Comprehensive Cancer Center
Tübingen-Stuttgart

Post ASH 2024 San Diego

Myeloproliferative Neoplasien / CML / nichtmaligne Hämatologie

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

EBERHARD KARLS
UNIVERSITÄT
TÜBINGEN

Comprehensive
Cancer Center
Tübingen - Stuttgart

Universitätsklinikum
Tübingen

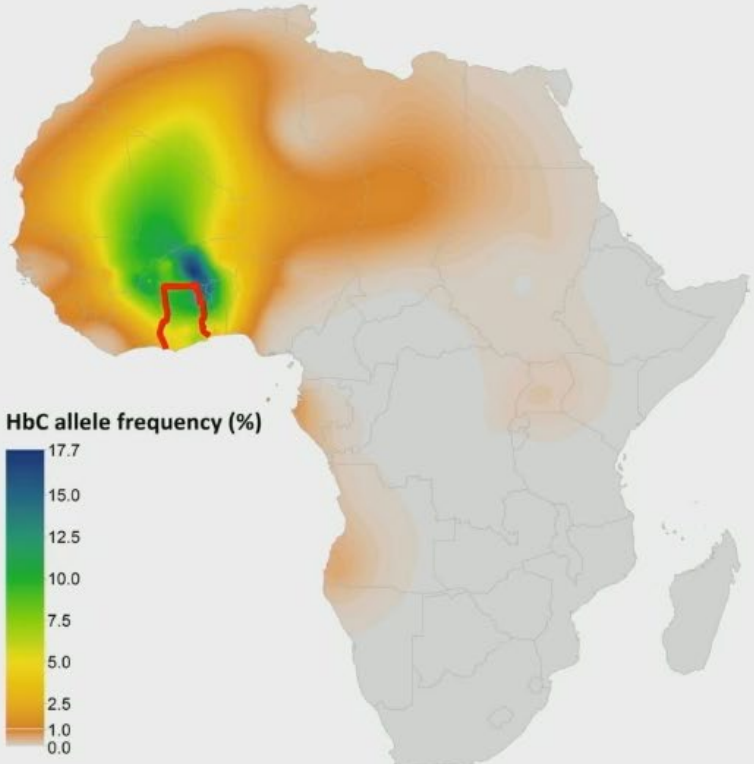
Sichelzellkrankheit:

Hydroxyurea …

3 Double-Blind, Placebo-Controlled Randomized Controlled Trial of Hydroxyurea for HbSC: Results of the Prospective Identification of Variables As Outcomes for Treatment (PIVOT) Trial. Y. Dei-Adomakoh, Accra, Ghana

Hemoglobin SC is the second most common sickle cell disease genotype

Hb S β6Glu-Val	Hb S β6Glu-Val	Hemoglobin SS disease Sickle Cell Anemia
Hb S β6Glu-Val	Hb C β6Glu-Lys	Hemoglobin SC disease



Piel F, *et al. Sci Rep*, 2013.
Bachir D and Galacteros F. Orphanet Encyclopedia, 2004.

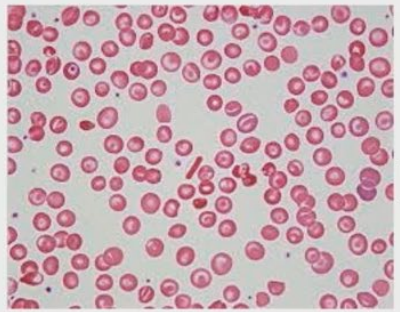
3 Double-Blind, Placebo-Controlled Randomized Controlled Trial of Hydroxyurea for HbSC: Results of the Prospective Identification of Variables As Outcomes for Treatment (PIVOT) Trial. Y. Dei-Adomakoh, Accra, Ghana

Patienten / Studiendesign

- 243 Patienten (5-50 Jahre alt) mit HbSC-Krankheit (Ghana)
- HU 20 mg/kg vs. Placebo
- Dosissteigerung in 2,5 mg/kg Schritten möglich

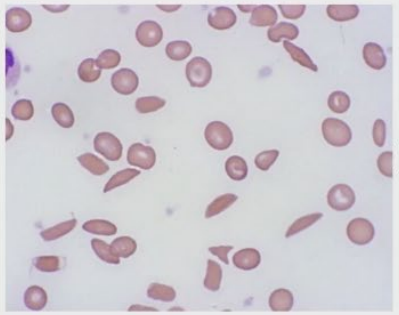
HbSC vs HbSS disease

HbSC erythrocytes
- Smaller size, dehydrated from water loss
- Rounder cells, often target shapes
- Denser cells (more Hb per cell)
- Milder anemia – hemolytic, compensated



HbSC

Clinical effects: sickling, anemia, viscosity
- Vaso-occlusion: pain, acute chest
- Spleen, Kidneys, Lungs are affected
- Eyes and hips may be more affected
- Brain is relatively protected



HbSS

3 Double-Blind, Placebo-Controlled Randomized Controlled Trial of Hydroxyurea for HbSC: Results of the Prospective Identification of Variables As Outcomes for Treatment (PIVOT) Trial. Y. Dei-Adomakoh, Accra, Ghana

Ergebnisse und Schlussfolgerungen

Clinical Adverse Events (per 100 person-years)

	Hydroxyurea			Placebo			IRR (95% CI)
	Pediatric N = 56	Adult N = 51	All N = 107	Pediatric N = 56	Adult N = 49	All N = 105	All
All Clinical AE	284.6	218.1	253.8	358.1	340.2	349.8	0.70 (0.48-0.92)
Vaso-occlusive pain	44.1	71.9	57.0	137.0	164.4	149.6	0.38 (0.28-0.52)
Malaria	30.1	32.3	31.2	27.4	52.5	39.0	0.80 (0.47-1.35)
Hospitalization	12.0	13.9	12.9	23.5	38.8	30.6	0.42 (0.22-0.81)
Any sickle related (N)	18	19	37	33	36	69	0.39 (0.26-0.59)

3 Double-Blind, Placebo-Controlled Randomized Controlled Trial of Hydroxyurea for HbSC: Results of the Prospective Identification of Variables As Outcomes for Treatment (PIVOT) Trial. Y. Dei-Adomakoh, Accra, Ghana

- **HU reduziert Schmerzkrisen und Hospitalisation, daher Einsatz sinnvoll auch bei HbSC**

Clinical Adverse Events (per 100 person-years)

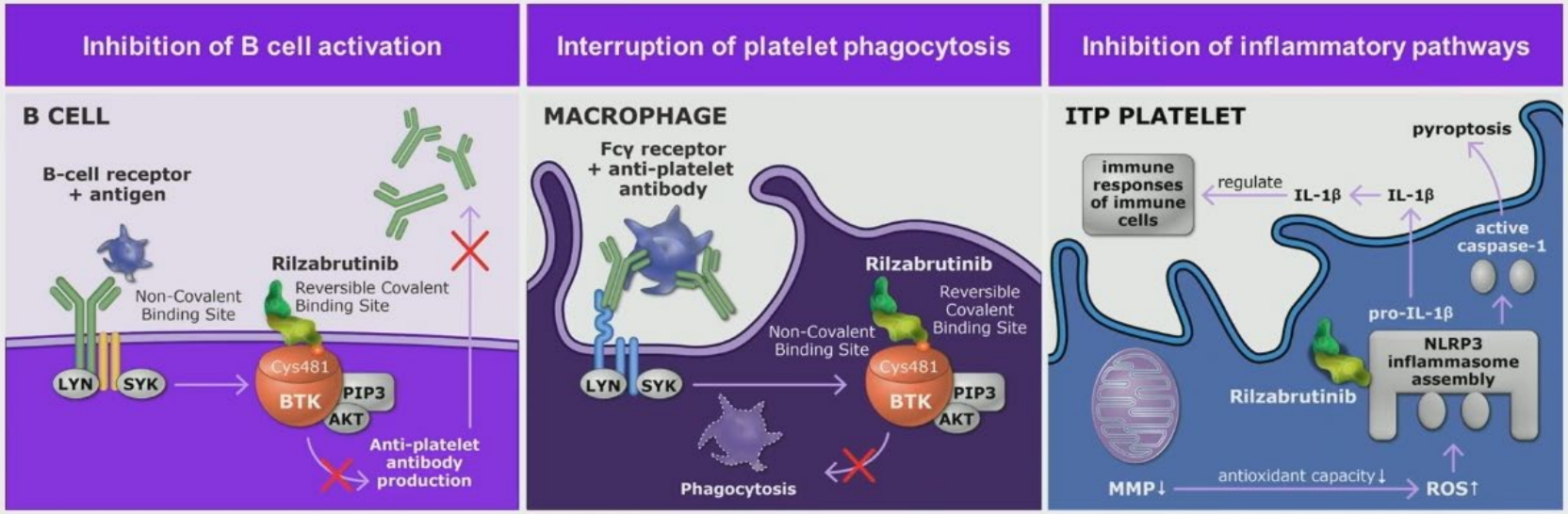
	Hydroxyurea			Placebo			IRR (95% CI)
	Pediatric N = 56	Adult N = 51	All N = 107	Pediatric N = 56	Adult N = 49	All N = 105	All
All Clinical AE	284.6	218.1	253.8	358.1	340.2	349.8	0.70 (0.48-0.92)
Vaso-occlusive pain	44.1	71.9	57.0	137.0	164.4	149.6	0.38 (0.28-0.52)
Malaria	30.1	32.3	31.2	27.4	52.5	39.0	0.80 (0.47-1.35)
Hospitalization	12.0	13.9	12.9	23.5	38.8	30.6	0.42 (0.22-0.81)
Any sickle related (N)	18	19	37	33	36	69	0.39 (0.26-0.59)

