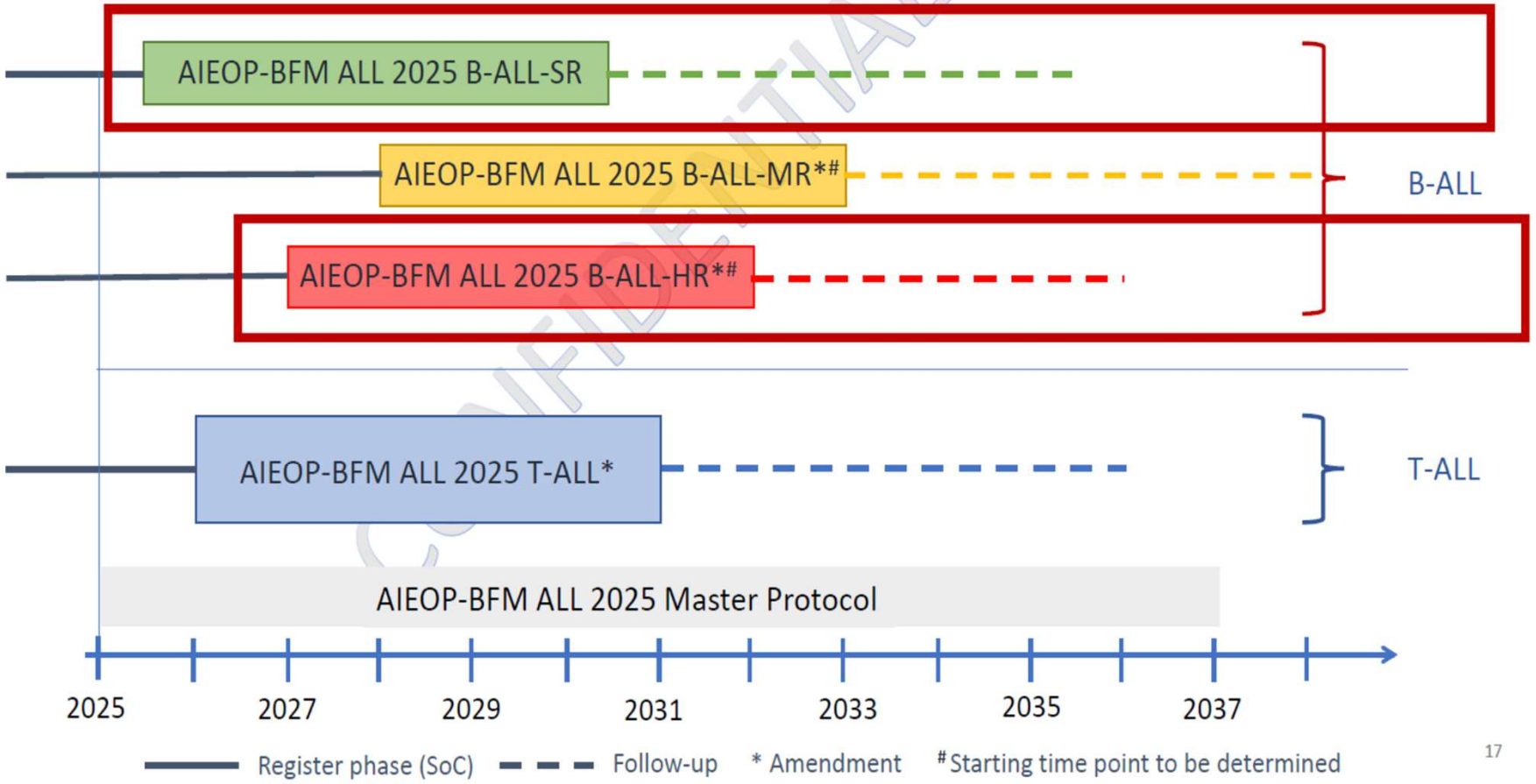
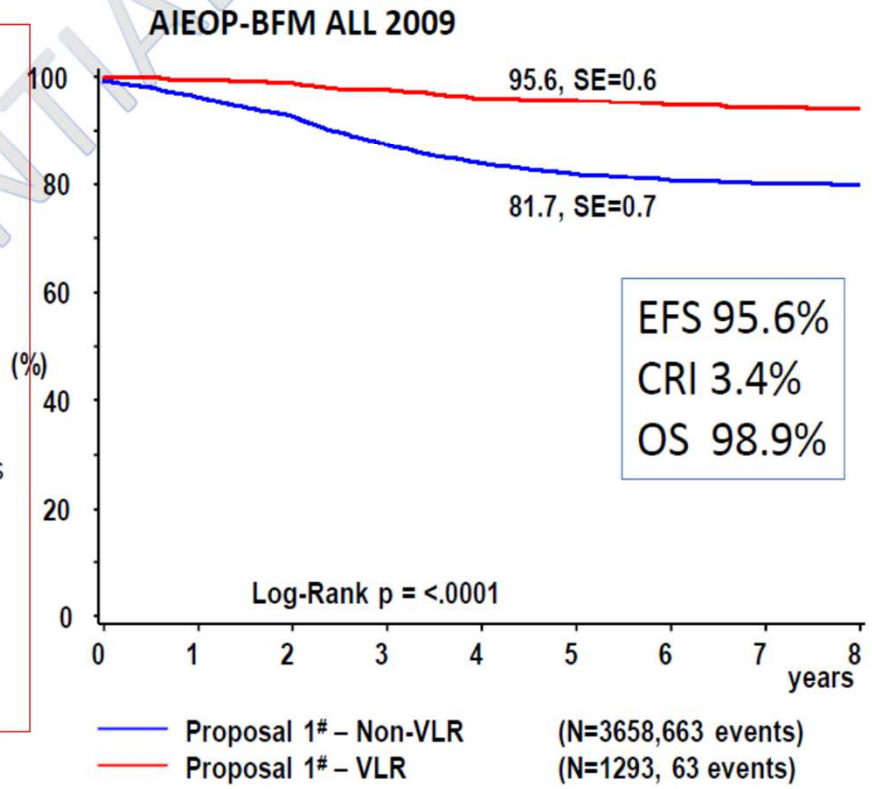
AIEOP-BFM ALL 2025
Overview of Trial and Sub-Protocols
Adaptation 09/23: Sequential start of B-ALL questions beginning with SR



