New therapeutic options in refractory and relapsed leukemia

with a **focus on acute and pediatric diseases**

Assoc. Prof. Dr. Michael N. **Dworzak,** M.D.

Chairman of the Austrian pediatric AML/CML-studies
Austrian representative at the I-BFM steering committee
St. Anna Children's Hospital, Vienna, Austria

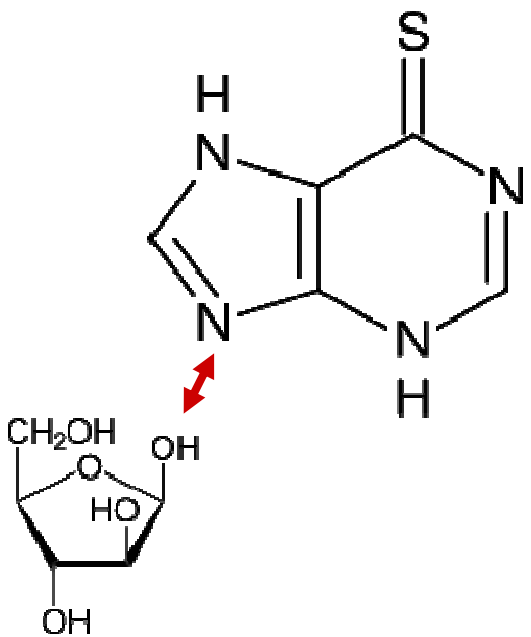
XVI Congress of The Chilean Society of Hematology
Coquimbo, **Chile**, September 24-27, 2008

New therapeutic options in refractory and relapsed leukemia

- New nucleoside analoga
- MRD-based treatment tailoring
- FLAMSA
- Antibodies
- Signal transduction inhibition

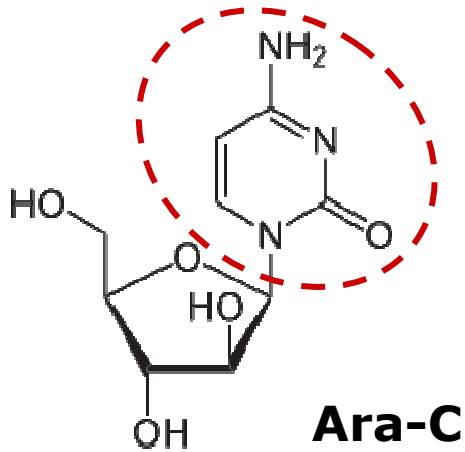
Nucleoside antimetabolites:
purine and pyrimidine analogs

6-mercapto-purine



β-D-Arabinofuranose

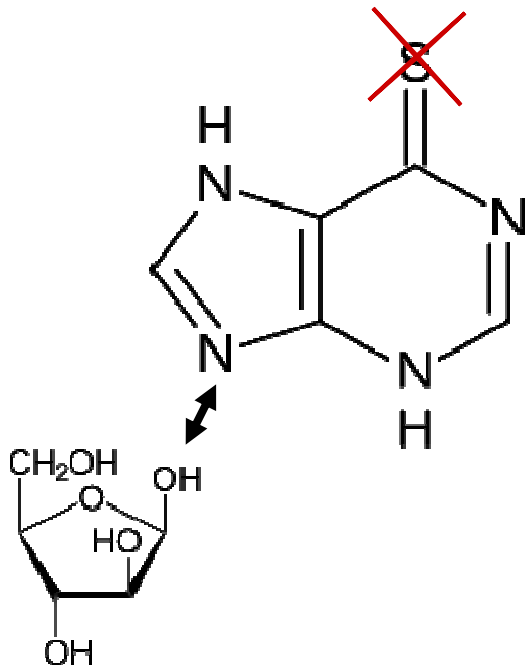
cytosine-*arabinoside*



Ara-C

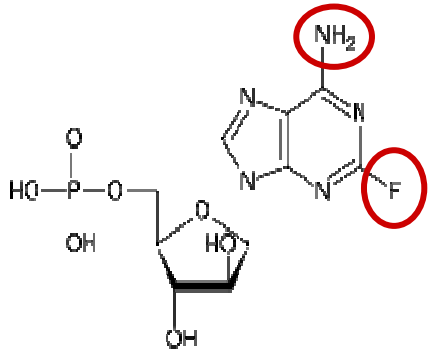
Nucleoside antimetabolites: **new purine** analogs