Ein Brutinib …

… auch für nichtmaligne hämatologische Erkrankungen: ITP

5 Efficacy and Safety of Oral Bruton Tyrosine Kinase Inhibitor (BTKi) Rilzabrutinib in Adults with Previously Treated Immune Thrombocytopenia (ITP): A Phase 3, Placebo-Controlled, Parallel-Group, Multicenter Study (LUNA 3). Kuter DJ, Boston, USA

Rilzabrutinib: Oral, Reversible, BTK Inhibitor



Kuter DJ, et al. Ther Adv Hematol. 2023; ***Langrish CL, et al. J Immunol. 2021; Wang S, et al. Thromb Res. 2021; Daak A, et al. Blood. 2024 (abstract 2482).***

Does not cause platelet dysfunction

LUNA-2: Open-label, dose-finding, Phase 1–2 trial of Rilzabrutinib in ITP *Kuter et al, NEJM 2022*

LUNA-3: Phase 3 trial, Rilzabrutinib vs. Placebo for previously treated ITP

5 Efficacy and Safety of Oral Bruton Tyrosine Kinase Inhibitor (BTKi) Rilzabrutinib in Adults with Previously Treated Immune Thrombocytopenia (ITP): A Phase 3, Placebo-Controlled, Parallel-Group, Multicenter Study (LUNA 3). Kuter DJ, Boston, USA

Patienten / Studiendesign

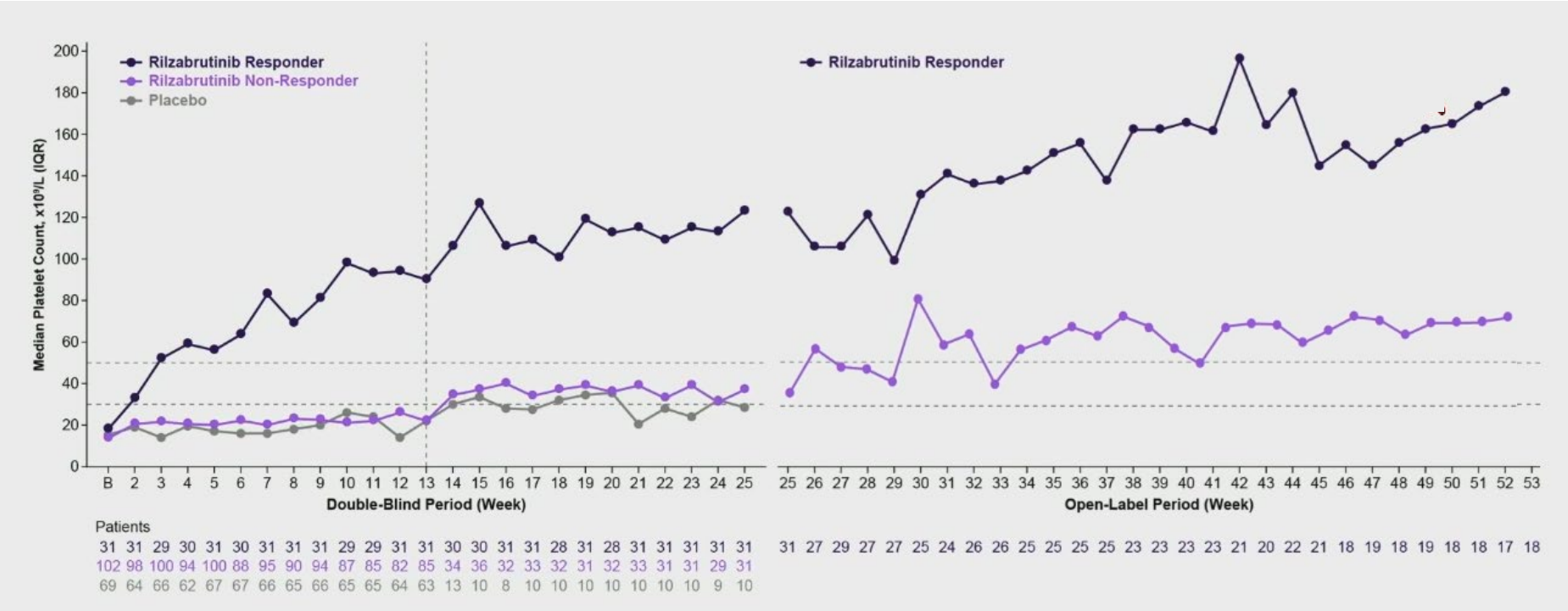
- Rilzabrutinib: Kein Effekt auf Plättchenaggregation, keine Blutungsneigung

- Chronische ITP, Thr. <30.000 /ul
- Parallele Behandlung mit Steroiden / TPO-RA erlaubt
- 133 Pat. erhielten Rilzabrutinib für knapp ½ Jahr, 69 Placebo
- danach „open-label period“, also auch Cross-over möglich

5 Efficacy and Safety of Oral Bruton Tyrosine Kinase Inhibitor (BTKi) Rilzabrutinib in Adults with Previously Treated Immune Thrombocytopenia (ITP): A Phase 3, Placebo-Controlled, Parallel-Group, Multicenter Study (LUNA 3). Kuter DJ, Boston, USA

Ergebnisse und Schlussfolgerungen

- **Thrombozyten > 50.000 /ul in 65% (Rilzabrutinib), 33% Placebo, auch Fatigue gebessert**
- **BTK Inhibitoren: Neue, potentielle Therapieoption bei ITP**



712 Updated Outcome from Biomarker MSC-C5b-9-Guided All-Trans Retinoic Acid Treatment for Resistant/Recurrent ITP: A Multicenter, Randomized, Open-Label, Phase 3 Clinical Trial. Li M, Peking, China

Patienten / Studiendesign

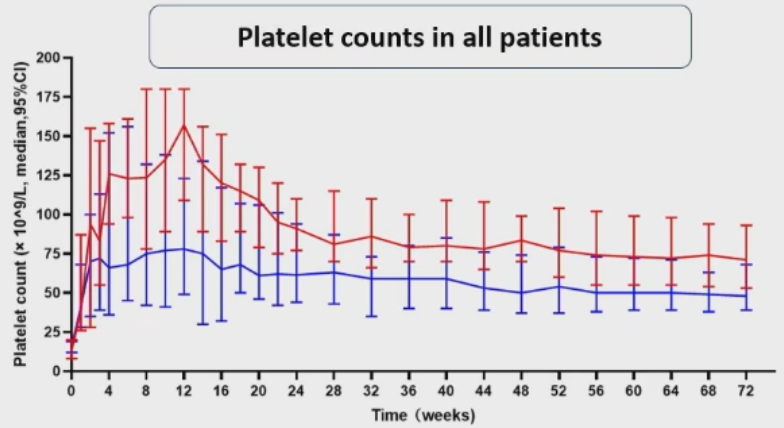
- 96 Pat. mit steroidresist./rezidivierter ITP, randomisiert 1:1 Eltrombopag ± ATRA
- ATRA: 10 mg 2x täglich
- Etwa 1/3 MSC-C5b-9 pos. (Knochenmarkanalyse)

