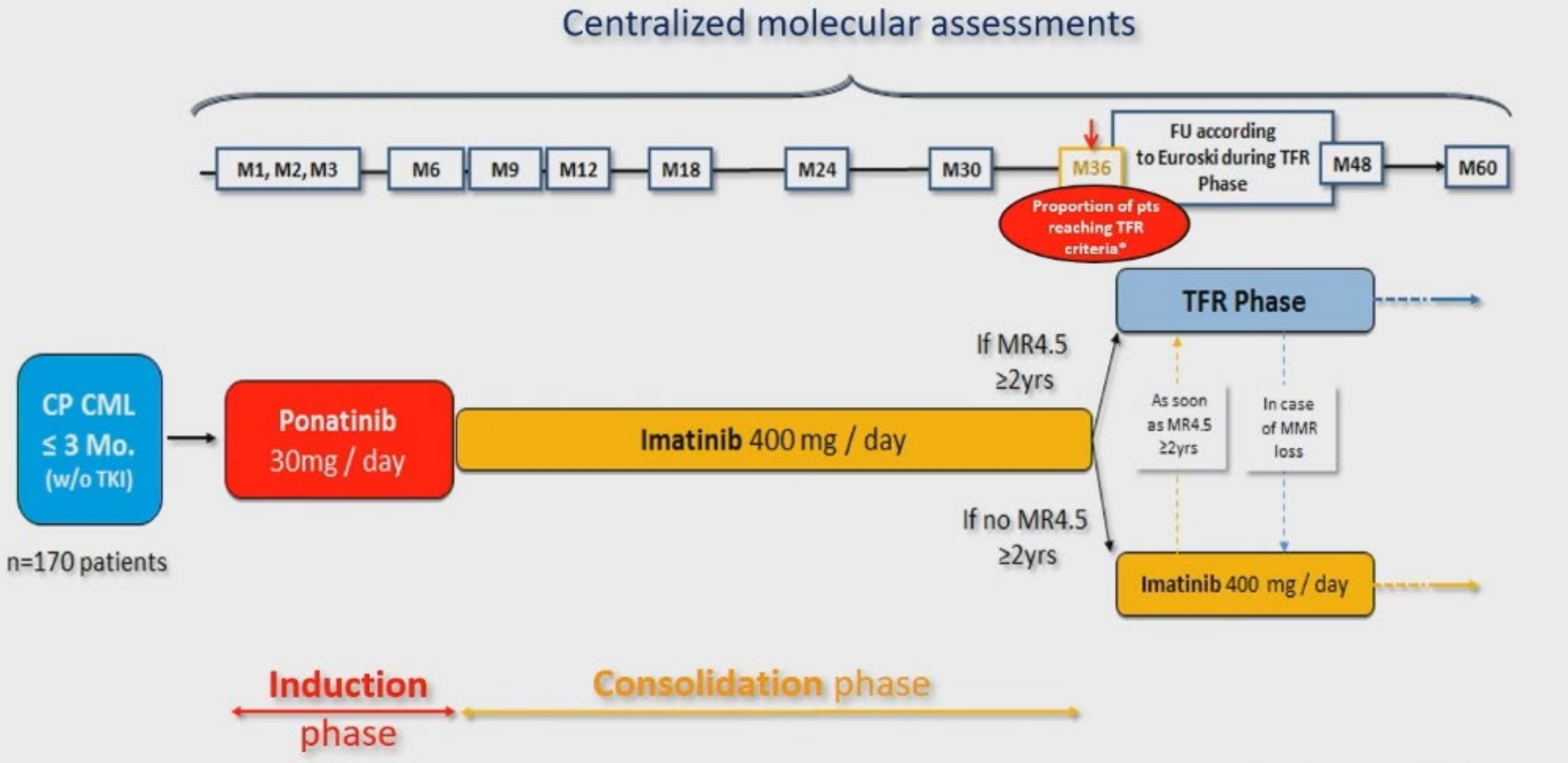


Cellular IC50s for *ABL-1* ATP-competitive inhibitors against 21 single mutants£

BCR-ABL Mutant	Ponatinib	Imatinib	Nilotinib	Dasatinib	Bosutinib
Native	3	201	15	2	71
M244V	3	287	12	2	147
L248R	8	10000	549	6	674
L248V	4	586	26	5	182
G250E	5	1087	41	4	85
Y253H	5	4908	179	3	40
E255K	6	2487	127	9	181
E255V	16	8522	784	11	214
V299L	4	295	24	16	1228
T315A	4	476	50	59	122
T315I	6	9773	8091	10000	4338
F317C	3	324	16	45	165
F317I	7	266	25	40	232
F317L	4	675	21	10	82
F317V	10	1023	26	104	1280
M351T	4	404	15	2	97
E355A	7	441	18	3	74
F359C	6	728	47	2	70
F359I	11	324	64	3	76
F359V	4	346	41	2	59
H396R	4	395	23	2	60
E459K	5	612	38	4	127

