Gemeinschaftsklinikum Mittelrhein

Post ASH 2023

AML

&

Hodgkin-Lymphom

Dirk Niemann

65TH ASH ANNUAL MEETING AND EXPOSITION

Offenlegung potentieller Interessenkonflikte

1. Anstellungsverhältnis

Gemeinschaftsklinikum Mittelrhein, Koblenz

2. Beratungstätigkeit

keine

3. Aktienbesitz

keiner

4. Honorare

Advisory Boards: Novartis, Roche

5. Kongress-/Fortbildungsunterstützung

Amgen, Novartis, Janssen, Jazz, Roche, Celgene

6. Gutachtertätigkeit

keine

7. Andere finanzielle Beziehungen

keine

AML
#969
Venetoclax kombiniert mit Daunorubicin und Cytarabin (2 + 6) in AML

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide

Venetoclax combined with daunorubicin and cytarabine (2 + 6) in Acute Myeloid Leukemia: Updated Results of a Phase II Trial

Xiaohui Suo[1#], Dongmei Wang[2#], Fang Zheng[3#], Suping Zhang[4#], Congcong Zhang[1], Yinling Li[1], Rui Shi[2], Yan Wu[2], Sisi Yang[3], Xuemei Zhao[3], Liyun Zhao[5], Zongjiu Jiao[5], Jiaojie Song[5], Jie Liu[6], Ling Zhang[6], Ling Li[7], Zhihua Zhang[8], Xinxiao Lu[9], Linyu Yuan[9], Sifeng Gao[10], Jilei Zhang[10] ,Xingli Zhao[9*], Guanchen Bai[10*], Kaiqi Liu[11*], Yingchang Mi[11*]

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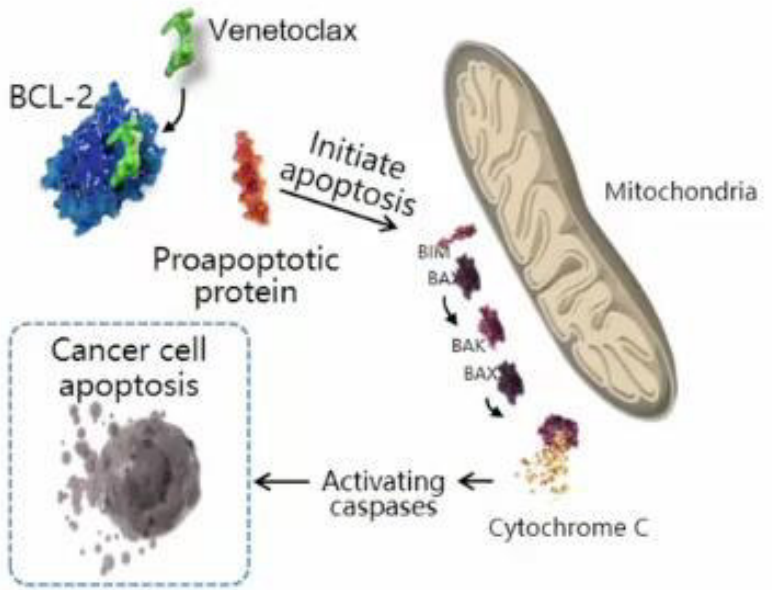
AML
#969
Hintergrund

- **Venetoclax**:
  - Oraler BCL-2-Inhibitor, bindet selektiv an BCL-2, um
  - Proapoptotische Proteine freizusetzen

- **Multicenter, einarmige Phase-2-Studie**
  - Zur Untersuchung der Sicherheit und Effektivität von Venetoclax in Kombination mit DA (2+6)
    in der Induktionstherapie bei neu diagnstizierter AML



Cancer Res. 2016 October 15; 76(20): 5914–5920.

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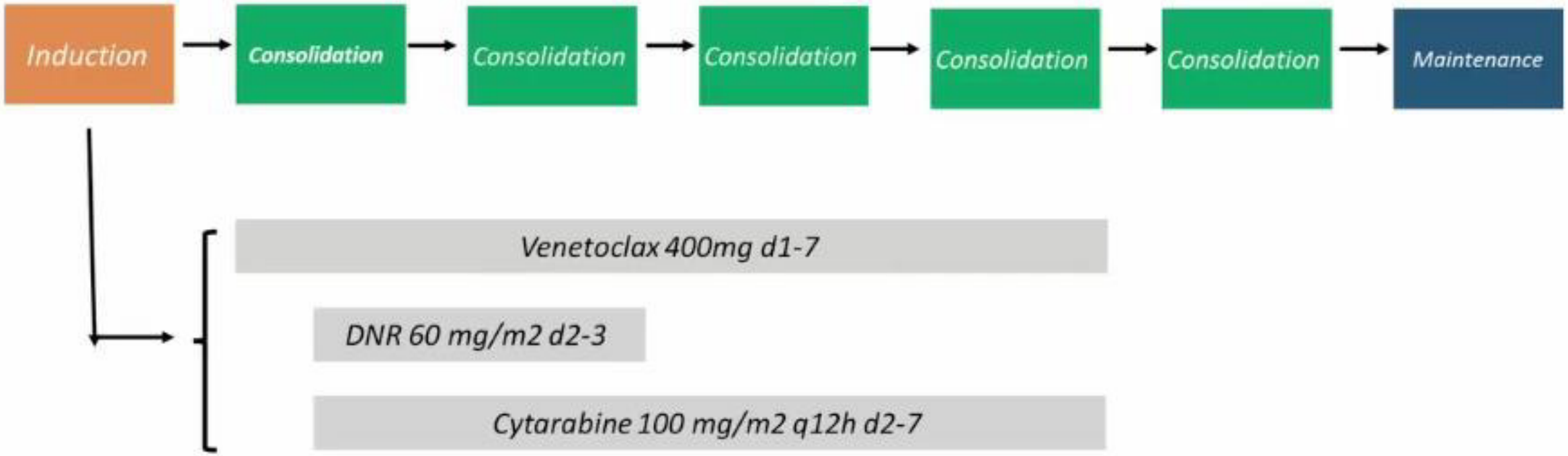
Studiendesign



- White cell counts, hydroxyurea and cytarabine were permitted for cytoreduction before induction therapy to decrease the possibility of tumor lysis syndrome until the white cell count (WBC) was≤30× 109 /L.
- Patients receiving potent CYP3A inhibitors, such as voriconazole and posaconazole, Ven reduced to 100mg.

Exp Hematol Oncol. 2023 May 12;12(1):45.

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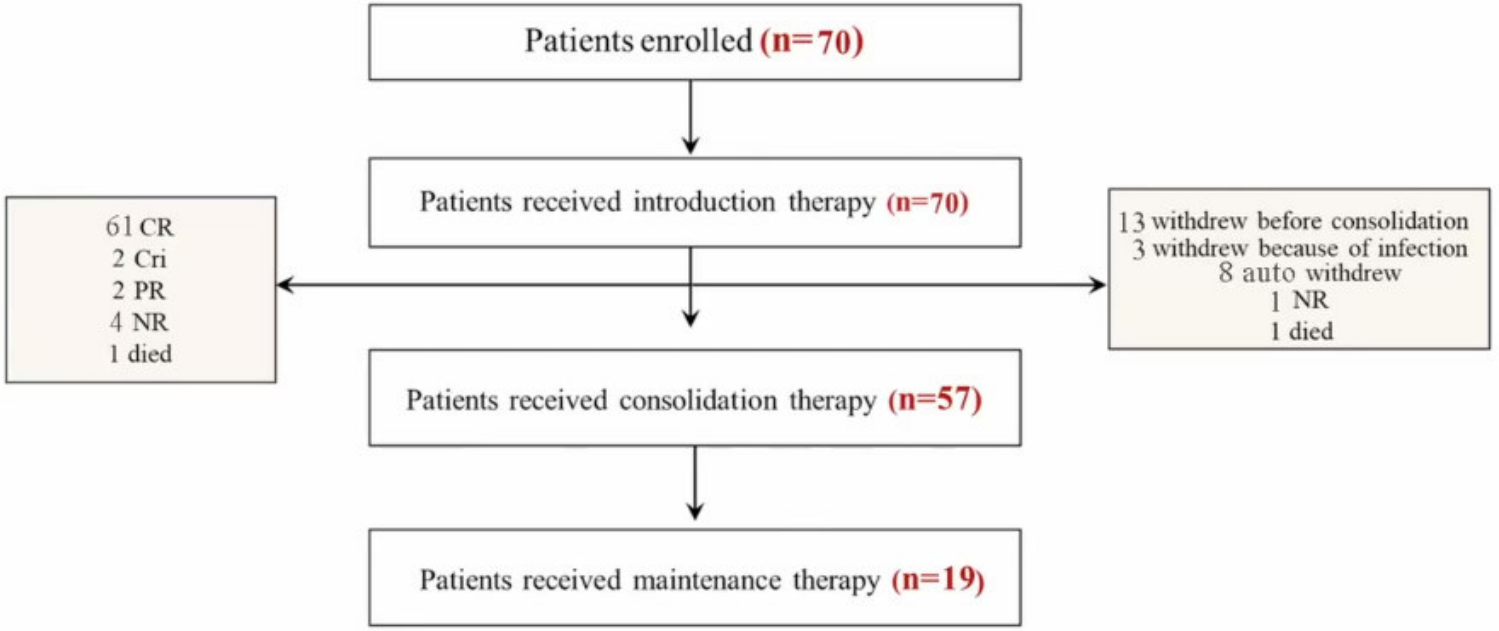
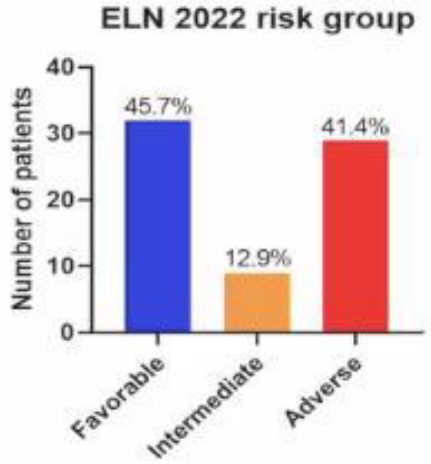
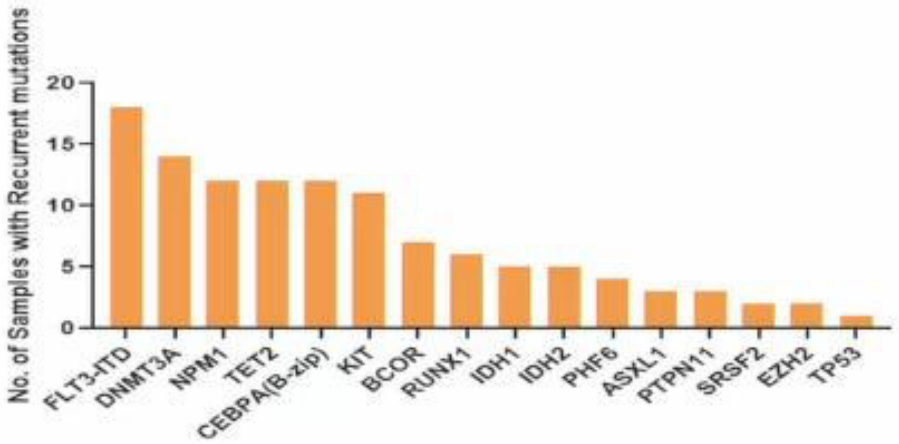
Flowchart und Patientencharakteristika







Medianes Alter	44 (16 – 61)
Männer	37 (52,9%)
Frauen	33 (47,1)

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Ergebnisse nach Induktion

	Overall(n=70)	Favorable risk(n=32) *	Intermediate risk(n=9) *	Adverse risk(n=29) *
Overall response rate (CR+CRi+PR)	92.9% (65/70)	96.0% (31/32)	77.8% (7/9)	93.1% (27/29)
composite complete remission rate	90.0% (63/70)	96.0% (31/32)	77.8% (7/9)	86.2% (25/29)
CR	87.1% (61/70)	96.0% (31/32)	77.8% (7/9)	79.3% (23/29)
CRi	2.9% (2/70)	0	0	6.9% (2/29)
PR	2.9% (2/70)	0	0	6.9% (2/29)
Died	1.4% (1/70)	0	0	3.4% (1/29)
MRD (-) after induction by flow cytometry		89.5% (51/57)		
Responders that received allo-HSCT		6/69 (8.7%)		
Time to blood cell count recovery after induction, days				
Time to absolute neutrophil count $\geq 0.5\times10^9$/L, days	13 (5-36)			
Time to absolute platelet count $\geq 30\times10^9$/L, days	13 (8-48)			
Evenfreesurvival,				
Median, months	NR	NR	NR	NR
12-month, %(95% CI)	81.0%			
Overall survival				
Median, months	NR	NR	NR	NR
12-month, %(95% CI)	84.9%			