AIEOP-BFM ALL 2025 B-ALL – SR - Definition

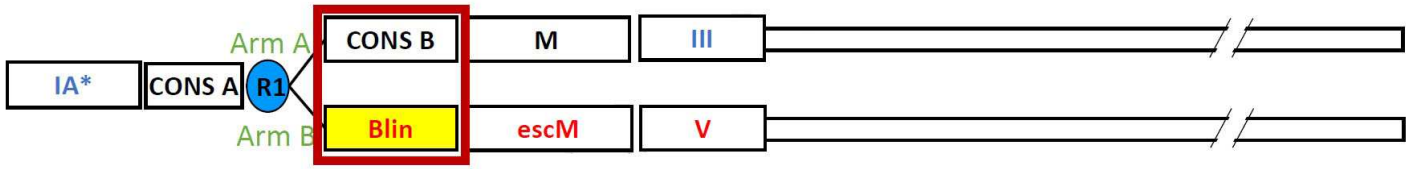
- CNS 1/2 and no testicular involvement *and*
- no evidence of any of the following genetics:
  - any KMT2A rearrangement
  - Hypodiploidy
  - TCF3::HLF
  - TCF3::PBX1
  - iAMP21
  - IKZF1plus *and*
- FCM-MRD in BM on day 15 < 10% *and*
- PCR-MRD at TP1 negative for all investigated markers *and*
- at least one of the following criteria:
  - ETV6::RUNX1
  - High Hyperdiploidy*
  - Age < 10 yrs. + FCM-MRD d15 < 0.1%

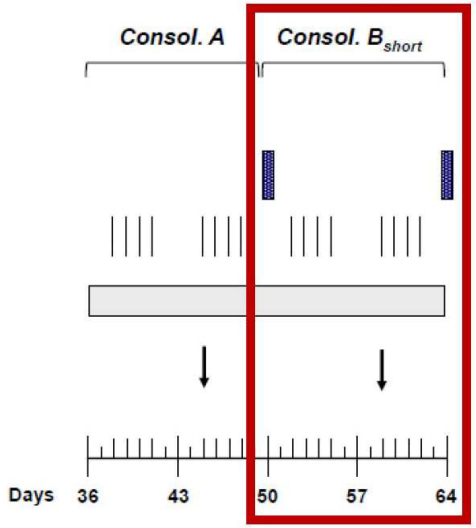


no unfavorable genetics: No *KMT2A-AFF1* and no hypodiploidy, no consideration of other *KMT2Ar, TCF3/PBX1, IKZF1*+ or iAMP21

