Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

EHA2024 HYBRID

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PD Dr. med. Lukas Frenzel
Innere Medizin I | Uniklinik Köln

Leukämie SPECIAL

Offenlegung potentieller Interessenskonflikte

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Honorare	Otsuka, JAZZ, Abbvie, KML, Delbert Pharma
Finanzierung wissenschaftlicher Untersuchungen	
Andere finanzielle Beziehungen	
Immaterielle Interessenkonflikte	

Kapitel 1

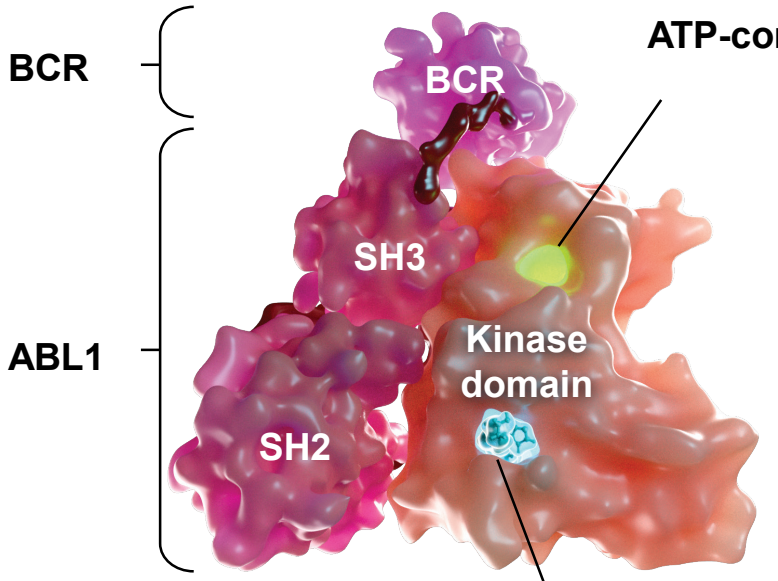
Erstlinientherapie der CML – Ergebnisse der Phase III Studie ASC4FIRST

Asciminib Provides Superior Efficacy and Excellent Safety and Tolerability vs Tyrosine Kinase Inhibitors in Newly Diagnosed Chronic Myeloid Leukemia in the Pivotal ASC4FIRST Study

Plenary Session – Abst #S103

Andreas Hochhaus, Timothy P. Hughes, Jorge E. Cortes, Ghayas C. Issa, Richard A. Larson, Felice Bombaci, Jianxiang Wang, Dong-Wook Kim, Dennis Dong Hwan Kim, Jiri Mayer, Yeow-Tee Goh, Philipp le Coutre, Inho Kim, Gabriel Etienne, Shruti Kapoor, Tracey McCulloch, Kamel Malek, Lillian Yau, Sophie Ifrah, Naoto Takahashi

Asciminib: intentionally designed to improve efficacy and reduce off-target effects vs current ATP-competitive TKIs



Asciminib Specifically Targets the ABL Myristoyl Pocket (STAMP)

ASC4FIRST, a head-to-head study comparing asciminib vs all standard-of-care TKIs in newly diagnosed CML patients

NCT04971226

Key inclusion criteria

- Newly diagnosed Ph+ CML-CP with ***no*** prior TKIs[a]
- Age ≥18 years

Prerandomization TKI selection

- The TKI a patient will take if randomized to the investigator-selected (IS-TKI) arm
- Selected by the physician in consultation with the patient

Stratification by:

- Prerandomization TKI selection (IMA or 2G TKI)
- ELTS risk category

R 1:1

N=405

Asciminib (ASC) 80 mg QD

Imatinib stratum: **ASC^{IMA}**

2G TKI stratum: **ASC^{2G}**

Imatinib stratum: **IS-TKI^{IMA}**

2G TKI stratum: **IS-TKI^{2G}**

Data cutoff: Nov. 28, 2023

Primary endpoints:

- MMR at week 48 for asciminib vs all investigator-selected TKIs
- MMR at week 48 for asciminib vs investigator-selected TKI within the imatinib stratum

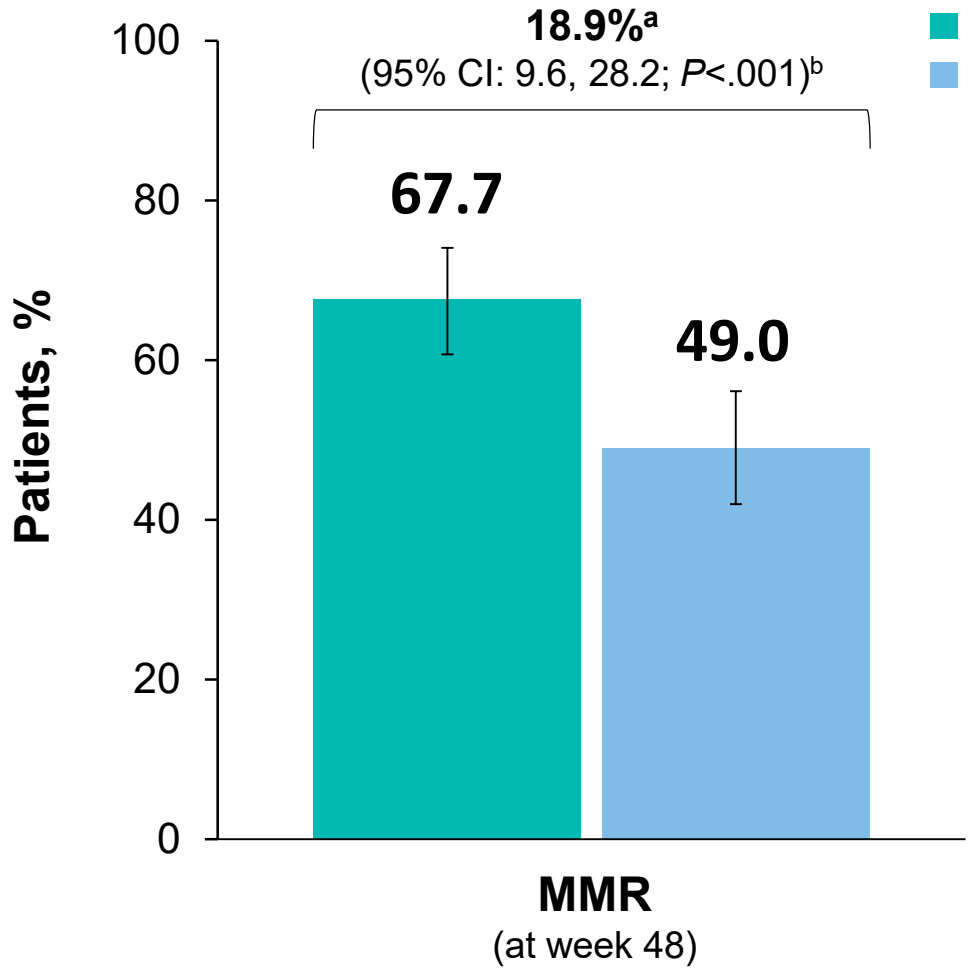
Baseline characteristics were well balanced between asciminib and all IS-TKIs