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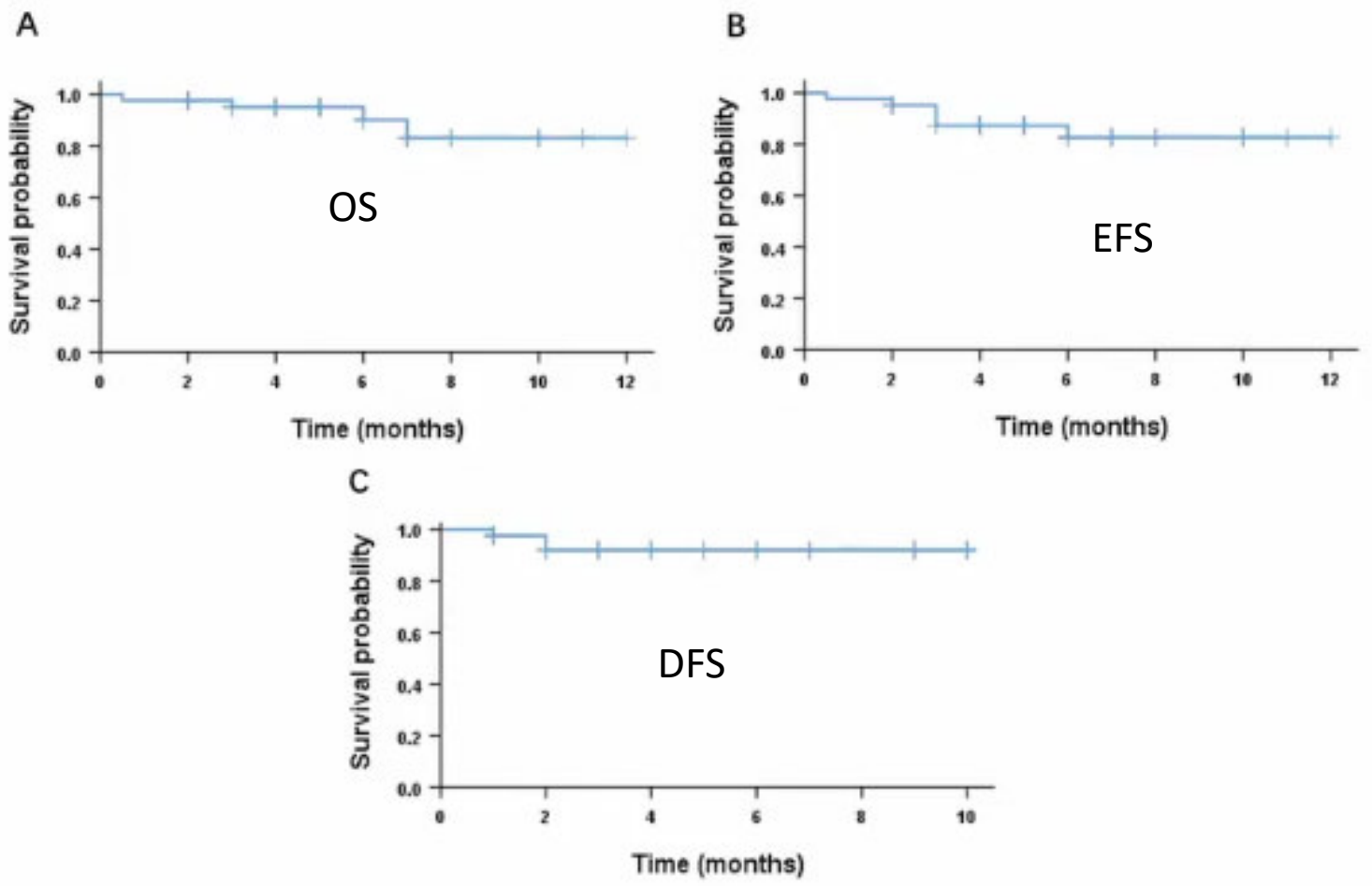
OS, EFS & DFS



Medianes Folow up 9 Monate (1 – 18)

6 Pat. mit Allo-HSCT

12 Monate OS	84,9%	(A)
12-Monate EFS	81,0%	(B)
12-Monate DFS	81,6%	(C)

AML
#833
Decitabine/Cedarudizine plus Venetoclax in AML

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Abstract #833

A Phase 2 Study of the Fully Oral Combination of ASTX727 (Decitabine/Cedazuridine) Plus Venetoclax for Older and/or Unfit Patients with Acute Myeloid Leukemia

Alexandre Bazinet, Guillermo Garcia-Manero, Nicholas J. Short, Yesid Alvarado, Alex Bataller, Tareq Abuasab, Rabiul Islam, Kathryn Montalbano, Ghayas Issa, Abhishek Maiti, Musa Yilmaz, Nitin Jain, Lucia Masarova, Steven Kornblau, Elias Jabbour, Guillermo Montalban-Bravo, Sherry Pierce, Courtney D. DiNardo, **Tapan Kadia**, Naval Daver, Marina Konopleva, Hagop Kantarjian, Farhad Ravandi

Department of Leukemia

University of Texas MD Anderson Cancer Center

65th ASH Annual Meeting and Exposition. San Diego, California. December 11th, 2023.

AML
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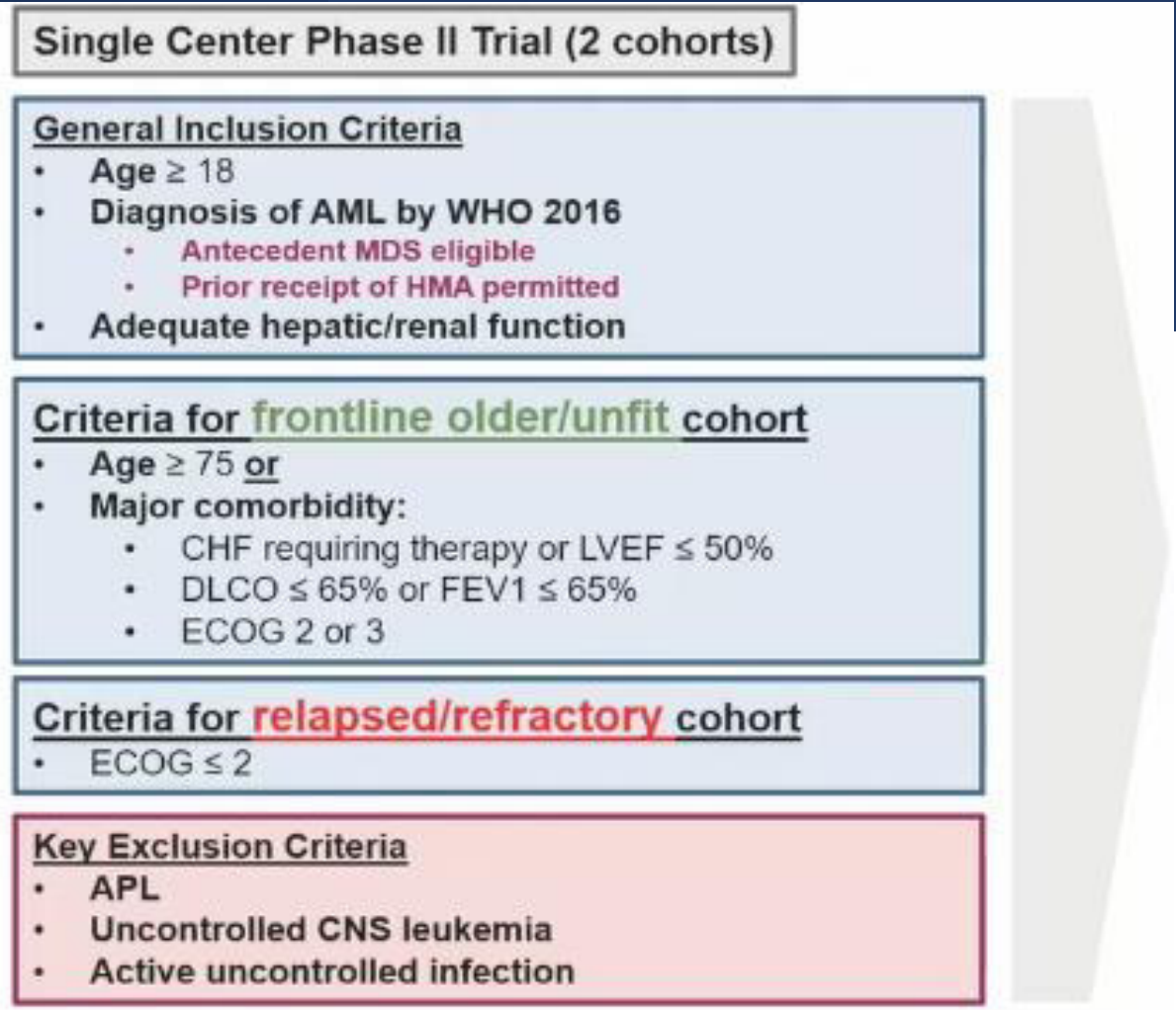
Rationale & Studiendesign

- AML Erkrankung der Älteren
  - Komorbiditäten, geringere physiolog. Reserven
  - Höhere Inzidenz von Hochrisiken
  - Keine Kandidaten für Intensive Therapien oder Allo-PBSCT

- VIALE A-Studie
  - Azacitidine + Venetoclax als Standard in AML für ältere/nicht fitte Patienten

- ASTX727 (Decitabine/Cedazuridine)
  - Äquivalente, orale Formulierung für i.v. Decitabine

- Phase II-Studie zur Evaluation von Effektivität und Sicherheit einer komplett oralen Kombination aus ASTX727 und Venetoclax in älteren/nicht fitten Patienten mit AML



- Primärer Endpunkt: Overall response rate
- Sek. Endpunkte
  - Overall Survival (OS)
  - Relapse free survival (RFS)
  - Duration of response (DOR)
  - Safety

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Therapieplan

28-day cycles, up to 24 cycles)

INDUCTION

- **ASTX727** 35/100 mg PO on **D1-5**
- **Venetoclax:**
  - Adjusted for concomitant CYP3A4 inhibitors
  - 100 mg PO on D1, 200 mg on D2, 400 mg on **D3-28**
  - **Held on D21** if blast clearance in bone marrow)

CONSOLIDATION

- **ASTX727** 35/100 mg PO on **D1-5**
  - Dose reduction to **D1-3** permitted for toxicity
- **Venetoclax** 400 mg on **D1-21**
  - Dose reduction to **D1-14** days permitted for toxicity

Antibacterial, mold-active antifungal, and antiviral prophylaxis provided.

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Patientencharakteristika

n (%) or median [range]	Frontline Cohort (n=49)	Relapsed/Refractory Cohort (n=13)
Age	80 [50-92]	72 [46-82]
ECOG Performance Status		
0-1	27 (55)	8 (62)
2+	22 (45)	5 (38)
Cytogenetics		
Normal	17 (35)	4 (31)
Other intermediate	12 (24)	2 (15)
11q23-rearranged	2 (4)	2 (15)
inv(3)/t(3;3)	2 (4)	0 (0)
-5/5q-	9 (18)	4 (31)
-7/7q-	9 (18)	2 (15)
-17/17p-	4 (8)	2 (15)
Complex	12 (24)	6 (46)
ELN 2022 risk		
Favorable	7 (14)	0 (0)
Intermediate	3 (6)	4 (31)
Adverse	39 (80)	9 (69)
Prognostic Risk Signature[1]		
Higher benefit	28 (57)	8 (62)
Intermediate benefit (*FLT3*-ITD/*RAS*)	13 (27)	2 (15)
Lower benefit (*TP53*)	8 (16)	3 (23)
Prior MDS/MPN, untreated	11 (22)	1 (8)
Prior MDS/MPN, treated	10 (20)	2 (15)
Therapy-related AML	7 (14)	3 (23)

1. Döhner, H, et al. ELN Risk Stratification Is Not Predictive of Outcomes for Treatment-Naïve Patients with Acute Myeloid Leukemia Treated with Venetoclax and Azacitidine. ASH 2022.

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Ergebnisse

Median follow-up time: 18.3 months

n (%) or median [range]	Frontline Cohort (n=47)	Relapsed/Refractory Cohort (n=13)
ORR	**30 (64)**	**6 (46)**
CR	16 (34)	4 (31)
CRi	11 (23)	2 (15)
PR	0 (0)	0 (0)
MLFS	3 (6)	0 (0)
CRc (CR + CRi)	**27 (57)** (Viale A: 66%)	**6 (46)**
MRD-negative (MFC)	12/27 (44)	1/5 (20)
Cycles given	3 [1-16]	3 [1-10]
Cycles to first response	1 [1-4]	1 [1-2]
Cycles to best response	1 [1-7]	2 [1-6]
4-week mortality	**5 (11)**	0 (0)
8-week mortality	**8 (17)**	0 (0)

Rate of transition to SCT: 5% (3/62)

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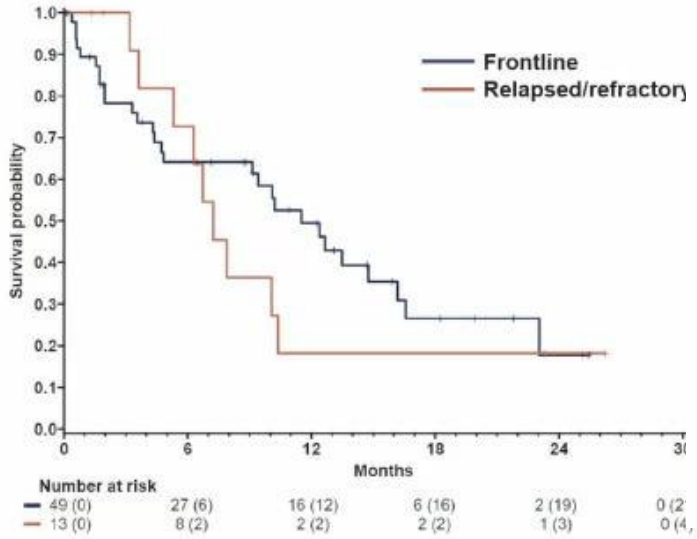
OS,RFS, DOR