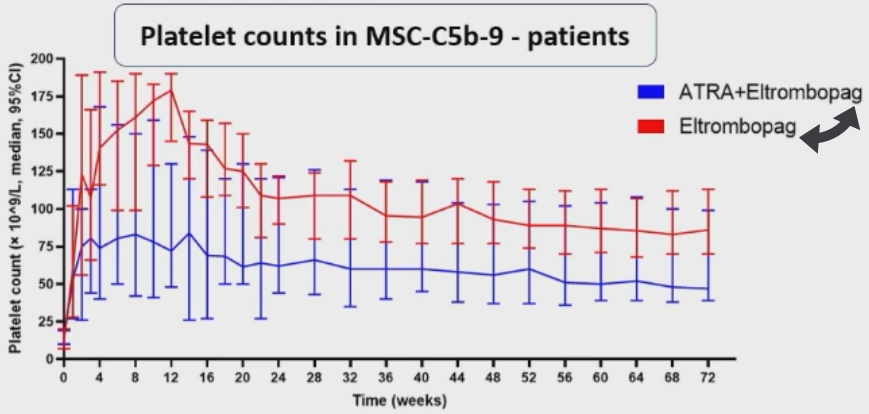
Ergebnisse

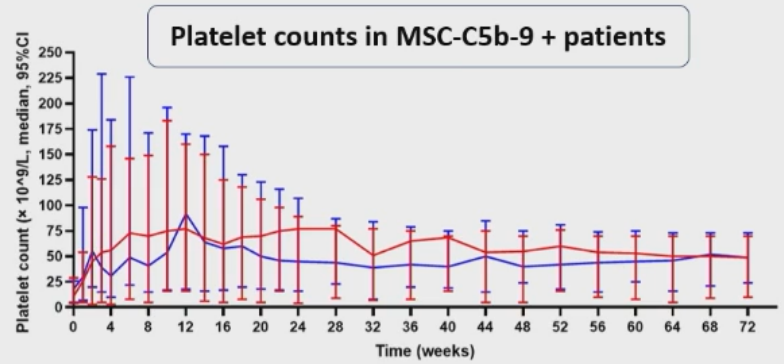
- Anhaltende Remission (18 Monate) in 2/3 der ATRA Gruppe, nur 1/3 ohne ATRA
- AEs in beiden Gruppen gleich häufig

712 Updated Outcome from Biomarker MSC-C5b-9-Guided All-Trans Retinoic Acid Treatment for Resistant/Recurrent ITP: A Multicenter, Randomized, Open-Label, Phase 3 Clinical Trial. Li M, Peking, China

Result—Platelet counts at weeks







Platelet count of the ATRA group higher than the monotherapy group

- Total cases: **p<0.0001**
- MSC-C5b-9 +: p=0.1517
- MSC-C5b-9 -: **p<0.0001**

Schlussfolgerungen

- ATRA 2 x 10 mg als Add-on zu TPO-RA (?)

ITP: Gefährliche Blutungen sind selten.
Aber wie häufig ist “selten” ?

547 Critical Bleeding in Adults and Children with Immune Thrombocytopenia: A Multicentre Cohort Study. Chowdhury S, Hamilton, Canada

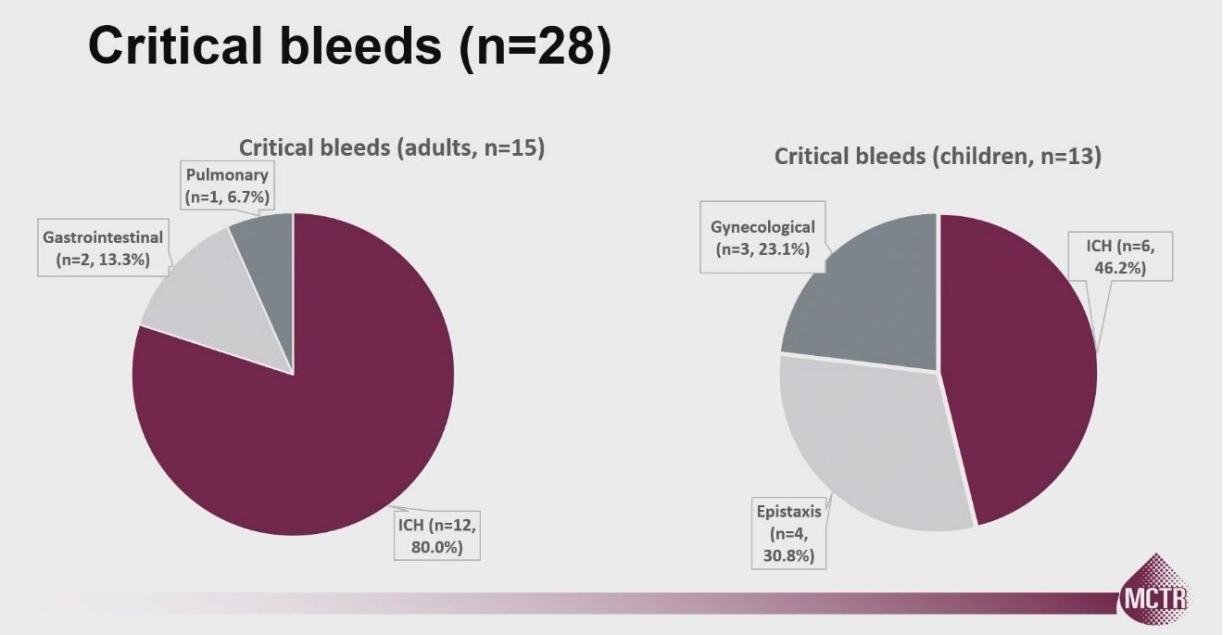
Patienten / Studiendesign

- 1226 Patienten mit ITP (296 davon Erwachsene) mit ITP
- in der Notaufnahme mit < 20.000 /ul Thrombozyten
- Definition kritische Blutung: intrazerebral, spinal, intraokulär, retroperitoneal, Kompartmentsyndrom, hämodynamisch instabil, Dyspnoe

Ergebnisse

5,1% bei Erwachsenen (47% letal)

1,4% bei Kindern (15% letal)



Schlussfolgerungen

- Kritischen Blutungen bei Erw. mit ITP in der Notaufnahme sind gar nicht so selten (5%)

- Höhere Letalität bei Erwachsenen (ca. die Hälfte), meist intrazerebrale Blutung

- Corticoide, IvIGs und Thrombozytentransfusionen häufigste Therapie

- Insbesondere bei ältere Patienten und bei spätem Therapiebeginn hohe Letalität

Eine AML ist selten bei ITP-Patienten
Erhöhtes Risiko durch TPO-Rezeptor-Agonisten?

549 Risk of Acute Myeloid Leukemia in Adults with Primary Immune Thrombocytopenia Treated with Thrombopoietin Receptor Agonists: A French Nationwide Population-Based Study. Zadro Y, Toulouse, Frankreich

Patienten / Studiendesign

- 8.172 Patienten mit ITP, 31.410 Patientenjahre Beobachtung

Ergebnisse / Schlussfolgerungen

- 20% hatten jemals TPO-RA bekommen, gleiche Beobachtungszeit wie die übrigen Pat.
- Auftreten von AML gleich häufig: jeweils in 0,6% beobachtet

TPO-RA sind kein Risikofaktor für das Auftreten einer AML

iTTP:

Oder mit OBI?

139 Obinutuzumab in Rituximab Refractory or Intolerant Immune-Mediated Thrombotic Thrombocytopenic Purpura. Weisinger J, Paris, Frankreich

Patienten / Studiendesign

- 60 Patienten mit iTTP, refraktär (56%) oder intolerant (44%) gegenüber Rituximab

- 1000 mg Obinotuzumab d1 (geteilte Dosis), 8, 15, 28, 56

- Compassionate Use

- In den meisten Fällen im präemtiven Setting

139 Obinutuzumab in Rituximab Refractory or Intolerant Immune-Mediated Thrombotic Thrombocytopenic Purpura. Weisinger J, Paris, Frankreich