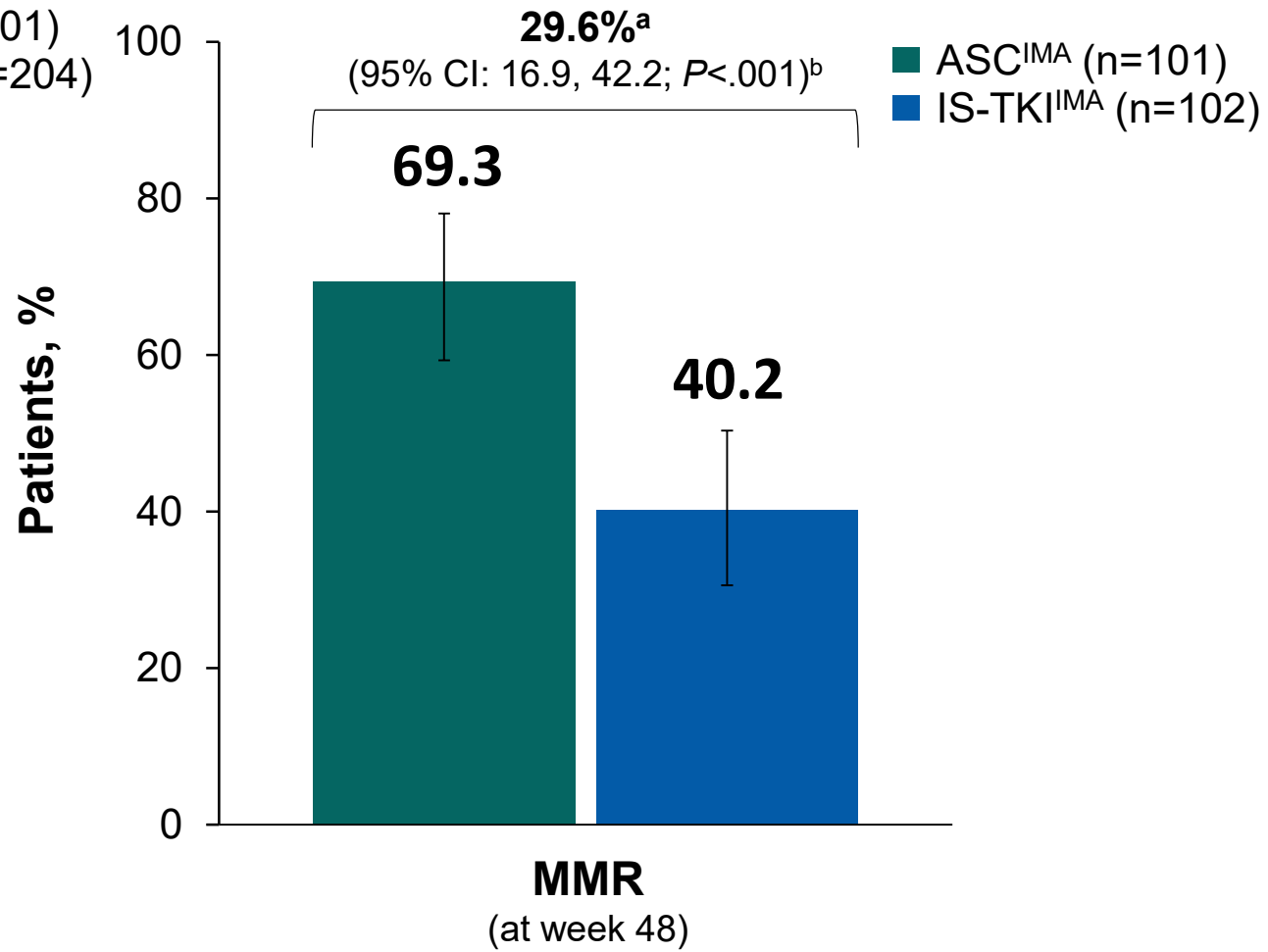
Variable	Asciminib			IS-TKI		
	All asciminib (n=201)	Imatinib stratum (n=101)	2G TKI stratum (n=100)	All IS-TKI (n=204)	Imatinib stratum (n=102)	2G TKI stratum (n=102)
Median age (range), years	52.0 (18.0-79.0)	56.0 (21.0-79.0)	43.0 (18.0-76.0)	50.5 (19.0-86.0)	54.5 (20.0-86.0)	43.0 (19.0-83.0)
Age group, %						
18 to <65 years	77.1	68.3	86.0	76.0	68.6	83.3
65 to <75 years	17.9	23.8	12.0	16.7	21.6	11.8
≥75 years	5.0	7.9	2.0	7.4	9.8	4.9
Male, %	65.2	61.4	69.0	61.3	63.7	58.8
Framingham CV risk score, %[a]						
Low risk (<10%)	54.2	40.6	68.0	54.9	39.2	70.6
Intermediate risk (10%-20%)	15.9	20.8	11.0	21.6	28.4	14.7
High risk (≥20%)	29.9	38.6	21.0	23.5	32.4	14.7
ELTS, %[b]						
Low	60.7	61.4	60.0	61.3	62.7	59.8
Intermediate	27.9	29.7	26.0	27.9	29.4	26.5
High	11.4	8.9	14.0	10.8	7.8	13.7

- More patients in the imatinib stratum vs 2G TKI stratum were aged ≥65, with higher cardiovascular disease risk, **reflecting physician preference for imatinib in these subgroups**