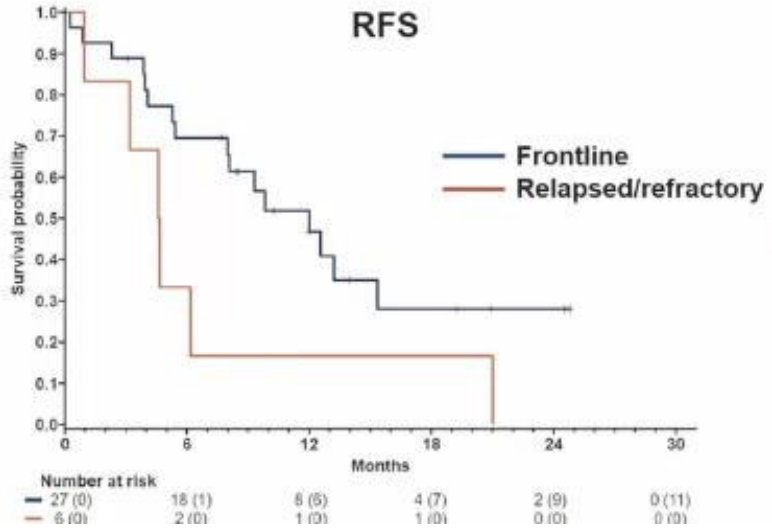
OS: Defined as enrollment to death
Median follow-up time: 18.3 months



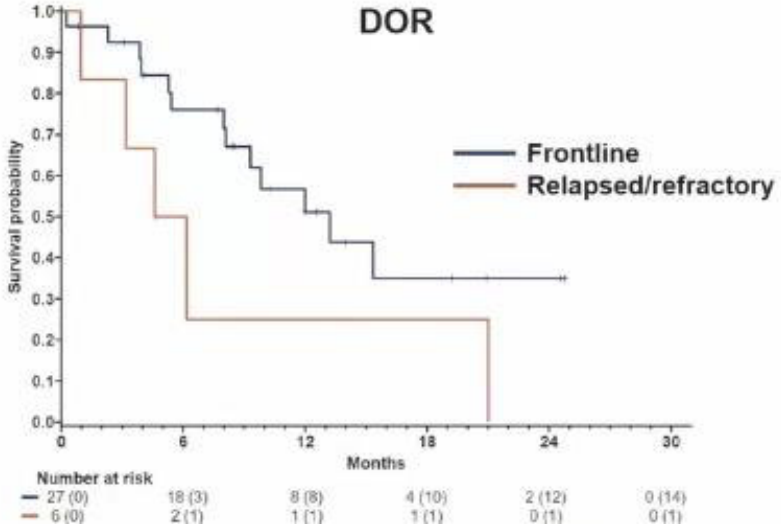
	N	Median OS	1-year
Frontline	49	13,5 months	49.5%
Relapsed/refractory	13	7.2 months	18.2%

Viale A: 14,7 months

RFS: Defined as response to relapse or death; **DOR:** Defined as response to relapse
Median follow-up time: 18.3 months



	N	Median RFS	1-year
Frontline	27	12.0 months	46.7%
Relapsed/refractory	6	4.6 months	16.7%



	N	Median DOR	1-year
Frontline	27	13.2 months	51.0%
Relapsed/refractory	6	5.4 months	25.0%

AML
833
Nebenwirkungen

Non-infectious TEAEs

Adverse Event	Grade 1-2	Grade 3-5	Any
Constipation	14 (23)	0	14 (23)
Oral mucositis	12 (19)	2 (3)	14 (23)
Diarrhea	9 (15)	1 (2)	10 (16)
Nausea	10 (16)	0	10 (16)
Headache	8 (13)	0	8 (13)
ALT increased	5 (8)	2 (3)	7 (11)
Fatigue	3 (5)	2 (3)	5 (8)
Respiratory failure	0	5 (8)	5 (8)
Thromboembolic event	2 (3)	3 (5)	5 (8)
Abdominal pain	3 (5)	1 (2)	4 (6)
Anorexia	3 (5)	1 (2)	4 (6)
Altered mental status	1 (2)	2 (3)	3 (5)
Dyspnea	2 (3)	1 (2)	3 (5)
Leukocytosis	0	3 (5)	3 (5)
Neutrophil count decreased	0	3 (5)	3 (5)
Platelet count decreased	0	3 (5)	3 (5)

TEAEs occurring in ≥ 5% of patients shown.
Data displayed as n (%)

Infectious TEAEs

	Grade 1-2	Grade 3-5	Any
Febrile neutropenia	0	11 (18)	11 (18)
Pneumonia	0	8 (13)	8 (13)
Bacteremia	1 (2)	4 (6)	5 (8)
Sepsis	0	4 (6)	4 (6)
Cellulitis	0	2 (3)	2 (3)
Sinusitis	0	2 (3)	2 (3)
Urinary tract infection	0	2 (3)	2 (3)
Other infectious	0	4 (6)	4 (6)

Data displayed as n (%)

- **37%** of patients experienced at least one infectious TEAE
- **Most common grade ≥ 3:**
  - Febrile neutropenia (18%)
  - Pneumonia (13%)
  - Respiratory failure (8%)
  - Bacteremia (6%)
  - Sepsis (6%)
- Four **grade 5 TEAEs** occurred
  - 1 Respiratory failure (in CR)
  - 1 Cerebral hemorrhage (non-responder)
  - 1 Gastrointestinal hemorrhage (in CRi without platelet recovery)
  - 1 Sepsis (in CR)

AML
LBA-5

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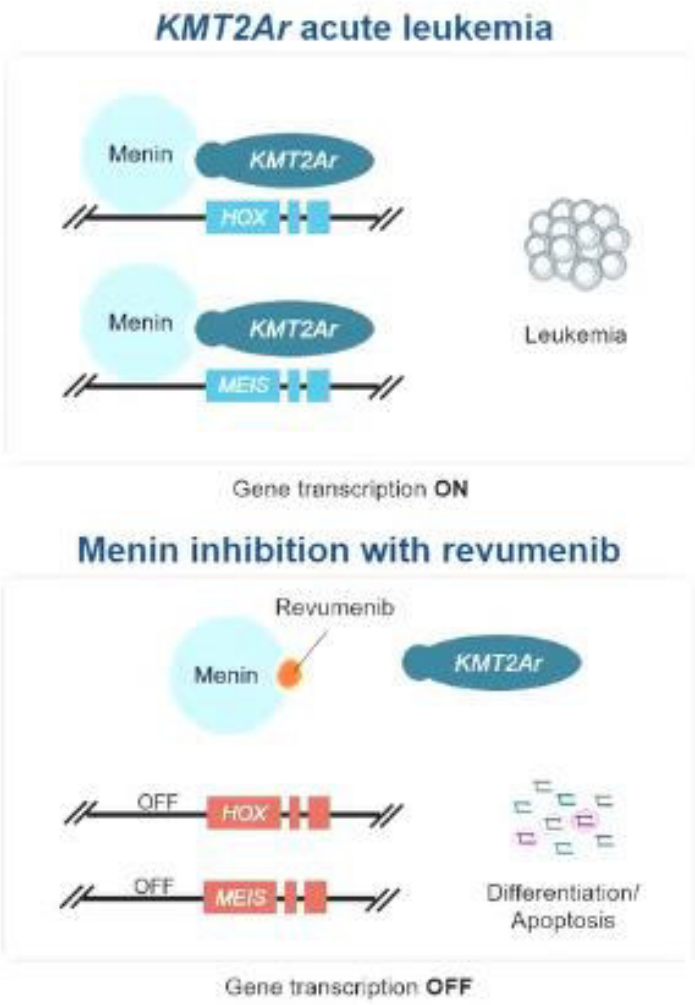
Revumenib Monotherapy in Patients with Relapsed/Refractory *KMT2Ar* Acute Leukemia: Topline Efficacy and Safety Results from the Pivotal AUGMENT-101 Phase 2 Study

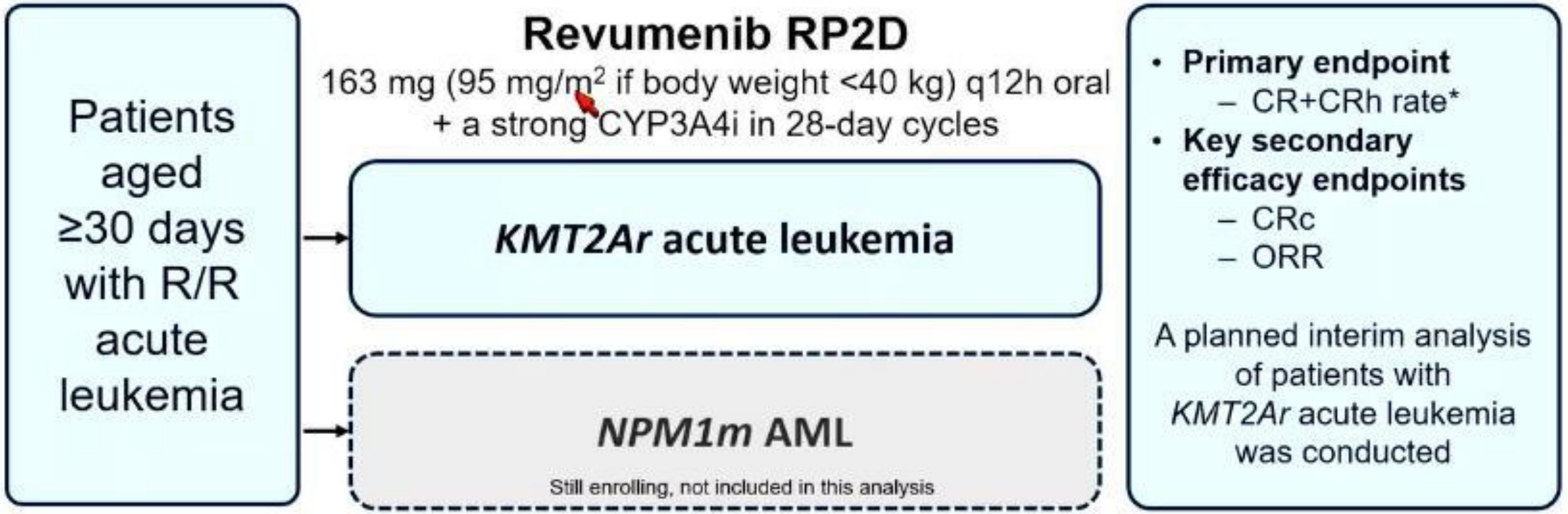
Ibrahim Aldoss, Ghayas C. Issa, Michael Thirman, John DiPersio, Martha Arellano, James S. Blachly, Gabriel N. Mannis, Alexander Perl, David S. Dickens, Christine M. McMahon, Elie Traer, C. Michel Zwaan, Carolyn Grove, Richard Stone, Paul J. Shami, Ioannis Mantzaris, Matthew Greenwood, Neerav Shukla, Branko Cuglievan, Yu Gu, Rebecca G. Bagley, Kate Madigan, Soujanya Sunkaraneni, Huy Van Nguyen, Nicole McNeer, Eytan M. Stein

AML
LBA-5
KMT2Ar & Revunemib

- KMT2Ar starker leukämische Treiber
  Histon-Lysin-N-Methyltransferase 2A-Rearrangements
- In 10% aller AL-Fälle
- Schlechte Prognose nach Rezidiv
- NPM1-Mut. Bei ca. 30% der AML-Fälle
- Bislang keine zugelassenen bei
  KMT2Ar-Rearrangements
- Menin-KMT2A-Interaktion
  Schlüssel-Treiber der Leukämogenese
- Positive Effekte von Revumenib bei
  r/r KMT2Ar u. NPM1m AL



AML
LBA-5
Studiendesign
AUGMENT-101 Phase 2



*CR+CRh rate >10% in adult evaluable population considered lower efficacy bound

AML, acute myeloid leukemia; CR, complete remission; CRc, CR composite (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; CYP3A4i, cytochrome P450 3A4 inhibitor; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; *NPM1m*, nucleophosmin 1-

AML
LBA-5
Patientencharakteristika

Parameter	Efficacy population (n=57)	Safety population (n=94)[a]
Leukemia type, n (%)		
AML	49 (86)	78 (83)
ALL	7 (12)	14 (15)
MPAL/Other	1 (2)	2 (2)
Co-mutations[b], n (%)		
FLT3	5 (9)	7 (7)
RAS	9 (16)	12 (13)
p53	4 (7)	5 (5)
Primary refractory, n (%)	14 (25)	18 (19)
Number of prior lines of therapy, median (range)	2 (1–11)	2 (1–11)
1, n (%)	17 (30)	25 (27)
2, n (%)	14 (25)	28 (30)
>3, n (%)	26 (46)	41 (44)
Prior venetoclax, n (%)	41 (72)	61 (65)
Prior HSCT, n (%)	26 (46)	47 (50)

Data cutoff: July 24, 2023. [a]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib. [b]In patients that had co-mutation status reported.

Parameter	Efficacy population (n=57)	Safety population (n=94)[a]
Median age, y (range)	34.0 (1.3–75)	37.0 (1.3–75)
Age <18 y, n (%)	13 (23)	23 (25)
Age ≥18 y, n (%)	44 (77)	71 (76)
Sex, n (%)		
Female	33 (58)	56 (60)
Race, n (%)		
White	43 (75)	68 (72)
Non-White	10 (18)	14 (15)
Unknown	4 (7)	12 (13)

Data cutoff: July 24, 2023. [a]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib.

AML
LBA-5
Ergebnisse

Parameter	Efficacy population (n=57)
ORR, n (%)	**36 (63)**
CR+CRh rate, n (%)	13 (23)
95% CI	12.7–35.8
P value, 1-sided	0.0036
CRc	25 (44)
95% CI	30.7–57.6
Negative MRD status[a]	
CR+CRh	7/10 (70)
CRc	15/22 (68)

Parameter	Efficacy population (n=57)
Best response, n (%)	
CR	10 (18)
CRh	3 (5)
CRi	1 (1.8)
CRp	11 (19)
MLFS	10 (18)
PR	1 (1.8)
PD	4 (7)
No response	14 (25)
Other[b]	3 (5)

Data cutoff: July 24, 2023. [a]MRD done locally; not all patients had MRD status reported. [b]Includes patients without postbaseline disease assessment.