*T. O'Hare et al. Cancer Cell 2009; 6(5): 401-412
£A. Eiring et al. Genome Biology 2014; 15:461-472
$T. O'Hare et al. Blood. 2004; 104: 2532-2539
& A. Hochhaus et al. Leukemia 2020; 34:966-984

TIPI design



*according to D. Rea et al. Cancer; 2018;124:2956-2963

EudraCT Number: 2018-001789-41 - Sponsor ID: ET18000120
Clinical Trial: NCT04070443

Fundings and Ponatinib drug supply
Incyte Biosciences Europe

Ergebnisse:

Unter Pona 30 mg werden molekulare Remissionen sehr schnell erreicht (“doppelt so schnell wie bei Nilo”)

Aber: Auch bei kurzer Therapiedauer können kardiovaskuläre Ereignisse auftreten

Results: Comparisons EPIC trial vs TIPI

Cardio-vascular toxicities

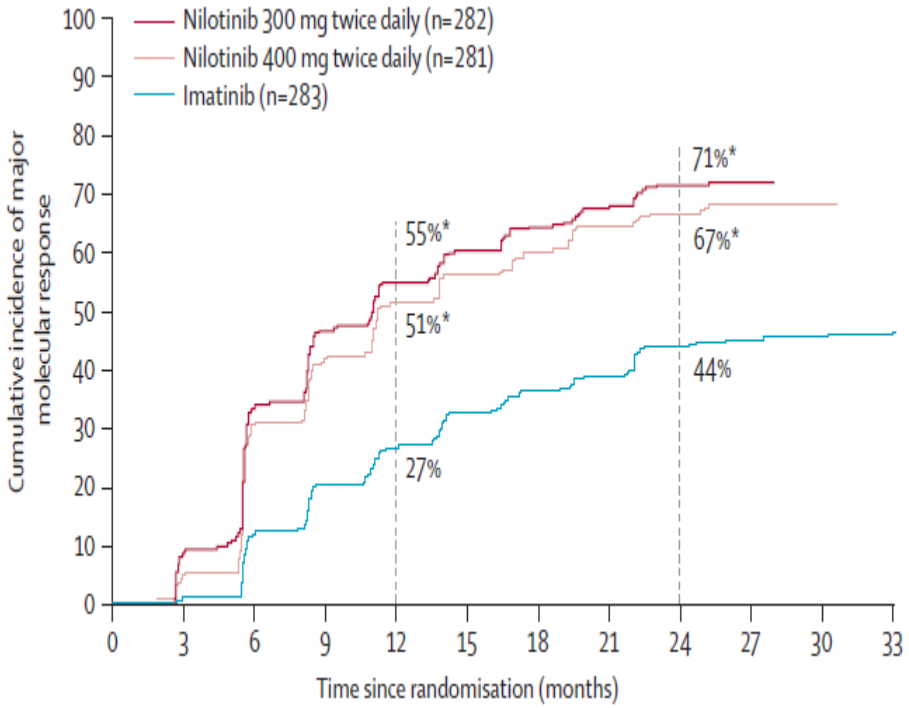
	EPIC* (n=154)		TIPI (n=169)	
Median follow-up (Months)	5.0 (3.5-7.5)		18 (3-33)	
	All AEs	**SAEs**	**All AEs**	**SAEs**
Cardio-vascular	5 (3%)	4 (3%)	8 (5%)	5 (3%)
Cerebro-vascular	3 (2%)	3 (2%)	1 (0.5%)	0
Peripheral vascular	3 (2%)	3 (2%)	1 (0.5%)	1 (0.5%)
Total	**11 (7%)**	**10 (7%)**	**10 (6%)**	**6 (3.5%)**
Hypertension	27 (18%)	7(5%)	15 (9%)	0

Molecular efficacy

	TIPI M6 (Pona 30 mg) n=169	EPIC M6** (Pona 45 mg) n=73
MMR	57%	62%
MR4	30%	32%
MR4.5	11%	16%
MR5	8.3%	NA