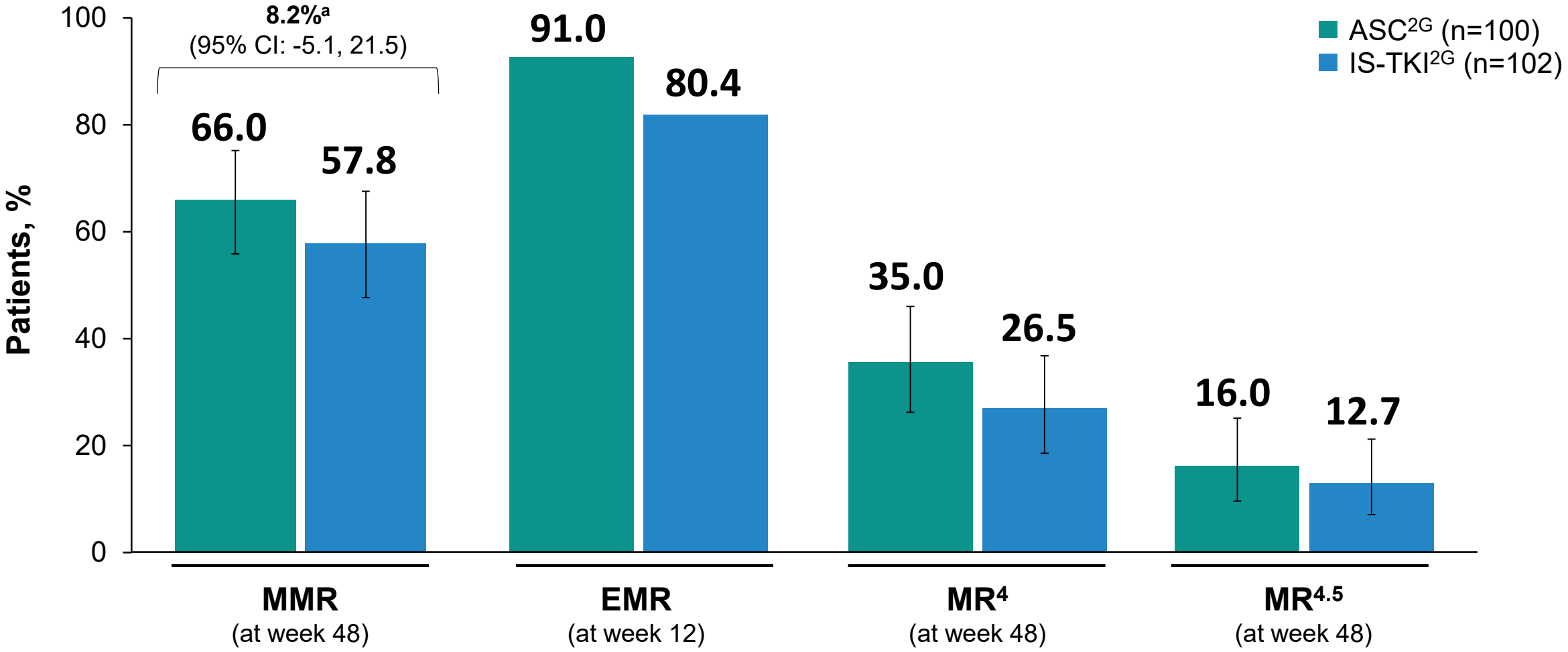
- [a] Framingham estimated 10-year cardiovascular disease risk categories.
- [b] Based on randomization data.

MMR rate (<0.1%) at week 48 was superior with asciminib vs all IS-TKIs and ASC^{IMA} vs IS-TKI^{IMA}, meeting both primary endpoints



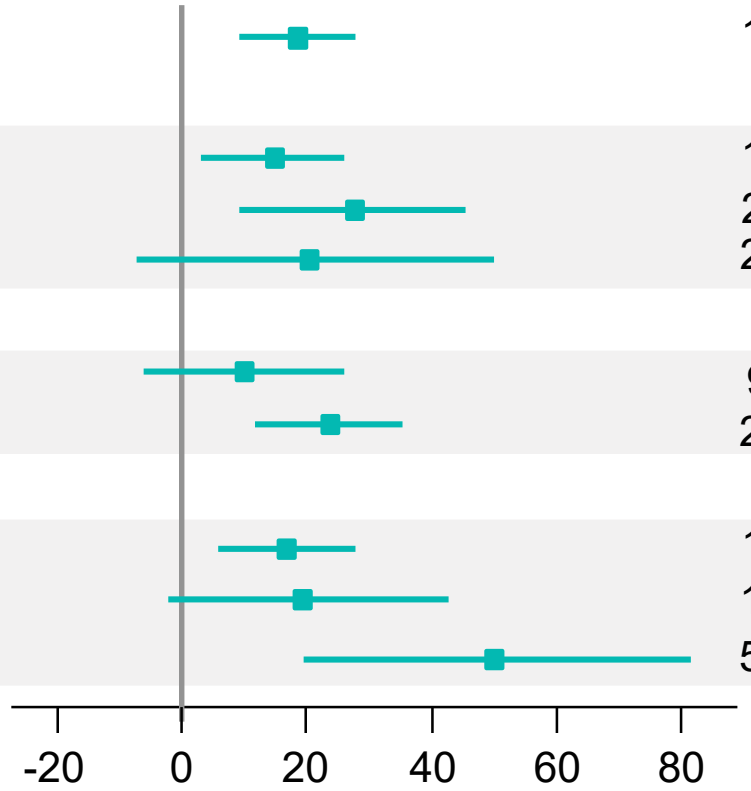


A numerically higher proportion of patients with ASC^{2G} achieved major, early, and deep molecular responses vs IS-TKI^{2G}

