CAALL-F01

OVERVIEW, OUTLINES

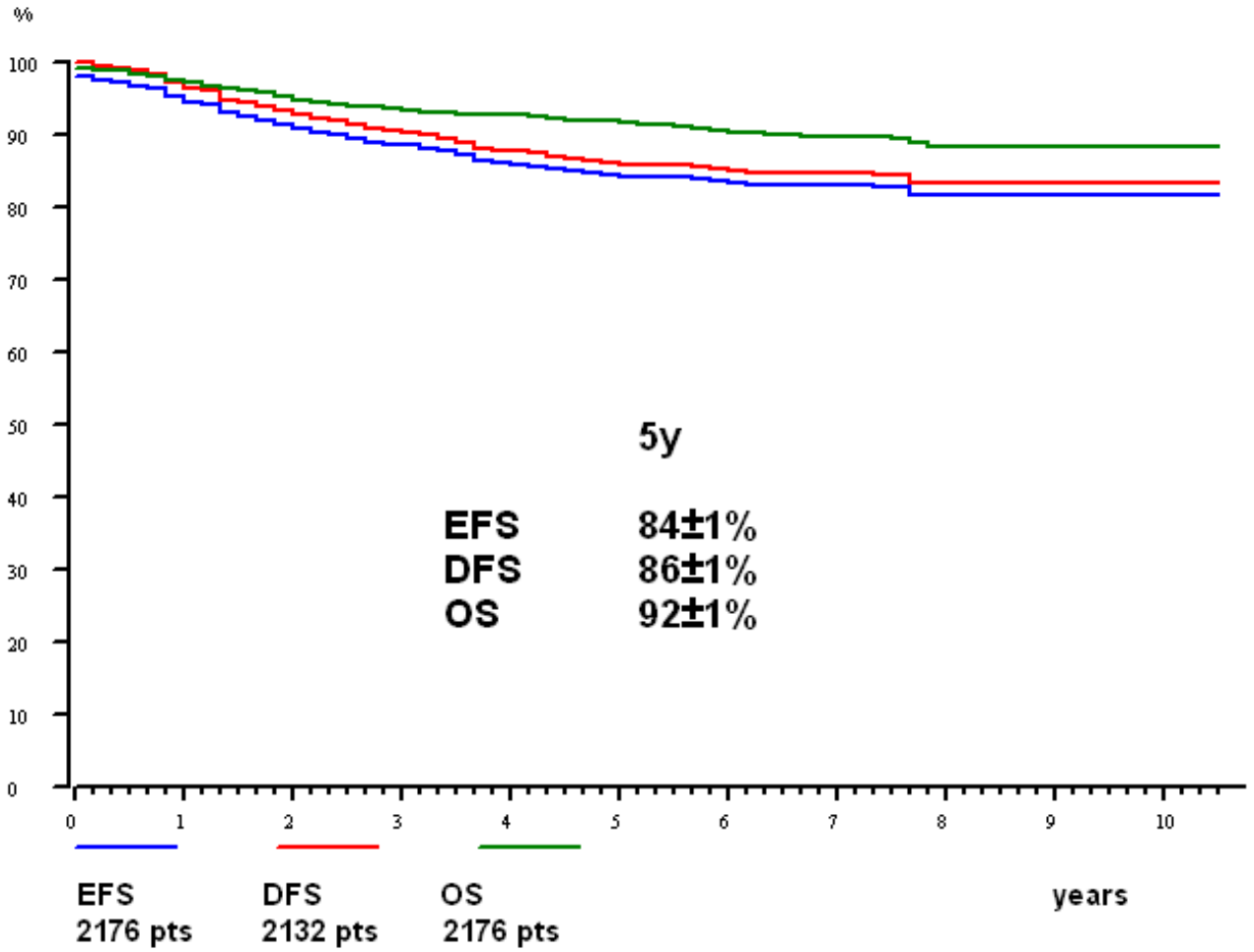
COMITE LEUCEMIES

19 NOVEMBRE 2015

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Current outcomes in childhood and adolescent ALL:

FRALLE 2000 protocol: 2176 pts; 1-20 years



FRALLE Group

	Event-Free Survival		Overall Survival	
	5 years	8 years	5 years	8 years
FRALLE 2000 (2146 pts)	84.0%	82%	91%	89%
EORTC 58951 (1947pts)	82.6%,	81.3%	89.7%	88.1%

A more complex reality (1) ?

- Lack of efficacy
  - ~15% of the pts overall still relapse

- Excessive toxicity:
  - deaths in CR
  - some «EFS» pts have more sequelae than CR2 pts
  - no global indicator of the burden of therapy

More is no more better for most of the patients!

- Both:
  - some early deaths
  - absence of plateau in B-lineage ALL

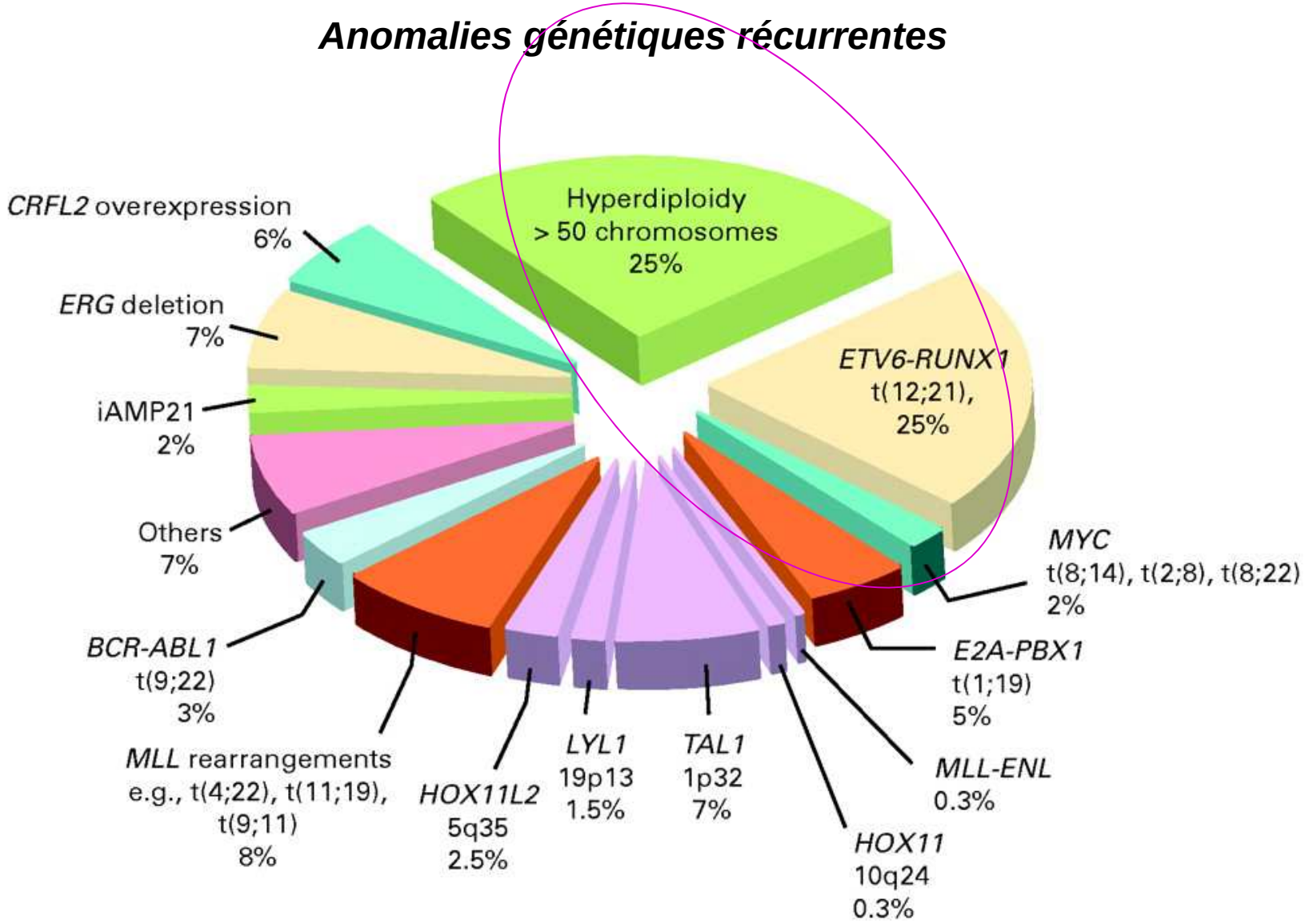
A more complex reality (2) ?

- In absolute numbers, most of the relapses come from the SR and MR groups
  - even defined by MRD
  - ++ in the B-lineage ALL

A challenge for MRD only?

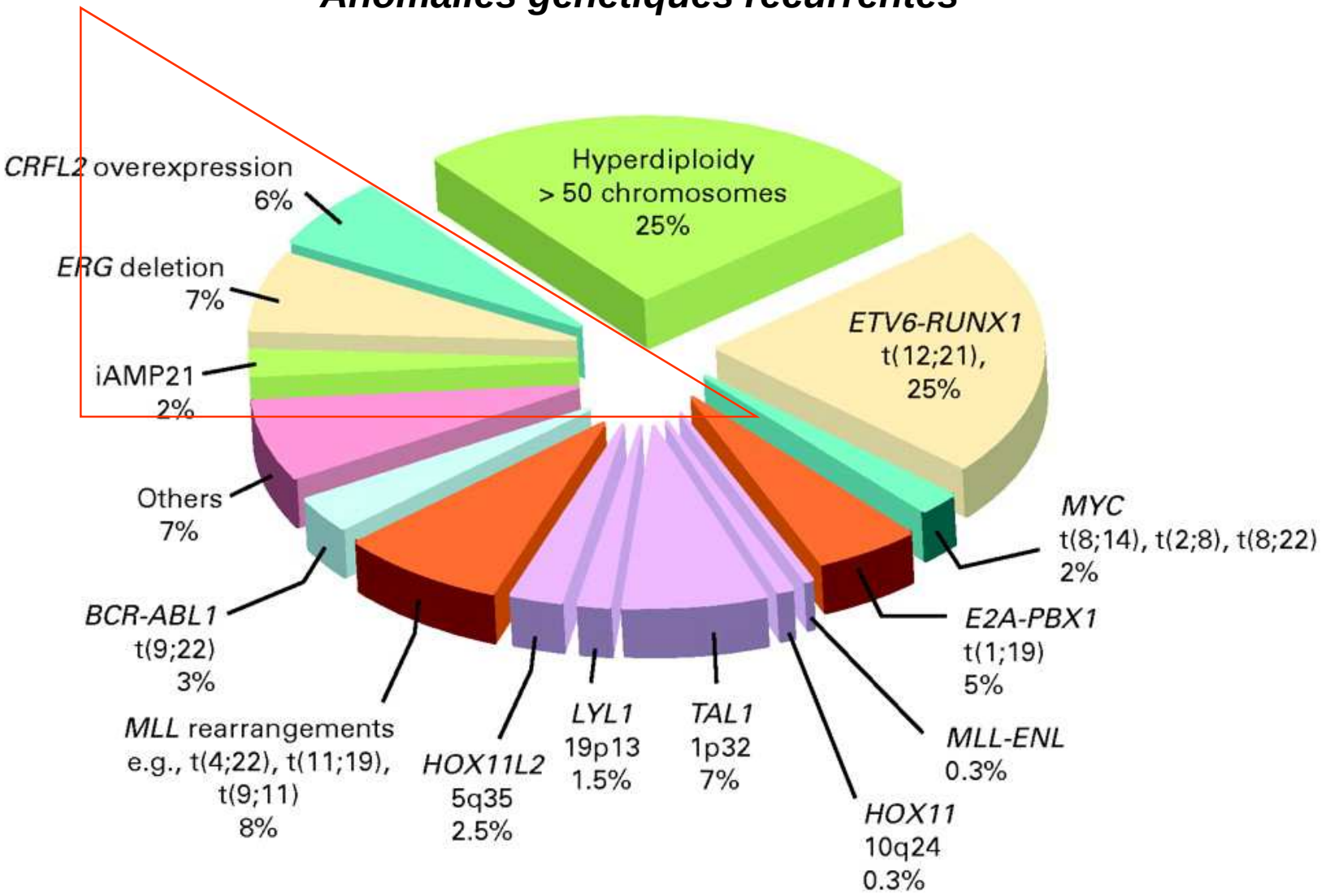
- 94 % of the pts have SR or MR MRD features
- represent 81% of the events
- Need to add-on upfront biologic features
  - **IKAROS deletions (IKZF1) ++**
  - BCR-ABL like / B-other?
  - High/very-high CRLF2?
  - Others?

Anomalies génétiques récurrentes



Pui C et al. JCO 2011

Anomalies génétiques récurrentes



Pui C et al. JCO 2011

A more complex reality (3) ?

- In absolute numbers, most of the relapses come from the SR and MR groups (even defined by MRD)

- Increasing complexity of biology
  - the leukemia
  - the host
  - their interactions

- 80% of the children in the world :
  - outside privileged countries

How to increase efficacy?

- Better detect a high risk of relapse (genetics + MRD / MRD NGS?)
- Better treat
  - Better conventional drugs: e.g. pegylated asparaginase, new nucleoside analogues
  - Increase compliance (educational programs)
  - New drugs

Rationale

Different API/ dosing / schedules of ONCASPAR® during induction therapy in first-line ALL protocols around the world

- 2500 IU/m^2 one infusion: COG/DFCI protocols(US) (ONCASPAR LONZA)
- 3500 IU/m^2 one infusion: St Jude protocol (US) (ONCASPAR LONZA)
- 2500 IU/m^2 two infusions: AIEOP-BFM (Europe) (ONCASPAR KH)
- 2500 IU/ m^2 two infusions: EORTC (Belgium) (ONCASPAR KH)
- 2500 IU/ m^2 one infusion : Interfant 06(mainly Europe) (ONCASPAR KH)
- 1000 IU/m^2 two infusions: UKALL 2010 (UK) (ONCASPAR KH)
- 1500 IU/m^2 two infusions : DCOG protocol (NL) (ONCASPAR KH)

Rationale

Interesting results of the UKALL 2003 Protocol:

- 5 year EFS 86% , 5 y OS 92%
  - Vora A et al, Lancet Oncol 2013 and 2014.
- obtained using a low dosage per infusion of Oncaspar KH (1000 IU/m^2 IM) but repeated at 15 day intervals for induction.
- in a subgroup of 482 patients treated in UKALL 2003, CYK Fong et al (ASH 2011) show that the dose that provides adequate asparaginase activity (> 100 IU/L) in 86% of samples studied after the 1st and second injection.

Proposal

- A new CAALL-F01 only integrating pegasparagase (the US product with API from LONZA)

CAALL-F01 : Experimental design

- Nation-wide French prospective multicentric study in 28 centers
  - SFCE centers
  - AYA units
- Stratification based on type of ALL
  - B vs T
  - risk classification
    - 3 risk-groups for BCP-ALL
    - 2 risk-groups for T-cell-ALL

CAALL-F01: main objectives

1. **Adequate asparaginase activity at D33 of induction (≥100 IU/L)**

   (21 days after Pegaspargase n°1, 7 Days after Pegaspargase n°2)

2. **Toxicity: incidence of targeted grade 3-4 toxicities asparaginase-related** (CNS thrombosis, pancreatitis, anaphylaxis, hyperbilirubinemia)
   - From D12 to D49 of induction (or before D8 of consolidation)

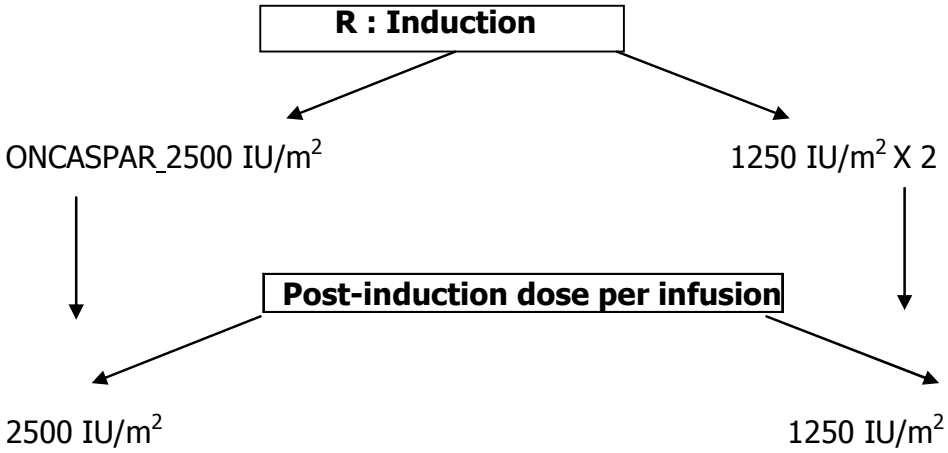
CAALL-F01: randomisations

1. **For the B-SR, B-MR and T-SR groups (83-85% of the pts):** to compare the PK (asparaginase activity) and targeted toxicities in pts receiving either **one infusion** of ONCASPAR® 2500 IU/m^2 at D12 (ARM 1) or **2 infusions** of ONCASPAR® 1250 IU/m^2 at D12 and D26 (ARM 2) during induction therapy.

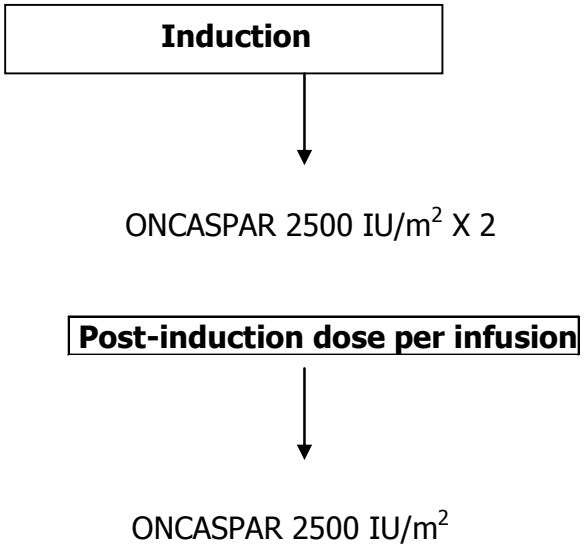
2. **For the high-risk/very high risk group (B-HR/VHR and T-HR/VHR) (15-17% of the pts):**

   no randomisation but evaluation of the PK (asparaginase activity) and targeted toxicities in pts receiving **2 infusions** of ONCASPAR® 2500 IU/m^2 given at D12 and D26 during induction therapy.