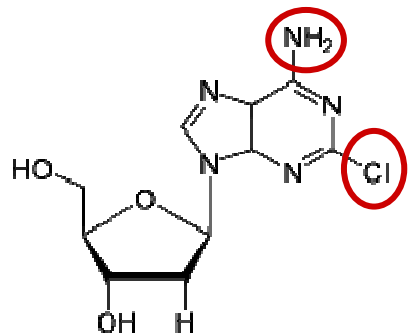
6-mercapto-purine



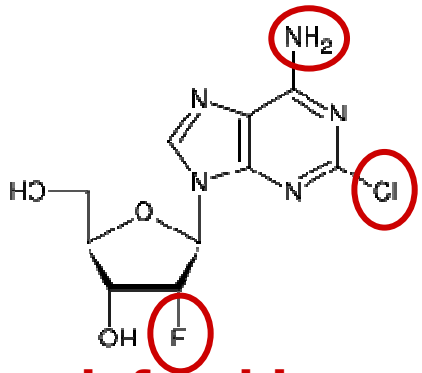
β-D-Arabinofuranose

fludarabine



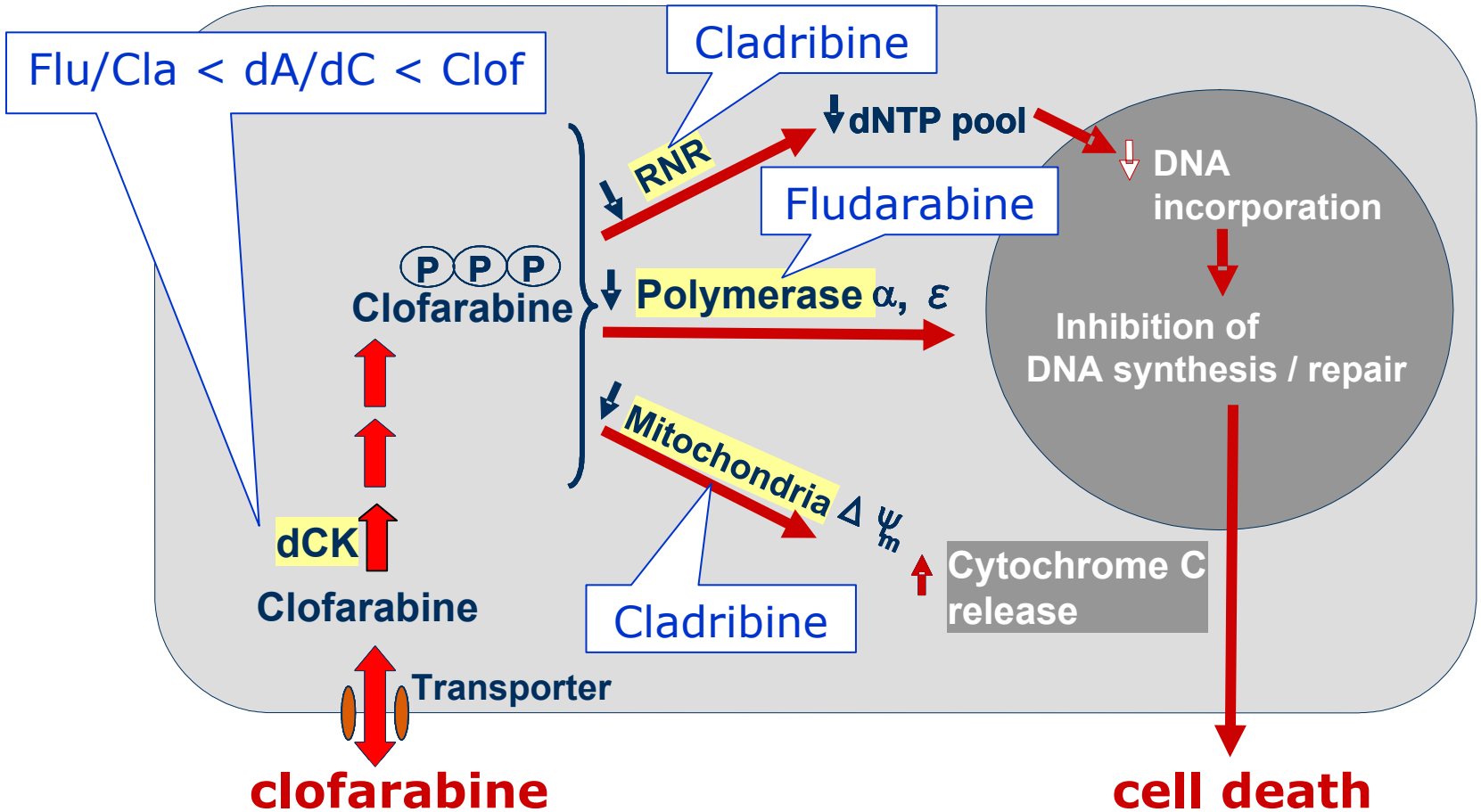


cladribine



clofarabine

Clofarabine (Clolar™, Evoltra™): mode of action

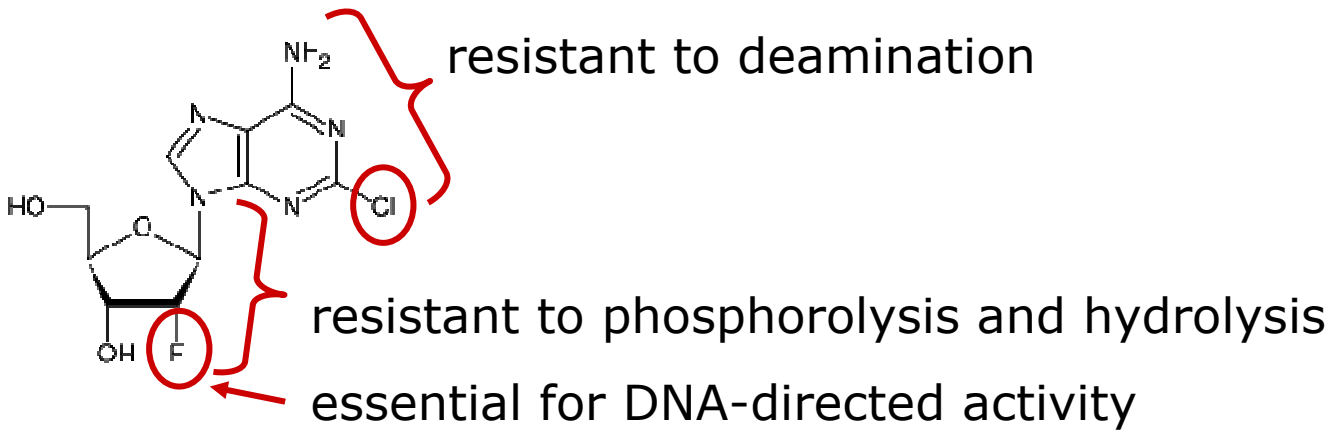


Parker, Cancer Res 1991, 51: 2386-2394
Xie and Plunkett, Cancer Res 1996;56:3030-3037
Genini, Blood 2000, 96: 3537-43

Clofarabine (Clolar™, Evoltra™)

- **rationally designed** to overcome disadvantages of cladribine AND fludarabine and to combine advantages of both
- **2004/6: accelerated* FDA/EMEA approval** for treatment of **relapsed/refractory pediatric ALL** after ≥ 2 prior regimens

*only by surrogate end-point like response rate
company still needs to establish the clinical benefit (phase IV)



Clofarabine (Clolar™, Evoltra™)

- **short half-life**
- **negligible accumulation** with once daily dosing
- **elimination via urine** (unchanged 49-60% of dose)
- **no cytochrome p450 interactions**
- **potentially enters CSF**
- **low neurotoxic potential** – best tolerated with 2 h infusion
- Potentialities for **rational drug combinations:**

  increases **Ara-C**TP accumulation via RNR-inhibition
  increases **cyclophosphamide** effect by DNA-repair inhibition

Clofarabine (Clolar™, Evoltra™): studies in **adults**

- **single agent** (**salvage**):

  Kantarjian et al., JCO (phase 1), Blood 2003 (phase 2)
  n=62 pts. (31 refractory/relapsed **AML**)
  40 mg/m^2 BSA days 1 – 5, every 3 - 6 weeks
  ORR 48% (CR 20, CRp 9, PR 1)
  ORR AML 55% (9/19 in 1st relapse, 8/12 ≥2nd relapse)
  ORR ALL 17% (2/12)

  Foran et al., JCO abs ASCO 2003 (phase 2, multicentric)
  n=40 pts. refractory (28%)/relapsed (early 55%) **AML**
  only 1 CR/40 pts.