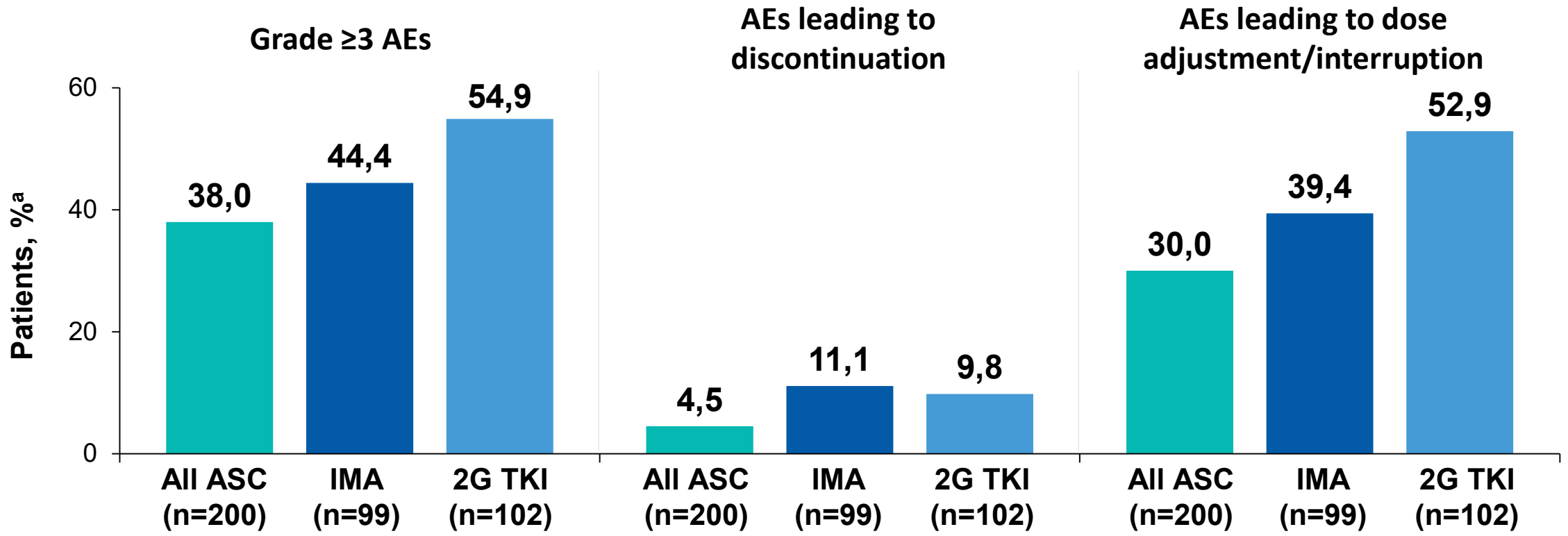


Asciminib had higher MMR rates across all demographic and prognostic subgroups vs all IS-TKIs

Subgroup	MMR		Favors all IS-TKIs	Favors ASC	Treatment difference (95% CI)
	ASC, %	All IS-TKIs, %			
All patients	67.7	49.0			18.6 (9.2 to 28.1)
ELTS					
Low	72.1	57.6			14.5 (2.8 to 26.3)
Intermediate	64.3	36.8			27.4 (9.7 to 45.2)
High	52.2	31.8			20.4 (-7.9 to 48.6)
Sex					
Female	64.3	54.4			9.9 (-5.8 to 25.6)
Male	69.5	45.6			23.9 (12.1 to 35.6)
Age category					
18 to <65 years	64.5	48.4			16.1 (5.2 to 27.0)
65 to <75 years	75.0	55.9			19.1 (-2.8 to 41.0)
≥75 years	90.0	40.0			50.0 (19.0 to 81.0)



Asciminib demonstrated favorable safety and tolerability vs IMA and 2G TKIs



- The median dose intensity was 80.0 mg/day with ASC, 400.0 mg/day with IMA, 595.1 mg/day with NIL, 98.9 mg/day with DAS, and 341.8 mg/day with BOS
- The most common AEs leading to treatment discontinuation were increased lipase with ASC (1.5%), diarrhea and lymphopenia with IMA (2.0% each), and pleural effusion with 2G TKIs (2.0%)

- BOS, bosutinib; DAS, dasatinib; NIL, nilotinib. [a] Safety analyses consisted of 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.

Summary

In CML at diagnosis, specific BCR::ABL1 inhibition is efficacious and well tolerated

Asciminib demonstrated superior efficacy vs all standard-of-care frontline TKIs

Both **primary objectives in ASC4FIRST were met** with high statistical significance

1. Asciminib demonstrated superior MMR rates at week 48 vs all investigator-selected TKIs (**67.7% vs 49.0%,** *P*<0.001)
2. Asciminib demonstrated superior MMR rates at week 48 vs investigator-selected TKIs, within the imatinib stratum (**69.3% vs 40.2%,** *P*<0.001)

Asciminib had a markedly favorable safety and tolerability profile, with fewer grade ≥3 adverse events and half the rate of adverse events leading to treatment discontinuation vs all investigator-selected TKIs

Kapitel 2

Erstlinientherapie der Hochrisiko APL (AML M3)

– (Zwischen)Ergebnisse der randomiserten Phase III Studie APOLLO

FIRST RESULTS OF THE APOLLO TRIAL: A RANDOMIZED PHASE III STUDY TO COMPARE ATO COMBINED WITH ATRA VERSUS STANDARD AIDA REGIMEN FOR PATIENTS WITH NEWLY DIAGNOSED, HIGH-RISK ACUTE PROMYELOCYTIC LEUKEMIA

Plenary Session – Abst #S102

Uwe Platzbecker, Lionel Adès, Pau Montesinos, Emanuele Ammatuna, Pierre Fenaux, Claudia Baldus, Céline Berthon, Monica Bocchia, Caroline Bonmati, Erika Borlenghi, Martin Bornhauser, Diana Carp, Sylvain Chantepie, Fatiha Chermat, Fabio Ciceri, Enrico Crea, Hartmut Döhner, Gerhard Ehninger, Jordi Esteve Reyner, Jamilé Frayfer, Gianluca Gaidano, Ana Garrido Diaz, Cristina Gil, Livia Gorreo Renzulli, Anna Franziska Hamm, Maël Heiblig, Daniela Heidenreich, Madlen Jentzsch, Alwin Johannes Krämer, Marie-Pierre Ledoux, Valentina Mancini, Klaus Metzeler, Maria Cristina Miggiano, Carsten Müller-Tidow, Dietger Niederwieser, Pierre Peterlin, Kathrin Rieger, Christoph Röllig, Giovanni Rossi, Miguel A Sanz, Hubert Serve, Maaike Sohne, Karsten Spiekermann, Emmanuelle Tavernier-Tardy, Christian Thiede, Susana Vives Polo, Wichard Vogel, Michaela Weier, Patrizia Zappasodi, Pauline Ziller-Walter, Sven Zukunft, Francesco Lo Coco, Maria Teresa Voso