Population : B-SR, B-MR AND T-SR



Population B-HR/B-VHR AND T-H/VHR



STRATIFICATION

CAALL- F01: stratification overview

- BCP- ALL: 3 groups
  - B-standard risk
  - B-medium risk
  - B-high/very high risk
- T-cell ALL: 2 groups
  - T: standard risk
  - T: high/very high risk

Asparaginase studies

- Asparaginase activity
  - all the pts (during 5 years)
  - plasma
  - centralized in Robert Debré Hospital: ~20,000 samples
- Asparagine depletion:
  - 3 centers only (Paris x2 and Lyon) during 2 years
  - CNS and plasma
  - centralized in Lyon: ~ 1500-2000 samples
- Antibodies
  - All the pts during 2 years
  - Serum
  - Centralized in US or Europe: ~2000-2500 samples

Sampling for CAALL-F01 (all centers)

	Induction*	Consolidation	M phase	Delayed Intensification	M phase	Delayed intensification n°2	Total sampling
ALL B-SR 1000 pts	**D12** D19 D26 D33 D40	D8 **D8** D15 D43 D71		**D4** D8 D15			Ase: 10 AB: 3
ALL B-MR 480 pts	**D12** D19 D26 D33 D40	D22 **D22** D50		**D4** D8 D15 D50			Ase: 9 AB: 3
ALL B-HR 230 pts	**D12** D19 D26 D33 D40	D22 **D22** D50		**D4** D8 D15 D50		**D4** D8 D15 D50	Ase: 12 AB: 4
ALL T-SR 150 pts	**D12** D19 D26 D33 D40			**D4** D8 D15			Ase: 6 AB: 2
ALL T-HR 110 pts	**D12** D19 D26 D33 D40	**D43** D43		**D4** D8 D15 D50		**D4** D8 D15 D50	Ase:11 AB: 4

Dxx: antibodies (AB) (first 2 years only)

Dxx: asparaginase activity (Ase)(whole study duration)

B-Standard-risk : inclusion criteria

- **NCI standard–risk ALL (SR)**
  - BCP-ALL
  - 365d <age< 10y AND WBC < 50 G/L
  - Without
    - Ph1/BCR-ABL, iAMP21, MLL rearrangement, hypodiploidy<44 chr, monosomy 7, t(1;19)/TCF3-PBX1, t(17;19)/TCF3-HLF,

AND

- No CNS-3 or testis involvement
- D8 Good Prednisone response

B-Medium-risk : inclusion criteria

- **NCI SR with D8 Poor Prednisone response**
- **NCI HR with D8 Good Prednisone Response**
- t(1;19)/TCF3-PBX1
- monosomy 7
- testis involvement

if no HR criteria

AND

- No CNS-3

B- High/Very High-risk : inclusion criteria

- **NCI HR and D8 poor prednisone response**

AND/OR

- MLL gene rearrangement
- hypodiploidy (<44 chr)
- iAMP21
- t(17;19)(q22;p13) / TCF3-HLF*

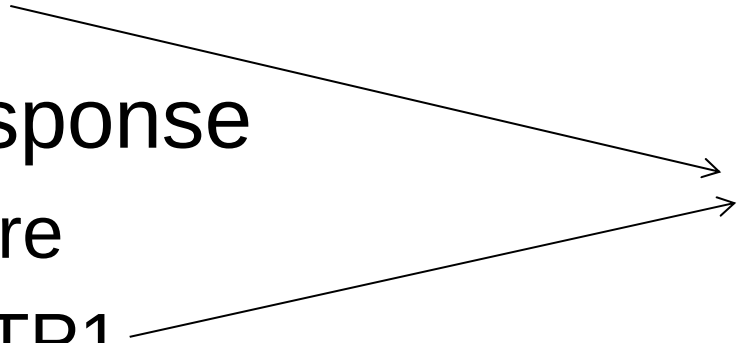
AND/OR

- **CNS-3**

STRATIFICATION SWITCHES
after induction therapy in B lineage-ALL

Can be linked to:

- IKZF1 status
- Inadequate response
  - Induction failure
  - High MRD at TP1
  - High MRD at TP2



Must be available at D42-50

STRATIFICATION SWITCHES
LINKED TO IKZF1 & MRD IN PTS WITH B lineage-ALL

	TP1		TP2
	IKZF1 No del	**IKZF1 del**	
B-SR	< 10^{-3}: SR	< 10^{-3}: MR	< 10^{-4}: stay in group defined after TP1 **≥ 10^{-4} <10^{-3}: HR** **≥ 10^{-3}: VHR**
	≥10^{-3} <10^{-2}: MR	≥10^{-3} <10^{-2}: HR	
	≥ 10^{-2}: HR	≥ 10^{-2}: HR	
B-MR	< 10^{-3}: MR	< 10^{-3}: MR	< 10^{-4}: stay MR **≥ 10^{-4} <10^{-3}: HR** **≥ 10^{-3}: VHR**
	≥ 10^{-3}: HR	≥ 10^{-3} HR	**< 10^{-3}: stay HR** **≥ 10^{-3}: VHR**
B-HR/VHR	HR/VHR	HR/VHR	**< 10^{-3}: HR** **≥ 10^{-3}: VHR**

SR,HR,VHR: standard, high, very high risk groups; TP: Time Point
HSCT: hematopoietic stem cell transplantation (only VHR pts go to HSCT)

NB: MR/HR pts presenting an induction failure confirmed by a MRD-TP1 ≥ 5 x10^{-2} go to VHR

T-cell Standard risk : inclusion criteria

- T-cell ALL
- AND D8 good prednisone response

  AND no CNS3

  AND D35 Complete remission

  AND MRD TP2 < 10^{-4}

High risk/VHR T-cell ALL : inclusion criteria

T-cell ALL and D8 PPR

AND/OR

CNS 3

AND/OR

No CR at D35

AND/OR

T-SR and MRD TP2 ≥ 10^{-4}

Table 4: stratification switches linked to MRD in patients with T-ALL

	TP1	TP2 (post consolidation)	TP3 (post VANDA course i.e. HR or VHR pts)
T-SR	**not decisional**	$<10^{-4}$: stay SR	***NA***
		$10^{-4} \leq MRD < 10^{-3}$: HR	$<10^{-4}$: stay HR
			$\geq 10^{-4}$: T-VHR
		$\geq 10^{-3}$: VHR	to be done for HSCT timing
T-HR	$<10^{-2}$: stay HR	$<10^{-3}$: stay HR	$<10^{-4}$: stay HR
			$\geq 10^{-4}$: VHR
	$\geq 10^{-2}$ & D8 PPR: VHR	$\geq 10^{-3}$: VHR	to be done for HSCT timing

SR,HR,VHR: standard, high, very high risk groups
PPR: Poor Prednisone Response
TP: Time Point; HSCT: hematopoietic stem cell transplantation (only VHR pts got o HSCT)

Table 5: MRD Time Points according to risk-groups

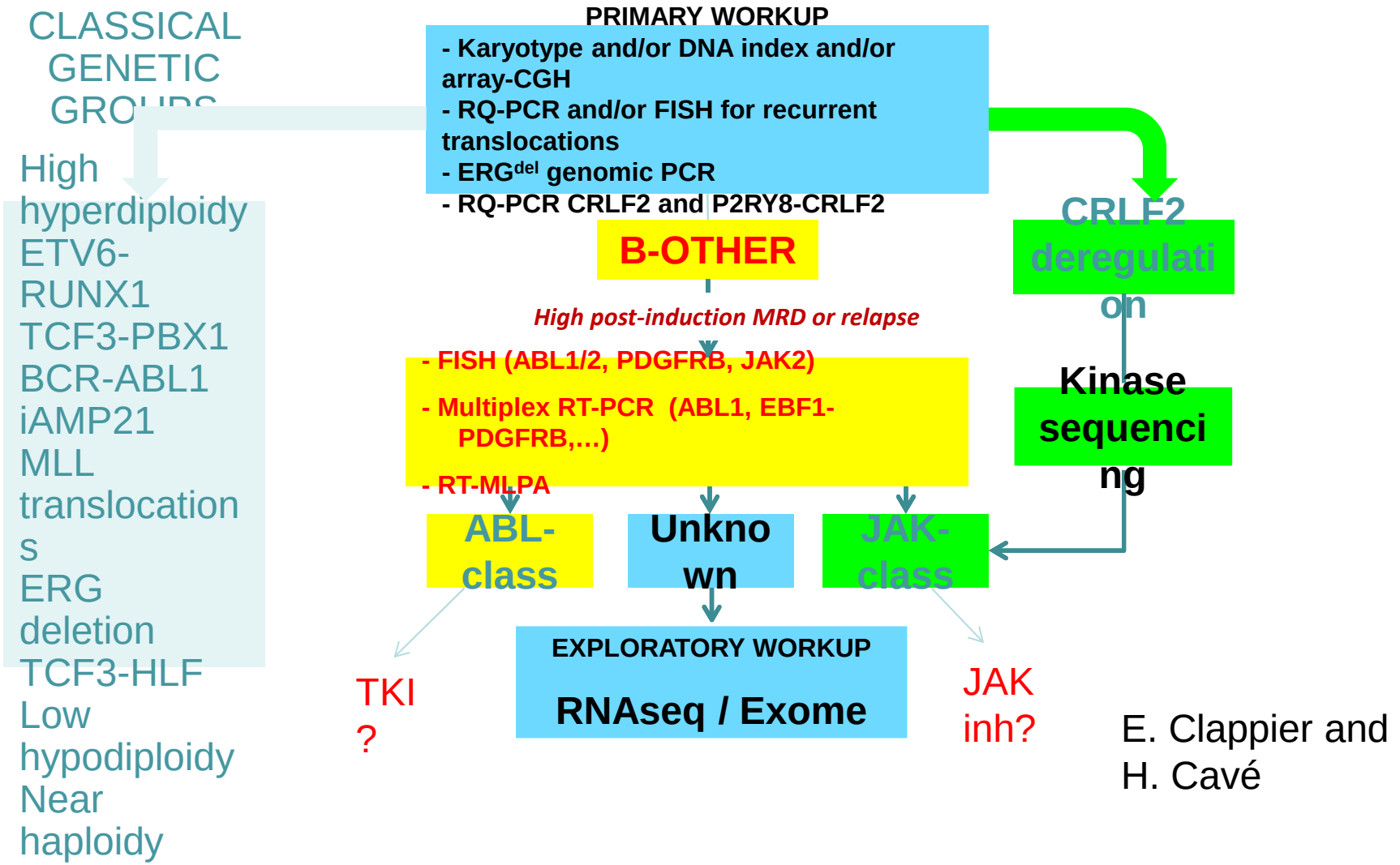
	TP1 (post induction)	TP2 (post consolidation)	TP3*
B-SR	D35-42	D65-75	NA
B-MR	D35-42	D95-105	NA
B-HR/VHR	D35-42	D95-105	D125-135
T-SR	D35-42	D85-95	NA
T-HR/VHR	D35-42	D95-105	D125-135

MRD samplings are to be performed after sufficient hematological recovery (at least PNN >0,5 G/L & platelets> 50 G/L)

* Only if indicated:
  - B-lineage: patients with TP2≥10^{-3}
  - T- lineage: patients with TP2 ≥10^{-4}

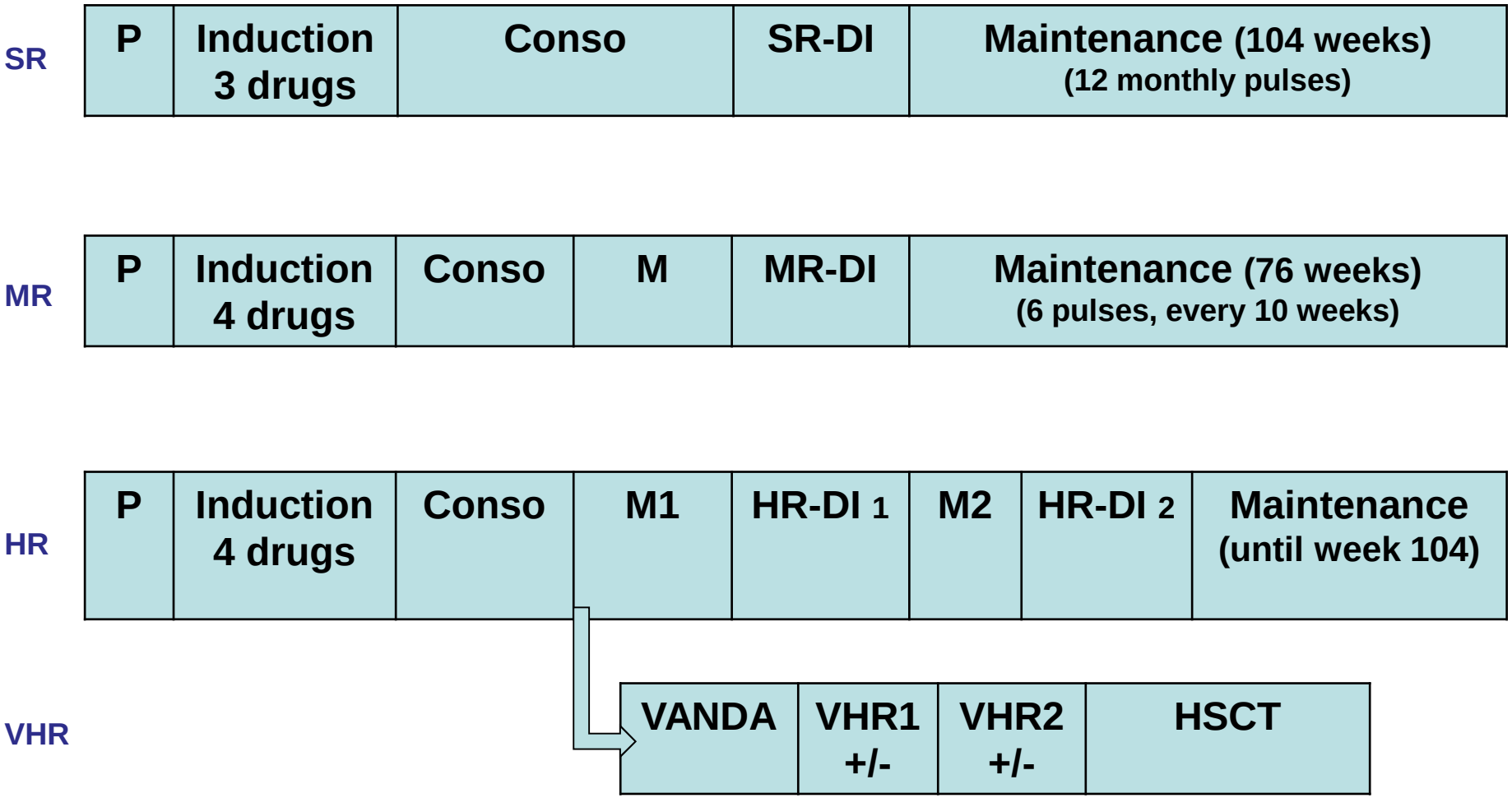
Prospective Diagnosis of BCR-ABL like ALL in the upcoming French Studies

(children, adolescents and adults) : CALL-F01, INTREALL, GRAALL



E. Clappier and H. Cavé

CAALL-F01: B-lineage ALL groups

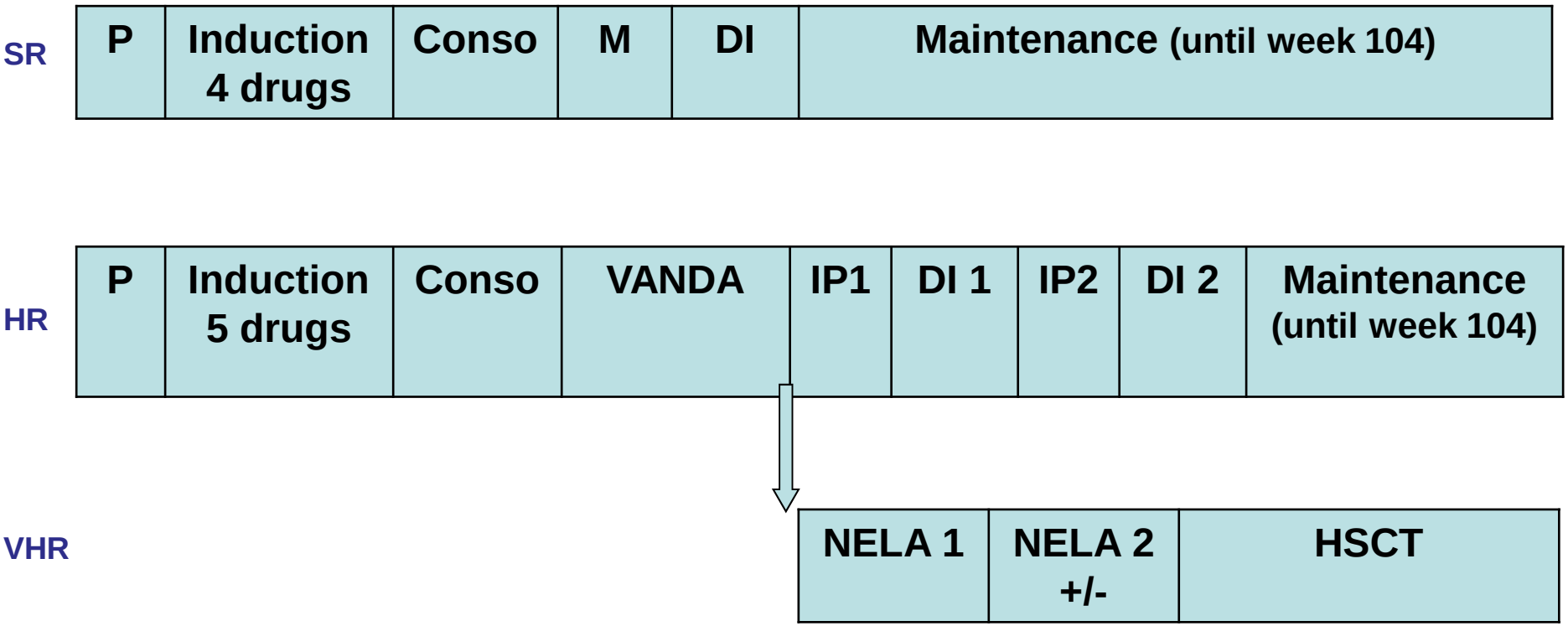


P: Prednisone prephase; Conso: consolidation course

DI: delayed intensification; M: high dose MTX cycles;

HSCT: hematopoietic stem cell transplantation; VANDA/VHR1V/HR2: intensive courses pre HSCT

CAALL-F01:T-cell ALL groups



P: Prednisone prephase; Conso: consolidation course; M: high dose MTX cycles; IP: intermediate phase with high dose MTX cycles

DI: delayed intensification; VANDA: intensive chemotherapy course: NELA: nelarabine course

HSCT: hematopoietic stem cell transplantation;

Indications of hematopoietic stem cell transplantation

- ***Indications according to genetics:***
  - B lineage:
    - Hypodiploidy < 40 chromosomes
    - t(17;19)/E2A-HLF
    - MLL rearrangement and NCI-HR
- ***Indications according to response:***
  - B lineage:
    - MR/HR induction failure with MRD-TP1 ≥ $5x\ 10^{-2}$
    - MRD-TP2 ≥ 10^{-3}
  - T-lineage:
    - D8 PPR and MRD-TP1 ≥ 10^{-2}
    - MRD-TP2 ≥ 10^{-3}
    - MRD-TP3*≥ 10^{-4}

TP3: performed if TP2 ≥10^{-4}

Summary of Intrathecal injections for CNS1 patients (most frequent situation)

	Induction	Consolidation		M phase	Delayed Intensification	M phase n°2	Delayed intensification n°2	Maintenance	Total ITs
ALL B-SR	D1 D13 D24	D2 D30 D58			D4 D31			M1, M3, M5, M7, M9, M11, M13, M15	16
ALL B-MR	D1 D13 D24	D3 D31		D9 D23 D37 D51	D4 D31			M1, M3, M5, M7, M9, M11	17
ALL B-HR	D1 D13 D24	D3 D31		D9 D23 D37 D51	D4 D31	D9 D23 D37 D51	D4 D31	NO	17
ALL T-SR	D1 D13 D24	D3 D17		D9 D23 D37 D51	D4 D31			If WBC <100 G/L W2,W8,W14, W20,W26,W32	17
								If WBC ≥100 G/L MTX HD +IT W2,W8,W14, W20,W26,W32	17
ALL T-HR	D1 D13 D24	D3 D31	VANDA D5	D9 D23 D37	D4 D31	D9 D23 D37	D4 D31	If WBC <100 G/L W2,W8,W14, W20,W26,W32	22
								If WBC ≥100 G/L MTX HD +IT W2,W8,W14, W20,W26,W32	22