** Adapted from J. Lipton et al. Lancet Oncol 2016; 17: 612-621*

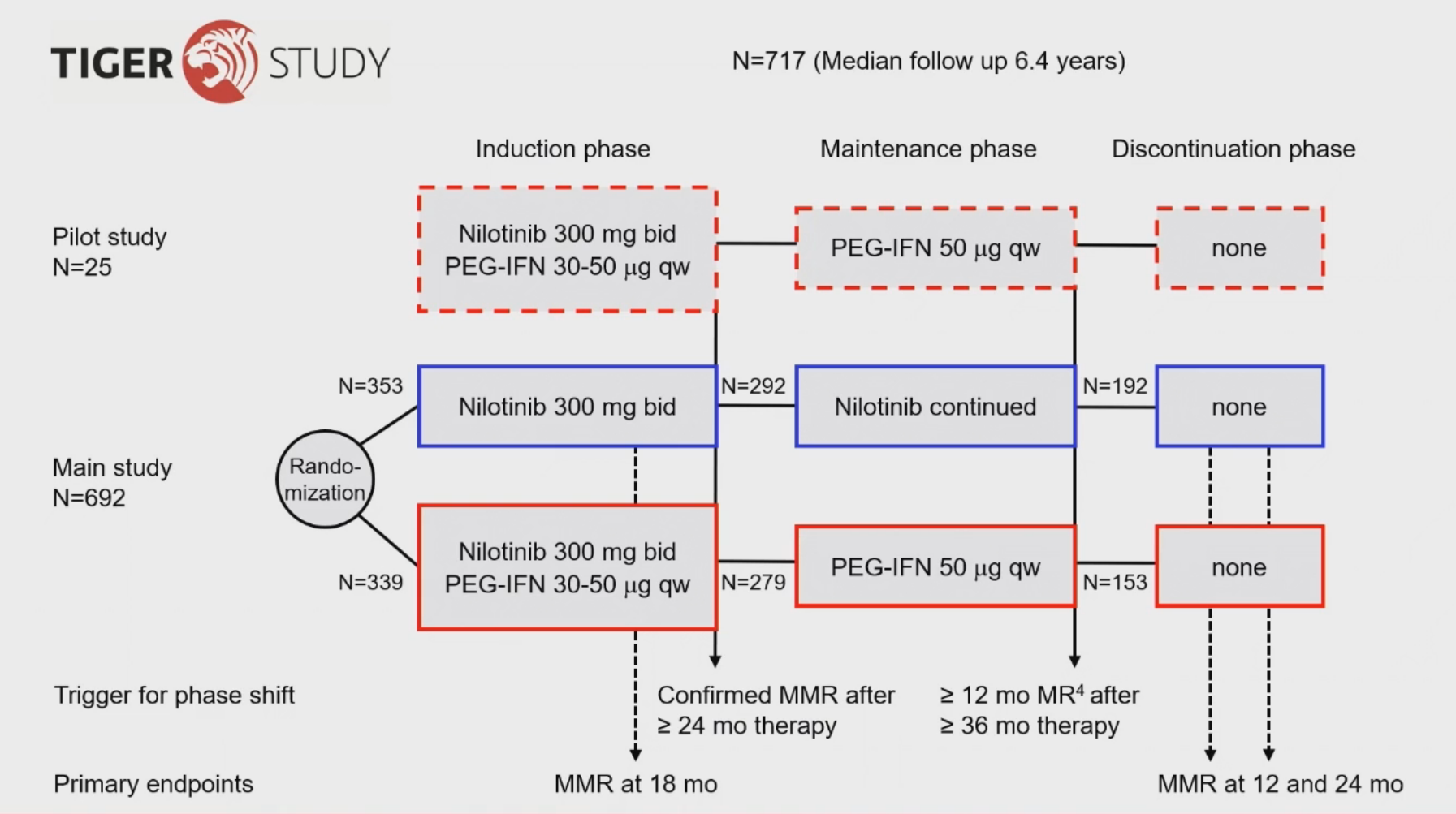
***J. Lipton et al. Lancet Oncol 2016, 17: 612-621*



(Kantarjian et al, Lancet Oncol 12:841, 2011)

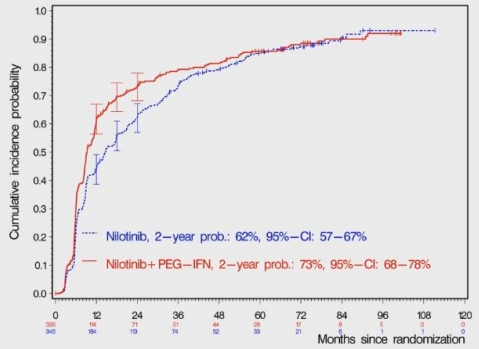
446 Treatment Free Remission after Nilotinib Plus Peg-Interferon Alpha Induction and Peg-Interferon Alpha Maintenance Therapy for Newly Diagnosed Chronic Myeloid Leukemia Patients; The Tiger Trial