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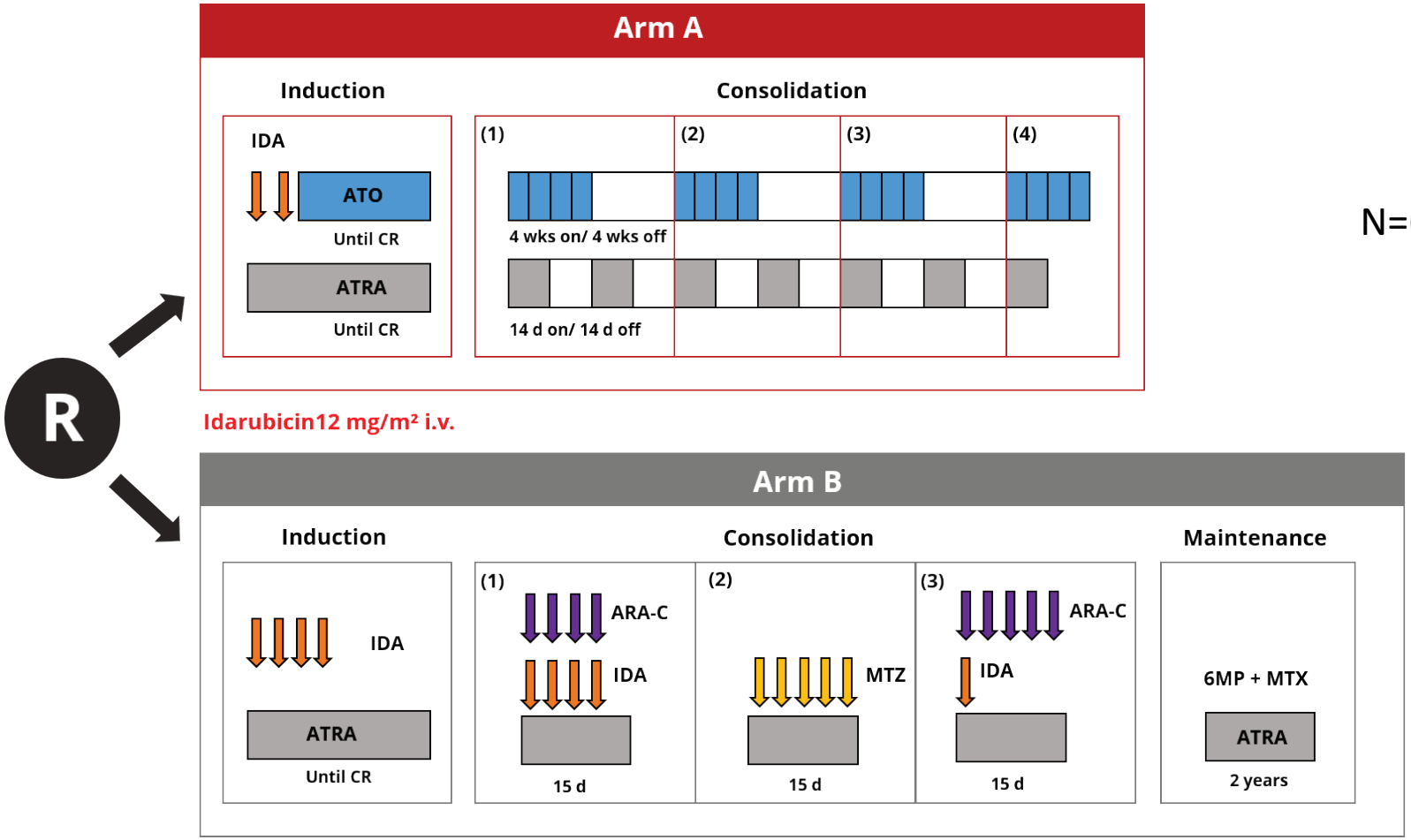
APOLLO – Treatment



N=68

N=63

Sanz et al. Blood 2019

Endpoints

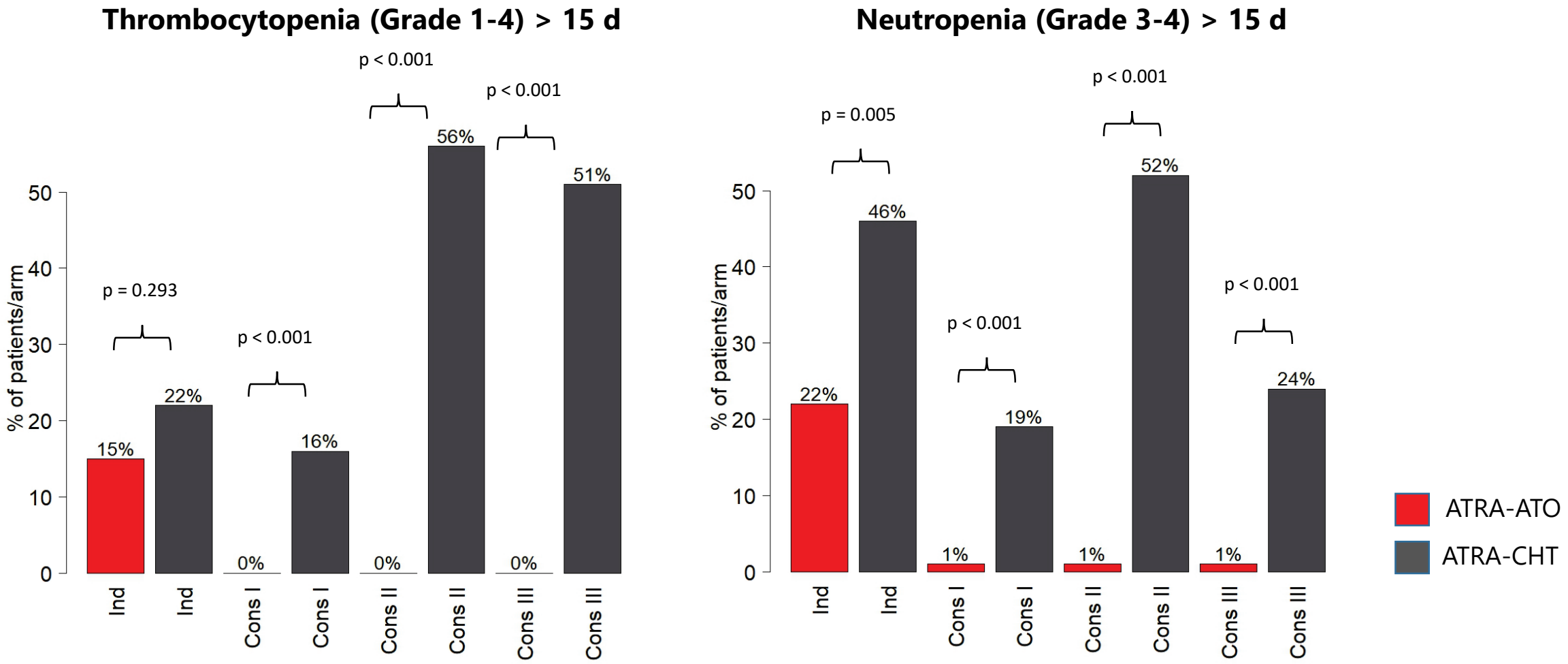
EFS at 2 years with:

- No CR after induction
- No molecular remission after consolidation
- Relapse (molecula/hematological)
- Death (including early death)
- Development of secondary MDS or leukemia

APOLLO – Patient Characteristics

Value		ATRA-ATO (n = 68)	ATRA-CHT (n = 63)	Total (n = 131)	P value
Age years	Median Range	46.5 18 – 66	44.0 18 - 65	46.0 18 - 66	0.910
Sex n (%)	Female Male	34 (50.0 %) 34 (50.0 %)	29 (46.0 %) 34 (54.0 %)	63 (48.1 %) 68 (51.9 %)	0.650
WBC, $x10^9/L$	Median Range	33.450 10.41 – 489.0	36.410 10.12 – 339.0	35.705 10.12 – 489.0	0.866
ECOG	Median Range	1 0 - 3	1 0 - 3	1 0 - 3	0.381

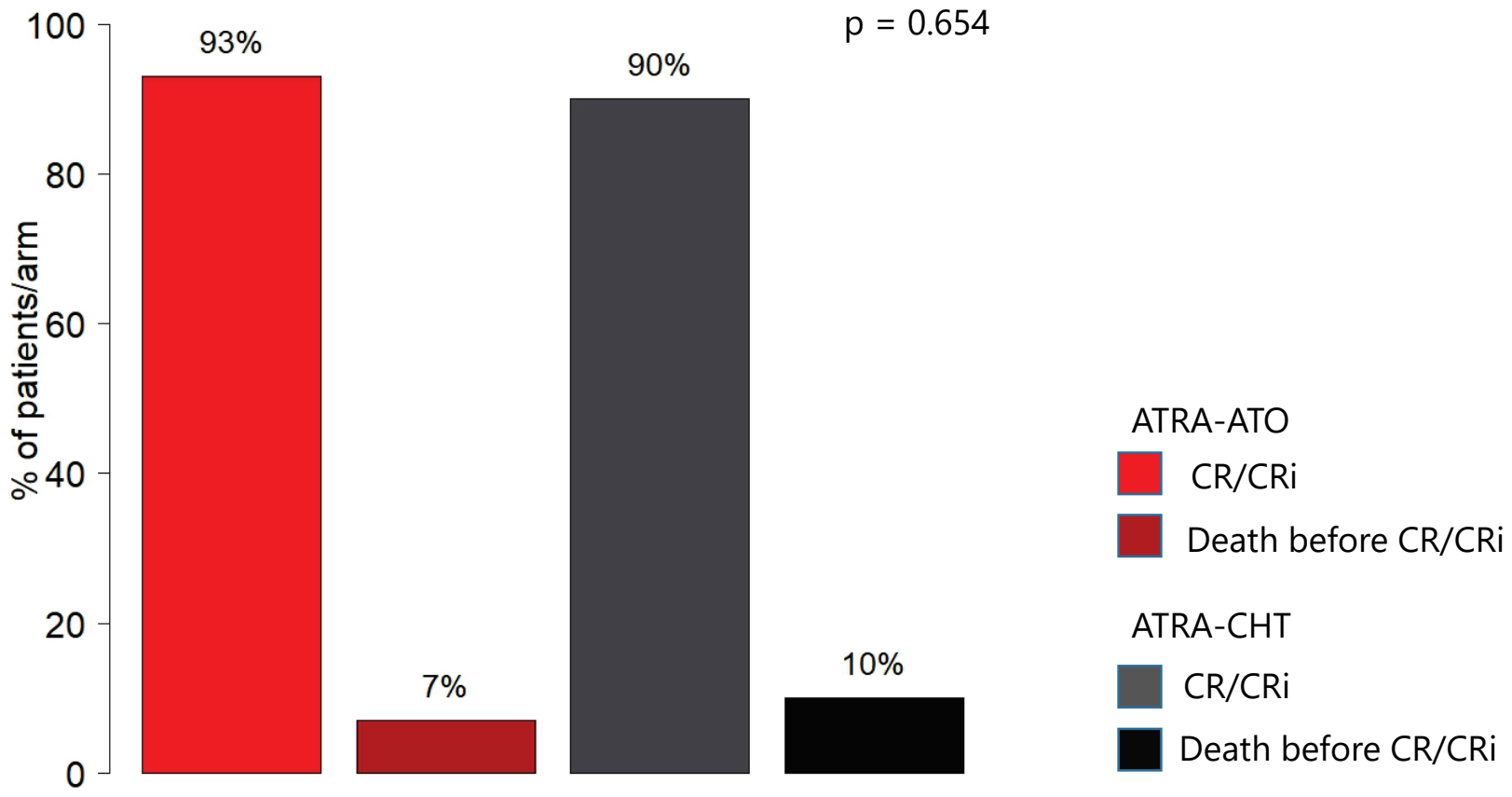
APOLLO – Hematologic Toxicity



APOLLO – Other Toxicities

Toxicity	ATRA-ATO	ATRA-CHT	P value
QTC prolongation (Grade 3 – 4); %	4.4	0	-
Hepatic toxicity (Grade 3 – 4); %	11.8	14.3	0.8
Differentiation syndrome; %	1.5	4.8	0.27