CR, complete remission; CRc, composite CR (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphological leukemia-free state; MRD, minimal residual disease; ORR, overall response rate (CRc+MLFS+PR); PD, progressive disease; PR, partial remission.

AML
LBA-5
Nebenwirkungen

Any grade TEAEs that occurred in ≥25% patients

All terms, n (%)	Safety population (n=94)[a]
Nausea	42 (45)
Febrile neutropenia	36 (38)
Diarrhea	33 (35)
Vomiting	29 (31)
Differentiation syndrome	26 (28)
Hypokalemia	26 (28)
Epistaxis	25 (27)
QTc prolongation	24 (26)

Grade ≥3 TEAEs that occurred in ≥10% patients

All terms, n (%)	Safety population (n=94)[a]
Febrile neutropenia	35 (37)
Decreased neutrophil count	15 (16)
Decreased white blood cell count	15 (16)
Decreased platelet count	14 (15)
Anemia	17 (18)
Differentiation syndrome	15 (16)
QTc prolongation	13 (14)
Sepsis	11 (12)
Hypokalemia	10 (11)

Data cutoff: July 24, 2023. [a]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib.

No patients discontinued due to differentiation syndrome, QTc prolongation, or cytopenias

AML
LBA-5
Duration of Response

Parameter	Patients achieving CR+CRh (n=13)
Median duration of CR+CRh, months (95% CI)	6.4 (3.4–NR)
Proceeded to HSCT, n (%)	14/36 (39)
Proceeded to HSCT in CR or CRh	6/14 (43)
Proceeded to HSCT in MLFS or CRp	8/14 (57)
Restarted revumenib post HSCT, n (%)	7/14 (50)*

Data cutoff: July 24, 2023
*3 additional patients remained eligible to initiate revumenib after HSCT at the time of data cutoff.

CR, complete remission; CRh, CR with partial hematologic recovery; CRp, CR with incomplete platelet recovery; HSCT, hematopoietic stem cell transplant; MLFS, morphological leukemia-free state; NR, not reached.

AML
#832

Publication Number: 832

QuANTUM-First Trial: *FMS*-Like Tyrosine Kinase 3-Internal Tandem Duplication (*FLT3*-ITD)–Specific Measurable Residual Disease (MRD) Clearance Assessed Through Induction and Consolidation Is Associated with Improved Overall Survival in Newly Diagnosed *FLT3*-ITD+ AML Patients

Alexander E. Perl,[1] Harry P. Erba,[2] Pau Montesinos,[3] Radovan Vrhovac,[4] Elżbieta Patkowska,[5] Hee-Je Kim,[6] Pavel Zak,[7] Po-Nan Wang,[8] Jaime E. Connolly Rohrbach,[9] Ken C.N. Chang,[9] Li Liu,[9] Yasser Mostafa Kamel,[9] Karima Imadalou,[9] Abderrahmane Laadem,[9] Arnaud Lesegretain,[9] Jorge Cortes,[10] Mikkael A. Sekeres,[11] Hervé Dombret,[12] Sergio Amadori,[13] Jianxiang Wang,[14] Richard F. Schlenk,[15] Mark J. Levis[16]

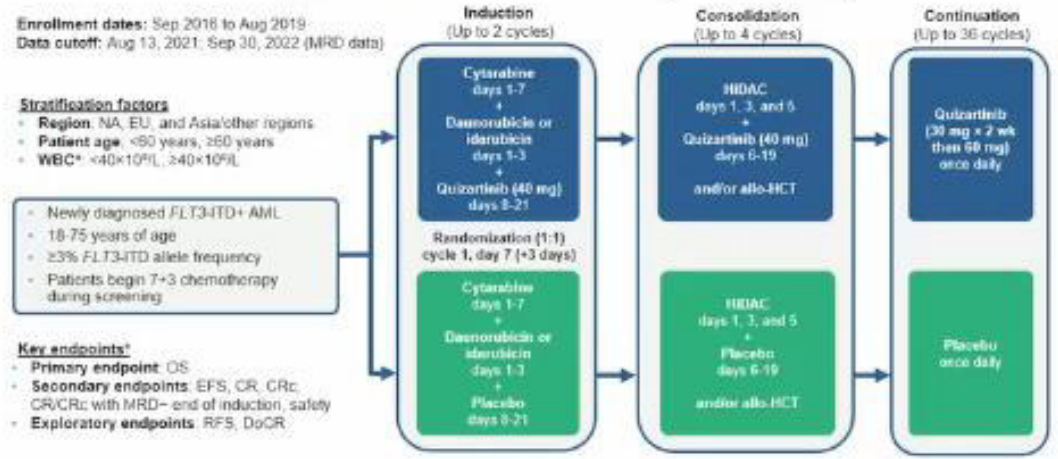
[1]University of Pennsylvania, Philadelphia, PA, USA; [2]Duke Cancer Institute, Durham, NC, USA; [3]La Fe University and Polytechnic Hospital, Valencia, Spain; [4]University Hospital Centre Zagreb, Zagreb, Croatia; [5]Institute of Hematology and Blood Transfusion, Warsaw, Poland; [6]Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; [7]University Hospital Hradec Kralove, Hradec Kralove, Czechia; [8]Chang Gung Medical Foundation, Linkou, Taiwan; [9]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [10]Georgia Cancer Center at Augusta University, Augusta, GA, USA; [11]Sylvester Cancer Center, University of Miami Health System, Miami, FL, USA; [12]Saint Louis Hospital, University of Paris, Paris, France; [13]Tor Vergata Polyclinic Hospital Rome, Rome, Italy; [14]Institute of Hematology and Blood Diseases Hospital, Tianjin, China; [15]Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany; [16]Johns Hopkins University, Baltimore, MD, USA

QuANTUM-FIRST STUDY

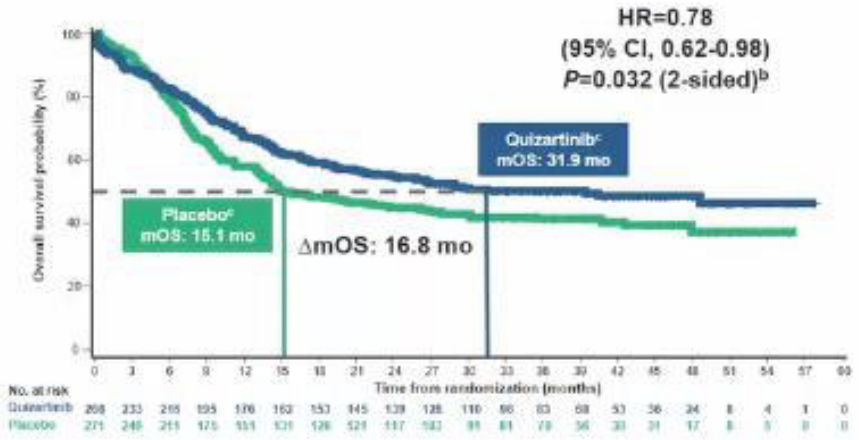
AML
#832
Quizartinib: Typ II FLT3-ITD-Inhibitor

Background: Addition of Quizartinib to Intensive Induction, Consolidation, and Continuation Therapy Improved OS in QuANTUM-First Phase 3 Trial

QuANTUM-First Trial Protocol (NCT02668653)[1]



Primary Endpoint: Overall Survival[1]



Rates of CR/CRi per IRC After 1-2 Courses of Induction

	CR (%)	CR/CRi (%)
Quizartinib	54.9	71.6
Placebo	55.4	64.9

- *FLT3*-ITD mutations:
  - Common in AML and are a negative prognostic marker[2-4]
- 3 FDA- and/or EMA-approved FLT3 inhibitors: midostaurin,[5] gilteritinib,[6] and quizartinib[1]
- Quizartinib:
  - Type II inhibitor[1,2] active against *FLT3*-ITD mutations[2,4]
  - More potent and selective than either midostaurin or gilteritinib[2,4]
  - Improved survival when added to induction, consolidation, and continuation therapy of newly diagnosed adults with *FLT3*-ITD+ AML[1]

*A hierarchical testing procedure was used to test the primary endpoint of OS, followed by EFS, CR, CRc, CR with *FLT3*-ITD MRD negativity, and CRc with *FLT3*-ITD MRD negativity. †*P* value was calculated using a stratified log-rank test. ‡Median follow-up time for both arms was 39.2 months. Allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; DoCR, duration of complete remission; EFS, event-free survival; EMA, European Medicines Agency; EU, European Union; FDA, United States Food and Drug Administration; FLT3-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; HiDAC, high-dose cytarabine; HR, hazard ratio; IRC, independent review committee; mOS, median overall survival; MRD, measurable residual disease; NA, North America; OS, overall survival; RFS, relapse-free survival; WBC, white blood cell.

1. Erba H, et al. *Lancet*. 2023;401(10388):1571-1583. 2. Aikawa T, et al. *Oncotarget*. 2020;11(11):943-956. 3. Levis M. *Hematology Am Soc Hematol Educ Program*. 2013;2013:220-226. 4. Pratz KW, et al. *Blood*. 2010;115(17):1425-1432. 5. Stone RM, et al. *N Engl J Med*. 2017;377(5):454-464. 6. Perl AE, et al. *N Engl J Med*. 2019;381(18):1728-1740.

AML

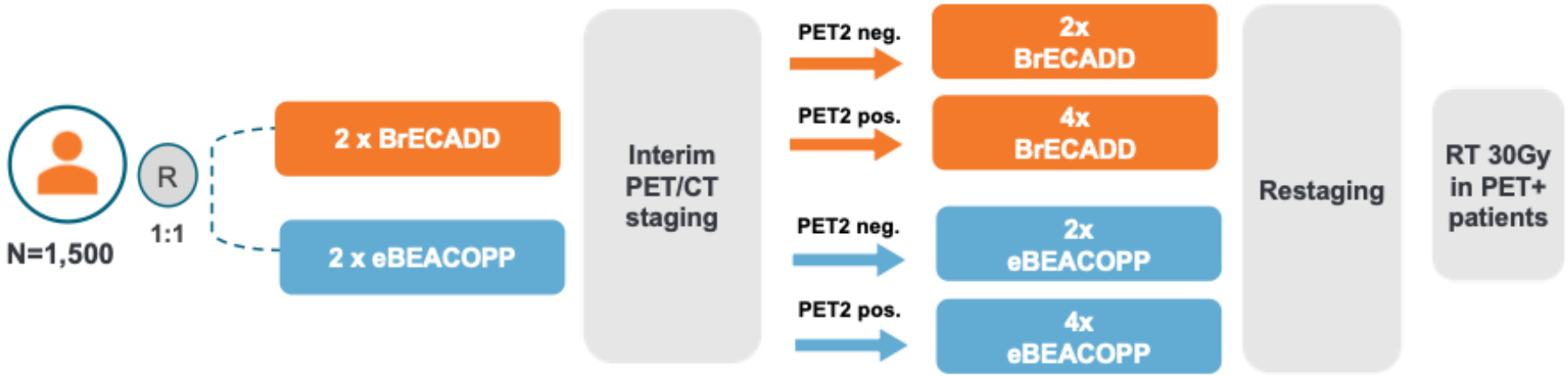
Schlussfolgerungen

# 969	Venetoclax kombiniert mit DA (2+6) ist eine hoch effektive und sichere Induktionstherapie für Erwachsene mit neu diagnostizierter AML
# 833	Eine komplett orale Therapie mit Decitabine/Cedazuridine ist eine sichere und effektive Therapie für ältere/nicht fitte Patienten mit nd AML, vergleichbar mit Daten der VIALE-A-Studie
LBA-5	Revumenib ist effektiv und sicher bei pädiatrischer u. adulter r/r KMT2Ar Akuter Leukämie mit dauerhaften MRD-negativen Remissionsraten und hohen Transplantationsraten unter den Respondern
#832	Quizartinib als spezifischer FLT3-ITD-Inhibitor in der Erstlinientherapie mit int. Chemotherapie und als Erhaltungstherapie bei nd AML zugelassen.

Hodgkin Lymphom
#3057
„Comprehensive Analysis of Treatment Related Morbidity and Progression-Free Survival in the GHSG Phase III HD 21 Trial“ , P. Borchmann et al.