- **single agent** (**first-line**; for pts. unfit for conventional therapy):

  Burnett et al., Blood 2004, n=30 AML >60y: ORR 56%
  Burnett et al., ASH 2006, n=66 AML >65y: ORR 44%
  Erba et al., ASCO 2008, n=116 AML >60: ORR 45%

Clofarabine (Clolar™, Evoltra™): studies in **adults**

- **combinations** (**salvage**):

  Faderl et al., Blood 2005 (phase 1-2)
  n=32 pts. (25 refractory/relapsed **AML**)
  clofarabine 40 mg/m²/d + ID-Ara-C 1 g/m²/d x5 days
  ORR AML 40% (CR 7, CRp 3); refractory/early Rx ORR 35%

  Faderl et al., Blood abs ASH 2006, + idarubicine/ ± ID-Ara-C

  Karp et al., Blood 2007 (phase 1)
  n=18 pts. (refractory 12 **AML**, 6 **ALL**)
  clofarabine 10-20 mg/m²/d + cyclophosph. 400 mg/m²/d x6 d
  ORR AML 25% (CR 2, PR 1), ORR ALL 67% (CR 3, PR 1)

- **combinations** (**first-line**):

  Faderl et al., + ID-Ara-C, n=60 AML >50y: ORR 60%
  Faderl et al., ± LD-s.c.-Ara-C, n=67 AML >60y: ORR 60%
  Burnett et al., + daunorubicin/mylotarg, n=37 AML: ORR 65%
  Agura et al., + ID-Ara-C, n=30 AML & cardiac risk: ORR 57%

Clofarabine (Clolar™, Evoltra™): **pediatric** studies

- **single agent:** **52** mg/m^2 BSA days 1 – 5

  Jeha et al., Blood 2004 (phase 1), JCO 2006 (phase 2)
  n=61 pts. refractory (57%)/relapsed **ALL**
  ORR 30% (CR 7, CRp 5, PR 6: 50% w CR(p) prev. refractory)
  SCT in 9/61 (7/9 responders): median CR 7 months
  remission by CHT only (if CR/CRp): 8 – 48 weeks

  Kearns et al., Blood abs ASH 2007 (phase 2, BIOV-111)
  n=65 pts. refractory/relapsed **ALL** (34% prev. SCT)
  ORR 28% (CR 6, CRp 11, PR 1: 11/18 had prev. SCT)
  SCT in 7/61 (7/7 responders)

  Jeha et al., Blood abs ASH 2006 (phase 2)
  n=42 pts. refractory (66%)/relapsed **AML**
  ORR 26% (CRp 1, PR 10: 6/11 w response prev. refractory)
  SCT in 13/42 (7/11 responders): 5 alive (+62 – 160 weeks)

Clofarabine (Clolar™, Evoltra™): **pediatric** studies

- **combinations:** (20-)**40** mg/m² BSA days 1 – 5

  Hijiya et al., Blood abs ASH 2007 (phase 1), (phase 2 ongoing)
  + cyclophosphamide 440mg/m²/d x5 days
  + etoposide 100mg/m²/d x5 days
  n=25 pts. refractory/relapsed **ALL** (n=20) or **AML** (n=5)
  ORR 64% (CR 10, CRp 6) „well tolerated"
  ORR ALL 55% (CR 9, CRp 2)
  ORR AML 100% (CR 1, CRp 4)

  phase 2 (CLO-218): **on hold** (excess of hepatotoxicity)
  n=8 pts.: 3 pts. **VOD**; 1 pt. ↑Bili °4 (prior SCT+TBI in 3)

  COG AAML0523 ongoing: clofarabine + cytarabine (1g/m²)

  I-BFM/ITCC CLARA-DNX upcoming**:** relapsed/refractory **AML**
  clofarabine + HD-cytarabine + lipos. daunorubicin