Summary of Intrathecal injections for CNS2 or TLP+ patients

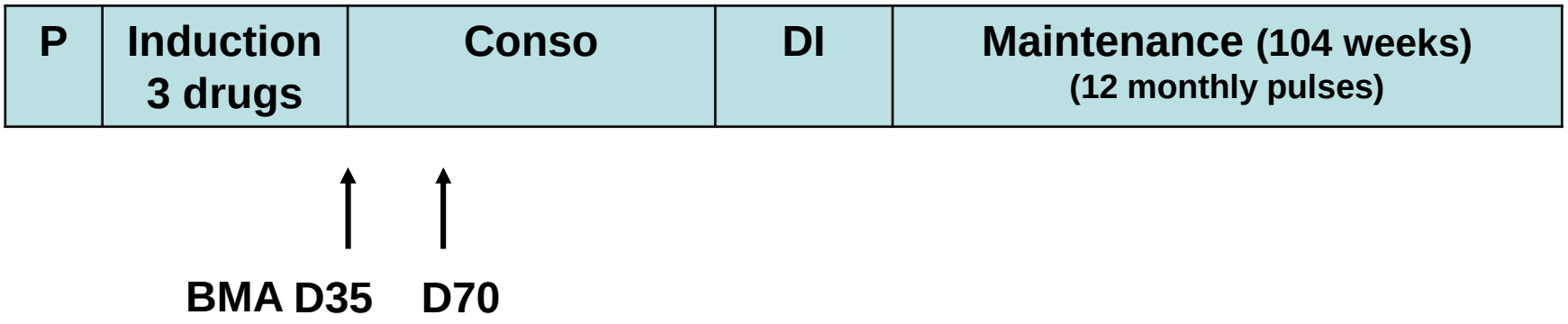
	Induction	Consolidation		M phase	Delayed Intensification	M phase2	DI n°2	Maintenance	Total ITs
ALL B-SR	D1 D13 D24 + D9 D18	D2 D30 D58			D4 D31			M1, M3, M5, M7, M9, M11, M13, M15	18
ALL B-MR	D1 D13 D24 + D9 D18	D3 D31		D9 D23 D37 D51	D4 D31			M1, M3, M5, M7, M9, M11	19
ALL B-HR	D1 D13 D24 + D9 D18	D3 D31		D9 D23 D37 D51	D4 D31	D9 D23 D37 D51	D4 D31	NO	19
ALL T-SR	D1 D13 D24 + D9 D18	D3 D17		D9 D23 D37 D51	D4 D31			If WBC <100 G/L W2,W8,W14, W20,W26,W32	19
								If WBC ≥100 G/L MTX HD +IT W2,W8,W14, W20,W26,W32	19
ALL T-HR	D1 D13 D24 +D9 D18	D3 D31	VANDA D5	D9 D23 D37	D4 D31	D9 D23 D37	D4 D31	If WBC <100 G/L W2,W8,W14, W20,W26,W32	24
								If WBC ≥100 G/L MTX HD +IT W2,W8,W14, W20,W26,W32	24

Summary of Intrathecal injections for CNS3

	Induction	Consolidation		M phase	Delayed Intensification	M phase n°2	Delayed intensification n°2	Maintenance	Total ITs
ALL B-HR	D1 D13 D24 D9 D4	D3 D31 D16 D46		D9 D23 D37 D51	D4 D31	D9 D23 D37 D51	D4 D31	4 supplementary TIT (M1, M4, M7, M10)	25
ALL T-HR	D1 D13 D24 D9 D4	D3 D31 D16 D46	VANDA D5 D20	D9 D23 D37	D4 D31	D9 D23 D37	D4 D31	6 MTX HD +IT W2,W8,W14, W20,W26,W32	27

CAALL-F01: B-SR
(BCP ALL standard-risk)

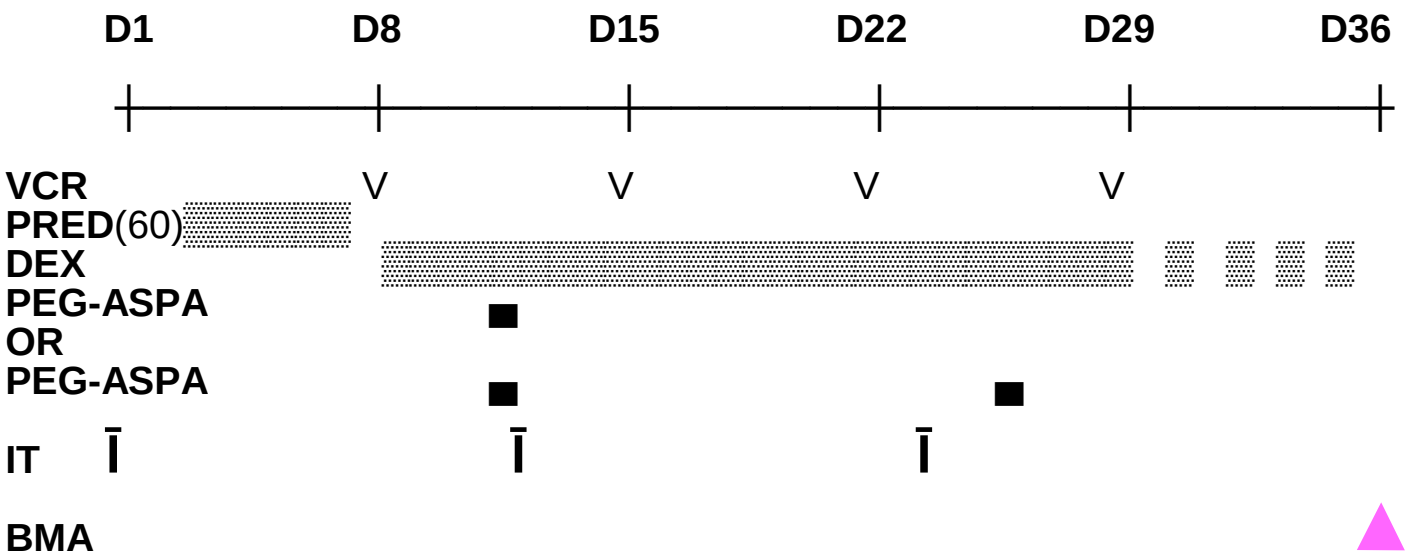
General design



P: Prednisone prephase; Conso: consolidation, DI: delayed intensification

BMA: bone marrow aspiration with MRD evaluation (TP1, TP2)

CAALL-F01: B-SR INDUCTION THERAPY



Vincristine (VCR)	**:** 1.5 mg/m^2 (IV)	D8, D15, D22, D29 (MAX 2 mg/infusion)
Pegaspargase (PEG-ASPA)	**: 2500 IU/m^2 (IV)**	**D12**
OR		
Pegaspargase (PEG-ASPA)	**: 1250 IU/m^2 (IV)**	**D12 and D26**
		dose per infusion according to randomisation
Prednisolone (PRED)	**:** 60 mg/m^2/d PO	D1-D7
Dexamethasone (DEX)	**:** 6 mg/m^2/d PO	D8-D28 then tapered over one week
Methotrexate (IT)	**:** see appendix 5	D1, D13, D24
Bone marrow aspiration (BMA): with MRD evaluation		D35 (no later than D42)

CAALL-F01: B-SR: CONSOLIDATION THERAPY

	D1	D8	D15	D22
Vincristine	V	V		
Dexamethasone	▨			
PEG-ASPA		PEG		
6 mercaptopurine	▒	▒	▒	
Methotrexate		m	m	m
IT	IT			

	D29 MRD-TP2*	D36	D43	D50
Vincristine	V	V		
Dexamethasone	▨			
PEG-ASPA		PEG		
6 mercaptopurine	▒	▒	▒	
Methotrexate		m	m	m
IT	IT			

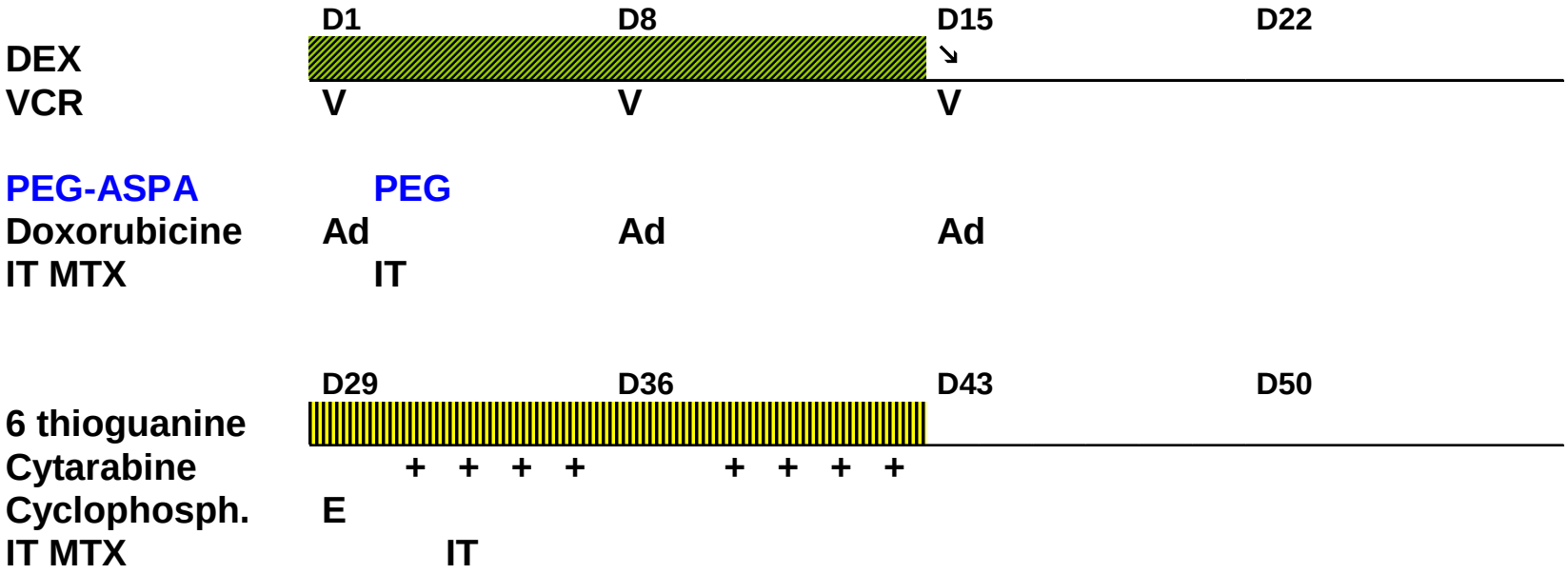
	D57	D64	D71	D78
Vincristine	V	V		
Dexamethasone	▨			
PEG-ASPA		PEG		
6 mercaptopurine	▒	▒	▒	
Methotrexate		m	m	m
IT	IT			

Vincristine	: 1,5 mg/m^2 (IV)	: D1, D8, D29, D36, D57, D64 (MAX 2 mg/infusion)
Dexamethasone	: 6 mg/m^2/d (PO)	: D1 to D5 / D29 to D33 /D57 to D61
Pegaspargase*(PEG-ASPA)	**: 1250 or 2500 IU/m^2(IV)**	**: D8, D36, D64**
6 mercaptopurine	: 50 mg/m^2/d (PO)	: D1 to D21;D29-D50;D57-D78
Methotrexate(m)	: 25 mg/m^2/w (PO)	: D8, D15, D22, D36, D43, D50, D64, D71, D78
IT	: MTX see Appendix 5	: D2, D30, D58

*** dose of pegaspargase per infusion according to unitary dose of the initial randomisation**

*** MRD-TP2: bone marrow aspiration for second evaluation of MRD**

CAALL-F01: B-SR DELAYED INTENSIFICATION



Dexamethasone (DEX)	: **<u>10</u>** mg/m^2/d (PO)	: D1 to D15 (in 3 takes/day) tapered from D15
Vincristine (VCR)	: 1,5 mg/m^2/infusion (IV)	: D1, D8, D15 (MAX 2 mg/infusion)
Pegaspargase*(PEG-ASPA)	**: 1250 or 2500 IU/m^2 (IV)**	**: D4**
Doxorubicine	: 25 mg/m^2/infusion (IV)	: D1, D8, D15
6 thioguanine	: 60 mg/m^2/d (PO)	: D29 to D42
Cytarabine	: 75 mg/m^2/infusion (IV)	: D31, 32, 33, 34 and D38, 39, 40, 41 (total: 8)
Cyclophosphamide	: 1 g/m^2/infusion(IV)	: D29
Methotrexate IT	: see appendix5	: D4, D31

*** dose of pegaspargase per infusion according to unitary dose of the initial randomisation**

CAALL-F01: B-SR
Continuation therapy «maintenance»

- 104 weeks (i.e. total duration of ALL treatment: ~30 months)
- 12 pulses: one cycle every 4 weeks during the first year of maintenance
  - VCR: 1.5 mg/m^2/infusion: D1 (MAX 2mg per infusion)
  - DEX: 6 mg/m^2/day: D1 to D5
  - IT MTX: D15 (see appendix 5)

- 6MP: 50 mg/m^2/day
- MTX: 25 mg/m^2/week

NB: Bactrim® is to be given during the whole duration of maintenance and at least 3 months after stopping of 6MP/MTX

CAALL-F01: B-SR
Continuation therapy «maintenance»

Continuation therapy with 6 mercaptopurine (6-MP) and methotrexate (MTX) is an essential component of the treatment of childhood ALL.

The objective is to maintain the total leucocyte count between 2000 and 3000/mm^3. But this should be associated to neutrophils above 500/mm^3 and lymphocytes above 300/mm^3 and platelets above 50.000 mm^3

Liver function tests will not be decisional except if ALAT ≥ 10N and /or bilirubin ≥ 3N (Arico M et al, Leukemia 2005). In such cases other causes such as viral hepatitis or Gilbert syndrome should also be considered.

ii) Monitoring frequency

CBC should be evaluated every 2 weeks for the first 3 months and then monthly

CBC should be evaluated in case of fever or clinical problem.

CAALL-F01: B-SR
Continuation therapy «maintenance»

Table 15: Dose adaptation

Leucocyte/neutrophils (PN) /mm^3	% 6-Mercaptopurine dose	Methotrexate dose
< 1000 and/or PN < 500	0	0
1000-1999	66%	66%
2000-2999	100%**	100%***
3000-4000*	125%	125%
> 4000 *	150%	150%

Lymphocytopenia occurs frequently during maintenance treatment. A severe lymphocytopenia (< 300/mm^3) should lead to a 25-33% reduction of 6-MP without MTX modification.

Any increase of the dose should lead to a control CBC not earlier than one month after.

ALAT impact on conduct of maintenance treatment

- *If ALAT ≥ 10N and neutrophils ≤ 800/mm^3: Stop 6-MP/MTX for one week.*
- *If ALAT ≥ 10N and neutrophils > 800/mm^3: Stop MTX only for one week*

Any stopping of the treatment should not exceed one week and lead to at least weekly control of CBC count. If recovery is not observed within 2 weeks after stopping of the treatment, a bone marrow evaluation should be discussed.

Patients homozygous for TPMT deficiency: begin 6-MP at 7.5 mg/m^2/day. Patients heterozygous for TPMT deficiency: begin 6-MP at 30 mg/m^2/day and control as for other patients the CBC after 15 days.

CAALL-F01:
in case of allergy

Erwiniase

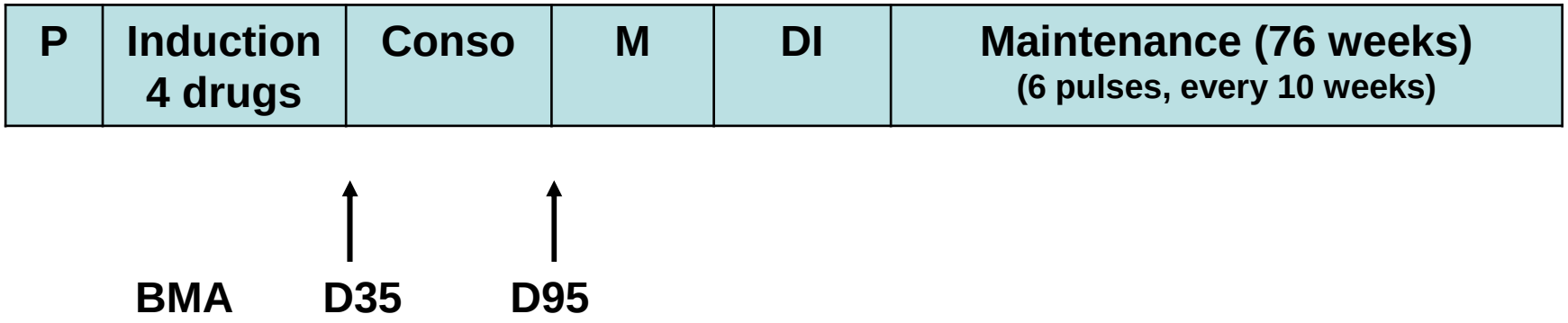
As dose/peak does not seem to influence the length of depletion, the choice in CAALL F01, where asparaginases are to be infused IV, is to recommend that

a) a single administration of 2500 IU/m^2 of pegaspargase is to be substituted by seven doses of 20,000 IU/ m^2 crisantaspase administered IV every other day for two weeks.

b) a single dose of 1250 IU/ m^2 is also to be substitued by seven doses of 20,000 IU/ m^2 crisantaspase administered IV every other day for two weeks.