GHSG HD21 study design and primary endpoints

HD21 is an ongoing, randomized, open-label, Phase 3 study of BrECADD versus eBEACOPP in patients with previously untreated, advanced cHL

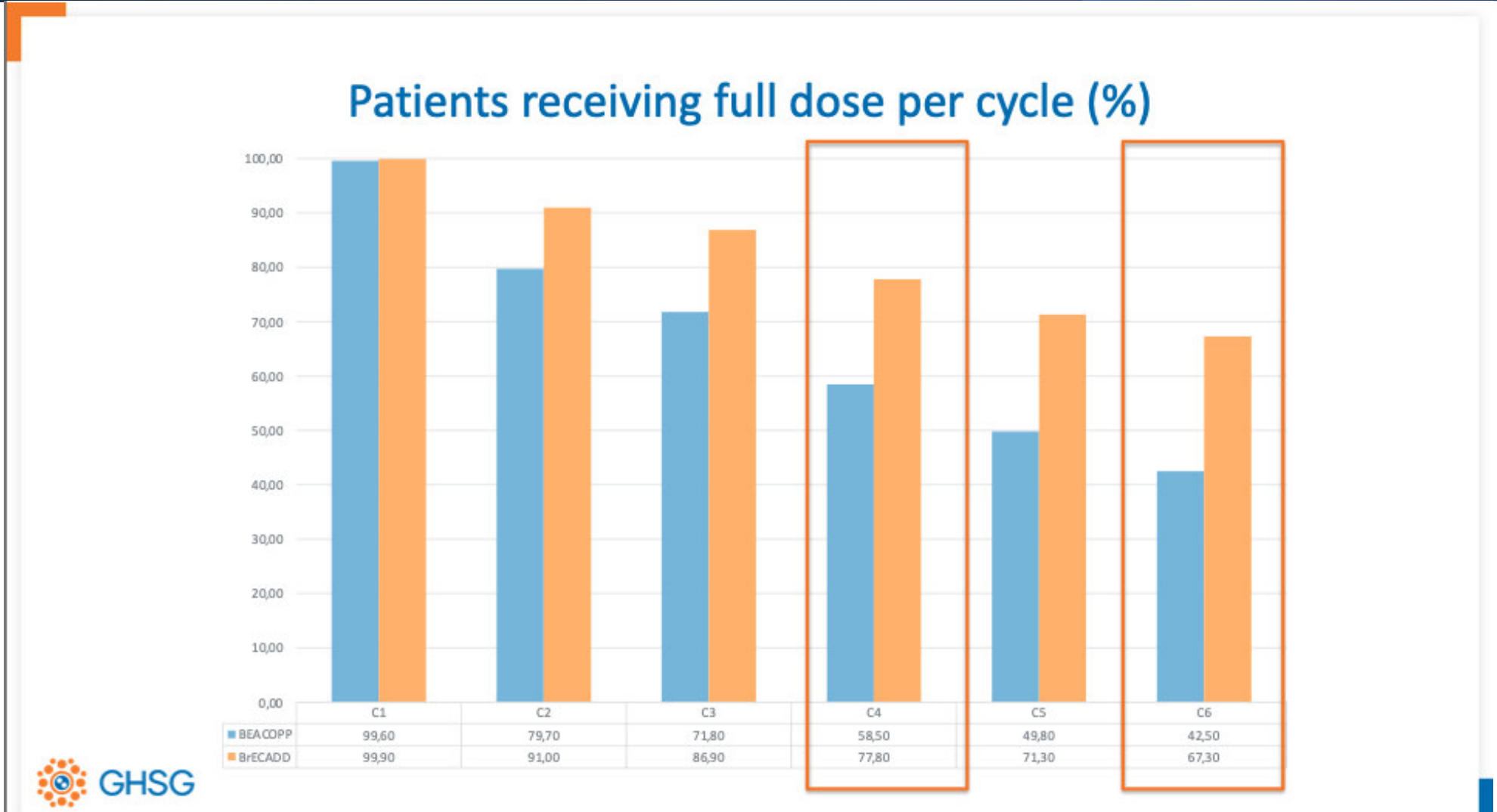


Co-primary objectives achieved:

1. Reduced treatment-related morbidity (TRMB) with BrECADD highly significant.
2. Non-inferiority of 4-6 x BrECADD in terms of PFS already at interim analysis shown

GHSG

Hodgkin Lymphom
#3057
Volle Dosis pro Zyklus eBEACOPP vs. BrECADD

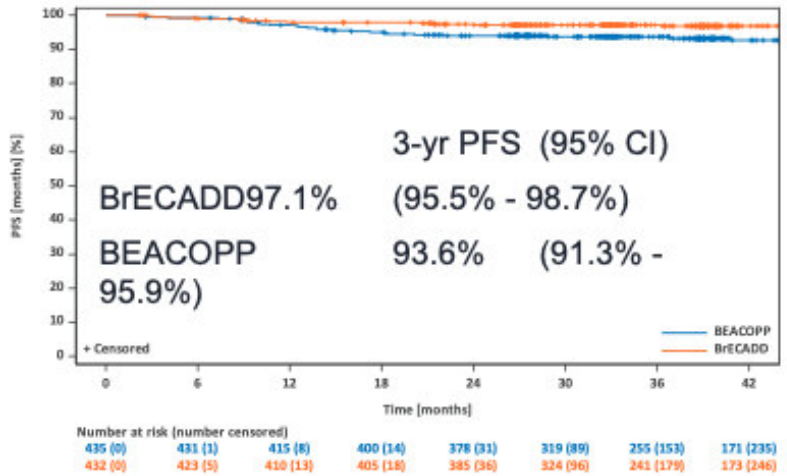


GHSG

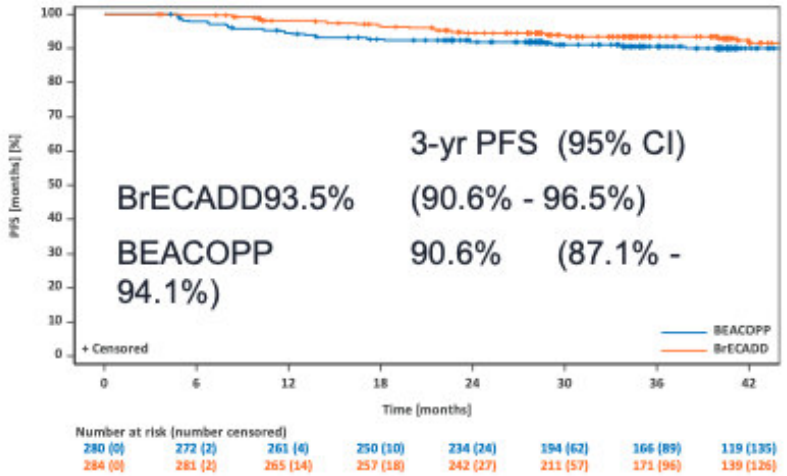
Hodgkin Lymphom
#3057
3y PFS in Abhängigkeit vom PET2-Status

HD21: 3y progression-free survival and PET2-status by treatment arm

PET2-negative (4 cycles)



PET2-positive (6 cycles)



Hodgkin Lymphom
#181

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Abstract #181

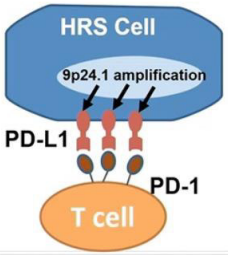
Nivolumab-AVD is better tolerated and improves PFS vs Bv-AVD in older patients (aged ≥60 years) with advanced stage Hodgkin lymphoma (cHL) on S1826

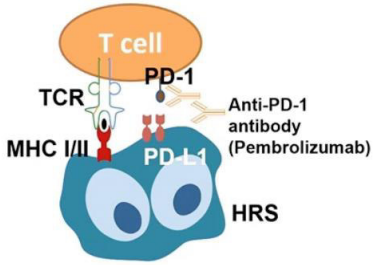
Sarah C. Rutherford MD[1], Hongli Li MS[2], Alex F. Herrera MD[3], Michael Leblanc PhD[2], Sairah Ahmed MD[4], Kelly L. Davison MD, PhD[5], Carla Casulo MD[6], Nancy L. Bartlett MD[7], Joseph M. Tuscano MD[8], Brian Hess MD[9], Pallawi Torka MD[10], Pankaj Kumar MD[11], Ryan W. Jacobs MD[12], Joo Y. Song MD[13], Sharon M. Castellino MD, MSc[14], Brad S. Kahl MD[15], John P. Leonard MD[1], Sonali M. Smith MD[16], Jonathan W. Friedberg MD, MMSc[6] and Andrew M Evens DO, MBA, MMSc[17]

[1]Weill Cornell Medicine, New York, NY; [2]Fred Hutchinson Cancer Center, Seattle, WA; [3]City of Hope, Duarte, CA; [4]Department of Lymphoma/Myeloma and Stem Cell Transplantation, The University of Texas MD Anderson Cancer Center, Houston, TX; [5]Royal Victoria Hospital, McGill University Health Centre, Montreal, QC, CAN; [6]Wilmot Cancer Center, University of Rochester, Rochester, NY; [7]Siteman Cancer Center, Washington University School of Medicine, Saint Louis, MO; [8]University of California, Davis Medical Center, Sacramento, CA; [9]Medical University of South Carolina, Charleston, SC; [10]Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [11]Illinois CancerCare, Bloomington, IL; [12]Atrium Health Levine Cancer Institute, Charlotte, NC; [13]City of Hope National Medical Center, Duarte, CA; [14]Department of Pediatrics, Emory University School of Medicine, Atlanta, GA; [15]Siteman Cancer Center, Division of Oncology, Washington University School of Medicine in St. Louis, St. Louis, MO; [16]Department of Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, IL; [17]Division of Blood Disorders, Rutgers Cancer Institute New Jersey, New Brunswick, NJ

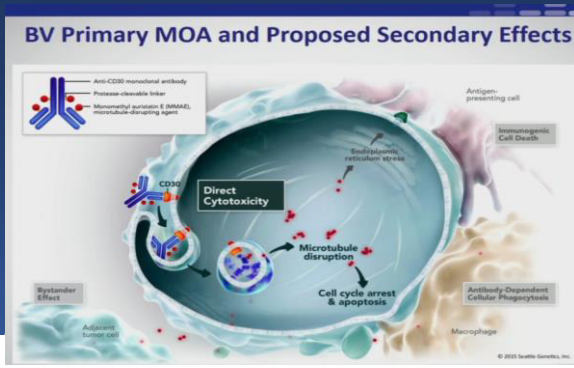
Hodgkin Lymphom
#181
Probleme für Patienten ab 60 Jahre

- Ca. 15 – 25% aller Patienten mit klassischem Hodgkin-Lymphom
- Schlechtere Toleranz gegenüber Chemotherapien aufgrund von Komorbiditäten und Medikamentennebenwirkungen
- Häufig Dosisreduktionen oder weniger Therapiezyklen
- Behandlungsbedingte Mortalität
- Weniger Überlebensvorteile als jümgere Patienten





Hodgkin Lymphom
#181
S1826 Studiendesign



Newly Diagnosed Stage III-IV Classic Hodgkin Lymphoma

RANDOMIZE

1:1

N-AVD x 6 cycles
Nivolumab 240mg days 1,15[a]
Doxorubicin, Vinblastine, Dacarbazine days 1,15[b]
*G-CSF optional

470 pts

Bv-AVD x 6 cycles
Bv 1.2mg/kg days 1,15
Doxorubicin, Vinblastine, Dacarbazine days 1,15[b]
*G-CSF required

470 pts

EOT RT (30-36 Gy)
(residual FDG-avid lesions)

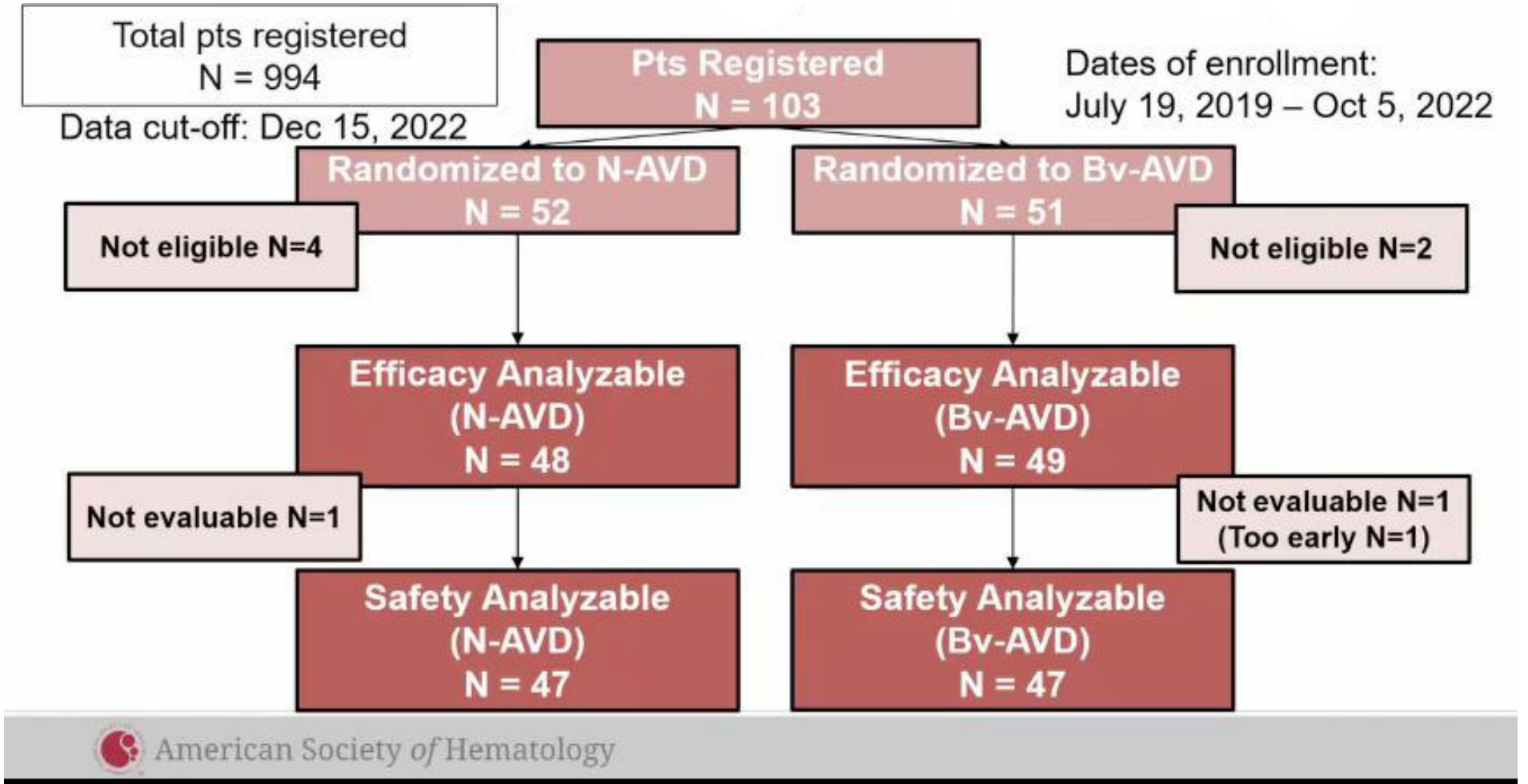
Stratification:
- Age (12-17/18-60/>60)
- IPS (0-3/4-7)
- EOT RT intended (Y/N)

- Primary endpoint: PFS
- Secondary endpoints: EFS, OS, EOT CMR rate, PROs

Herrera et al. ASCO and ICML 2023.