APOLLO – Induction Outcome

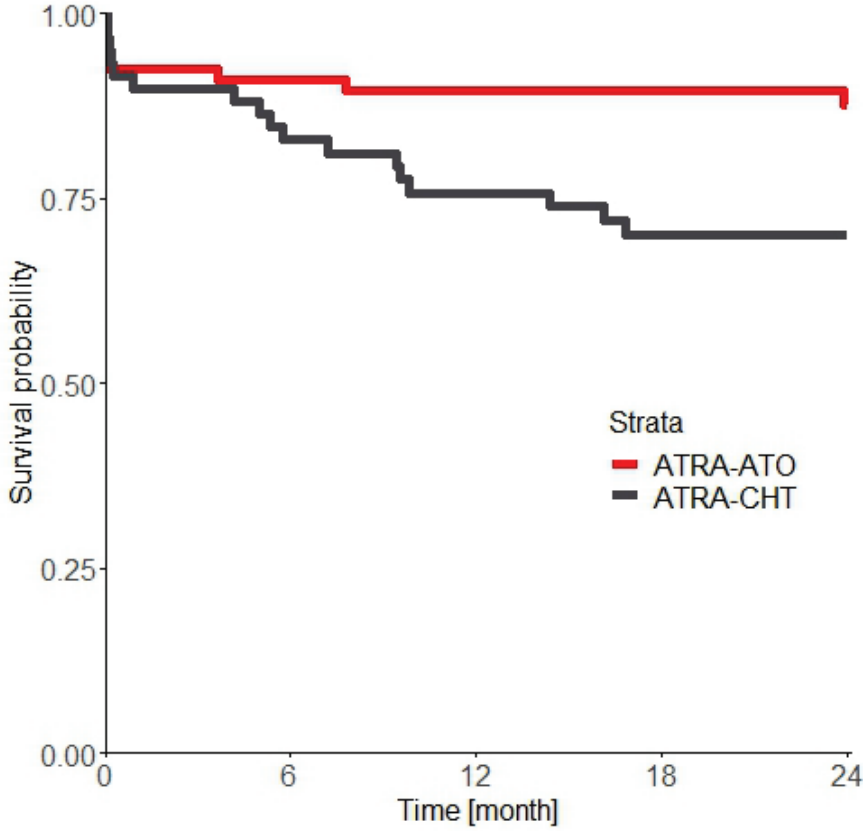


APOLLO – Molecular resistance

Therapy	Molecular resistance		P value
ATRA-ATO	1.7%	1/60	0.268
ATRA-CHT	5.5%	3/55	

No achievement of molecular remission after the last consolidation course

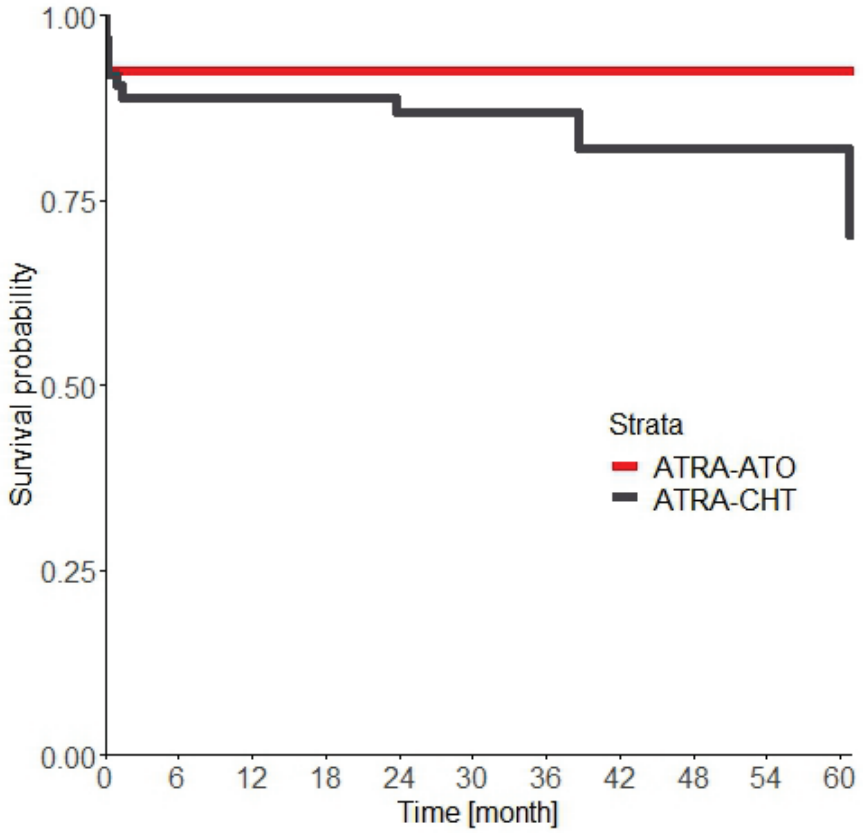
APOLLO – Event-free Survival



Therapy	2-year survival	95% cofidence interval	P value
ATRA-ATO	88%	80% – 96%	0.02
ATRA-CHT	70%	59% - 83%	

Main factors for the significantly better EFS are incidence of molecular relapse and molecular resistance.

APOLLO – Overall Survival



Therapy	2-year survival	95% cofidence interval	P value
ATRA-ATO	93%	87% – 99%	0.17
ATRA-CHT	87%	78% - 96%	

APOLLO – Conclusion

- **First-line therapy ATRA-ATO with superior EFS compared to conventional ATRA-CHT in patients with HR-APL**
- **Shorter Treatment**
- **Less toxic**
- Further analysis of the APOLLO trial may support the implementation of this regimen as the **new standard of care in patients with HR-APL**.

Kapitel 3

Erstlinientherapie des HR-MDS – zwei negative Phase III Studien

PRIMARY RESULTS OF THE PHASE III STIMULUS-MDS2 STUDY OF SABATOLIMAB + AZACITIDINE VS PLACEBO + AZACITIDINE AS FRONTLINE THERAPY FOR PATIENTS WITH HIGHER-RISK MDS OR CMML-2

Abst #S180

Amer M. Zeidan, Zhijian Xiao, Guillermo Sanz, Aristoteles Giagounidis, Mikkael A. Sekeres, Zhentang Lao, Dries Deeren, Sujun Gao, Marta Riva, Je-Hwan LEE, Fei Ma, Alexandre Weiller, Marlies Van Hoef, Hans D. Menssen, Valeria Santini

MAGROLIMAB (MAGRO) + AZACITIDINE (AZA) VS PLACEBO (PBO) + AZA IN PATIENTS (PTS) WITH UNTREATED HIGHER-RISK (HR) MYELODYSPLASTIC SYNDROMES (MDS): PHASE 3 ENHANCE STUDY FINAL ANALYSIS

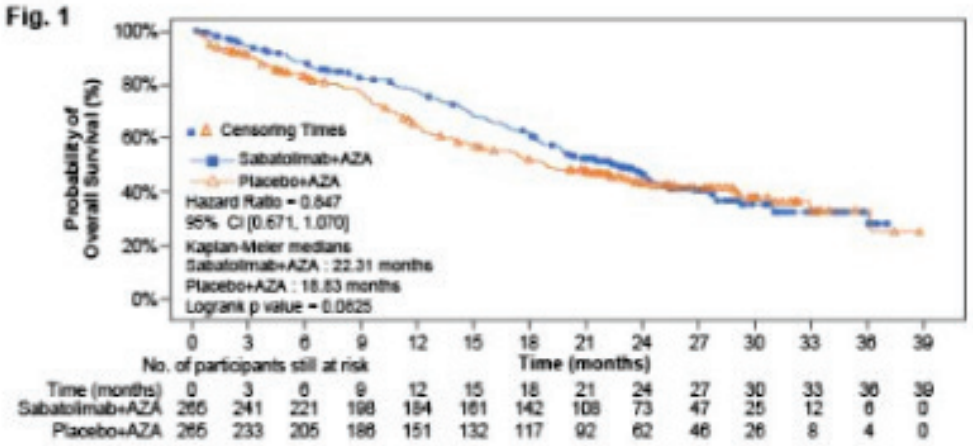
Abst #S181

David Sallman, Guillermo Garcia-Manero, Naval Daver, Camille Abboud, Eytan Stein, Karilyn Larkin, Anna B. Halpern, Shannon McCurdy, Monzr Al Malki, Guru Subramanian Guru Murthy, Lewis R. Silverman, Richard Larson, Peter Greenberg, Ivana Gojo, Tomasz Wróbel, Uwe Platzbecker, Cecily Forsyth, Pankit Vachhani, Mei Dong, Jiang Shao, Anderson Tan, Parul Doshi, Paresh Vyas, Andrew Wei