Ergebnisse / Schlussfolgerungen

- 85% - ADAMTS13 >20%

- 72% - ADAMTS13 >50%

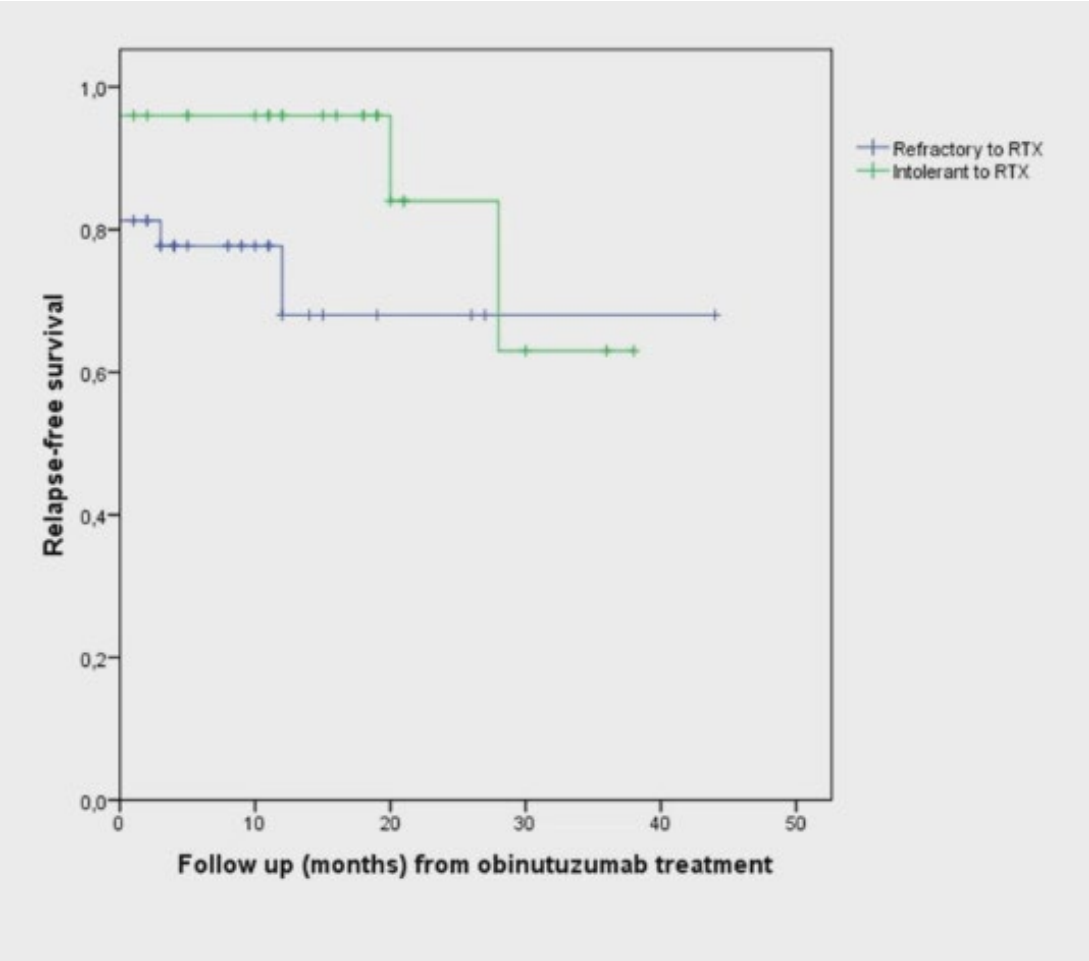
- 15% No response

- Rückfallfreies Überleben:

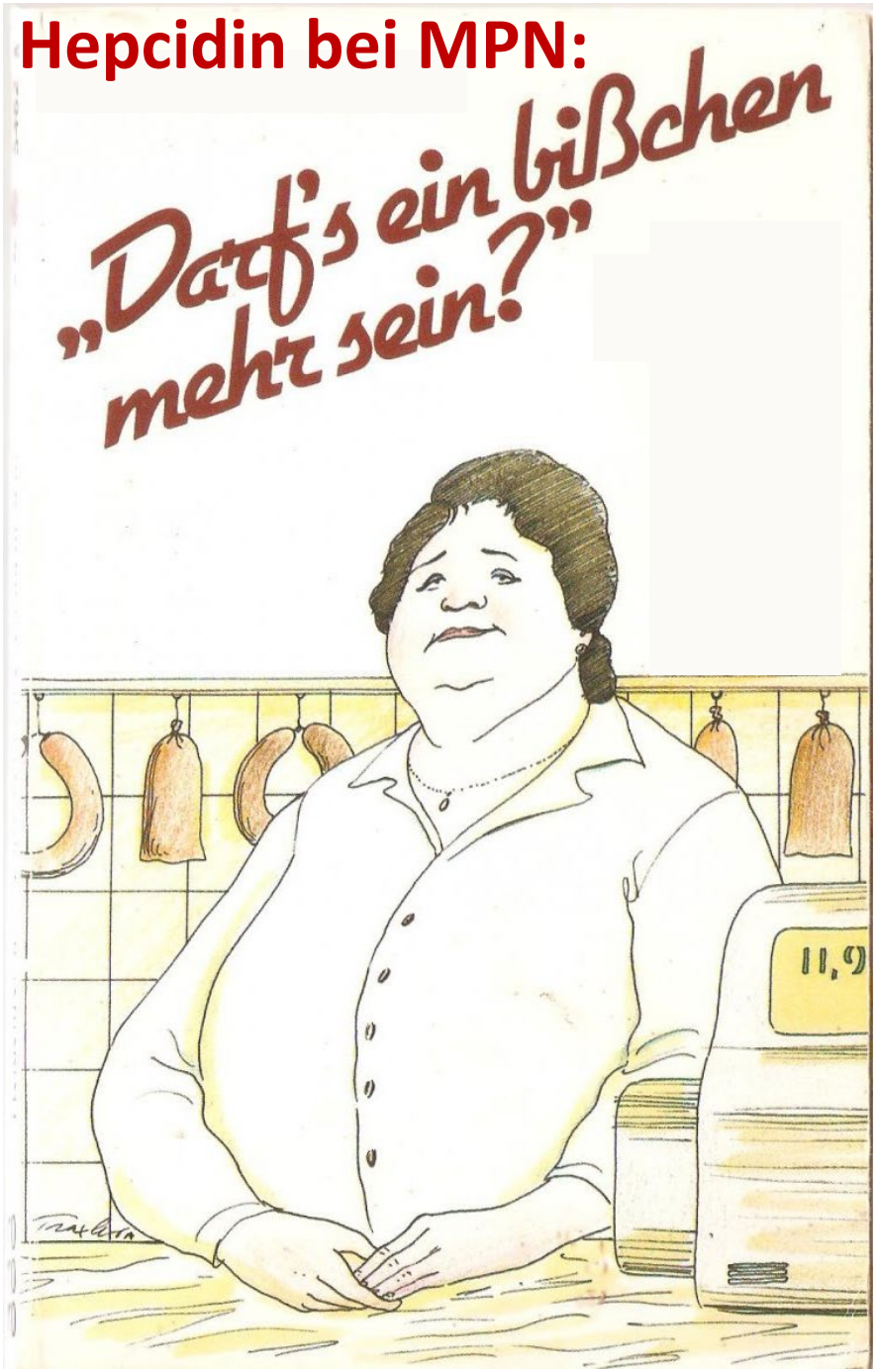
  Kein Unterschied zwischen

  Rituximab intolerant bzw. refraktär

- Obinutuzumab: Effektiv bei TTP



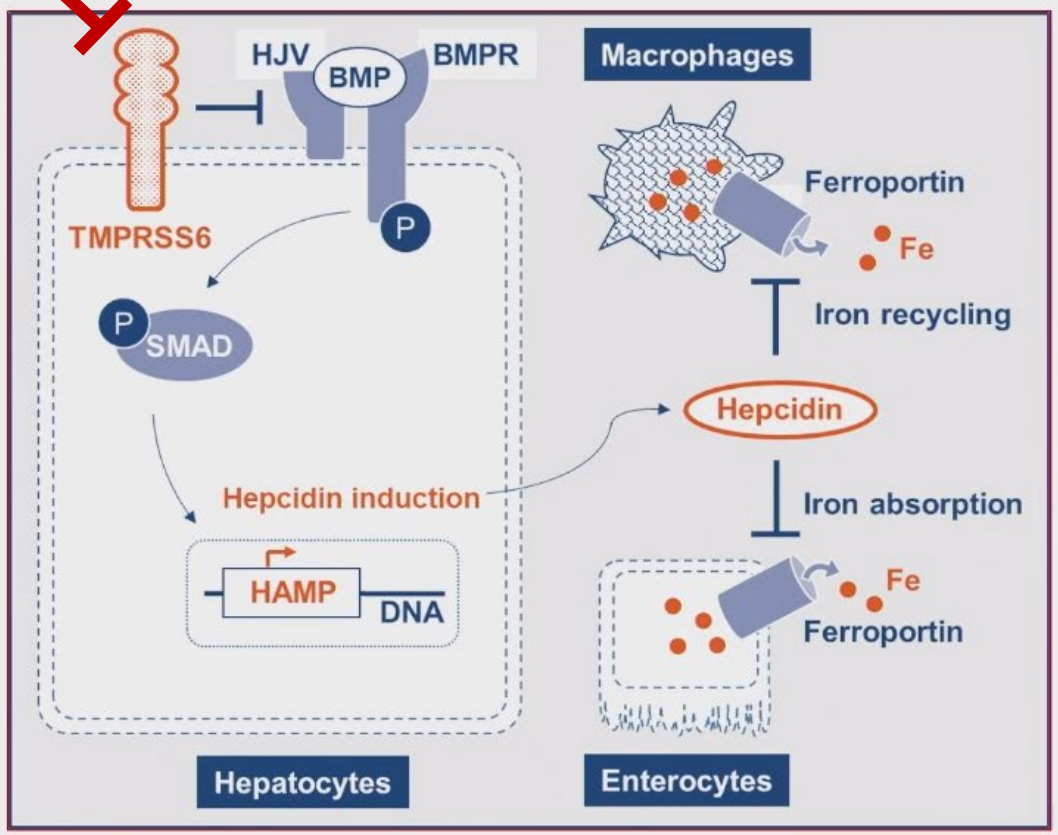
Hepcidin bei MPN:



… oder doch lieber etwas weniger?

656 Initial Results from a Phase 1/2 Study Evaluating Divesiran, a Novel Galnac Conjugated siRNA, in Patients with Polycythemia Vera (SANRECO). Kremyanskaya M, New York, USA

Inhibition of TMPRSS6 Elevates Hepcidin and Redistributes Iron



- **Hepcidin** reduces uptake of dietary iron and release of iron from storage cells.
- **HJV/BMP/SMAD** signaling pathway induces hepcidin expression. **TMPRSS6** is a **negative** regulator of this pathway. It is a serine protease which cleaves HJV
- **Hepcidin** levels are low to normal in patients with Polycythemia Vera
- **Therapeutic hypothesis:** inhibition of TMPRSS6 will raise hepcidin and reduce iron delivery to the bone marrow resulting in reduced erythropoiesis.