[a] Nivolumab 3mg/kg for ages ≤ 17, max 240mg
[b] Conventional doses of AVD: Stephens DM et al Blood 2019, Ansell SM et al NEJM 2022

Hodgkin Lymphom
#181
Patientenrandomisation



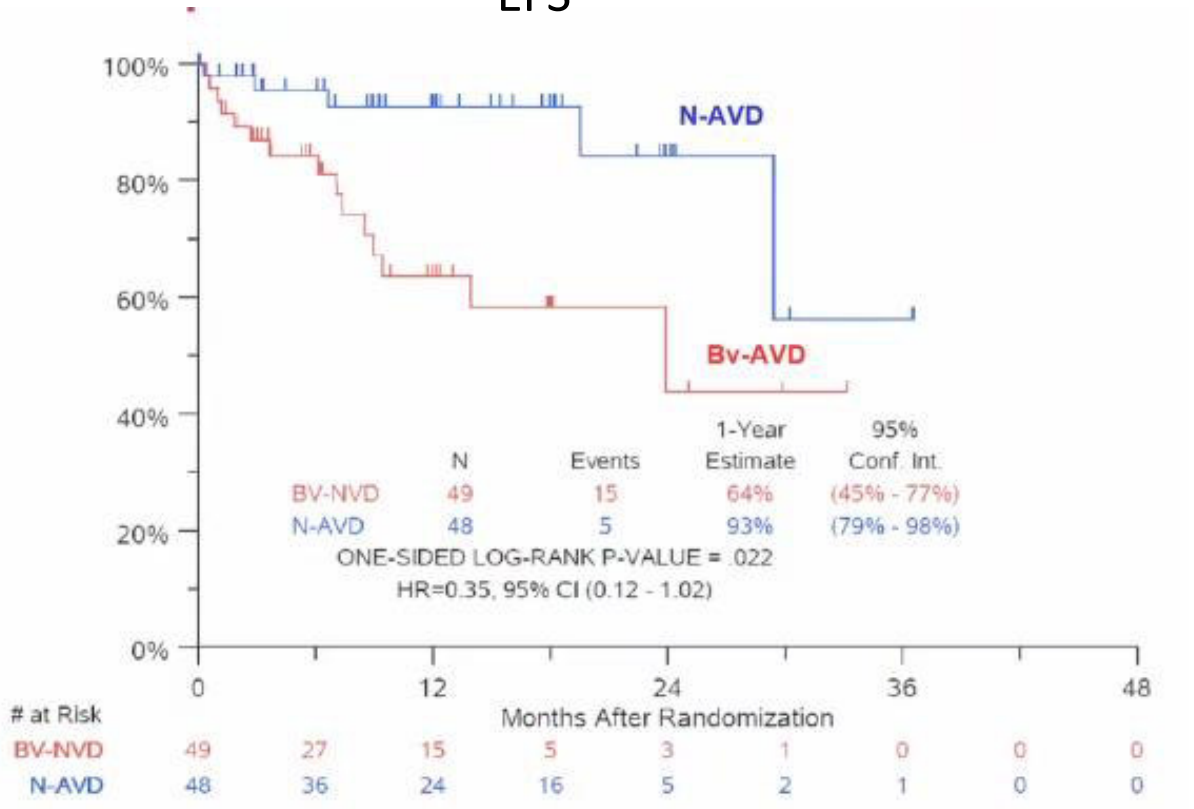
Hodgkin Lymphom
#181
Patientencharakteristika

Baseline characteristics	N-AVD N = 48 N (%)	Bv-AVD N = 49 N (%)
Age, median (range)	66.4 (60-84 y)	67.1(60-87 y)
Age 60-69	31 (65%)	36 (74%)
Age 70-79	14 (29%)	12 (24%)
Age ≥80	3 (6%)	1 (2%)
Female Sex	19 (40%)	18 (37%)
Race		
White	43 (90%)	40 (82%)
Black	1 (2%)	2 (4%)
Asian	1 (2%)	1 (2%)
Other/Unknown	3 (6%)	6 (12%)
Hispanic	5 (10%)	5 (10%)

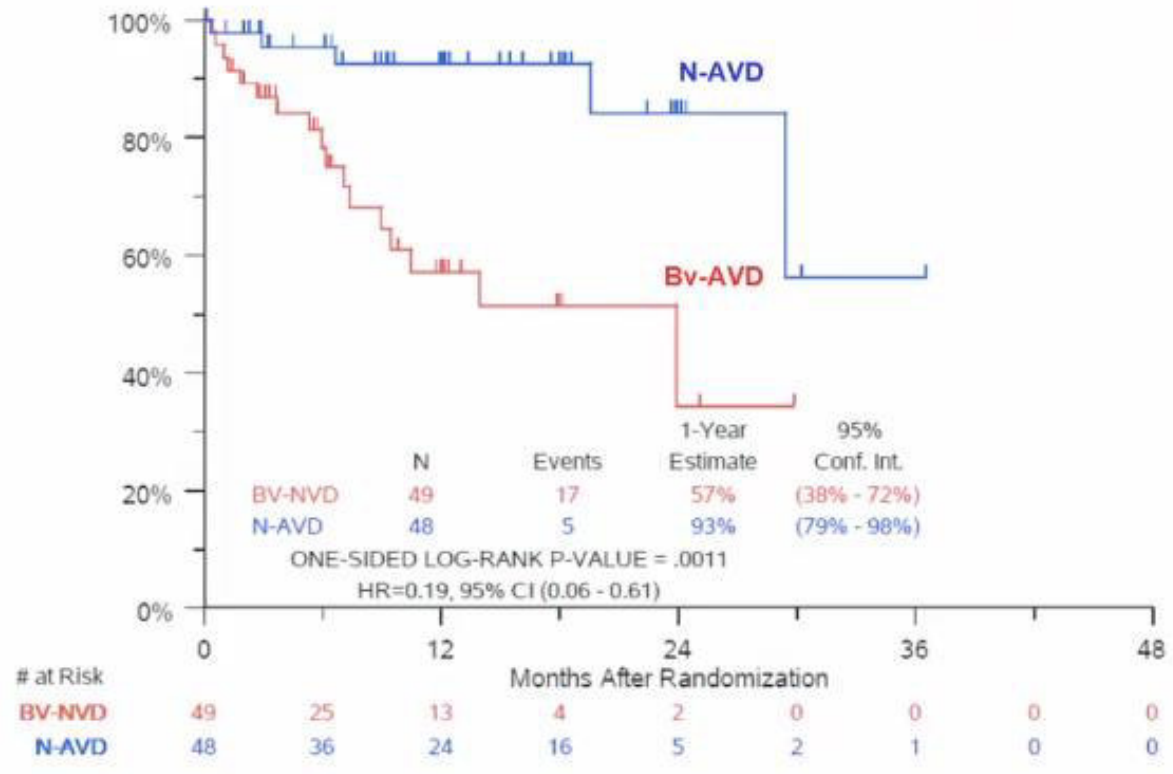
Baseline characteristics	N-AVD N = 48 N (%)	Bv-AVD N = 49 N (%)
Stage		
III	16 (33%)	22 (45%)
IV	32 (67%)	27 (55%)
B symptoms present	25 (52%)	27 (55%)
IPS Score		
0-3	24 (50%)	27 (55%)
4-7	24 (50%)	22 (45%)
Bulky disease > 10cm	7 (15%)	5 (10%)
HIV+	0 (0%)	1 (2%)
Elevated bilirubin	4 (8%)	4 (8%)

Hodgkin Lymphom
#181
Ergebnisse EFS & PFS

EFS



PFS



Hodgkin Lymphom
#181
Nebenwirkungen

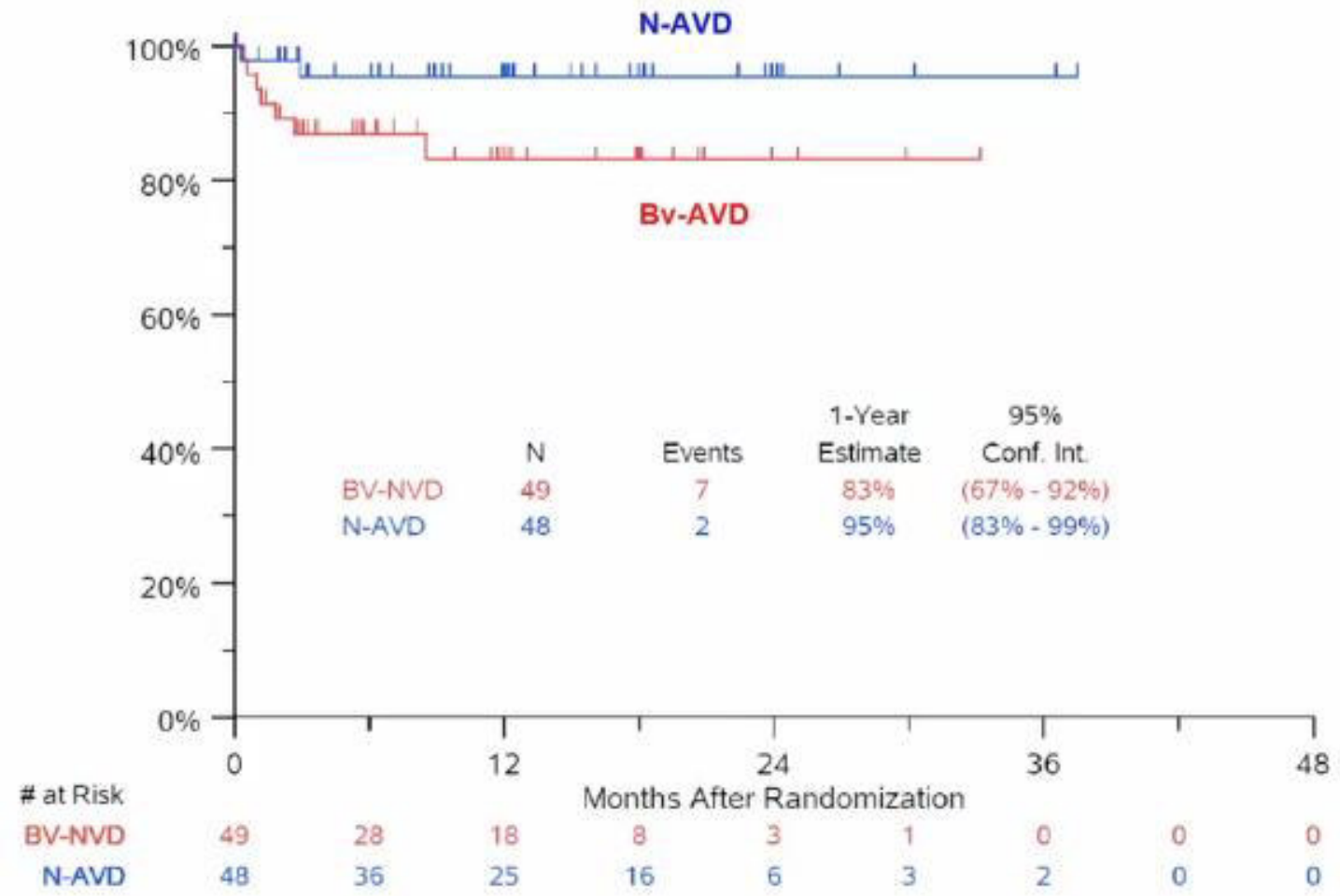
Toxicity	N-AVD N = 47	Bv-AVD N = 47	p-value*	N-AVD N = 47	Bv-AVD N = 47	p-value*
	Any grade N (%)	Any grade N (%)		Gr ≥ 3 N (%)	Gr ≥ 3 N (%)	
Febrile Neutropenia	6 (13%)	9 (19%)	0.57	6 (13%)	9 (19%)	0.57
Sepsis	3 (6%)	10 (21%)	0.07	3 (6%)	10 (21%)	0.07
Infections/ Infestations	9 (19%)	16 (34%)	0.16	3 (6%)	10 (21%)	0.07

Toxicity	N-AVD N = 47	Bv-AVD N = 47	p-value*	N-AVD N = 47	Bv-AVD N = 47	p-value*
	Any grade N (%)	Any grade N (%)		Gr ≥ 3 N (%)	Gr ≥ 3 N (%)	
Peripheral sensory neuropathy#	15 (32%)	31 (66%)	0.0018	1 (2%)	5 (11%)	0.20
Peripheral motor neuropathy+	4 (9%)	7 (15%)	0.52	0 (0%)	1 (2%)	1.00

Toxicity	N-AVD N = 47		Bv-AVD N = 47	
	Any Grade N (%)	Grade ≥ 3 N (%)	Any Grade N (%)	Grade ≥ 3 N (%)
ALT increased	9 (19%)	4 (9%)	11 (23%)	1 (2%)
AST increased	7 (15%)	3 (6%)	11 (23%)	1 (2%)
Hypothyroidism	7 (15%)	1 (2%)	0 (0%)	0 (0%)
Rash maculo-papular	5 (11%)	0 (0%)	1 (2%)	0 (0%)
Rash acneiform	3 (6%)	0 (0%)	0 (0%)	0 (0%)
Pneumonitis	3 (6%)	1 (2%)	3 (6%)	3 (6%)
Gastritis	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Colitis	0 (0%)	0 (0%)	1 (2%)	0 (0%)