Clofarabine (Clolar™, Evoltra™): **pediatric** studies

- **case reports**: **Steinherz** et al., J Ped Hemat Oncol 2007
  Gidwani et al., Chemotherapy 2008

  case 1, **pB-ALL**, **3rd BM-relapse** (after 2x SCT), refractory
  clofarabine 52-26mg/m$^{2\ BSA}$ x5 days: 12 cycles
  CR after cycle 1: 47 weeks (24 days in-patient)

  case 2, **pB-ALL**, **3rd (BM)-relapse** (prev. 2x CNS; 25 Gy)
  clofarabine 52-26mg/m$^{2\ BSA}$ x5 days: 12 cycles
  CR after cycle 1: 59 weeks

  case 3, **AML**, 1st late BM-relapse, refractory to FLAG
  clofarabine 52-30mg/m$^{2\ BSA}$ x5 days: 8 cycles
  PR after cycle 1, CR after cycle 3: for 64 weeks
  in-patient: 35 days

  case 4, **T-ALL, mult. relapses**, refractory (3 attempts)
  clofarabine + cytarabine; CR after cycle 1

Clofarabine (Clolar™, Evoltra™): **toxicity profile**

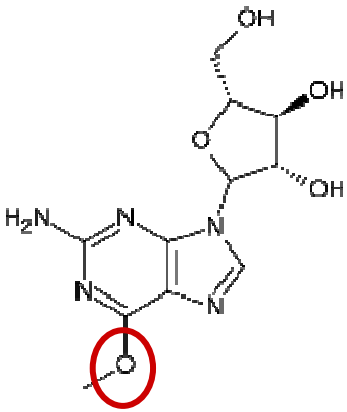
- **pediatric reports**:

>50% of patients:	myelosuppression
>10-50% of pts.:	febrile neutropenia, nausea, headache liver enzyme elevation, hyperbilirubinemia diarrhea, hypotension
≤ 10% of pts.:	pleural effusion, capillary leak syndrome cytokine-release syndrome (i.e. SIRS) tumor lysis syndrome skin rash, hand-foot syndrome decline in cardiac function (& sepsis or SIRS)

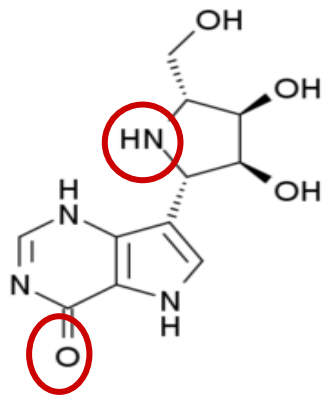
- **adult reports:** **additional toxicities**

  renal insufficiency, prolonged aplasia (comb.)