CAALL-F01: B-MR
(BCP-ALL medium risk)

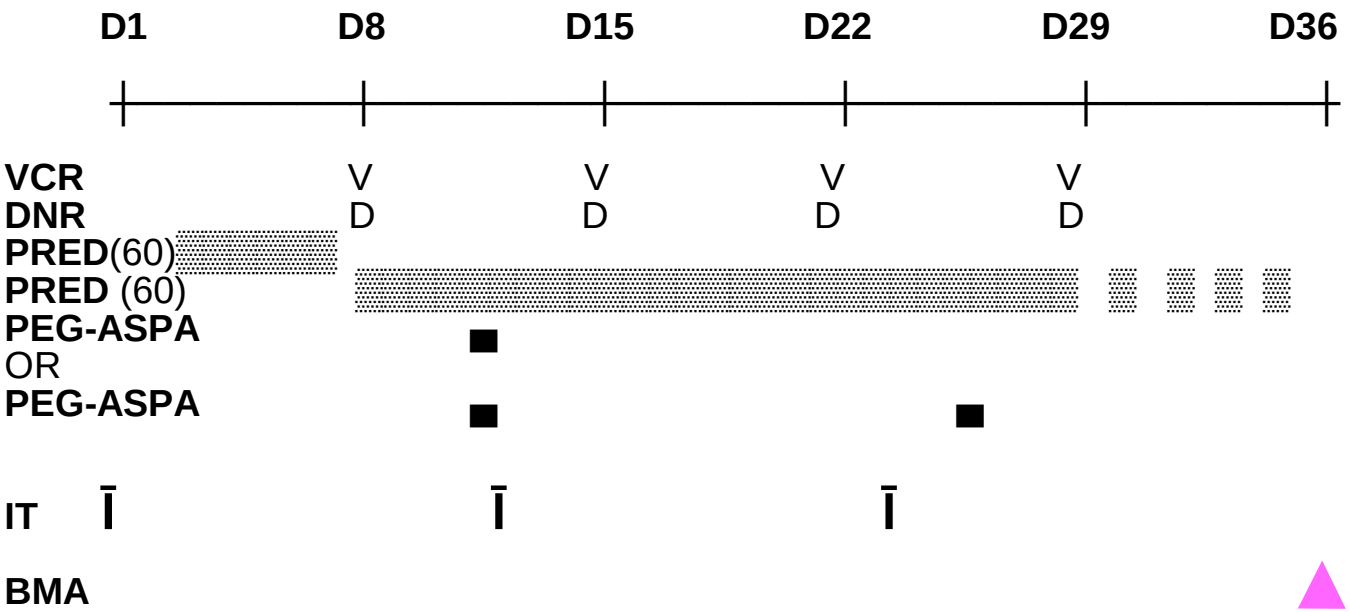
General design



Conso: consolidation course; M: high dose MTX cycle; DI: delayed intensification

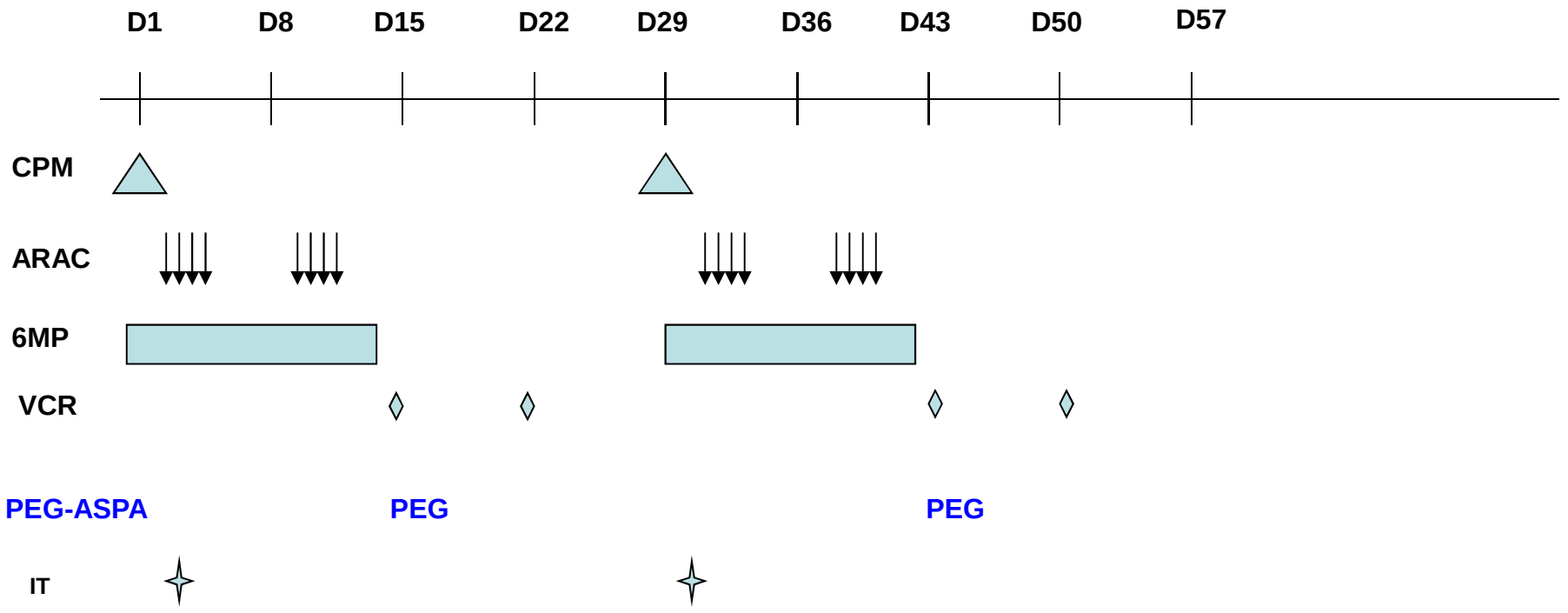
BMA: bone marrow aspiration with MRD evaluation (TP1, TP2)

CAALL-F01: B-MR INDUCTION THERAPY



Vincristine (VCR)	**:** 1.5 mg/m^2	D8, D15, D22, D29 (MAX 2 mg/infusion)
Daunorubicine (DNR)	: 30 mg/m^2	D8, D15, D22, D29
Pegaspargase (PEG-ASPA)	**: 2500 IU/m^2 IV**	**D12**
OR		
Pegaspargase (PEG-ASPA)	**: 1250 IU/m^2 IV**	**D12 D26 according to randomisation**
Prednisolone (PRED)	: 60 mg/m^2/d PO	D1-D7
Prednisolone (PRED)	: 60 mg/m^2/d PO	D8-D28 then tapered over one week
Methotrexate (IT)	: see appendix 5	D1
Triple IT	: see appendix 5	D13, D24
Bone marrow aspiration (BMA): with MRD evaluation		D35 (no later than D42)

CAALL-F01: B-MR CONSOLIDATION

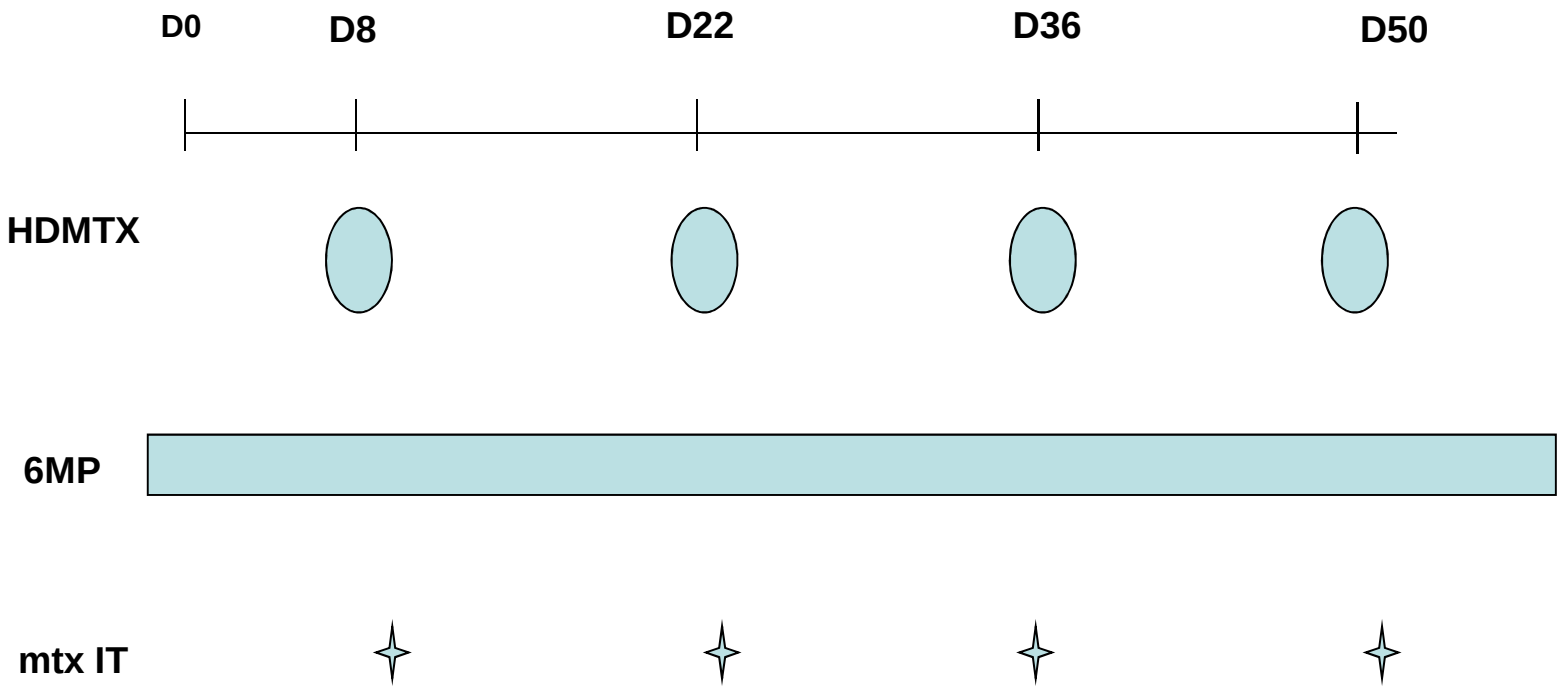


BMA with MRD TP2

6 mercaptopurine	60 mg/m²	PO	28 days	D1-14, D29-42
Cyclophosphamide	1g/m²	IV	2 infusions	D1, D29
Pegaspargase (PEG-ASPA)*	**1250 or 2500 IU/m²**	**IV**	**2 infusions**	**D15, D43**
Vincristine	1.5 mg/m²	IV	4 infusions	D15, D22, D43, D50 (MAX 2 mg/infusion)
Cytarabine	75 mg/m²	IV	16 infusions	D3-6, D10-13, D31-34, D38-41
Triple IT	See appendix 5	IT	2 injections	D3, D31

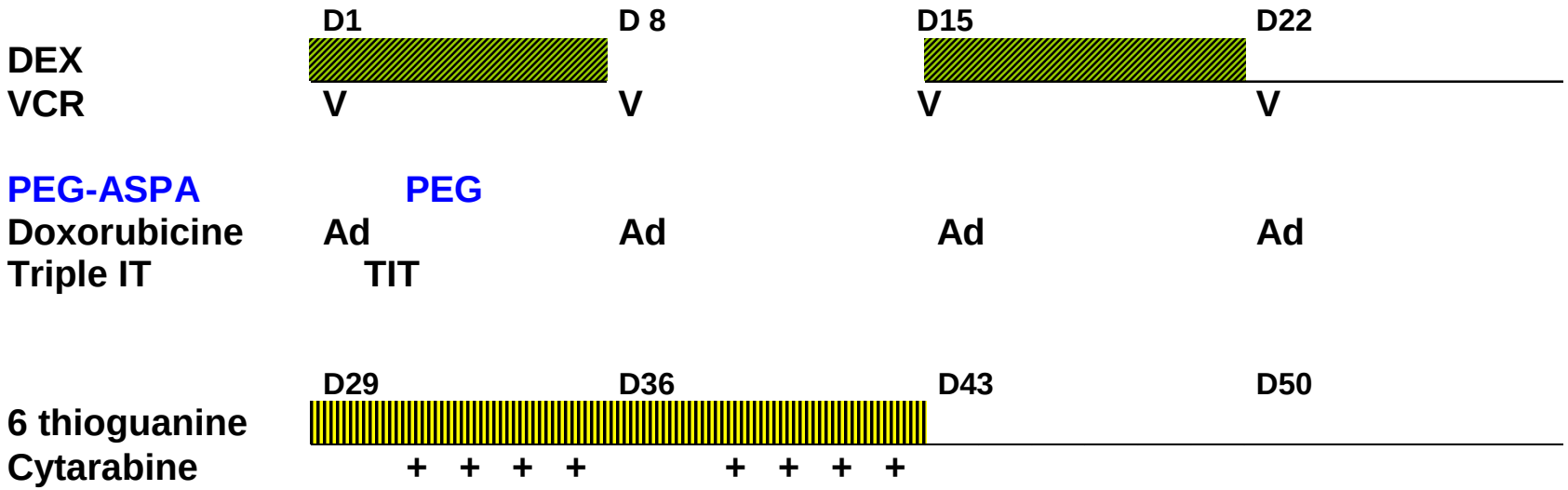
*** dose of pegaspargase per infusion according to unitary dose of the initial randomisation**

CAALL-F01: B-MR M phase



Methotrexate (HDMTX)	5 g/m²	IV 24h	4 infusions	D8,22,36,50; leucovorin rescue beginning at H42
6 mercaptopurine (6MP)	25 mg/m²	Per os	56 days	D1-56
Methotrexate IT	appendix 5	IT	4 days	D9,23,37,51

CAALL-F01: B-MR DELAYED INTENSIFICATION



Dexamethasone (DEX)	: **<u>10</u>** mg/m^2/d (PO)	**:D1 to D7, D15 to D21** (in 3 takes/d)
Vincristine (VCR)	: 1,5 mg/m^2/infusion (IV)	: **D1, D8, D15, D22**(MAX 2 mg/infusion)
Pegaspargase*(PEG-ASPA)	**: 1250 or 2500 IU/m^2(IV)**	**: D4**
Doxorubicine	: 25 mg/m^2/infusion (IV)	: **D1, D8, D15, D22**
6 thioguanine	: 60 mg/m^2/d (PO)	: **D29 to D42**
Cytarabine	: 75 mg/m^2/infusion (IV)	: **D31, 32, 33, 34 and D38, 39, 40, 41** (total: 8)
Cyclophosphamide	: 1 g/m²/infusion(IV)	: **D29**
Triple IT	: see appendix 5	: **D4, D31**

*** dose of pegaspargase per infusion according to unitary dose of the initial randomisation**

CAALL-F01: B-MR
Continuation therapy «maintenance»

- 76 weeks (i.e. total duration of ALL treatment: ~2 years)
- 6 pulses (one cycle every 10 weeks):

  Warning: these pulses are different from the pulses of the SR group

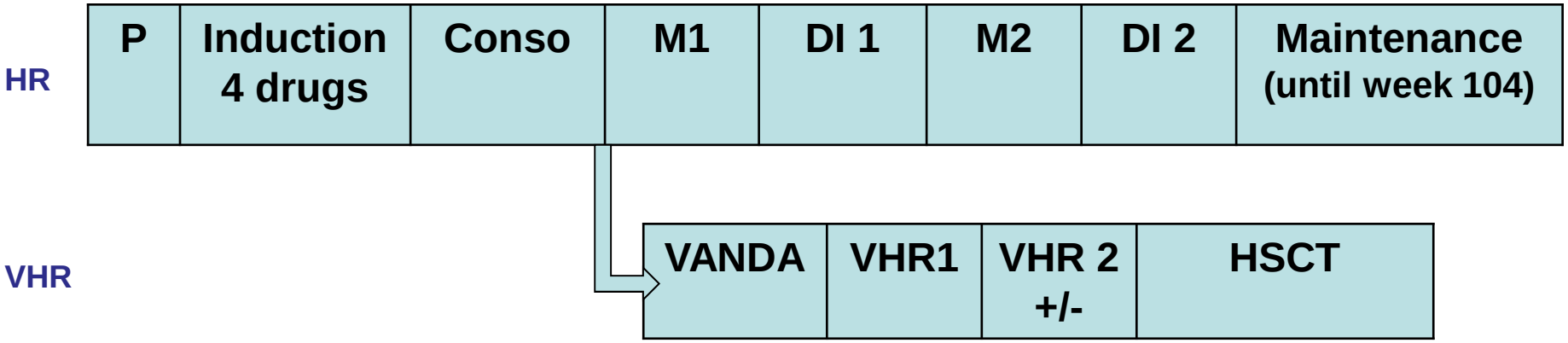
  – VCR: 1.5 mg/m^2/infusion: D1,D8 (MAX 2mg per infusion)
  – DEX: 6 mg/m^2/day: D1 to D7
  – IT MTX: D15 (see appendix 5)

- 6MP: 50 mg/m^2/day
- MTX: 25 mg/m^2/week

NB: Bactrim® is to be given during the whole duration of maintenance and at least 3 months after stopping of 6MP/MTX

CAALL-F01: B-HR/VHR
(BCP ALL high/very high risk)

General design

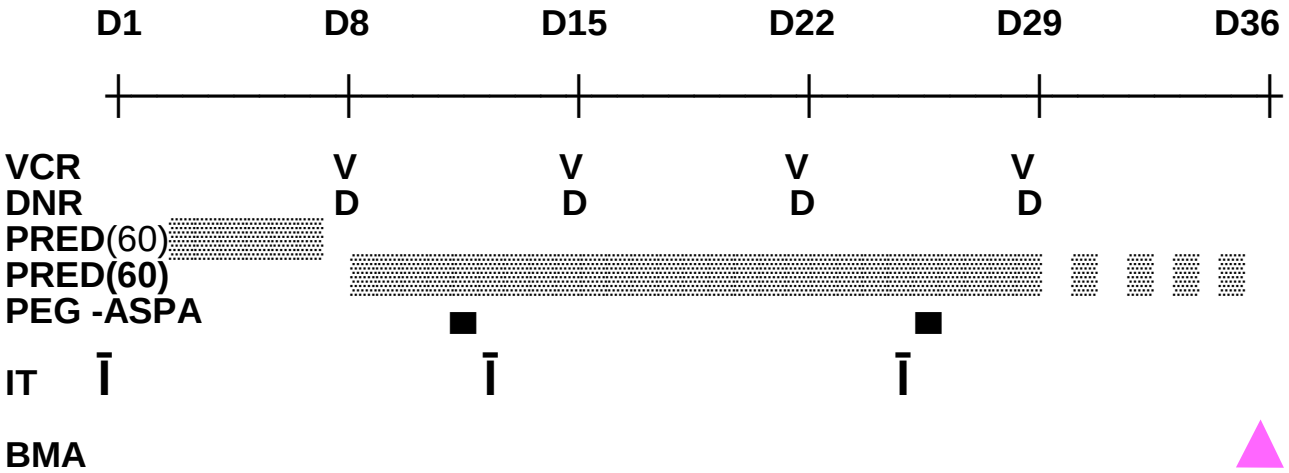


P: Prednisone prephase; Conso: consolidation course

DI: delayed intensification; M: high dose MTX cycles;

HSCT: hematopoietic stem cell transplantation; VANDA/HR1/HR2: intensive courses pre HSCT