656 Initial Results from a Phase 1/2 Study Evaluating Divesiran, a Novel Galnac Conjugated siRNA, in Patients with Polycythemia Vera (SANRECO). Kremyanskaya M, New York, USA

Patienten / Studiendesign

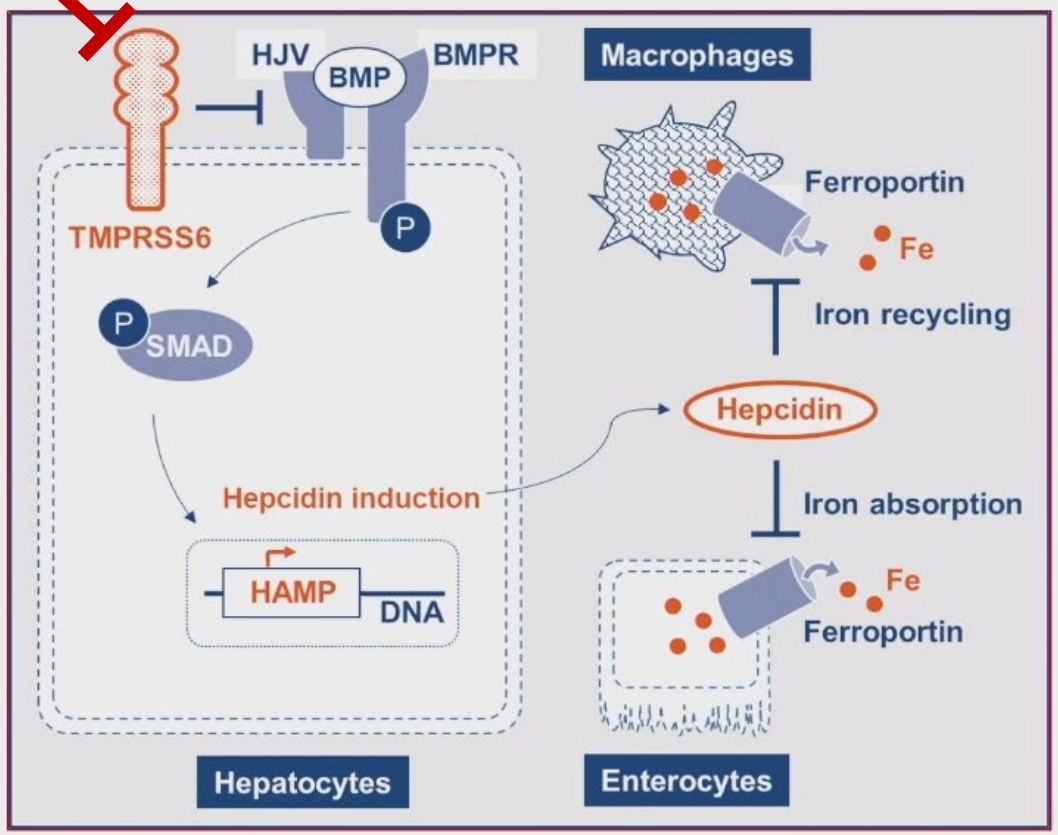
- 19 Pat. mit PV, teilweise (12) mit zytoreduktiver Therapie
- sc. Gabe der siRNA in 6-wöchigen Abständen, gut verträglich

Ergebnisse / Schlussfolgerungen

- 15/19 Pat. kein Aderlass mehr erforderlich, HKT fällt, Anstieg der Hepcidin-Spiegel
- Interessanter Therapieansatz, weitere Studien erforderlich

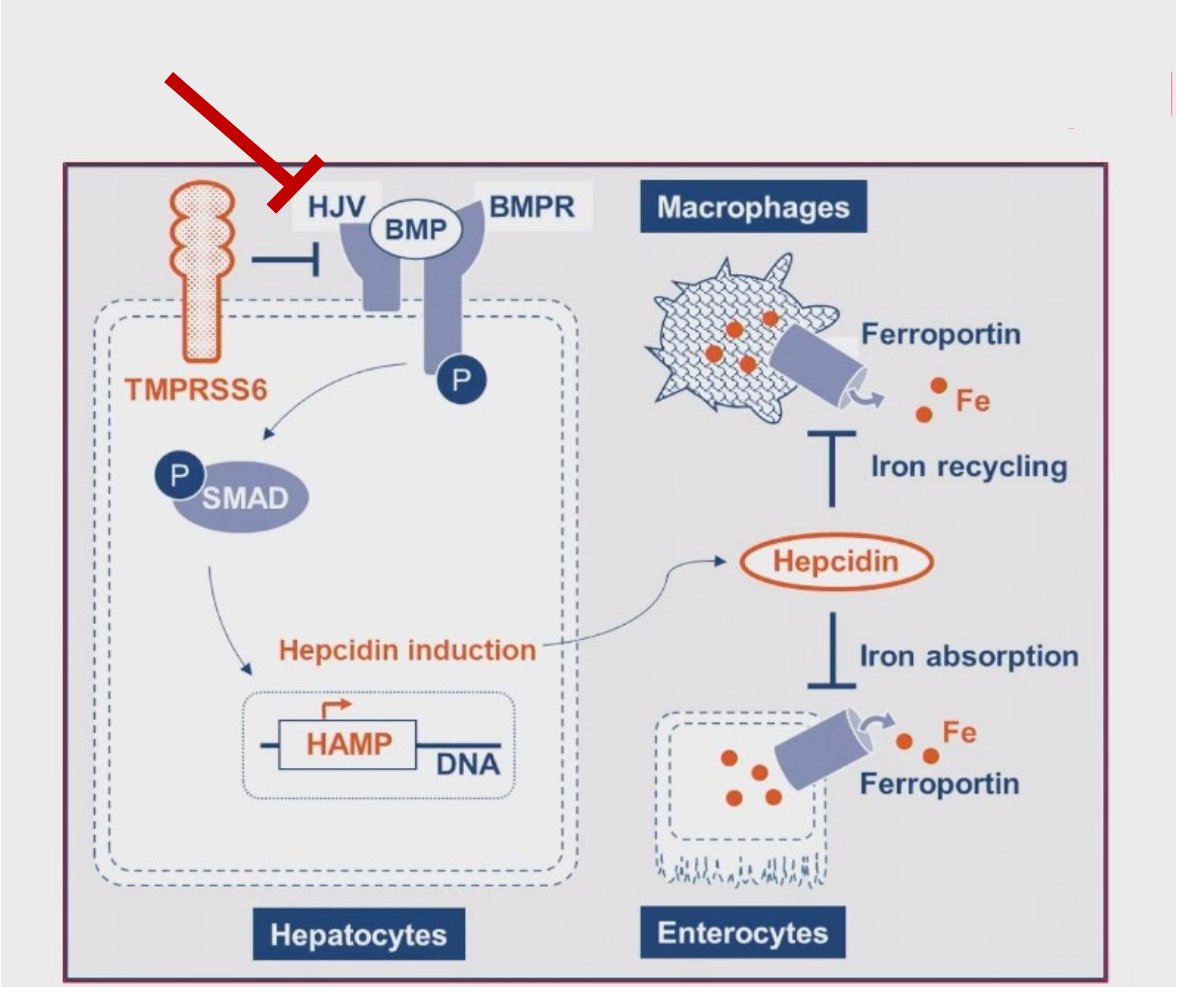
656 Initial Results from a Phase 1/2 Study Evaluating Divesiran, a Novel Galnac Conjugated siRNA, in Patients with Polycythemia Vera (SANRECO). Kremyanskaya M, New York, USA

Inhibition of TMPRSS6 Elevates Hepcidin and Redistributes Iron



- **Hepcidin** reduces uptake of dietary iron and release of iron from storage cells.
- **HJV/BMP/SMAD** signaling pathway induces hepcidin expression. **TMPRSS6** is a **negative** regulator of this pathway. It is a serine protease which cleaves HJV
- **Hepcidin** levels are low to normal in patients with Polycythemia Vera
- **Therapeutic hypothesis:** inhibition of TMPRSS6 will raise hepcidin and reduce iron delivery to the bone marrow resulting in reduced erythropoiesis.