Nucleoside antimetabolites:
very new **purine** analogs

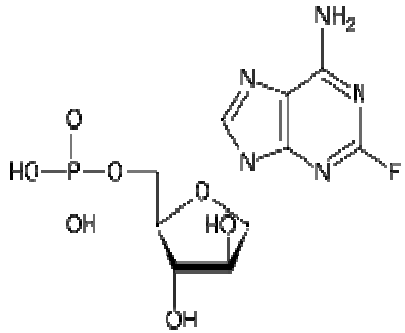


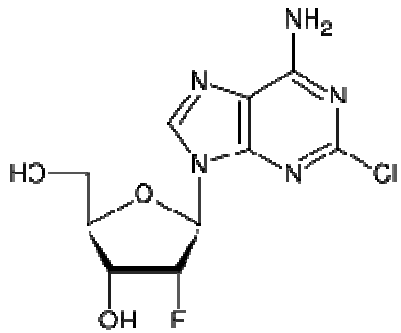
nelarabine



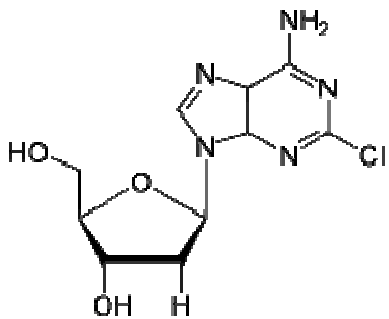
forodesine

fludarabine





clofarabine



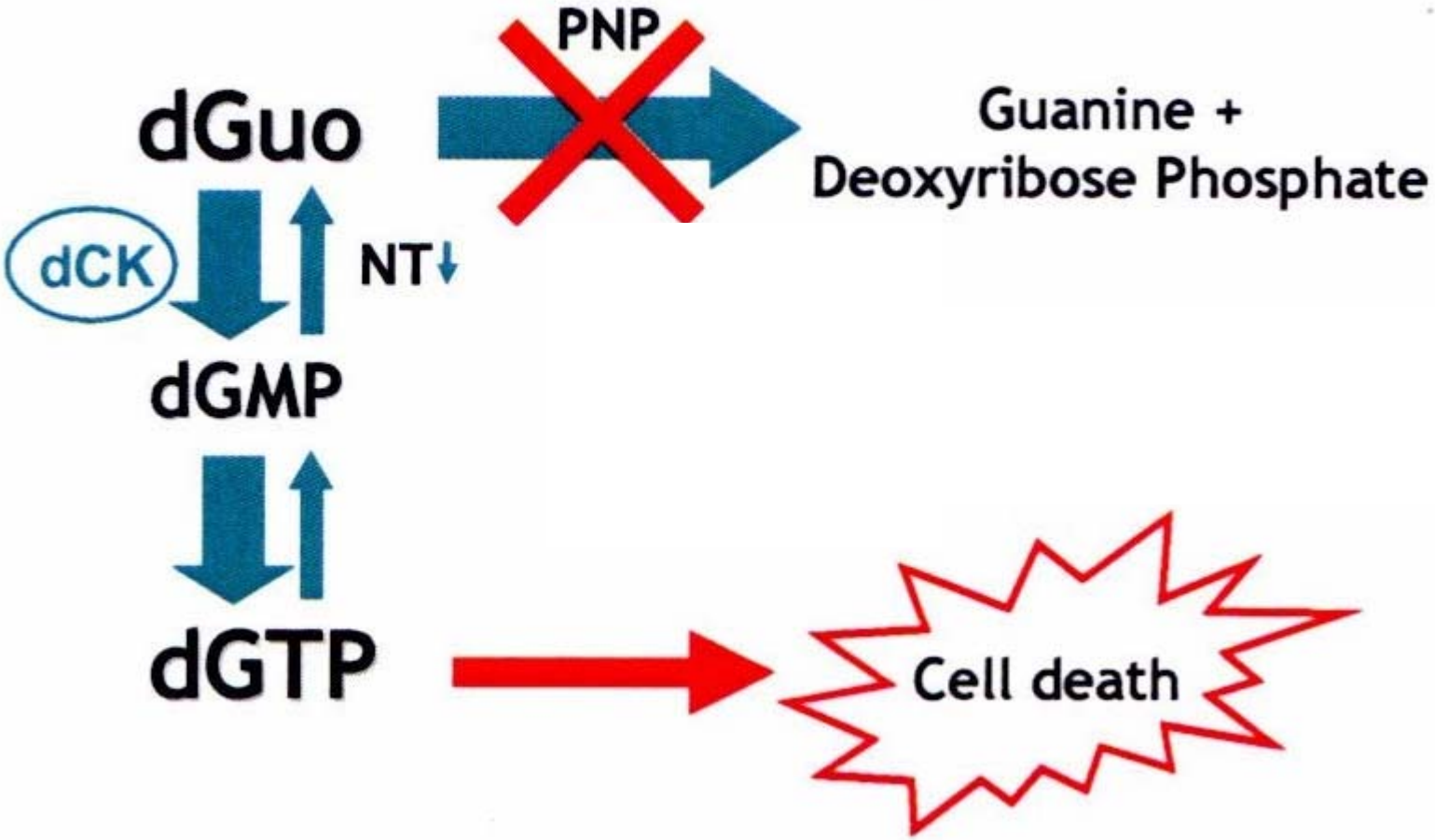
cladribine

Inherited PNP Deficiency

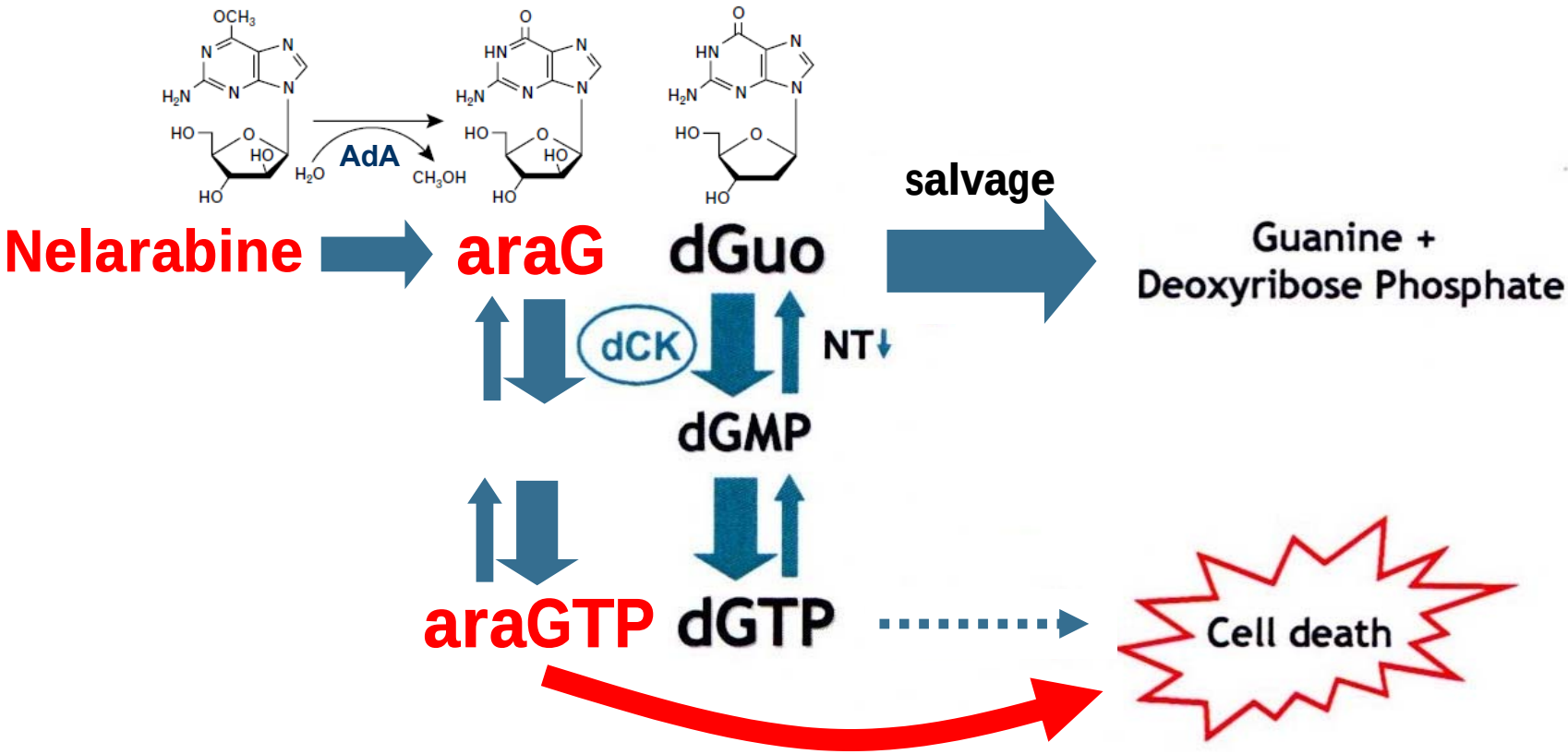
- Disease model: *Severe Combined Immunodeficiency Syndrome (SCID)*
  - Around 40 children characterised
- PNP deficiency is characterised by:
  - Low number of circulating T cells
  - Normal or reduced number of B cells
  - PNP activity <5% of normal level leading to:
    - High plasma deoxyguanosine (dGuo)
    - High intracellular dGTP level
    - ➢ Imbalance of nucleotides!

first described in 1975

Purine Nucleoside Phosphorylase (PNP) Inhibition Leads to Apoptosis



Nelarabine (Arranon™, Atriance™): mode of action



Nelarabine (Arranon™, Atriance™)

- dGTP: toxicity for T cells >> B cells
  due to greater accumulation/retention
- araG: dGTP analogon
  synthesized first in 1964
  not used because of poor solubility
- **nelarabine:** pro-drug of araG
  10x more water soluble than araG
  developed in 1995

  2005: accelerated* FDA approval for treatment of **relapsed/refractory T-ALL/T-LBL** after ≥ 2 prior regimens (**adults and children**)

  *only by surrogate end-point like response rate
  company still needs to establish the clinical benefit (phase IV)

Nelarabine (Phase 1, adults and children)