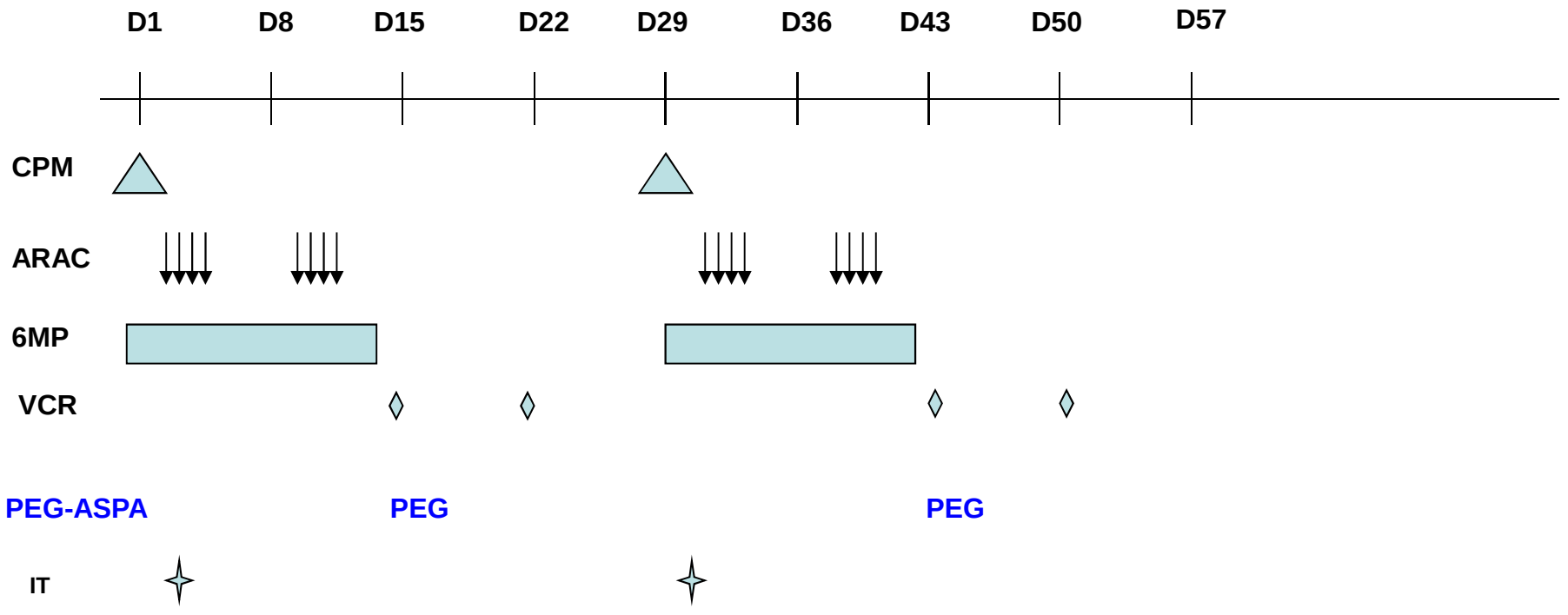
CAALL- F01: B-HR INDUCTION THERAPY



Vincristine (VCR)	**:** 1.5 mg/m^2 IV	D8, D15, D22, D29
Daunorubicine (DNR)	**:** 30 mg/m^2 IV	D8, D15, D22, D29
Prednisolone (PRED)	**:** 60 mg/m^2/d PO	D1-D7
Prednisolone (PRED)	**:** 60 mg/m^2/d PO	D8-D28, then tapered over one week
Pegaspargase (PEG-ASPA)	**: 2500 IU/m^2 IV**	**D12 D26**
Methotrexate (IT)	: see appendix 5	D1
Triple IT	: see appendix 5	D13, D24

Bone marrow aspiration (BMA): with MRD evaluation D35 (no later than D42)

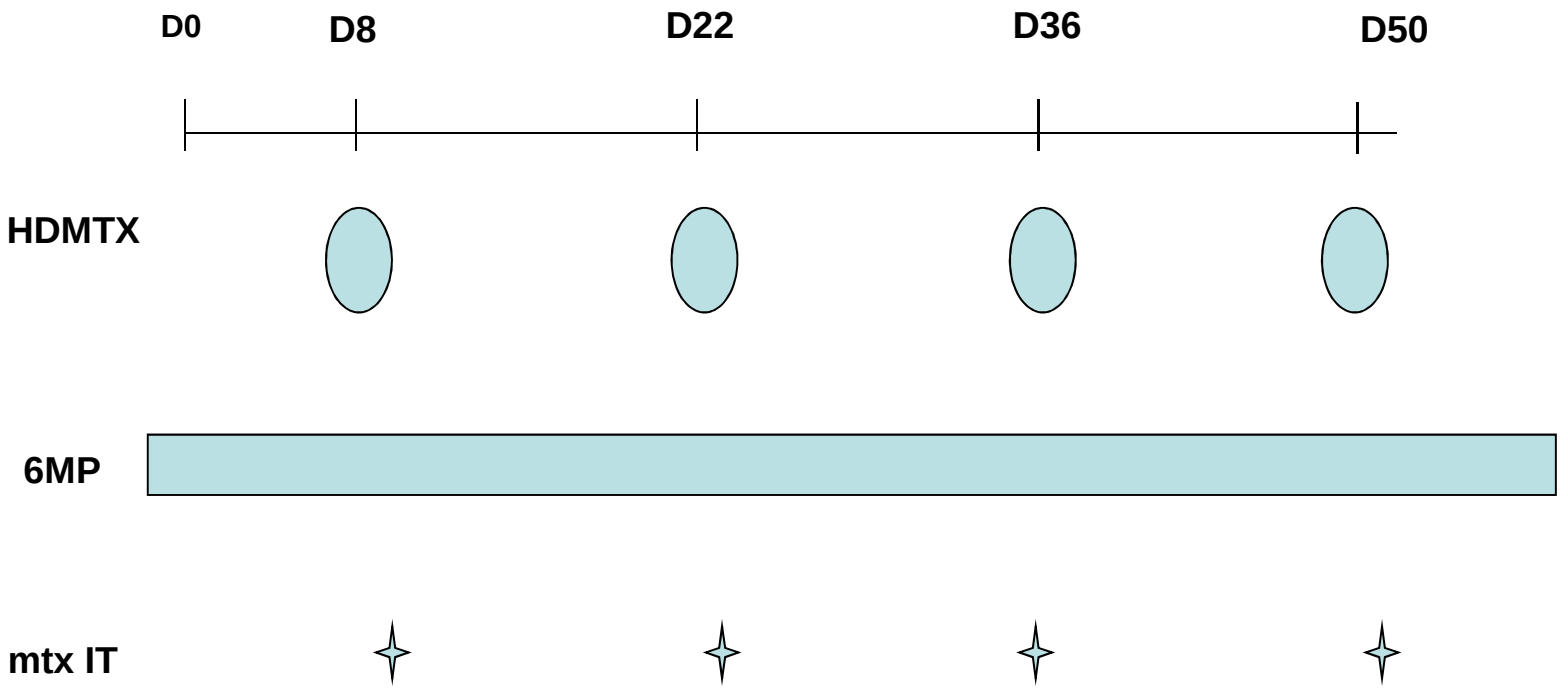
CAALL-F01: B-HR CONSOLIDATION



BMA with MRD TP2

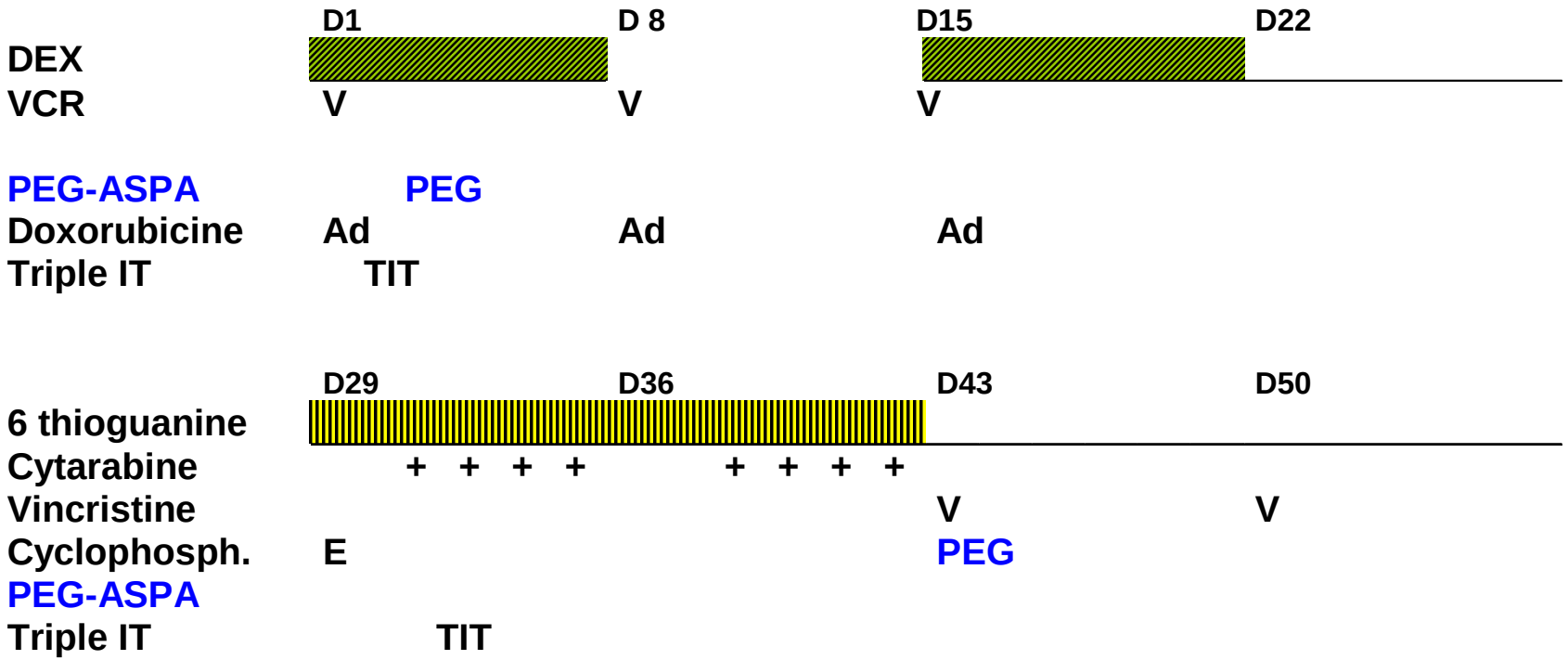
6 mercaptopurine	60 mg/m²	PO	28 days	D1-14, D29-42
Cyclophosphamide	1g/m²	IV	2 infusions	D1, D29
Pegaspargase (PEG-ASPA)*	**2500 IU/m²**	**IV**	**2 infusions**	**D15, D43**
Vincristine	1.5 mg/m²	IV	4 infusions	D15, D22, D43, D50 (MAX 2 mg/infusion)
Cytarabine	75 mg/m²	IV	16 infusions	D3-6, D10-13, D31-34, D38-41
Triple IT	See appendix 5	IT	2 injections	D3, D31

CAALL-F01: B-HR M1 phase



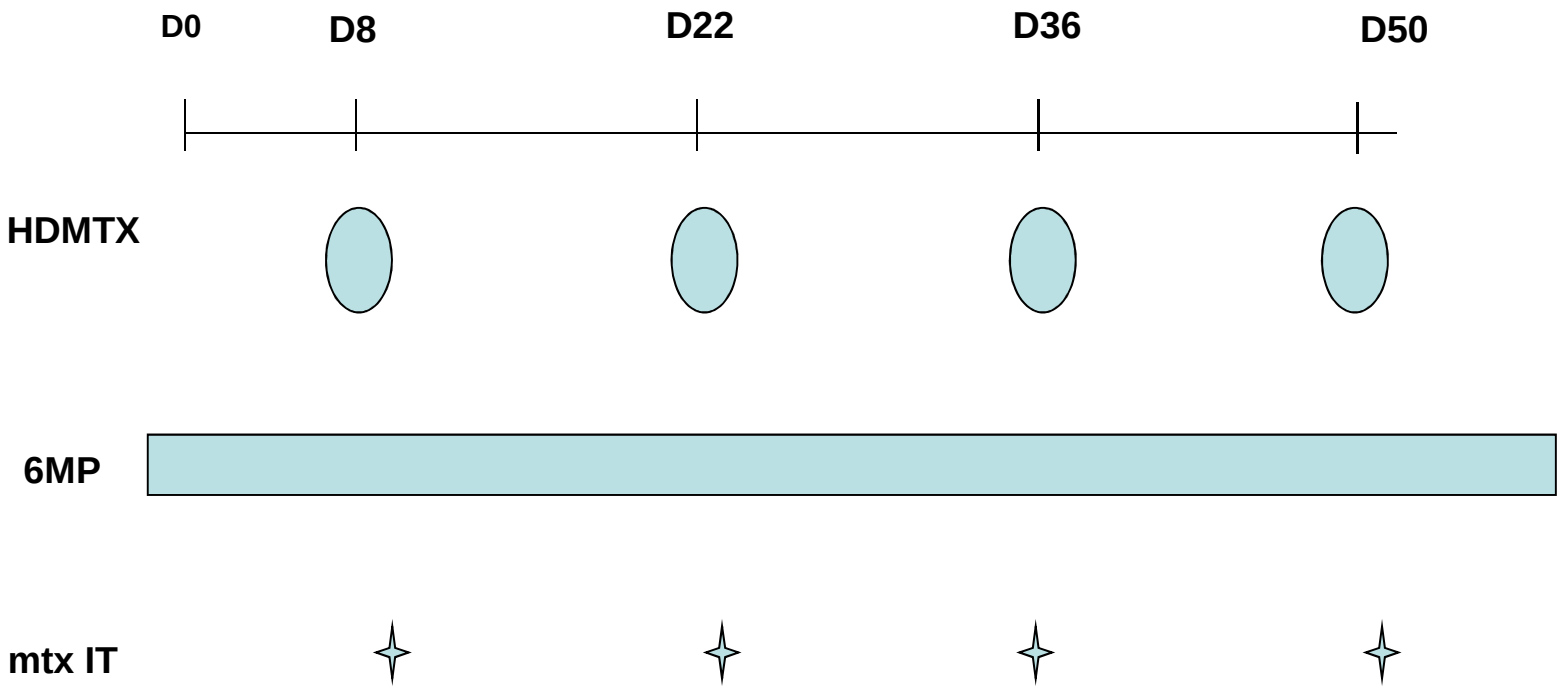
Methotrexate (HDMTX)	5 g/m²	IV 24h	4 infusions	D8,22,36,50; leucovorin rescue beginning at H42
6 mercaptopurine (6MP)	25 mg/m²	Per os	56 days	D1-56
Methotrexate IT	appendix 5	IT	4 days	D9,23,37,51

CAALL-F01: B-HR DELAYED INTENSIFICATION 1



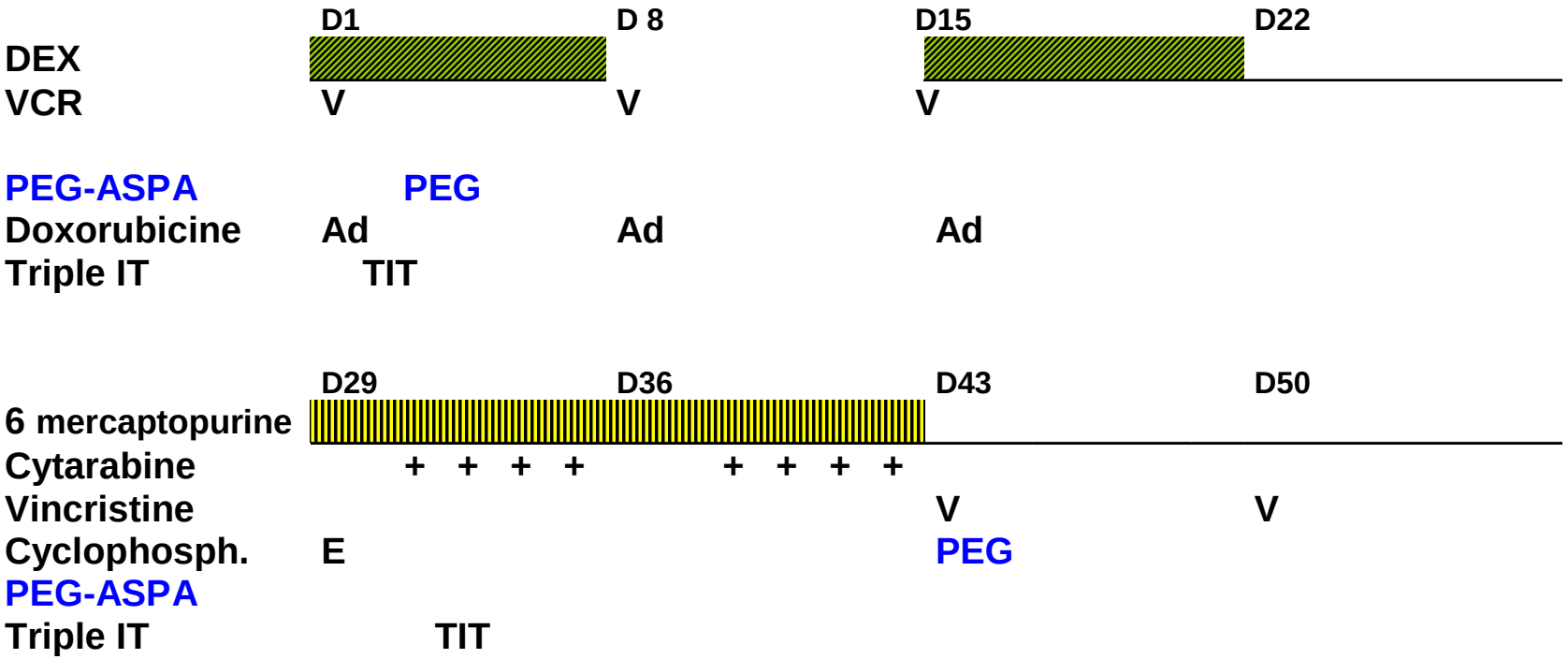
Dexamethasone (DEX)	: **<u>10</u>** mg/m^2/d (PO)	**:D1 to D7, D15 to D21** (in 3 takes/d)
Vincristine (VCR)	: 1,5 mg/m^2/infusion (IV)	: **D1, D8, D15, D43, D50** (MAX 2 mg/infusion)
Pegaspargase (PEG-ASPA)	**: 2500 IU/m^2/infusion (IV)**	**: D4, D43**
Doxorubicine	: 25 mg/m^2/infusion (IV)	: **D1, D8, D15**
6 thioguanine	: 60 mg/m^2/d (PO)	: **D29 to D42**
Cytarabine	: 75 mg/m^2/infusion (IV)	: **D31, 32, 33, 34 and D38, 39, 40, 41** (total: 8)
Cyclophosphamide	: 1 g/m²/infusion(IV)	: **D29**
Triple IT	: see appendix 5	: **D4, D31**

CAALL-F01: B-HR M2 phase



Methotrexate (HDMTX)	5 g/m²	IV 24h	4 infusions	D8,22,36,50; leucovorin rescue beginning at H42
6 mercaptopurine (6MP)	25 mg/m²	Per os	56 days	D1-56
Methotrexate IT	appendix 5	IT	4 days	D9,23,37,51

CAALL-F01: B-HR DELAYED INTENSIFICATION 2



Dexamethasone (DEX)	: **<u>10</u>** mg/m^2/d (PO)	**:D1 to D7, D15 to D21** (in 3 takes/d)
Vincristine (VCR)	: 1,5 mg/m^2/infusion (IV)	: **D1, D8, D15, D43, D50** (MAX 2 mg/infusion)
Pegaspargase (PEG-ASPA)	**: 2500 IU/m^2/infusion (IV)**	**: D4, D43**
Doxorubicine	: 25 mg/m^2/infusion (IV)	: **D1, D8, D15**
6 mercaptopurine	: 60 mg/m^2/d (PO)	: **D29 to D42**
Cytarabine	: 75 mg/m^2/infusion (IV)	: **D31, 32, 33, 34 and D38, 39, 40, 41** (total: 8)
Cyclophosphamide	: 1 g/m²/infusion(IV)	: **D29**
Triple IT	: see appendix 5	: **D4, D31**

CAALL-F01: B-HR
Continuation therapy « maintenance »

- Total duration: until week 104
- No pulses
- No ITs *(except for CNS3 pts see annex 5)*
- 6-MP: 50 mg/m^2/day
- MTX : 25 mg/m^2/week

NB: Bactrim® is to be given during the whole duration of maintenance and at least 3 months after stopping of 6MP/MTX