657 A Phase 1b Study of DISC-0974, an Anti-Hemojuvelin Antibody, in Patients with Myelofibrosis and Anemia. Gangat N, Rochester, USA



657 A Phase 1b Study of DISC-0974, an Anti-Hemojuvelin Antibody, in Patients with Myelofibrosis and Anemia. Gangat N, Rochester, USA

Hepcidin is a Key Driver of Myelofibrosis-Related Anemia

Anemia of MF

Etiology of Anemia

- High hepcidin from inflammation
- Inflammatory cytokine expression
- Ineffective erythropoiesis
- JAK inhibitors may worsen anemia

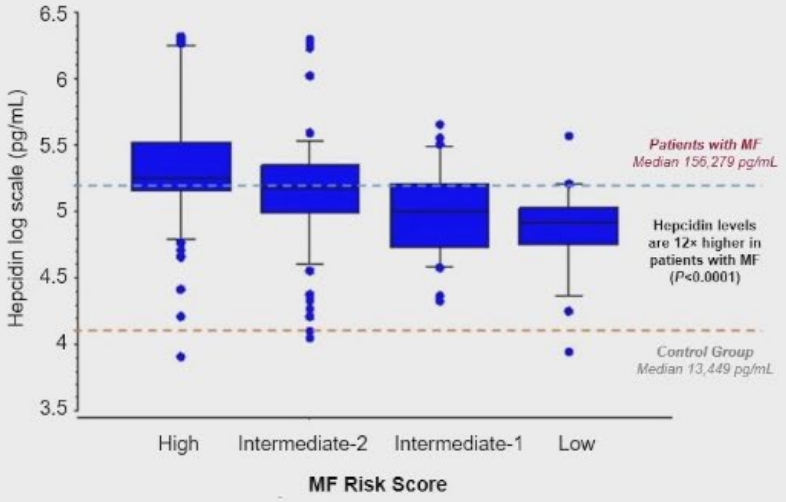
Estimated # of Patients

- 25,000 patients (US)
- ~87% have anemia

Unmet Medical Needs

- Anemia may limit optimal JAK inhibitor treatment
- No approved therapy specifically for anemia treatment
- Agents targeting TGF-β-BMP-SMAD pathway under investigation

Hepcidin Levels are Elevated in MF
~12× higher than control and associated with severity of anemia and transfusion burden



Source: Pardanani et al, Am J Hematol, 2013

657 A Phase 1b Study of DISC-0974, an Anti-Hemojuvelin Antibody, in Patients with Myelofibrosis and Anemia. Gangat N, Rochester, USA

Patienten / Studiendesign

- 35 Pat. mit PMF, ca. 1/3 unter JAKi, wenige unter Hydroxyurea
- ca. 1/3 transfusionsabhängig
- sc. Gabe des Antikörpers in monatlichen Abständen für ½ Jahr

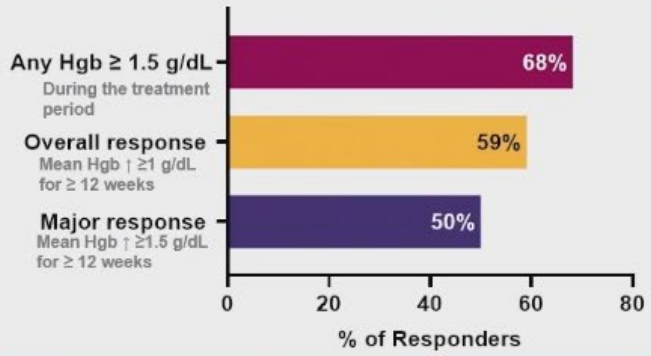
Ergebnisse / Schlussfolgerungen

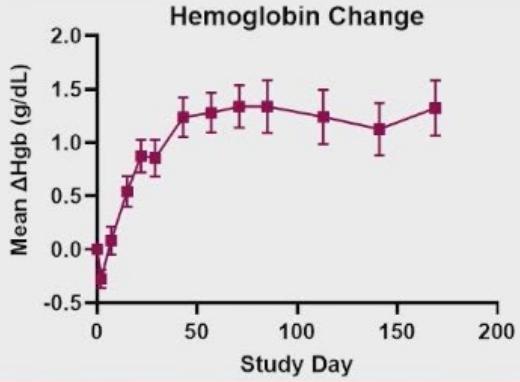
- Anstieg des Hbs, weniger Transfusionen, Besserung der Fatigue
- Abfall des Hepcidinspiegels, Anstieg des Serumeisens
- Perspektive: Kombination JAKi mit Anti-Hemojuvelin-AK

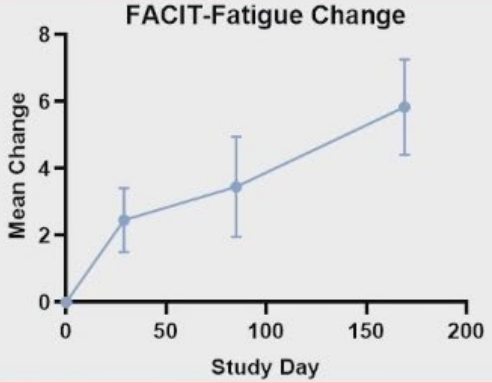
657 A Phase 1b Study of DISC-0974, an Anti-Hemojuvelin Antibody, in Patients with Myelofibrosis and Anemia. Gangat N, Rochester, USA

Hematologic Response: Non-Transfusion-Dependent Participants# (n=22)

68% of nTD participants achieved a Hgb Increase of ≥1.5 g/dL during study period
50% achieved a sustained Hgb response for ≥12 weeks







67% of participants (n=9) receiving concomitant JAKi therapy achieved durable response

nTD participants: Baseline Hgb <10 with 0 units PRBC in the 84 days prior to screening.

Response	Mean ± SD (days)
Time to first Hgb increase for major response	36 ± 18
Duration of major response during treatment period	150 ± 27

17 of 22 nTD participants have received continuation treatment with median response not reached. Follow-up ongoing (maximum 14.7 months)

Ein Stern im ASCendent:

475 Asciminib (ASC) Demonstrates Favorable Safety and Tolerability Compared with Each Investigator-Selected Tyrosine Kinase Inhibitor (IS TKI) in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) in the Pivotal Phase 3 ASC4FIRST Study. Cortes J, Augusta, USA

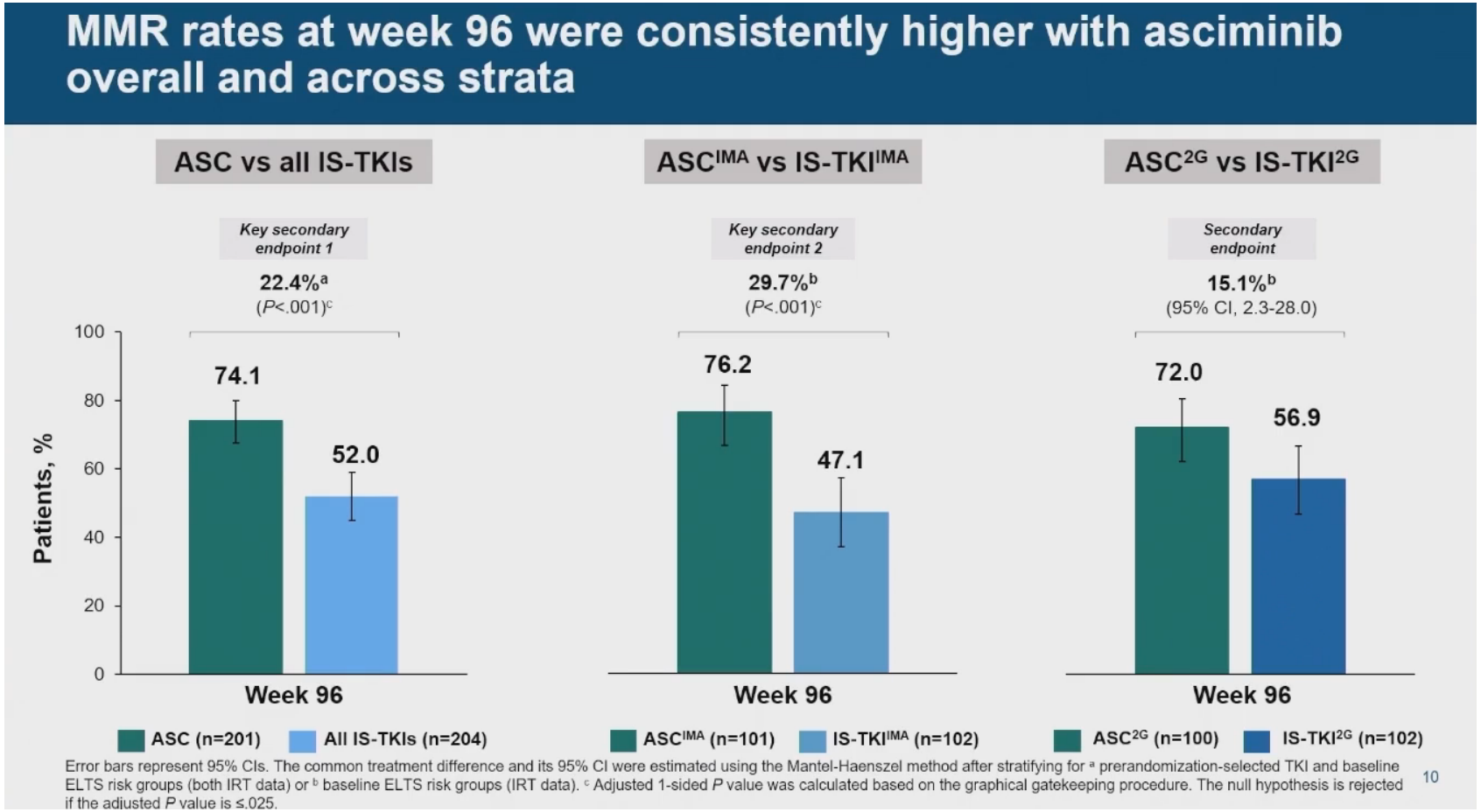
Patienten / Studiendesign

- CML chron. Phase: Randomisierung 201 Patienten Asciminib, 204 Patienten TKI
- Vor Randomisierung Entscheidung, welcher TKI (falls nicht im Asciminib-Arm)
- Somit besserer Vergleich möglich Asciminib vs. Imatinib bzw. 2nd Gen TKI