Disposition	N-AVD N = 48, N (%)	Bv-AVD N = 49, N (%)
Treatment ongoing	1 (2%)	2 (4%)
Completed treatment	42 (88%)	31 (63%)
Discontinued all treatment early	**5 (10%)**	**16 (33%)**
Adverse event	2 (4%)	7 (14%)
Refusal unrelated to AE	1 (2%)	2 (4%)
Progression/relapse	0 (0%)	1 (2%)
Death on treatment	**1 (2%)**	**5 (10%)**
Other – not protocol specified	1 (2%)	1 (2%)
Received protocol radiotherapy	0 (0%)	0 (0%)

Hodgkin Lymphom
#181
Gesamtüberleben



1-year OS
N-AVD 95%
Bv-AVD 83%

Median follow-up
12.1 months

p-value = 0.091
HR=0.35,
95% CI (0.07-1.75)

Hodgkin Lymphom
#182

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide

#182: PD-1 Blockade before Autologous Stem Cell Transplantation Improves Outcomes in Relapsed/Refractory Classic Hodgkin Lymphoma: Results from a Multicenter Cohort

Sanjal H. Desai, MBBS[1,2], Reid W. Merryman, MD[3], Harsh Shah, DO[4*], Levi D. Pederson, MS[2*], Susan M. Geyer, PhD[2], Nivetha Ganesan[5*], Tiffany Chang, MS[5*], Tamer Othman, MD[6], Ayo S Falade, MD, MBA[3], Gunjan L. Shah[5], Urshila Durani, MD, MPH[7], Kelsey Baron, MD[4], Shin Yeu Ong, MD, FRCPath[8*], Stephen M Ansell[7], Philippe Armand, MD, PhD[9], Siddharth Iyengar, MD[10*], Ivana Micallef, MD[2*], Alison Moskowitz, MD[5], Alex F. Herrera, MD[11], Robert Stuver, MD[5] and Matthew Genyeh Mei, MD[11*]

Hodgkin Lymphom
#182
Hintergrund & Methodik

- Klassische Hodgkin-Lymphome sind mittels Erstlinientherapie in 80 bis 90% heilbar

- Rezidivtherapien als konventionelle Chemotherapien oder auch in den letzten Jahren basierend auf Brentuximab-vedotin oder PD-1-Checkpointinhibitoren und anschliessender Hochdosischemotherapie mit autologer Stammzelltransplantation sind Basis der Therapie des r/r cHL

- Es gibt keine randomisierten Studien, die die neuen Substanzen mit konventionellen Chemotherapien im Rezidiv vergleichen

- Retrospektive Studie mit erwachsenen Patienten mit r/r cHL, die zwischen 2010 und 2021 in 5 US akademischen Institutionen eine Rezidivtherapie mit konventioneller Chemotherapie, PD-1-Checkpointinhibitorbasierter Therapie und/oder mit Brentuximab vedotin basiert erhalten habe und anschliessend eine HD-Therapie mit autologer PBSCT.

- Studienziele:
  - Progressionsfreies Überleben (PFS): Zeit von ASCT bis Progress oder Tod
  - Gesamtüberleben (OS): Zeit von ASCT bis zum Tod.

Hodgkin Lymphom
#182
Patientencharakteristika (N = 981) & Mediane Beobachtungszeit

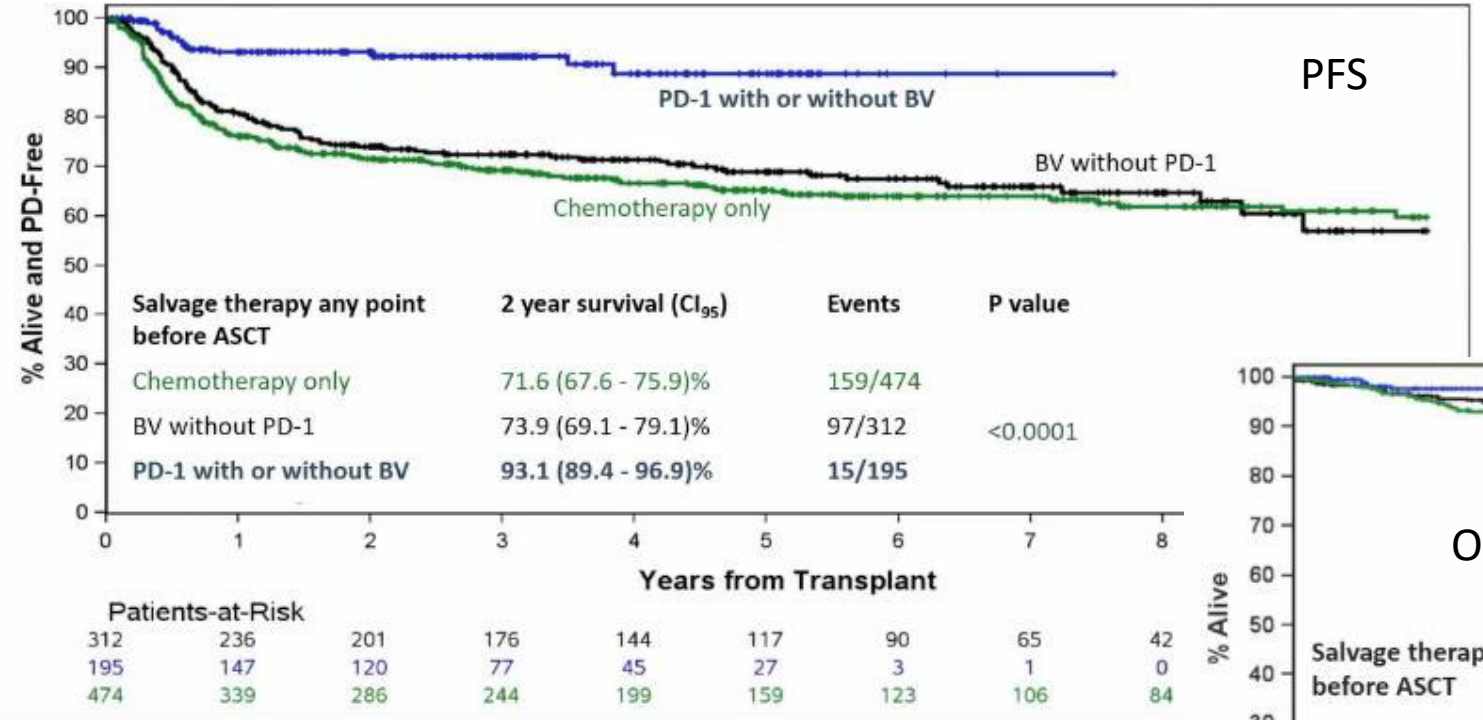
Relapse characteristics	N (%)
Age (median, IQR)	31 (21-43)
Male Sex	504 (52)
Advance stage	323 (32)
Extranodal disease	353 (35)
Primary refractory disease	345 (35)
Early relapse within 1 year	317 (32)
B symptoms	345 (35)
Post-ASCT consolidation	268 (27)
Peritransplant RT	239 (24)

Type of Salvage therapies at any point before ASCT:		N (%)
Salvage therapy (median, range)		2 (1-8)
>1 line of salvage therapies		308 (31)
Chemotherapy only without novel agents		474 (48)
BV based regimen without PD-1		312 (32)
PD-1+/-BV (N=195, 20)	PD-1+BV	83 (9)
	PD-1 without BV	112 (11)

Salvage Therapy (any line)	Median follow up (years, 95% CI)
BV only without PD-1	5.3 (5.0-6.0)
PD-1 with or without BV	2.8 (2.4-3.1)
Chemotherapy only	5.3 (5.0-5.7)

Hodgkin Lymphom
#182
PFS & OS

PFS

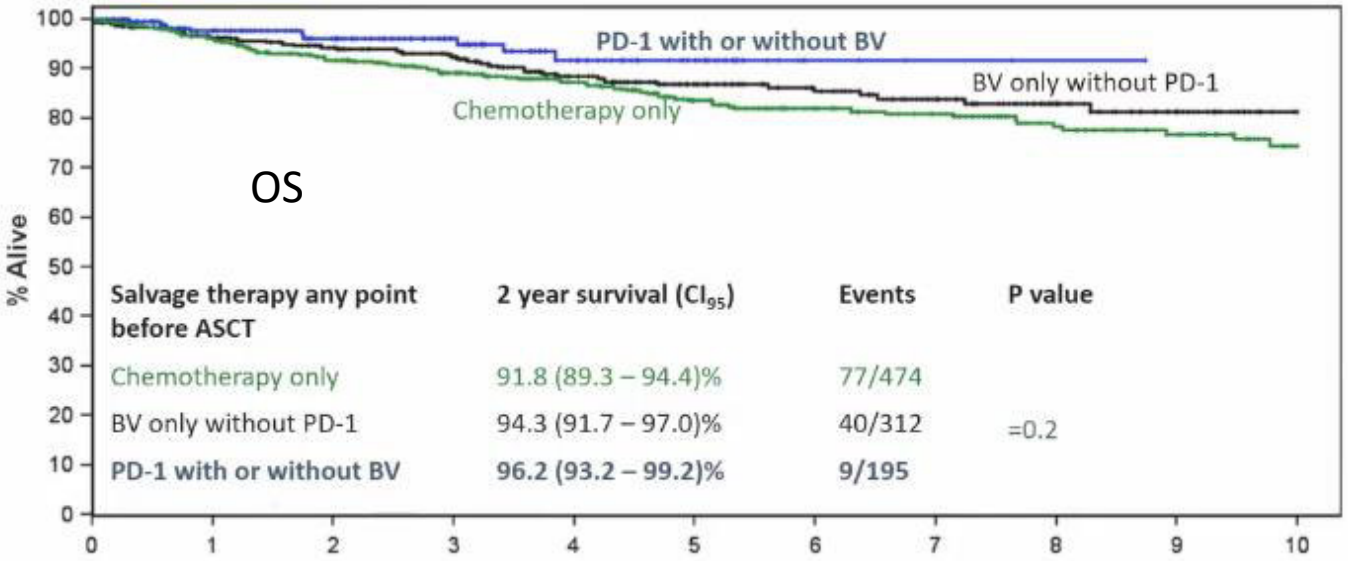


Salvage therapy any point before ASCT	2 year survival (CI_{95})	Events	P value
Chemotherapy only	71.6 (67.6 - 75.9)%	159/474	
BV without PD-1	73.9 (69.1 - 79.1)%	97/312	<0.0001
PD-1 with or without BV	**93.1 (89.4 - 96.9)%**	**15/195**	

Patients-at-Risk

312	236	201	176	144	117	90	65	42
195	147	120	77	45	27	3	1	0
474	339	286	244	199	159	123	106	84

OS



Salvage therapy any point before ASCT	2 year survival (CI_{95})	Events	P value
Chemotherapy only	91.8 (89.3 – 94.4)%	77/474	
BV only without PD-1	94.3 (91.7 – 97.0)%	40/312	=0.2
PD-1 with or without BV	**96.2 (93.2 – 99.2)%**	**9/195**	

Patients-at-Risk

312	283	260	227	186	150	118	89	60	32	7
195	154	125	83	47	29	4	2	1	0	
474	425	369	318	271	215	166	145	114	89	59

Hodgkin Lymphom
#612

Bleomycin affects lung function for at least 5 years after treatment for Hodgkin lymphoma: data from the international, randomised phase 3 RATHL trial

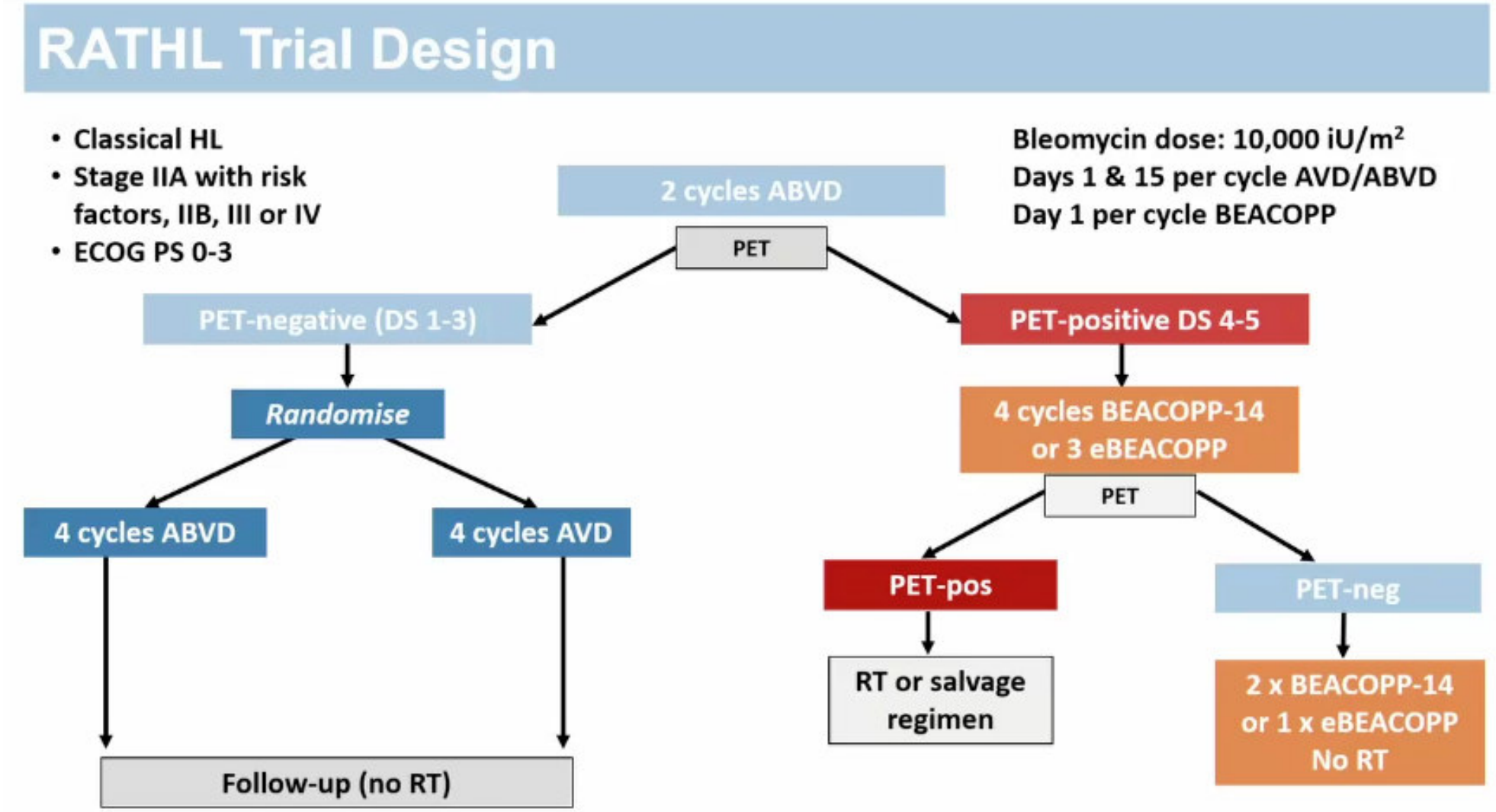
Elizabeth Phillips, Amy Kirkwood, Christina Hague, Jorgen Vestbo, Massimo Federico, Francesco D'Amore, Alexander Fosså, Judith Trotman, Leanne Berkahn, Daniel Molin, Stefano Luminari, Sally Barrington, Peter Johnson, John Radford