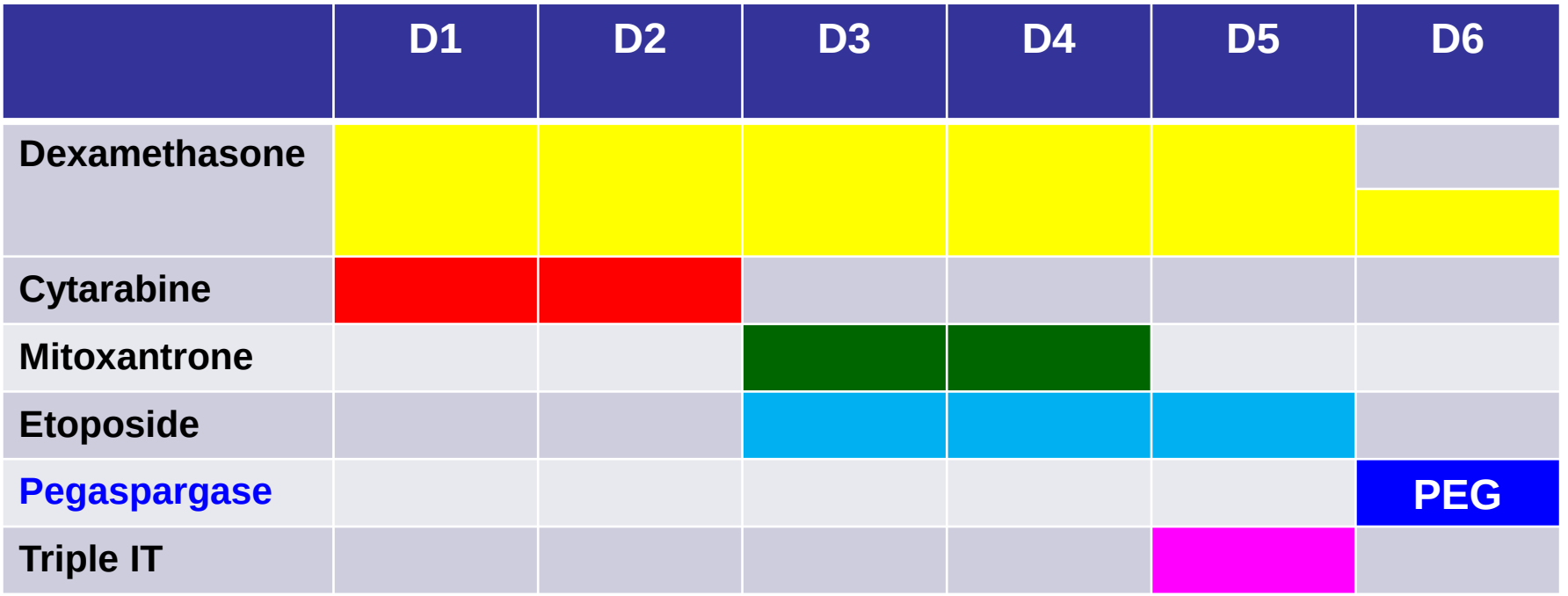
CAALL-F01: B-VHR (BCP-ALL/very high risk)

- If at least one criterium among:
  - poor risk-cytogenetics
  - induction failure confirmed by MRD-TP1 ≥ 5 $x10^{-2}$
  - MRD- TP2 ≥10^{-3}

→ indication of HSCT

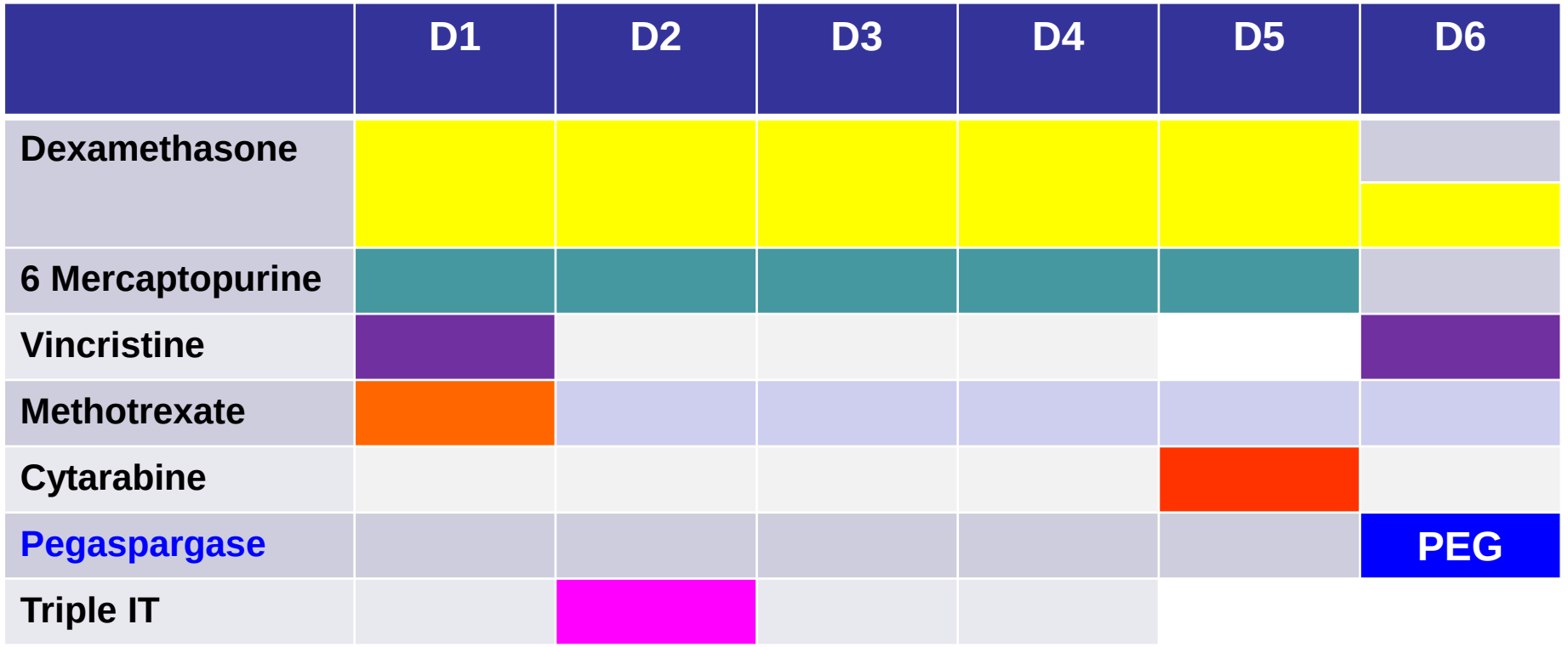
  - prior to HSCT, intensification of the treatment:
    - VANDA course
    - followed if necessary by VHR1 and VHR2 blocks
    - until HSCT which is to be performed according to ongoing international HSCT guidelines or protocol.

VANDA



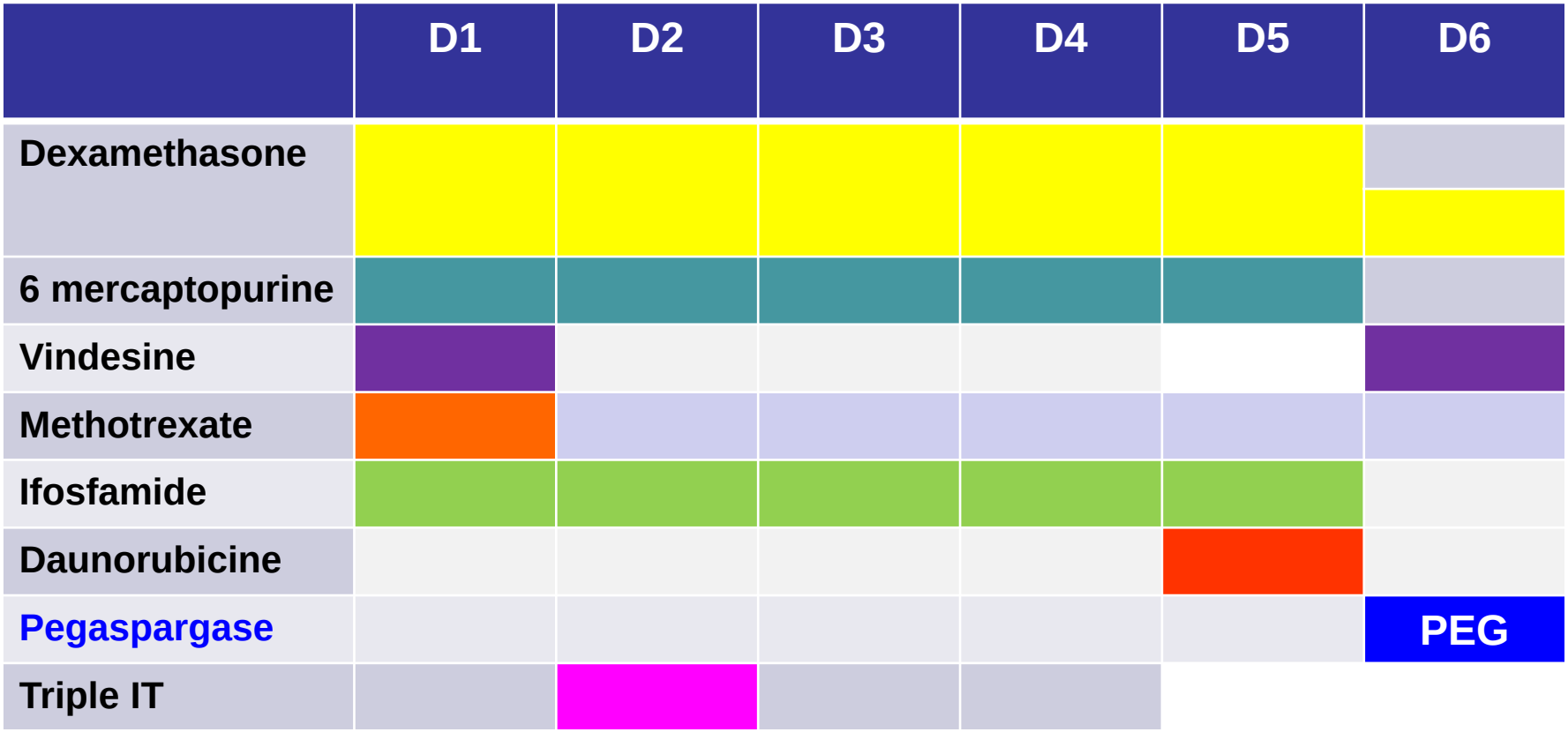
Dexamethasone	20 mg/m^2 in 2 takes	PO	5 days	**D1-D5**
Dexamethasone	10 mg/m^2 in 2 takes	PO	1 day	**D6**
Cytarabine	2 g/m^2 every 12 hours	IV (3h)	2 days	**D1 D2**
Mitoxantrone	8 mg/m^2	IV (1h)	2 days	**D3 D4**
Etoposide	150 mg/m^2			**D3 D4 D5**
Pegaspargase	**2500 IU/m^2**	**IV (1h)**	**1 day**	**D6**
Triple IT	see appendix 5	intrathecal	1 day	**D5**

VHR1 Block



Dexamethasone	20 mg/m^2 in 2 takes	PO	5 days	**D1-D5**
Dexamethasone	10 mg/m^2 in 2 takes	PO	1 day	**D6**
6 mercaptopurine	100 mg/m^2 in 1 take	PO	5 days	**D1-D5**
Vincristine	1.5 mg/m^2 (MAX 2mg)	IV direct	2 days	**D1 and D6**
Methotrexate	5g/m^2	IV (24h)	1 day	**D1**
Cytarabine	2 g/m^2 every 12 hours	IV (3h)	1 day	**D5**
Pegaspargase	**2500 IU/m^2**	**IV (1h)**	**1 day**	**D6**
Triple IT	see appendix 5	intrathecal	1 day	**D2**

VHR2 Block



Dexamethasone	20 mg/m^2 in 2 takes	PO	5 days	**D1-D5**
Dexamethasone	10 mg/m^2 in 2 takes	PO	1 day	**D6**
6 mercaptopurine	100 mg/m^2 in 1 take	PO	5 days	**D1-D5**
Vindesine	3 mg/m^2	IV push	2 days	**D1 and D6**
Methotrexate	5g/m^2	IV (24h)	1 day	**D1**
Ifosfamide	400 mg/m^2	IV (1h)	5 days	**D1-D5**
Daunorubicine	35 mg/m^2	IV (1h)	1 day	**D5**
Pegaspargase	**2500 IU/m^2**	**IV (1h)**	**1 day**	**D6**
Triple IT	see appendix 5	intrathecal	1 day	**D2**

Hematopoietic Stem Cell Transplantation in Very High Risk B-lineage ALL

- Should be performed according to:
  - international guidelines (I-BFM-HSCT)
  - or protocol (I-BFM «Forum trial»)
  - ongoing at CAALL-F01 opening

CAALL-F01: T-SR
(T-cell ALL standard risk)

General design

P	Induction 4 drugs	Conso	M	DI	Maintenance (until week 104)

BMA D35 **D85**

P: prednisone prephase; Ind: induction (« IA »);

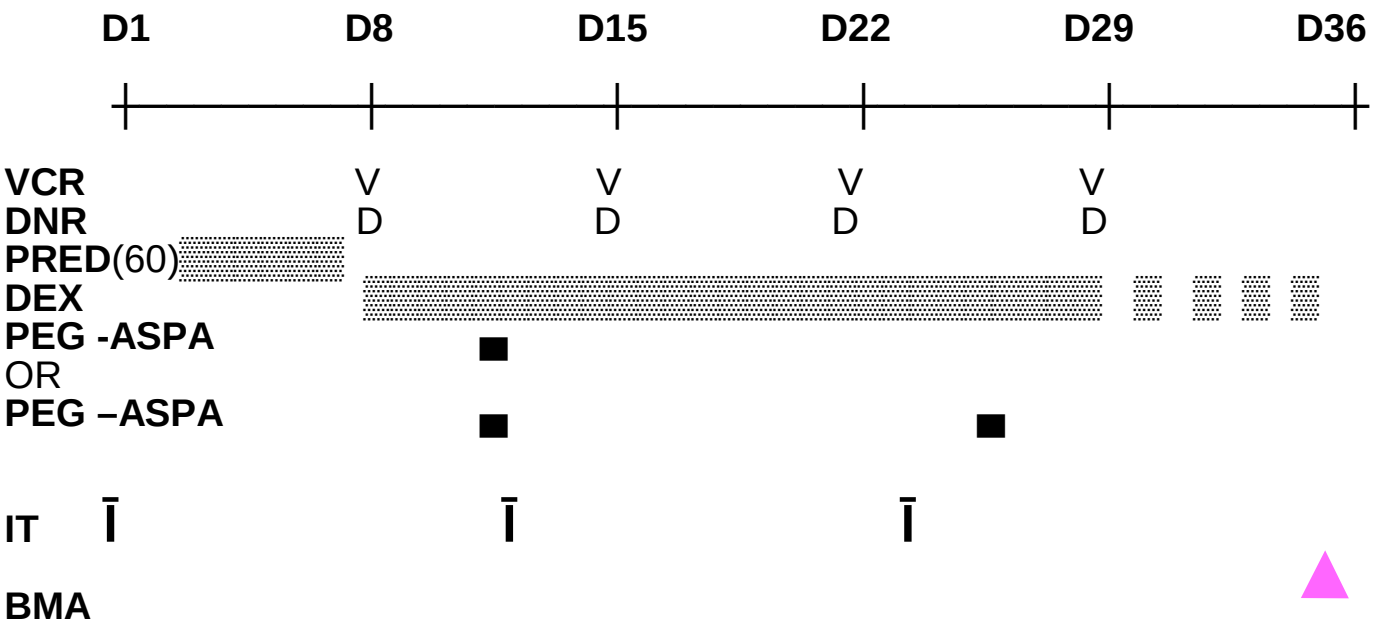
conso; consolidation (« IB »); M: M phase (high dose MTX cycles)

DI: delayed intensification (protocol « II »)

BMA: bone marrow aspiration with MRD evaluation

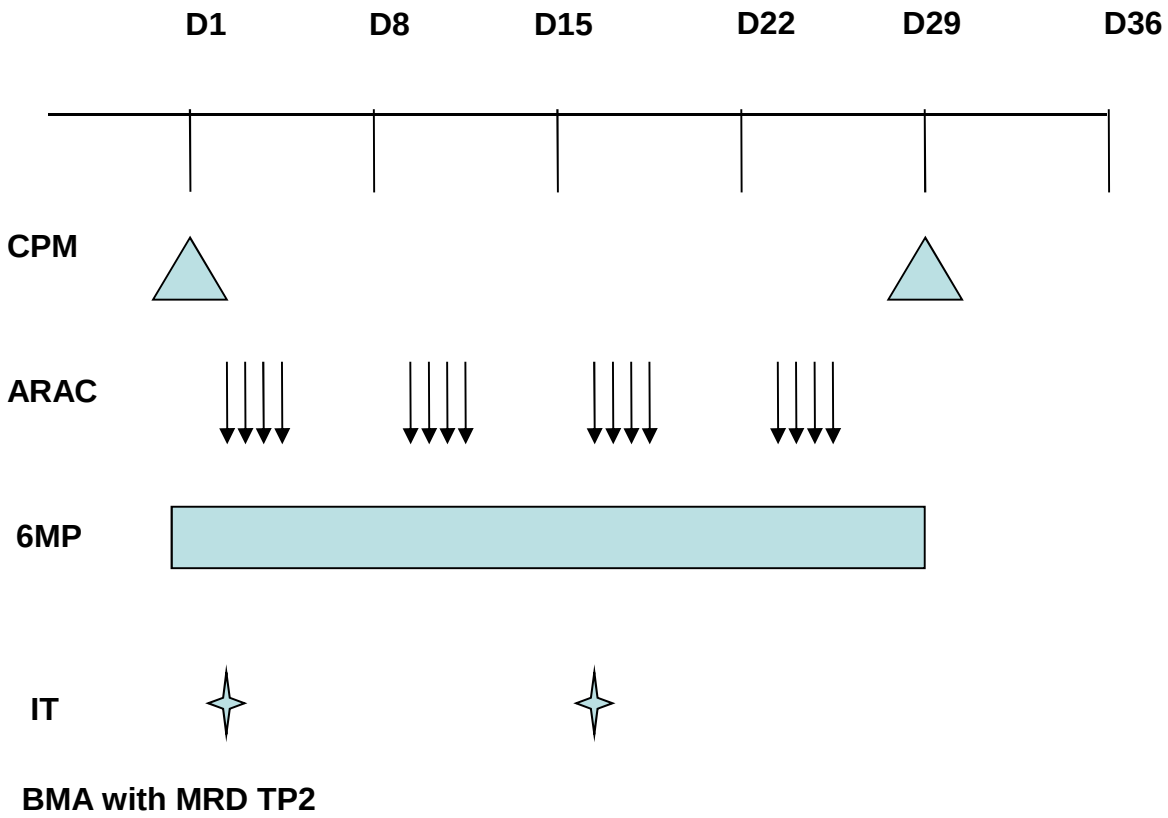
(++++ D85 MRD value decisional for SR, HR, VHR stratification)