475 Asciminib (ASC) Demonstrates Favorable Safety and Tolerability Compared with Each Investigator-Selected Tyrosine Kinase Inhibitor (IS TKI) in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) in the Pivotal Phase 3 ASC4FIRST Study. Cortes J, Augusta, USA

Ergebnisse

- **MMR wird schneller erreicht mit Asciminib, verglichen mit Imatinib und 2nd Gen TKI**



475 Asciminib (ASC) Demonstrates Favorable Safety and Tolerability Compared with Each Investigator-Selected Tyrosine Kinase Inhibitor (IS TKI) in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) in the Pivotal Phase 3 ASC4FIRST Study. Cortes J, Augusta, USA

- bei Asciminib treten Mutationen in der Myristoyl Binding Site auf

- Etwa ebenso häufig wie wie bei TKI in der ATP Binding Site

Postbaseline treatment-emergent *BCR::ABL1* gene mutations (by NGS)

Patients	Post-baseline mutations[a]	Discontinuation reason	Postprotocol therapy (2L+)	Last disease/survival status
Asciminib	**Myristoyl pocket**			
1	A433D	Treatment failure per ELN	Bosutinib, dasatinib	CP/alive
2	A337V, V506M[b]		Dasatinib	CP/alive
3	A337T, A344P,[b] P465Q,[b] I502N[b]		Dasatinib	AP/alive
4	A433D		Dasatinib, olverembatinib	AP/alive
5	A337T, V506M[b]		Ponatinib	Discontinued study
6	L340Q		Not available	Discontinued study
7[c]	A337T	Confirmed loss of MMR	Dasatinib	Discontinued study
8	A337T, L340Q	Unsatisfactory therapeutic effect (other)	Dasatinib	CP/alive
9	A337T,[b] F497L[b]	Progressive disease (BP)	Ponatinib	CP/death post HSCT
10[c]	A337V	Ongoing on study	Not applicable	
Imatinib	**ATP-binding domain**			
1	L248V, E255V,[b] G250E[b]	Treatment failure per ELN	Flumatinib, olverembatinib	BP/death post HSCT
2[c]	F317L[b]		Imatinib	CP/alive
3	L248V, E450G[b]		Nilotinib	CP/alive
4[c]	E459K	Confirmed loss of MMR	Dasatinib	CP/alive
Nilotinib	**ATP-binding domain**			
5[c]	Y253H	Treatment failure per ELN	Dasatinib	CP/alive
6	Y253H		Dasatinib, ponatinib	CP/alive
7	Y253H[b]	Ongoing on study	Not applicable	

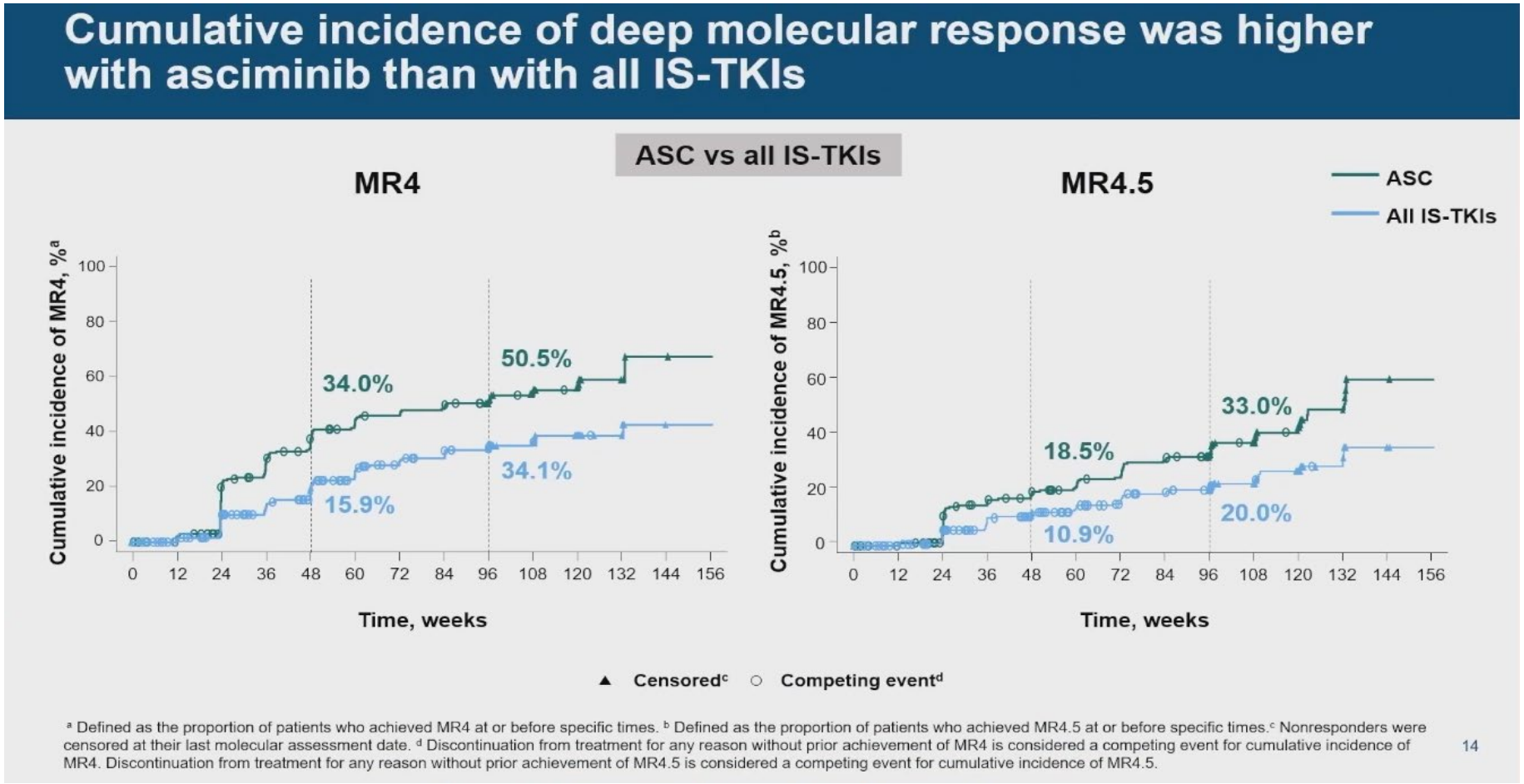
2L+, second line and beyond; AP, accelerated phase; BP, blast phase; CP, chronic phase; HSCT, hematopoietic stem cell transplant; NGS, next-generation sequencing.
[a] A patient with multiple mutations is only counted once. [b] Variant allele frequency was <20%. [c] Patients with new mutations since the week 48 data cutoff (November 28, 2023).

16

Oral presentation at: 66th ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA

475 Asciminib (ASC) Demonstrates Favorable Safety and Tolerability Compared with Each Investigator-Selected Tyrosine Kinase Inhibitor (IS TKI) in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) in the Pivotal Phase 3 ASC4FIRST Study. Cortes J, Augusta, USA