* Current version: >53 and ≤ 74 chromosomes or DNA-Index ≥ 1.16 and < 1.6

AIEOP-BFM ALL 2025 B-ALL - SR





CPM p.i. (1 h) 1000 mg/m²/dose

ARA-C i.v. 75 mg/m²/dose

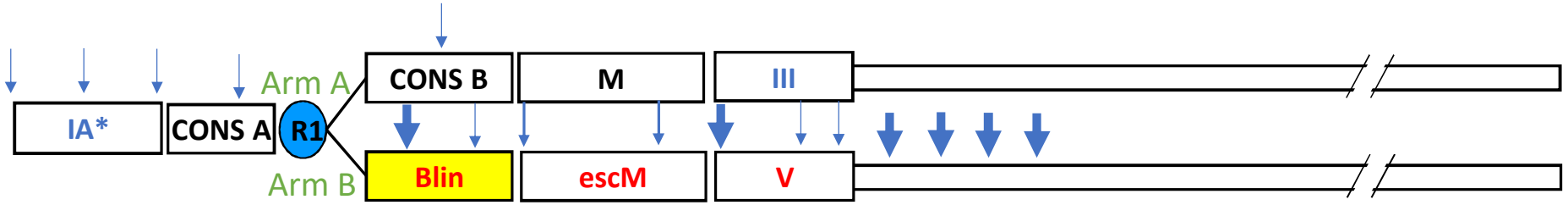
6-MP p.o. (28 d) 60 mg/m²/day

MTX i.th.

Age-adjusted dose:

< 1 year:	6 mg
1 to < 2 years:	8 mg
2 to < 3 years:	10 mg
≥ 3 years:	12 mg

SR-B-ALL



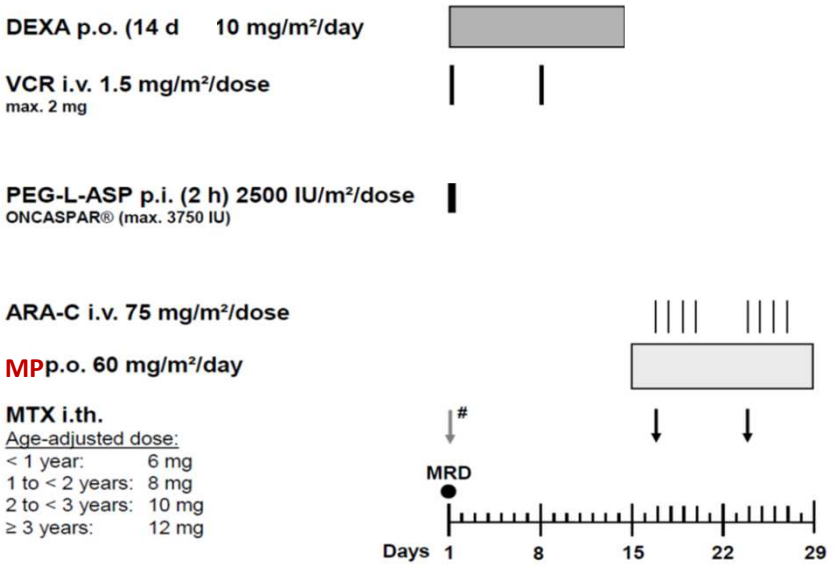
Consensus - investigational arm:
Intensified i.th. therapy according to the original escMTX scheme (COG) plus additional i.th.-doses in Maintenance treatment phase

Esc MTX

DRUG	ROUTE	DOSAGE	DAYS
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	1, 11, 21, 31 & 41
Intravenous Methotrexate (IV MTX)	IV over 2-5 min (undiluted) or 10-15 min (diluted)	___mg/m²/dose*	1, 11, 21, 31 & 41
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	1 & 31