CAALL-F01: T-SR INDUCTION THERAPY



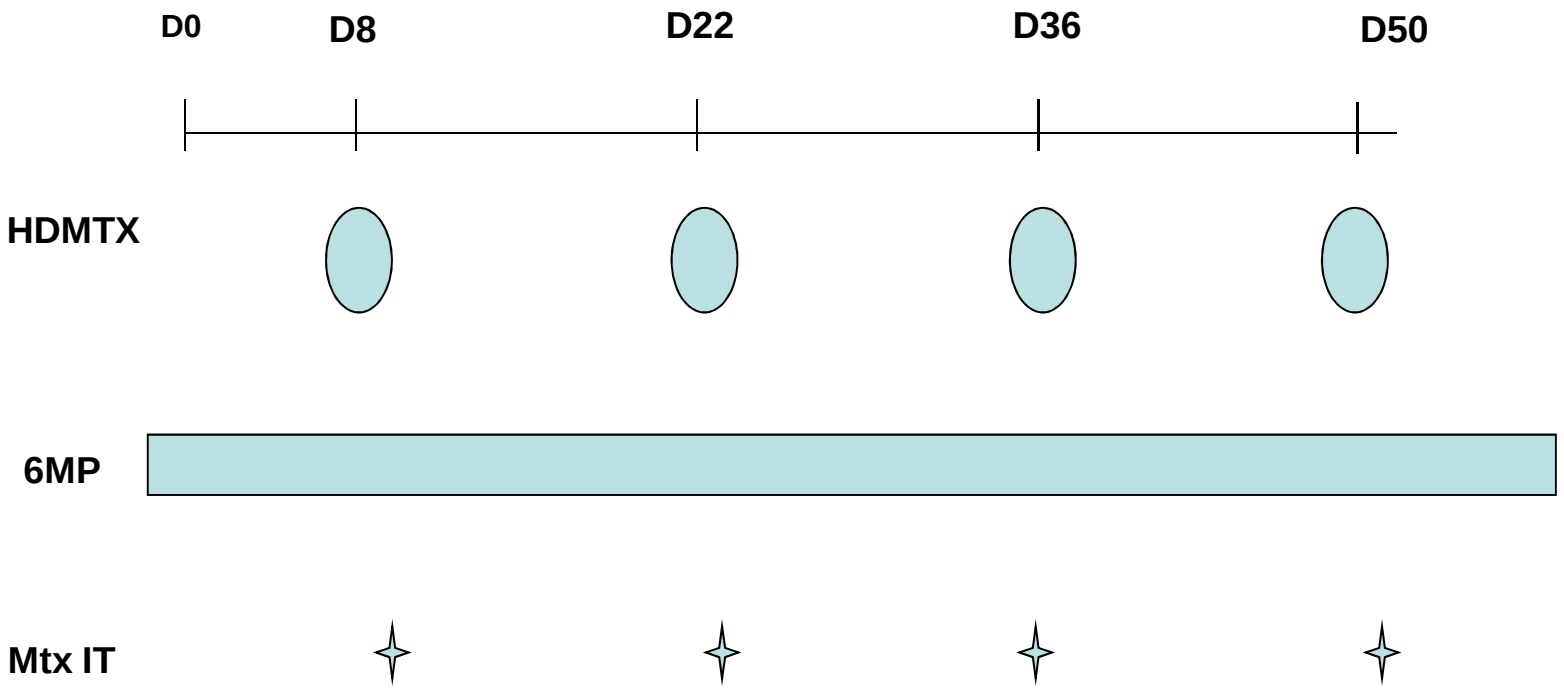
Vincristine (VCR)	: 1.5 mg/m^2 IV	D8, D15, D22, D29
Daunorubicine (DNR)	: 30 mg/m^2 IV	D8, D15, D22, D29
Pegaspargase (PEG-ASPA)	**: 2500 IU/m^2 IV**	**D12**
OR		
Pegaspargase (PEG-ASPA)	**: 1250 IU/m^2 IV**	**D12 D26 according to randomisation**
Prednisolone (PRED)	: 60 mg/m^2/d PO	D1-D7
Dexamethasone (DEX)	: **10** mg/m^2/j PO	D8-D28 then tapered over one week
Methotrexate (IT)	: cf appendix 5	D1, D13, D24
Bone marrow aspiration (BMA): with MRD evaluation		D35 (no later than D42)

CAALL-F01: T-SR CONSOLIDATION



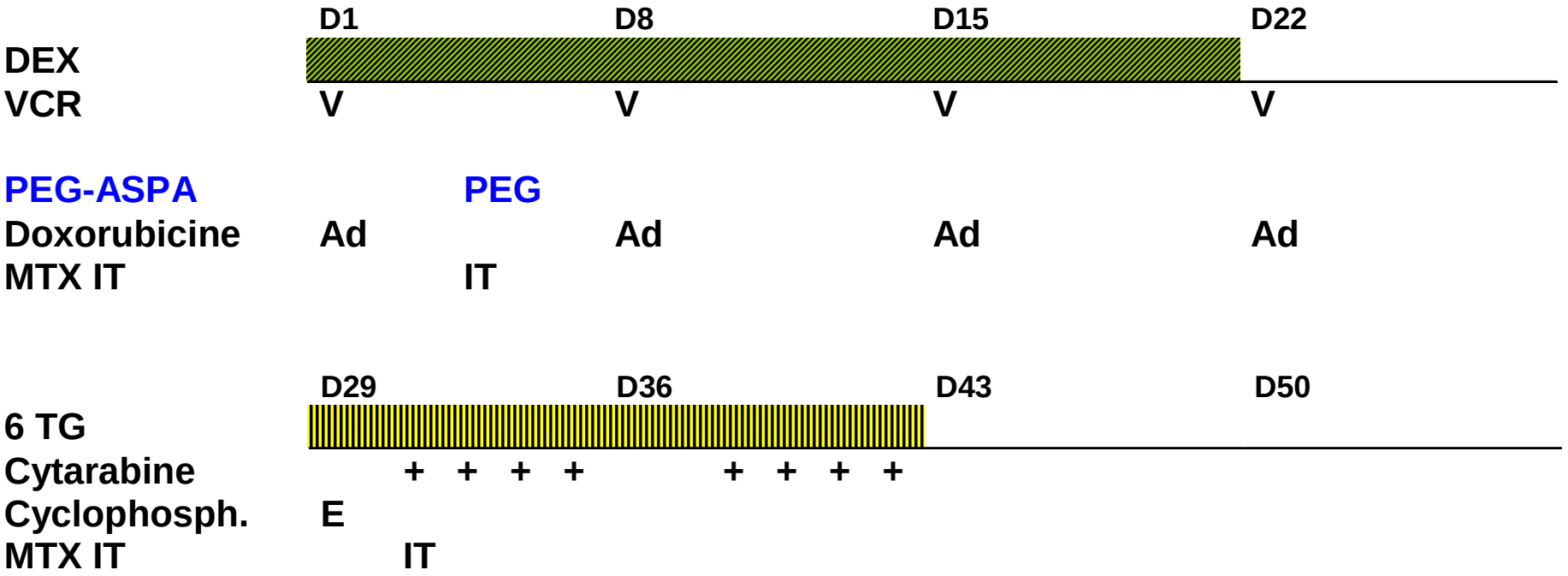
6 mercaptopurine (6MP)	60 mg/m²	PO	28 days	D1-28
Cyclophosphamide (CPM)	1g/m²	IV	2 infusions	D1, D29
Cytarabine (ARAC)	75 mg/m²	IV	16 infusions	D3-6, D10-13, D17-20, D24-27
Methotrexate (IT)	Appendix 5	IT	2 injections	D3, D17

CAALL-F01: T-SR M phase



Methotrexate (HDMTX)	5 g/m²	IV 24h	4 infusions	D8,22,36,50; leucovorin rescue beginning at H42
6 mercaptopurine (6MP)	25 mg/m²	Per os	56 days	D1-56
Methotrexate (IT)	See appendix 5	IT	4 days	D9, 23, 37, 51

CAALL-F01: T-SR Delayed intensification n°1 “protocol II”



Dexamethasone (DEX)	**:** **<u>10</u>** mg/m^2/d (PO)	**: D1 to D21** (in 3 takes)
Vincristine(VCR)	**:** 1.5 mg/m^2/infusion (IV)	: **D1, D8, D15, D22** (MAX 2mg/infusion)
Pegaspargase*(PEG-ASPA)	**: 1250 or 2500 IU/ m^2 (IV)**	**: D4**
Doxorubicin	**:** 30 mg/m^2/infusion (IV)	: **D1, D8, D15, D22,**
6 thioguanine (6TG)	**:** 60 mg/m^2/d (PO)	: **D29 to D42**
Cytarabine	**:** 75 mg/m^2/infusion (IV)	: **D31, D32, D33, D34 and D38, 39, 40, 4**
Cyclophosphamide	**:** 1 g/m² (IV)	: **D29**
MTX IT	**:** see appendix 5	: **D4, D31**

*** dose of pegaspargase per infusion according to unitary dose of the initial randomisation**

CAALL-F01:T-SR
Continuation therapy « maintenance »

- 76 weeks (total 104 weeks)
- No pulses
- 6MP 50 mg/m^2/day
- MTX 25 mg/m^2/week

Indications of cranial Radiotherapy (RT): **NO**

Patients with initial WBC <100 G/L:

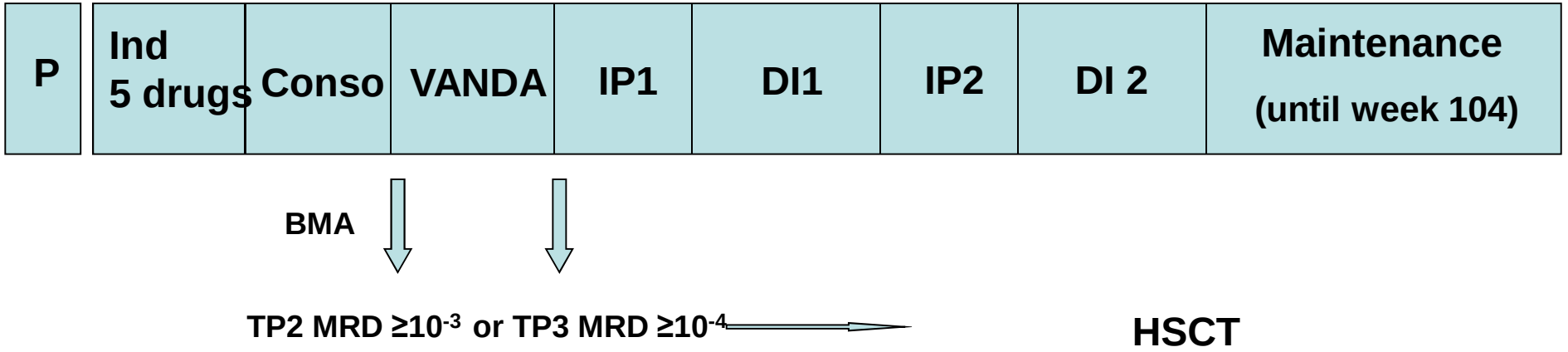
6 ITmtx: every 6 weeks beginning week 2 of maintenance

Patients with initial WBC ≥100 G/L:

6 HD-MTX + 6 ITmtx: every 6 weeks beginning week 2 of maintenance. *See annex 5*

NB: Bactrim® is to be given during the whole duration of maintenance and at least 3 months after stopping of 6MP/MTX

CAALL F01: T-HR/VHR
(T-cell ALL, high/very high risk)



Ind: induction ;Conso:consolidation course

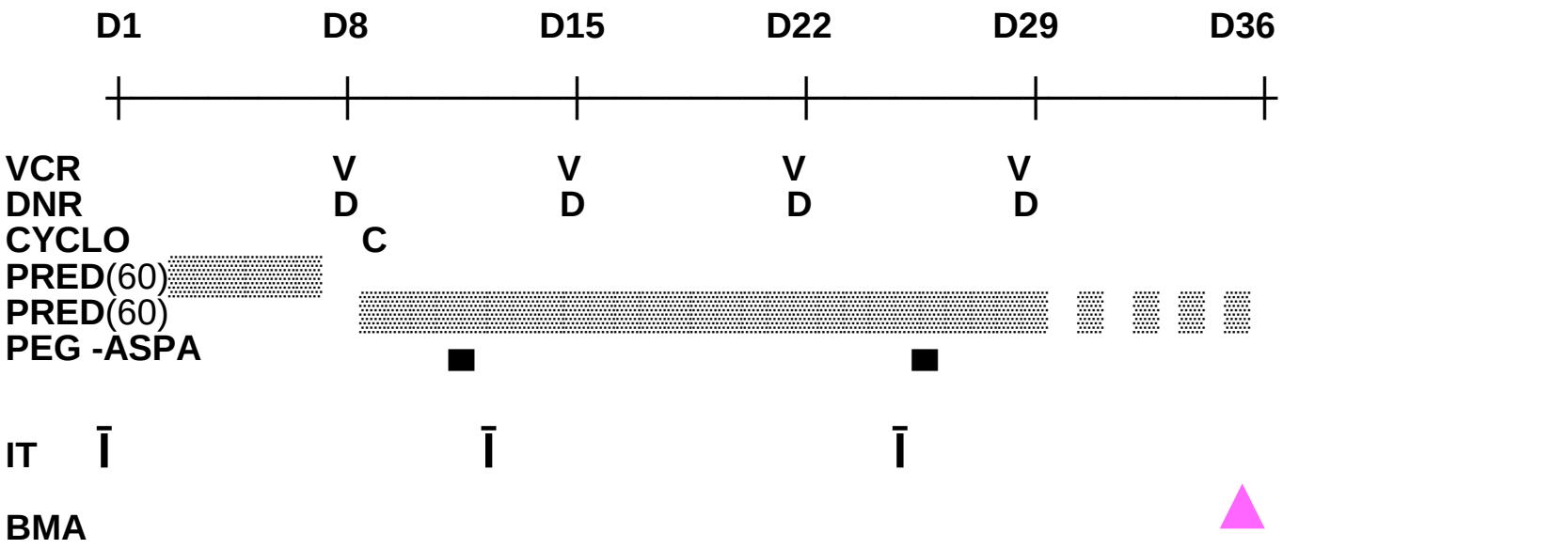
IP : intermediate phase with high dose MTX courses

DI: delayed intensification

BMA: bone marrow aspiration with MRD evaluation

HSCT: Hematopoietic stem cell transplantation (only VHR patients)

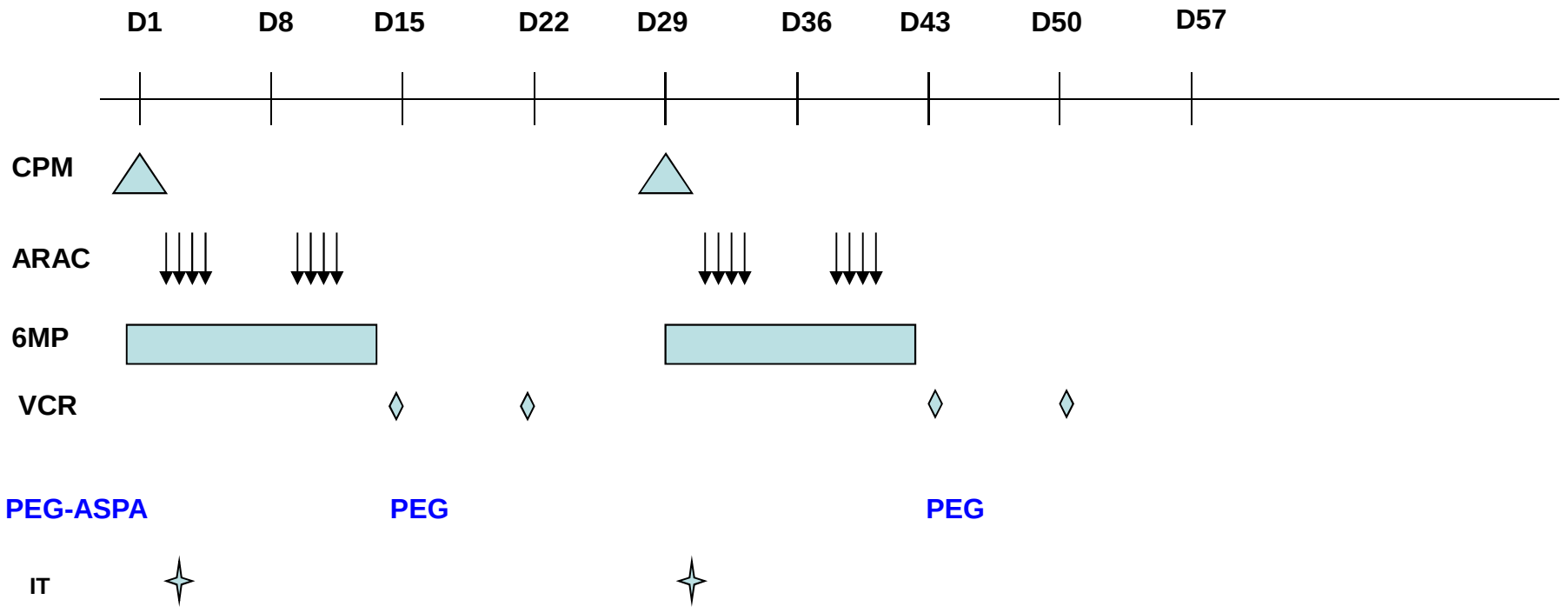
CAALL-F01: T-HR INDUCTION THERAPY



Vincristine (VCR)	: 1.5 mg/m^2 IV	D8, D15, D22, D29
Daunorubicine (DNR)	: 40 mg/m^2 IV	D8, D15, D22, D29
Pegaspargase (PEG-ASPA)	**: 2500 IU/m^2 IV**	**D12, D26**
Cyclophosphamide (CYCLO)	: 1 g/ m^2	D9
Prednisolone (PRED)	: 60 mg/m^2/d PO	D1-D28 then tapered over one week
Methotrexate (IT)	: see appendix 5	D1
Triple IT	: see appendix 5	D13, D24

Bone marrow aspiration (BMA) : **with MRD evaluation** D35 (no later than D42)