Hodgkin Lymphom
#612
Bleomycin Lungen Toxizität

- Inzidenz von bis zu 27% in unselektierten Patienten in Behandlung mit ABVD (1)
- Mortalitätsraten bis zu 25% (2)
- Alter (>40 – 60 J.), Anzahl der Zyklen, G-CSF als identifizierte Risikofaktoren (2,3)
- Publikationen fokussieren vornehmlich auf akute Lungentoxizität
- Langzeiteffekte von Bleomycin auf die Lungenfunktion sind nicht bekannt
- Keine etablierten Leitlinien für Screening und Monitoring
- Ziel: Evaluation der kurz- und langfristigen Effekte von Bleomycin auf die Lungenfunktionen von Patienten, die in der RATHL-Studie behandelt wurden.

1) WG Martin et al, J Clin Onc, 2005
2) A Evens et al, Blood, 2012
3) S Steiffer et al, Chest, 2001

Hodgkin Lymphom
#612
RATHL Studiendesign



Hodgkin Lymphom
#612
RATHL Studiendesign

		All (N=1201)	ABVD (N=469)	AVD (N=464)	BEACOPP (N=172)
Age (years), median (IQR)		**33 (25 - 46)**	32 (24 - 44)	32.5 (24 – 45)	32.5 (24 - 46)
DLCO (% predicted), median (IQR)		**82 (73-93)**	82 (73.9 – 93.9)	83 (73.3 – 93)	79 (70.5 – 90)
DLCO <75% predicted, N (%)		**327 (29.4)**	121 (27.3)	129 (29.1)	59 (38.1)
Sex	Male	**653 (54.4)**	259 (55.2)	251 (54.1)	92 (53.5)
Pulmonary history	No	**807 (84.9)**	330 (86.8)	314 (84.4)	105 (81.4)
	Yes	**144 (15.1)**	50 (13.2)	58 (15.6)	24 (18.6)
	Asthma	**80 (8.4)**	26 (6.8)	37 (9.9)	11 (8.5)
	COPD	**12 (1.3)**	6 (1.6)	3 (0.8)	1 (0.8)
	Missing	***250***	*89*	*92*	*43*
Smoking status	Never smoked	**535 (59.5)**	215 (60.9)	221 (62.1)	71 (57.7)
	Ex-smoker	**200 (22.2)**	68 (19.3)	81 (22.8)	31 (25.2)
	Current smoker	**164 (18.2)**	70 (19.8)	54 (15.2)	21 (17.1)
	Missing	***302***	*116*	*108*	*49*
Pack years, median (IQR)		**10 (4 - 20)**	11 (5 - 24)	8 (4 - 19)	8 (2 - 20)

Hodgkin Lymphom
#612
Behandlung und Akute Toxizität

	ABVD (N=469)	AVD (N=464)	BEACOPP (N=172)
Bleomycin doses: median (IQR)	12 (12-12)	4 (4-4)	8 (8-10)
Cycles with G-CSF: median (IQR)	0 (0-3)	0 (0-4)	5 (4-6)
G-CSF use (% pts)	40.7%	39.7%	98.3%
Grade ≥3 respiratory AE: N (%)	17 (3.6)	7 (1.5)	10 (5.8)
	p=0.041		
Grade 5 respiratory AEs: N (%)	1 (0.2)	0	0
Mean change in DLCO (95% CI)	-11.6 (-13.1 to -10.0)	-3.8 (-5.4 to 2.2)	-9.5 (-12.5 to -6.4)
	Difference* 7.1 (5.1 to 9.0), p <0.001		
DLCO <90% baseline	247/413 (59.8%)	167/411 (40.6%)	63/121 (52.1%)
	p<0.001		

*adjusted for baseline DLCO

Mean DLCO at EOT was 12.8% lower for pts with grade 3+ pulmonary events compared to those without (95% CI: -19.4 to -6.2; p<0.001)

Hodgkin Lymphom
#612
Erholung der Lungenfunktion (bei Pat. mit DLCO-Red. < 90% d. Basiswerts)

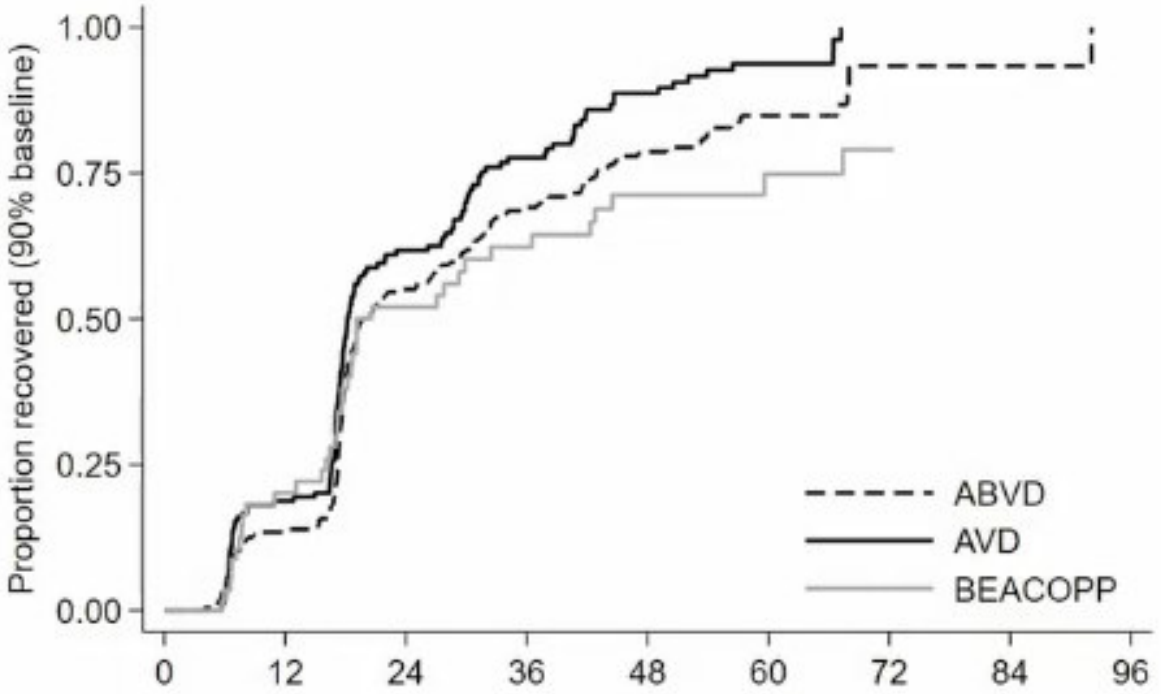
Time to recovery:
>90% baseline DLCO value

Slower recovery with:

- ABVD arm (HR 0.71, p=0.004)
- Male sex (HR 0.80, p=0.041)
- Respiratory history (HR 0.66, p=0.023)

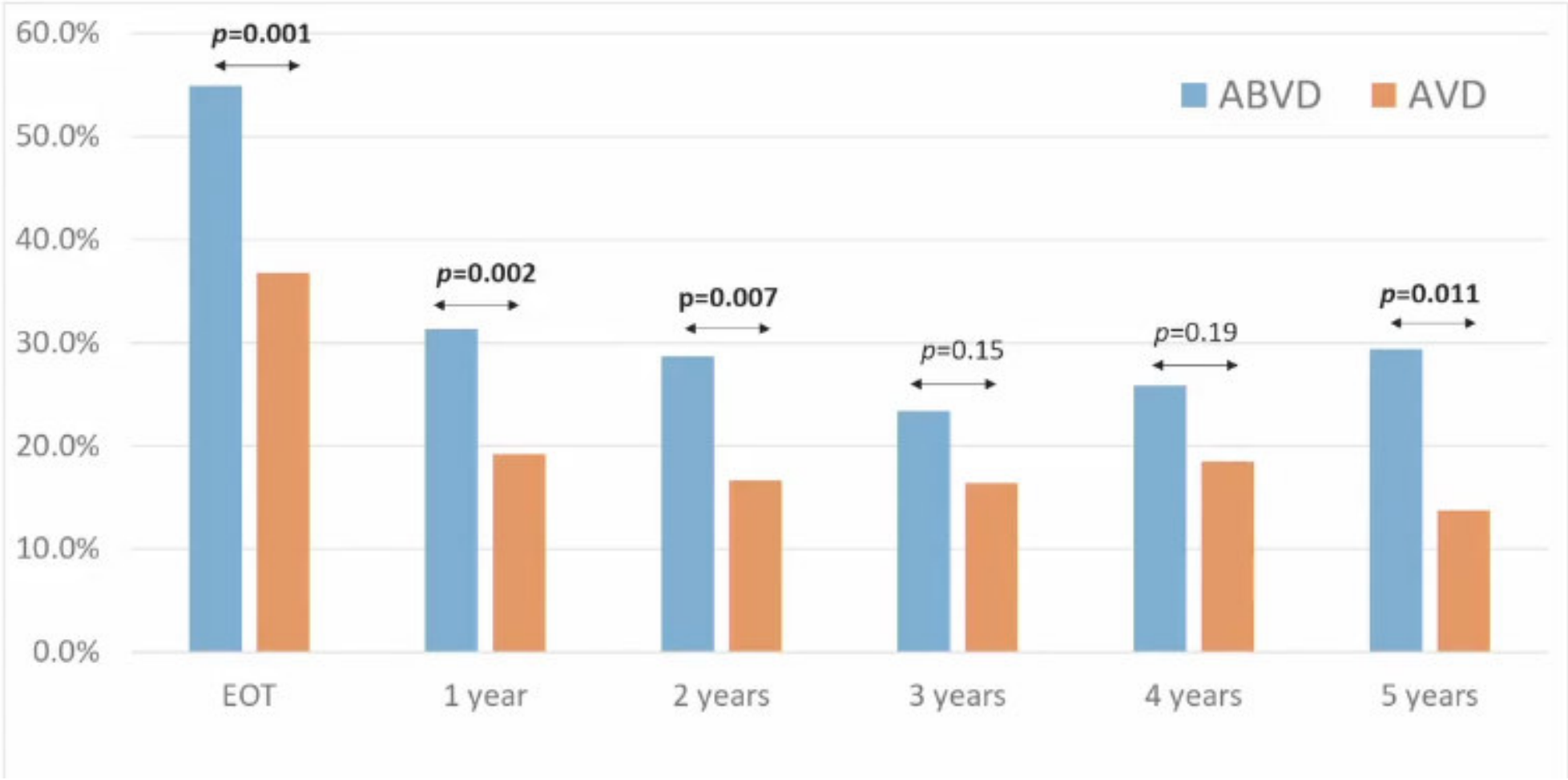
Recovery by 2 years:

- ABVD: 69.6% (64.9 – 74.1)
- AVD: 81.4% (77.4 – 85.2)
- BEACOPP: 68.5% (59.8 – 76.9)



Number at risk									
ABVD	244	188	87	52	29	14	2	2	0
AVD	165	117	52	28	12	6	0	0	0
BEACOPP	63	41	24	18	10	7	1	0	0

Hodgkin Lymphom
#612
Anteil der Patienten mit einer DLCO < 75%



Hodgkin Lymphom

Schlussfolgerungen

#3057 PET-2 adaptiertes BrECADD mit höchster 3-Jahres PFS Rate in einer randomisierten Studie für AS-cHL. Nutzen sowohl bei PET2-neg. als auch PET2-pos. Patienten.

#181 N-AVD wird von Pat. > 60 J. besser toleriert und verbessert das Progressionsfreie u. Ereignisfreie Überleben im Vergleich zu Bv-AVD.
Das Gesamtüberleben war in der Studie nicht signifikant unterschiedlich mit einem Trend zu weniger Todesfällen unter N-AVD.
N-AVD neuer Standard zur Therapie des fortgeschr. cHL bei Patienten > 60 Jahre?

#182 Die Vorbehandlung mit PD-1-Checkpointinhibitoren könnte bei r/r klassischen Hodgkinlymphomen, die mit HD-Therapie und auto PBSCT behandelt werden, das progressionsfreie Überleben erhöhen (Cave retrospektive Daten).

#612 Einschränkungen der Lungenfunktion im ABVD-Arm sind über einen Zeitraum von 5 Jahren nur partiell reversibel.
Aus den Daten ergibt sich, dass man die Anwendung von Bleomycin möglichst minimieren sollte.


Vielen Dank
für Ihre
Aufmerksamkeit
&
Einen schönen Abend