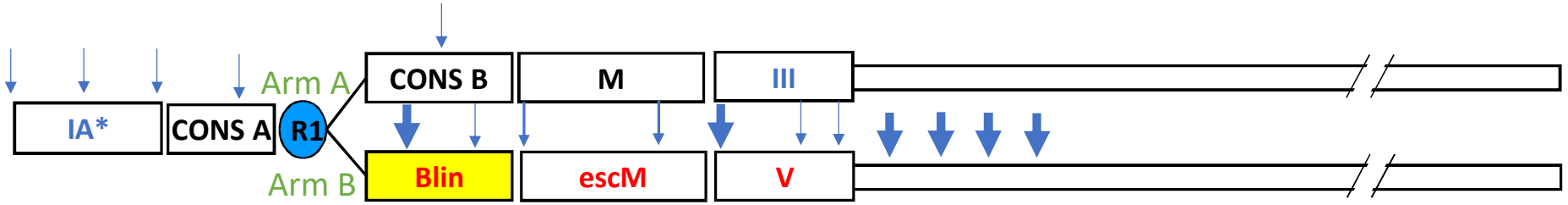
↓ i.th. MTX; *2xDNR

Protocol „V“



AIEOP-BFM
ALL Study group

SR-B-ALL

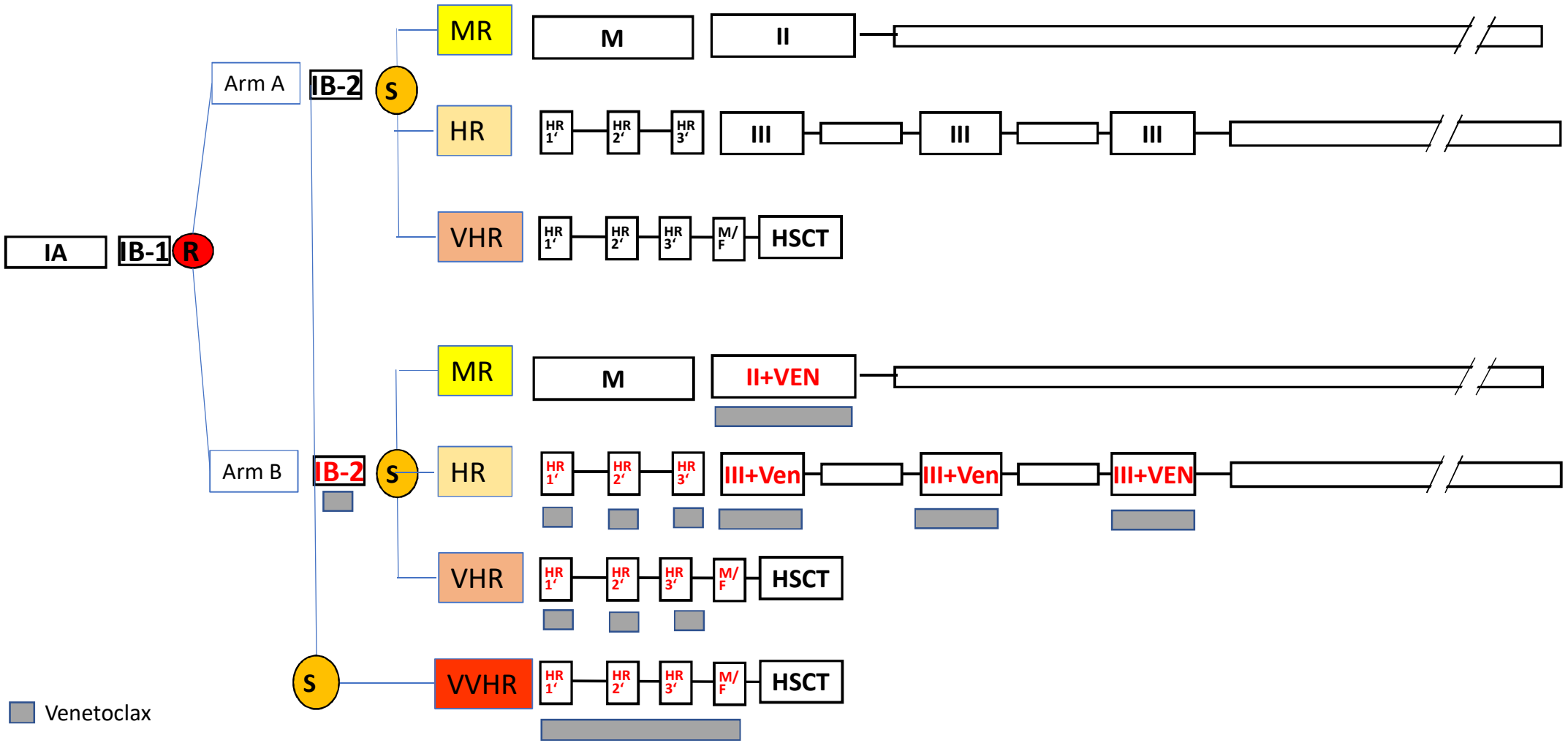


	Control Arm (PIII)	Blin Arm	Difference
Prednisolone**	2040 mg/m2	2040 mg/m2	-
Dexamethasone	165 mg/m2	140 mg/m2	-15%
Anthracycline	120 mg/m2	60 mg/m2	-50%
Vincristine	9 mg/m2	16.5 mg/m2	+83%
PEG-Asparaginase	7500 E/m2	7500 E/m2	-
6-MP***	3080 mg/m2	1680 mg/m2	-45%
6-TG	840 mg/m2	0	-100%
Cyclophosphamide	2500 mg/m2	0	-100%
Cytarabine	1800 mg/m2	900 mg/m2	-50%
Methotrexate**	20.000 mg/m2	Max. 1000 mg/m2	-95%
i.th. Methotrexate	11 doses	15 doses	+4

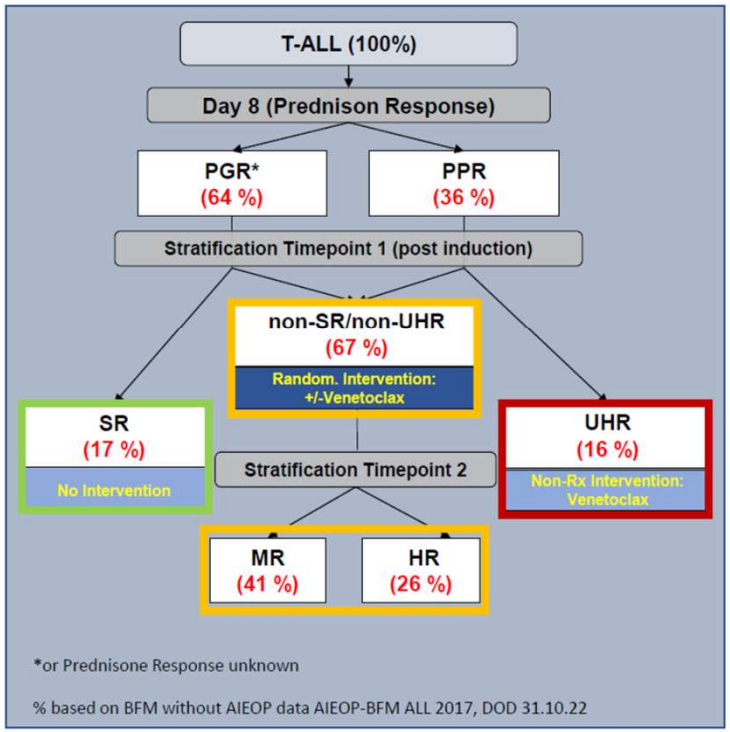
↓ i.th. MTX *2xDNR ** without prephase. ***without Maintenance

Venetoclax: to introduce the principle to sensitize blasts for chemo-induced apoptosis

Basis consent for Venetoclax-Randomization --- > Contact Abbvie



AIEOP-BFM ALL 2025 T-ALL - Risk stratification final



Stratification at TP1

Standard Risk (SR) (EFS ~91%)