STIMULUS-MDS2 (NCT04266301)

STIMULUS-MDS2 (NCT04266301) is a randomized, double-blind, PBO-controlled, Ph III trial that evaluated SABA+azacitidine (AZA) as frontline therapy in pts with higher-risk (I-, H- or vH) MDS or chronic myelomonocytic leukemia (CMML)-2.

- Sabatolimab (MBG453, SABA) is an immunotherapy targeting TIM-3, an immuno-myeloid regulator expressed on immune and leukemic stem cells.
- 530 pts were randomized (265 in each arm), median age was 71.0 years
- Primary endpoint OS not met



ENHANCE (NCT04313881)

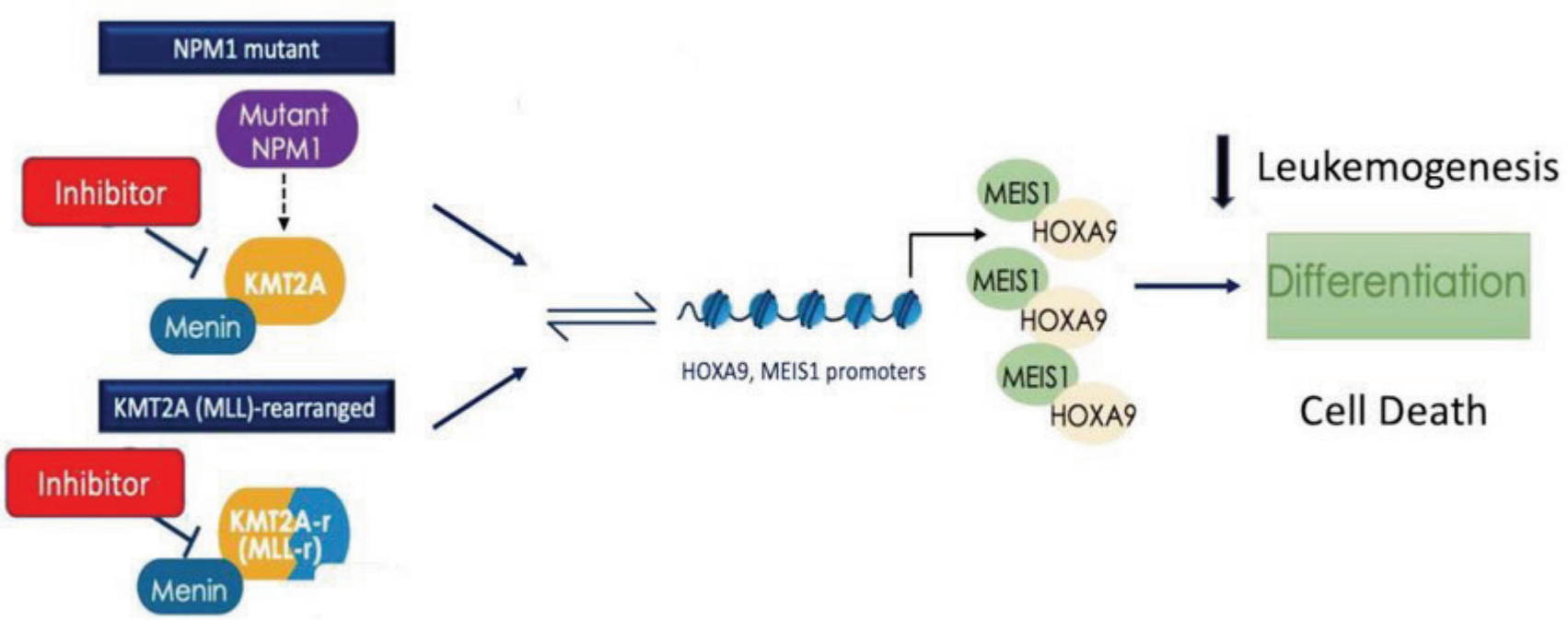
To evaluate the efficacy and safety of Magro+AZA vs PBO+AZA in pts with frontline HR-MDS in the randomized, double-blind, multicenter, phase 3 ENHANCE (NCT04313881) study.

- Magrolimab is a first-in-class monoclonal antibody that blocks CD47, an antiphagocytic signal overexpressed on cancer cells
- 539 pts were randomized into Magro+AZA (n=268) or PBO+AZA (n=271) arms
- Primary endpoints CRR and OS not met + inacceptable toxicity
- The study was discontinued due to futility at a prespecified interim analysis. Additional efficacy subgroup analyses will be presented.
- Findings highlight challenges of developing anti-CD47 therapies and other new treatments in HR-MDS.

Kapitel 4

Menin Inhibitoren – Ein Ausblick für die akuten Leukämien

Mode of action of Menin Inhibitors



Mahesh et al Cancer J 2022
doi: 10.1097/PPO.0000000000000571.

Challenges

- significant cardiac toxicities (QTc prolongation)
- sensitivity to cytochrome P450 inhibition
- acquired somatic mutations in MEN1 gene in patients with prolonged monotherapy menin inhibitor treatment (> 2 months)
- potential for differentiation syndrome

Take-Home-Messages

- Phase III CML-CP; ASC4FIRST: Ascimenib meets both endpoints against 2GN TKI/IMA
- Phase III APL; APOLLO: ATRA-ATO shows superior EFS in HR-APL against AIDA protocol
- Phase III HR-MDS: Vidaza still standard (2 negative trials)
- Menin inhibitors on the horizon to treat KMT2Ar and NPM1mut

Die Kurzpräsentationen sind online unter

www.lymphome.de/eha2024

Für den Inhalt verantwortlich:

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Uniklinik Köln

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

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