Andreas Hochhaus, Jena, Deutschland

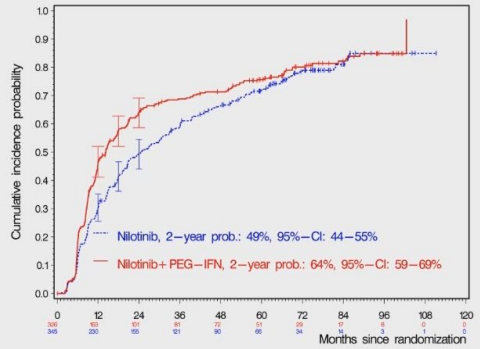


Cumulative incidences of DMR

MR^4

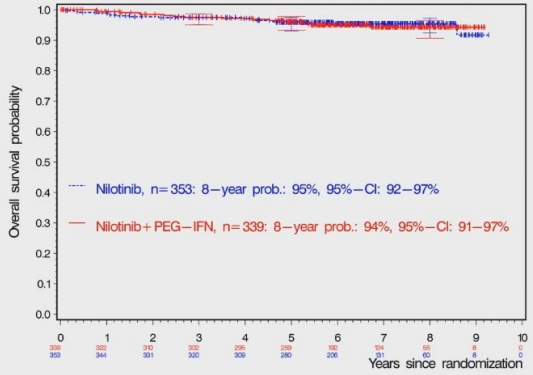


$MR^{4.5}$

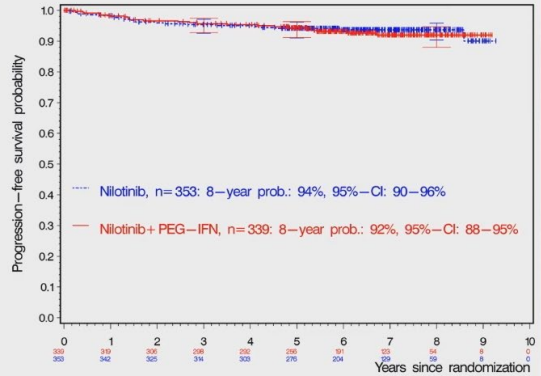


6 EUTOS IS standardized central labs; typical transcripts only

Overall and progression free survival by randomized therapy



8-year overall survival 95%



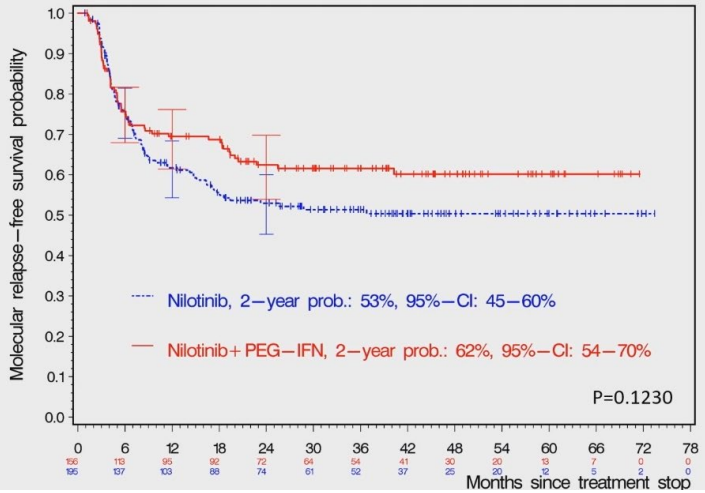
8-year progression free survival 93%

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%)



Adverse events of special interest, Grade 3-5

	Nilotinib monotherapy, N=353		Nilotinib-PEG-IFN combination, N=339	
	n	%	n	%
Arterial hypertension	37	10.5	21	6.2
Vascular disorders	59	16.7	31	9.1
Myocardial infarction	11	3.1	6	1.8
Stroke	5	1.4	4	1.2
Peripheral arterioocclusive disease	15	4.2	5	1.5
Pleural effusion	6	1.7	2	0.6
Depression	4	1.1	7	2.1
Fatigue	8	2.3	19	5.6
Flu like symptoms	1	0.2	7	2.1
Anemia	11	3.1	19	5.6
Neutropenia	14	4.0	39	11.5
Thrombocytopenia	73	20.7	61	18.0
ALAT increased	15	4.2	45	13.3
ASAT increased	7	2.0	20	5.9
Hyperbilirubinemia	12	3.4	13	3.8
Lipase increased	18	5.1	16	4.7

Quality of live analyses revealed decreased cognitive function and higher rates of fatigue in male and female patients in the NIL+IFN arm particularly in patients > 40 years.

Studien in Tübingen:

Asciminib vs. Nilotinib bei CML

ASC 4 START

Imetelstat vs. BAT bei PMF nach JAKI

IMpactMF

GRN163LMYF3001

Vielen Dank für Ihre Aufmerksamkeit!

Universitätsklinikum Tübingen