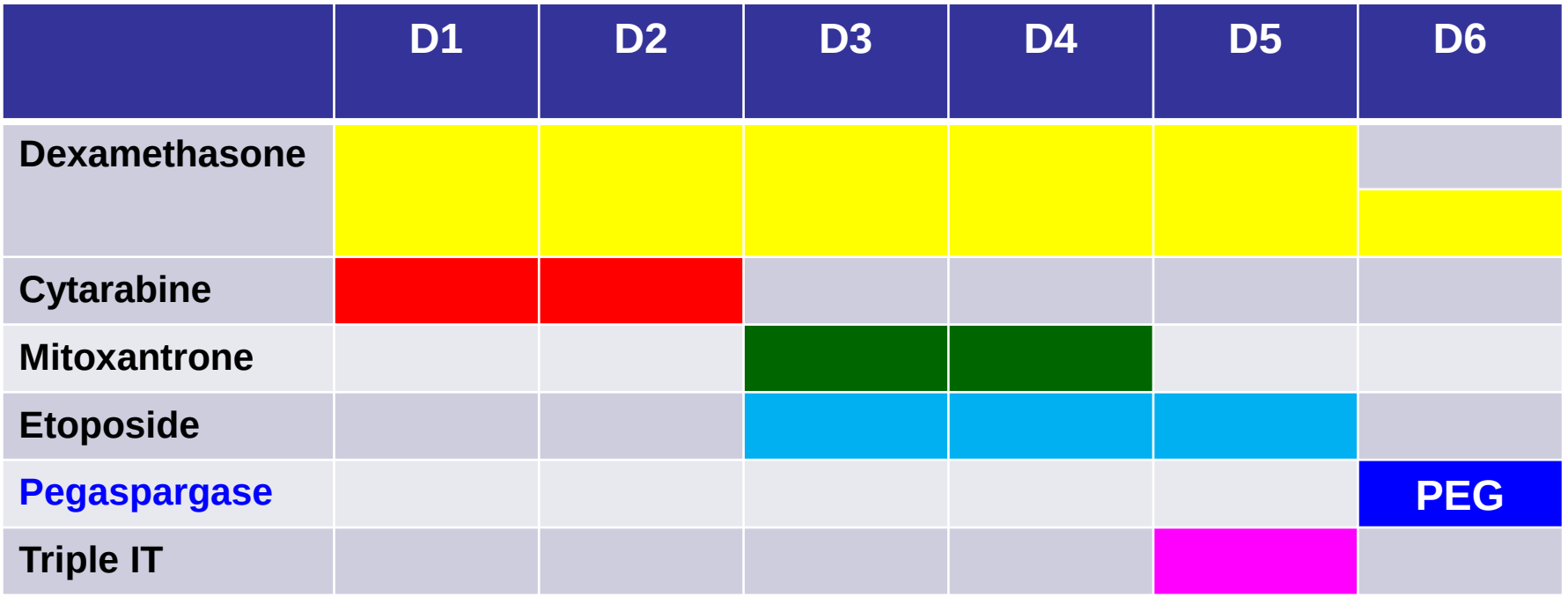
CAALL-F01: T-HR CONSOLIDATION



BMA with MRD TP2

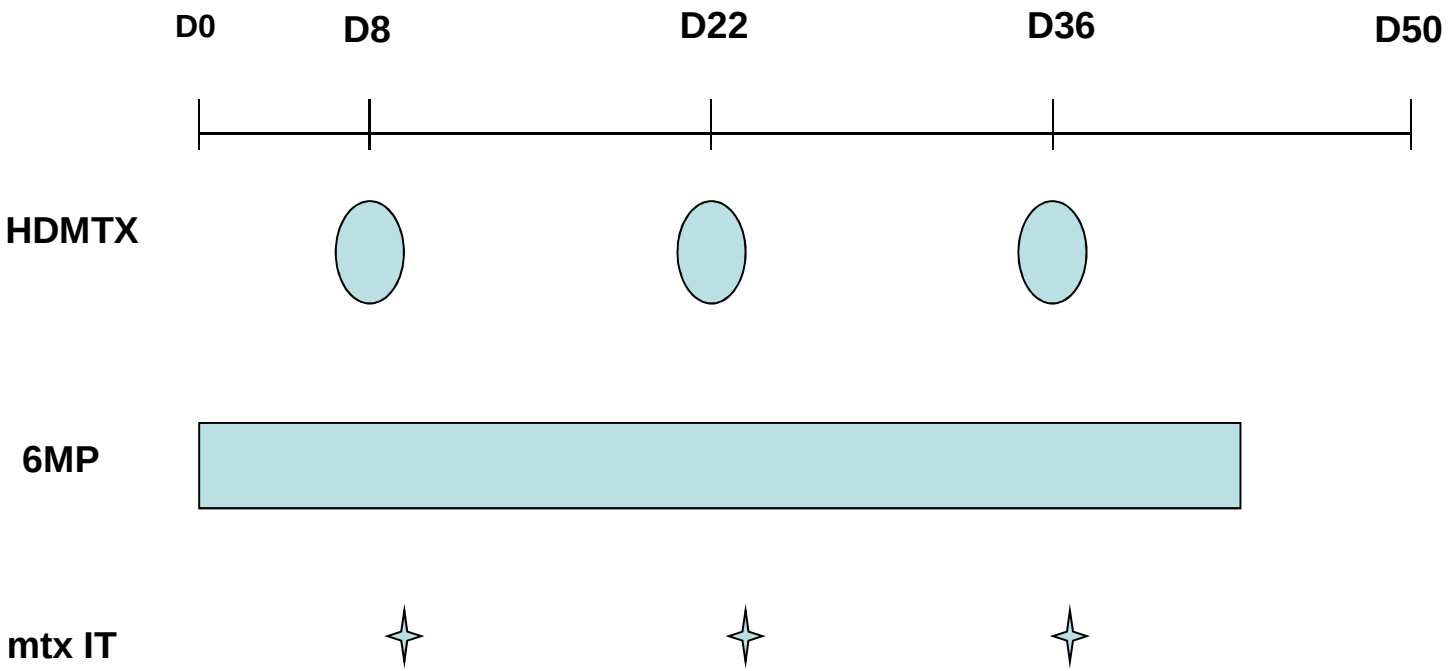
6 mercaptopurine	60 mg/m²	PO	28 days	D1-14, D29-42
Cyclophosphamide	1g/m²	IV	2 infusions	D1, D29
Pegaspargase (PEG-ASPA)*	**2500 IU/m²**	**IV**	**2 infusions**	**D15, D43**
Vincristine	1.5 mg/m²	IV	4 infusions	D15, D22, D43, D50 (MAX 2 mg/infusion)
Cytarabine	75 mg/m²	IV	16 infusions	D3-6, D10-13, D31-34, D38-41
Triple IT	See appendix 5	IT	2 injections	D3, D31

VANDA



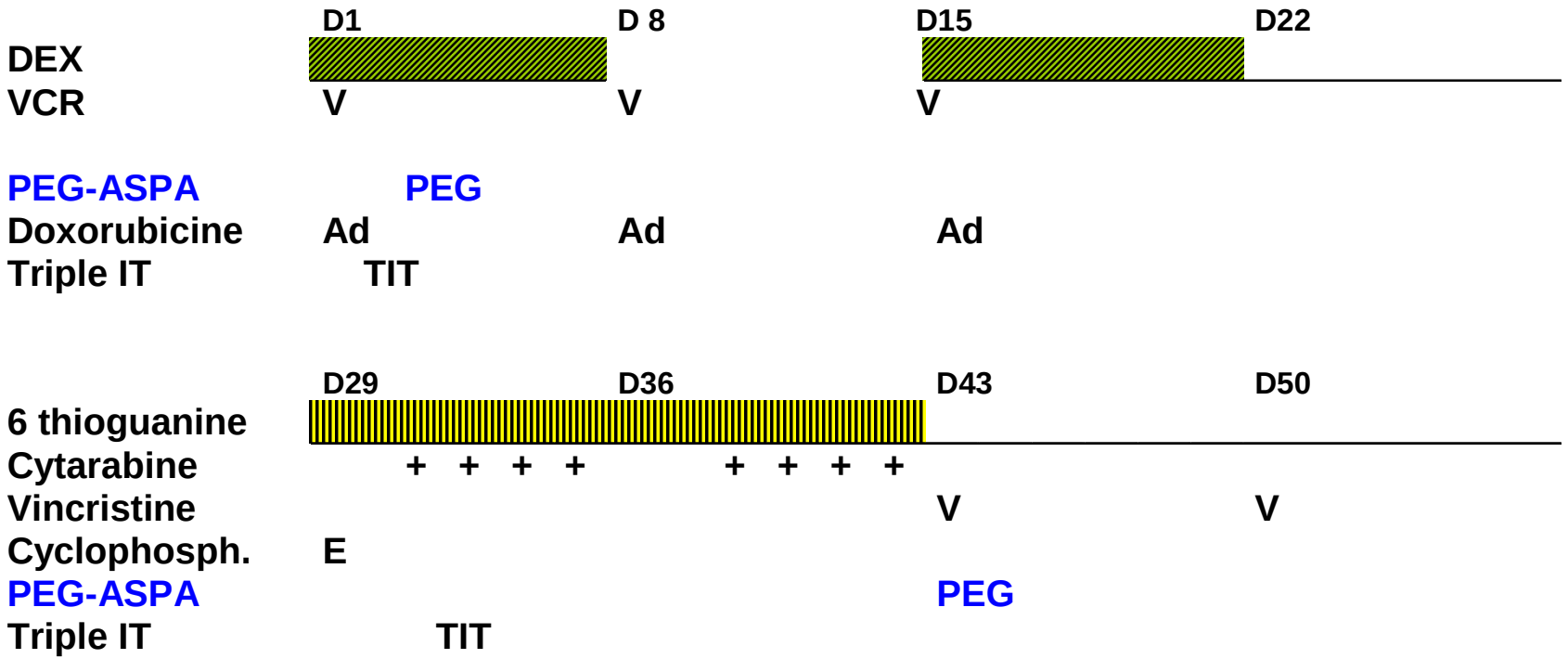
Dexamethasone	20 mg/m^2 in 2 takes	PO	5 days	**D1-D5**
Dexamethasone	10 mg/m^2 in 2 takes	PO	1 day	**D6**
Cytarabine	2 g/m^2 every 12 hours	IV (3h)	2 days	**D1 D2**
Mitoxantrone	8 mg/m^2	IV (1h)	2 days	**D3 D4**
Etoposide	150 mg/m^2			**D3 D4 D5**
Pegaspargase	**2500 IU/m^2**	**IV (1h)**	**1 day**	**D6**
Triple IT	see Appendix 5	intrathecal	1 day	**D5**

CAALL-F01: T-HR Interim Phase1



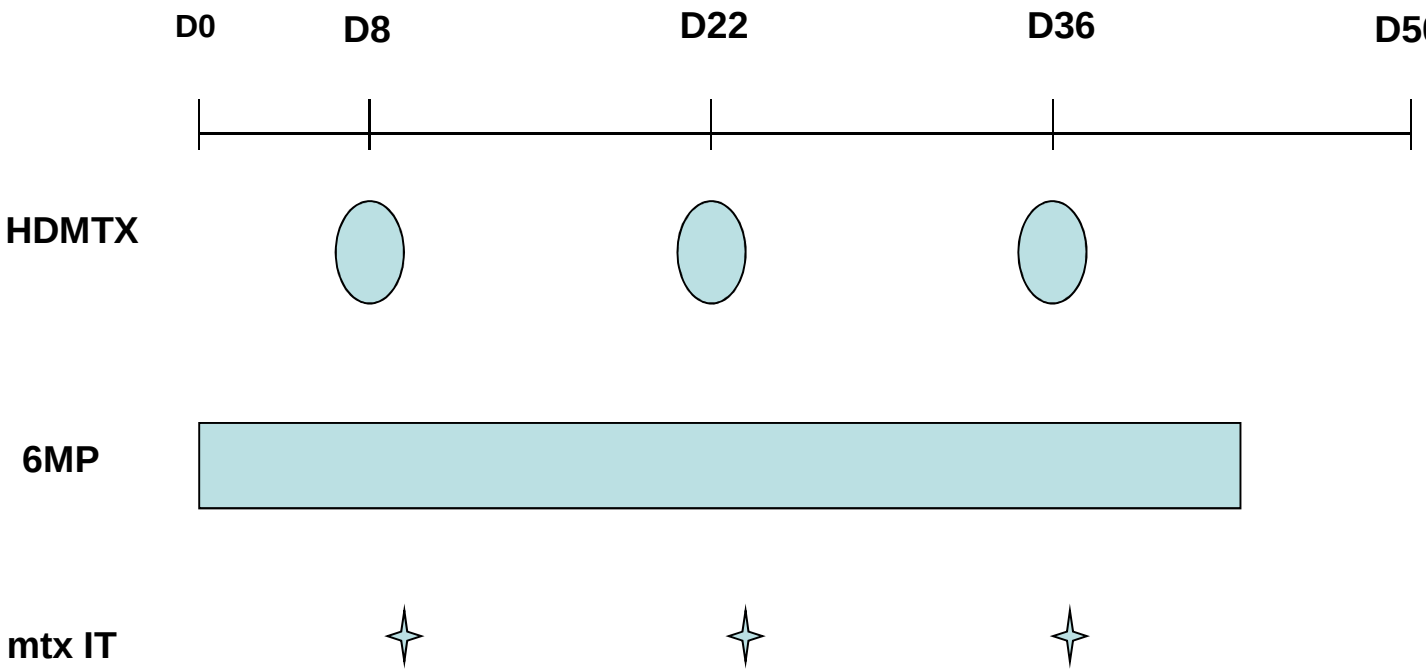
HD Methotrexate	5 g/m²	IV 24h	3 infusions	D8,22,36, leucovorin rescue beginning at H42
6 mercaptopurine	25 mg/m²	Per os	56 days	D1-42
Methotrexate IT	Appendix 5	IT	3 days	D9, 23, 37

CAALL-F01: T-HR DELAYED INTENSIFICATION 1



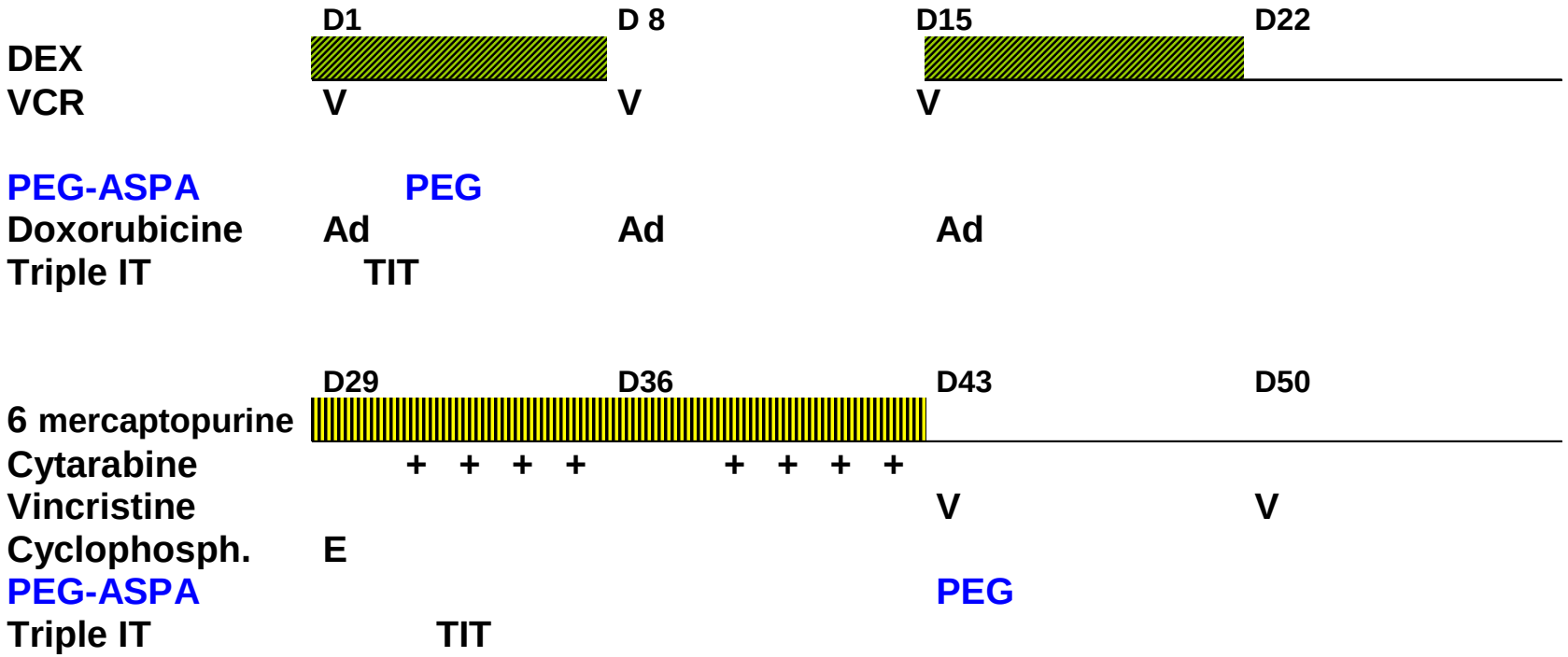
Dexamethasone (DEX)	: **<u>10</u>** mg/m^2/d (PO)	**:D1 to D7, D15 to D21** (in 3 takes/d)
Vincristine (VCR)	: 1,5 mg/m^2/infusion (IV)	: **D1, D8, D15, D43, D50** (MAX 2 mg/infusion)
Pegaspargase (PEG-ASPA)	**: 2500 IU/m^2/infusion (IV)**	**: D4, D43**
Doxorubicine	: 25 mg/m^2/infusion (IV)	: **D1, D8, D15**
6 thioguanine	: 60 mg/m^2/d (PO)	: **D29 to D42**
Cytarabine	: 75 mg/m^2/infusion (IV)	: **D31, 32, 33, 34 and D38, 39, 40, 41** (total: 8)
Cyclophosphamide	: 1 g/m²/infusion(IV)	: **D29**
Triple IT	: see appendix 5	: **D4, D31**

CAALL-F01: T-HR Interim Phase2



HD Methotrexate	5 g/m²	IV 24h	3 infusions	D8,22,36, leucovorin rescue beginning at H42
6 mercaptopurine	25 mg/m²	Per os	56 days	D1-42
Methotrexate IT	Appendix 5	IT	3 days	D9, 23, 37

CAALL-F01: T-HR DELAYED INTENSIFICATION 2



Dexamethasone (DEX)	: **<u>10</u>** mg/m^2/d (PO)	**:D1 to D7, D15 to D21** (in 3 takes/d)
Vincristine (VCR)	: 1,5 mg/m^2/infusion (IV)	: **D1, D8, D15, D43, D50** (MAX 2 mg/infusion)
Pegaspargase (PEG-ASPA)	**: 2500 IU/m^2/infusion (IV)**	**: D4, D43**
Doxorubicine	: 25 mg/m^2/infusion (IV)	: **D1, D8, D15**
6 mercaptopurine	: 60 mg/m^2/d (PO)	: **D29 to D42**
Cytarabine	: 75 mg/m^2/infusion (IV)	: **D31, 32, 33, 34 and D38, 39, 40, 41** (total: 8)
Cyclophosphamide	: 1 g/m²/infusion(IV)	: **D29**
Triple IT	: see appendix 5	: **D4,D31**

CAALL-F01:T-HR
Continuation therapy « maintenance »

- 76 weeks (total duration of the treatment: 104 weeks)
- No pulses
- 6MP 50 mg/m^2/day
- MTX 25 mg/m^2/week

Indications of cranial Radiotherapy (RT): **NO**

Patients with initial WBC <100 G/L:

6 ITmtx: every 6 weeks from beginning week 2 of maintenance

Patients with initial WBC ≥100 G/L:

6 HD-MTX + 6 ITmtx : every 6 weeks beginning week 2 of maintenance

See annex 5

NB: Bactrim® is to be given during the whole duration of maintenance and at least 3 months after stopping of 6MP/MTX

CAALL-F01:T-VHR
(T-cell ALL/Very High Risk)

- If T-cell ALL with inadequate reponse, i.e.
  - D8 poor PRED response and TP1 MRD ≥ 10^{-2}
  - SR/MRD-TP2 ≥ 10^{-3}
  - HR/MRD-TP2 ≥ 10^{-4}
  - MRD-TP3 (when indicated) ≥ 10^{-4}

⟹ indication of HSCT

  - prior to HSCT, intensification of the treatment:
    - VANDA course
    - followed by one or 2 cycles of nelarabine
    - until HSCT which is to be performed according to ongoing international HSCT guidelines or protocol.

CAALL-F01:T-VHR
(T-cell ALL/Very High Risk)

NELARABINE consolidation course

	D1	D2	D3	D4	D5
Nelarabine					

Nelarabine **650 mg/m^2/day** **IV (1h)** **5 days** **D1-D5**

NB: no IT is to be given during any nelarabine cycle from D-7 to D+15

- According to transplant availability one or two courses can be given.
- If a second course is given, it should begin at D21 after the first day of course 1

Hematopoietic Stem Cell Transplantation in Very High Risk T-cell ALL

- Should be performed according to:
  - international guidelines (I-BFM-HSCT)
  - or protocol (I-BFM «Forum trial»)
  - ongoing at CAAL-F01 opening