- Tiefe molekulare Remissionen: Schneller erreicht mit Asciminib als mit TKI

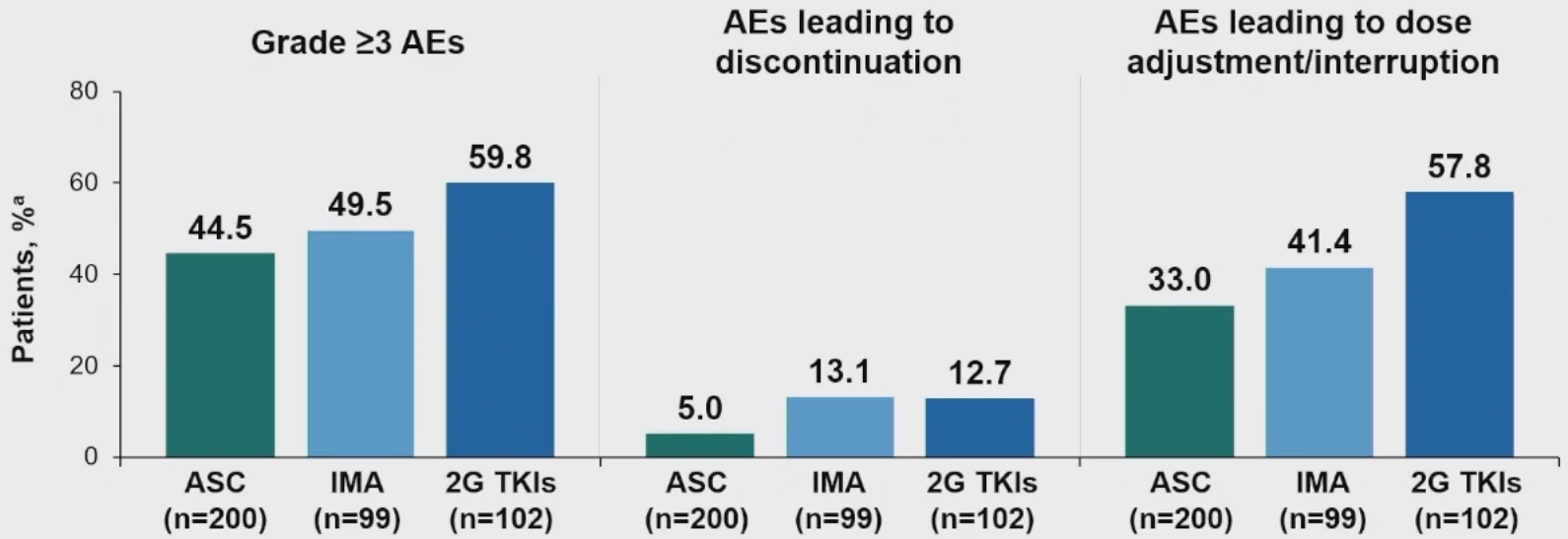


475 Asciminib (ASC) Demonstrates Favorable Safety and Tolerability Compared with Each Investigator-Selected Tyrosine Kinase Inhibitor (IS TKI) in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) in the Pivotal Phase 3 ASC4FIRST Study. Cortes J, Augusta, USA

- AEs mit Asciminib seltener als mit TKI

- insbes. solche, die zum Pausieren führen

Safety and tolerability continued to be more favorable with asciminib than with imatinib and 2G TKIs by the week 96 cutoff



- The median average daily dose was 80 mg/day with ASC, 400 mg/day with IMA, 600 mg/day with NIL, 100 mg/day with DAS, and 316 mg/day with BOS
- The hazard ratio for time to treatment discontinuation due to AEs (TTDAEs) for asciminib vs 2G TKIs was 0.46 (95% CI, 0.215-0.997)
  - There was a 54% lower risk of discontinuation due to AEs[b] with asciminib compared with 2G TKIs

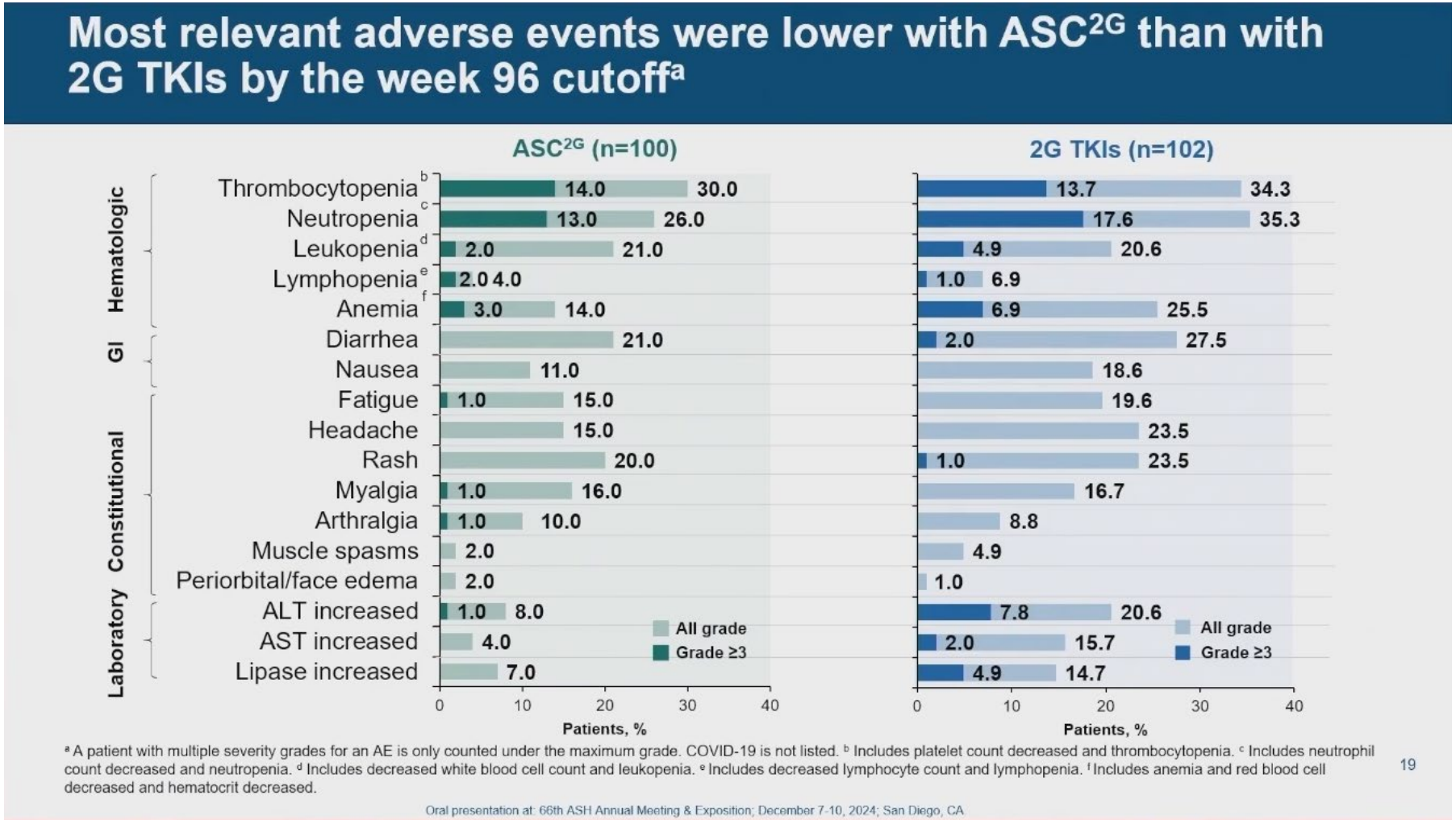
BOS, bosutinib; DAS, dasatinib; NIL, nilotinib; TTDAE, time to treatment discontinuation due to AE.
[a] Safety analyses were done in patients who received ≥1 dose of study drug. Patients were analyzed according to the study treatment received. A patient with multiple severity grades for an AE is only counted under the maximum grade. [b] Discontinuation for other reasons was a competing event.

17

475 Asciminib (ASC) Demonstrates Favorable Safety and Tolerability Compared with Each Investigator-Selected Tyrosine Kinase Inhibitor (IS TKI) in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) in the Pivotal Phase 3 ASC4FIRST Study. Cortes J, Augusta, USA

- Häufigste AEs bei Asciminib und TKI: Hämatologische Toxizitäten

- Erh. Leber- und / Pankreasenzyme nur bei TKI



479 Efficacy and Safety of Asciminib in Chronic Myeloid Leukemia in Chronic Phase (CML-CP): Interim Results from the Phase 2 ASC2ESCALATE Trial in the Cohort of Patients (Pts) after 1 Prior Tyrosine Kinase Inhibitor (TKI). Cortes J, Augusta, USA

- Asciminib in der Zweitlinie: 42% MMR und 24% MR4 nach 24 Wochen

476 Update of the Ascend-CML Study of Frontline Asciminib: High Rate of Optimal Response and Resistance Due to Mutations Is Rare. Yeung D, Adelaide, Australien

- Asciminib in der Erstlinie

- Bei Therapieversagen (u.a. >1% bcr-abl nach 12 Mo.): Hinzunahme (!) eines TKI

- Die Hälfte der Pat. erzielten eine MR4 nach 18 Mo.

Schlussfolgerungen der vorgestellten Asciminib-Studien

- Asciminib in der Erstlinie schnellere und höhere molekulare Ansprechraten als TKI
- Geringere Rate an unerwünschten Wirkungen: Neuer Standard für Erstlinie?
- Langzeit-Tox. (z.B. vaskuläre Ereignisse) kann noch nicht abschließend beurteilt werden
- Perspektive: Kombination von Asciminib und einem TKI

MPN Studien in Tübingen:

Imetelstat vs. BAT bei PMF nach JAKI

IMpactMF

GRN163LMYF3001

Und am Ende:

Vielen Dank für Ihre Aufmerksamkeit!

Universitätsklinikum Tübingen