- complete remission on day 33 and
- FCM-MRD in BM on day 15 <10% and
- Prednisone Good-Response and
- one of the following:
  - PCR-MRD at TP1 negative for all investigated markers with at least one marker with a quantitative range of ≤ 10^{-4} or
  - PCR-MRD result at TP1 inconclusive and FCM-MRD at TP1 NOT positive and FCM-MRD in BM d15 < 0.1%

non-Standard Risk/non-Ultra High Risk (non-SR/non-UHR) (EFS ~75%)
- No SR and no UHR criteria

Ultra High Risk (UHR) (EFS ~64%)
- PCR-MRD at TP1 ≥ $5x10^{-2}$ or
- Evidence of extramedullary non-remission at end of induction

Stratification at TP2 (only non-SR/non-UHR)

Medium Risk (MR)
- no HR criteria

High Risk (HR)
- CNS3 and no SR or
- Prednisone Poor-Response or
- No CR at TP1 or
- PCR-MRD# at TP2 ≥ $5x10^{-4\$}$

Indication for alloHSCT:
- MRD at TP2 ≥ $5x10^{-4}$
- Risk group UHR
- MRD increase during HR post-consolidation therapy to ≥ $5x10^{-4}$

#PCR-MRD can be replaced by FCM-MRD if PCR-MRD measurements are not available.