Table 7. Response Data by Disease Subtype

Disease Type	No. of Patients	CR		PR		CR+PR		NE		SD/NR/PD	
		No.	%	No.	%	No.	%	No.	%	No.	%
T-ALL/lymphoblastic lymphoma*	39	9	23	12	31	21	54	7	18	11	28
Pediatric T-ALL/lymphoblastic lymphoma	26	7	27	4	15	11	42	6	23	9	35
Adult T-ALL/lymphoblastic lymphoma	13	2	15	8	62	10	77	1	8	2	15
T-CLL/T-PLL	7	0	0	2	29	2	29	0	0	5	71
Other T-cell diseases	15	0	0	2	13	2	13	2	13	11	73
B-ALL/Pre-B ALL	10	0	0	1	10	1	10	3	30	6	60
B-CLL/B-PLL	4	0	0	1	25	1	25	0	0	3	75
B-NHL	6	0	0	1	17	1	17	1	17	4	67
AML/CML-BC	8	1	13	0	0	1	13	2	25	5	63
Other (Unknown immunotype, biphenotypic)	4	0	0	0	0	0	0	3	75	1	25
Total	93	10	11	19	20	29	31	18	19	46	49

Abbreviations: CR, complete response; PR, partial response; NE, not assessable; SD, stable disease; NR, no response; PD, progressive disease; CLL, chronic lymphocytic leukemia; PLL, prolymphocytic leukemia; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin's lymphoma; AML, acute myeloid leukemia; CML-BC, chronic myeloid leukemia blast crisis.

*Pediatric and adult T-ALL/lymphoblastic rows are subgroups of the data presented in the T-ALL/lymphoblastic lymphoma row.

MTD: **1.2** g/m^2 ^{BSA} in adults; **1.8** g/m^2 ^{BSA} in children

Kurtzberg et al., JCO 2005

Nelarabine (Phase 2, children/adolescents <21 a; COG)

Table 1. Response to Nelarabine by Stratum at All Dose Levels

Stratum/Dose (mg/m²)	Total Patients	Assessable Patients	CR	PR	Response Rate (CR + PR; %)	95% CI (%)
1 (T-ALL, first relapse)						
900	6	6	2	0	33	(0 to 71)
650	**34**	**33**	**16**	**2**	**55** ←	**(38 to 72)**
2 (T-ALL, second relapse)						
≥ 900	10	10	3	0	30	(2 to 47)
650	**36**	**30**	**7**	**1**	**27** ←	**(11 to 43)**
3 (CNS +)						
900	2	1	0	0	0	N/A
650	6	6	1	0	17	(0 to 47)
400	**24**	**21**	**5**	**2**	**33** ←	**(13 to 53)**
4 (lymphoma)						
650	8	7	1	2	43 ←	(6 to 80)
400	**27**	**22**	**0**	**3**	**14**	**(0 to 28)**
Overall	153	136	35	10	33	**(25 to 41)**

NOTE. The final dose levels used to determine response rate are indicated in bold.
Abbreviations: CR, complete response; PR, partial response; T-ALL, T-cell acute lymphoblastic leukemia; N/A, not applicable.

MTD: **650** mg/m² BSA as single agent; **400** mg/m² BSA in drug combinations

Berg et al., JCO 2005

Nelarabine - published studies

Alternate day regimen: to reduce neurotoxicity

First relapse 68% ! T-ALL: CR 76%

Table 1 Clinical trials of nelarabine

Population (Phase)	# of patients	Disease type	Nelar (g/m²)	Schedule	CR(%)	PR(%)	Reference
Adult and pediatric (I)	93	Leukemia + Lymphoma	escalating	Daily for 5 days	11	20	Kurtzbuerg et al 2005
Adult (II)	38	T-cell	1.5	Days 1, 3, 5	26	5	DeAngelo et al 2002
Adult (II)	53	T-cell	1.5	Days 1, 3, 5	47	13	Geokbuget et al 2005
Adult (II)	23	Non-Hodgkin's lymphoma	1.5	Days 1, 3, 5	11	36	Goy et al 2003
Adult (I) nelarabine/fludarabine	13	Indolent leukemia/ T-cell ALL	1.2	Days 1, 3, 5	15	31	Gandhi et al 2001
Pediatric (II)	136	T-cell	1.2, 0.6, 0.4	Daily for 5 days	35	10	Berg et al 2005
Pediatric (pilot) nelarabine/augmented BFM	87	T-cell	0.4, 0.6	Daily for 5 days	not published		Dunsmore et al 2006

Abbreviations: CR, complete remission; PR, CR without platel and partial remission; T-cell, T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma.

Both dosages well tolerated in combination with conventional therapy

review by Cooper-TM, 2007

Nelarabine - neurotoxicity (is dose-limiting)

in adults*: 72% total, 10% °3-4

Table 2 Nelarabine neurological toxicity in adult patients (n = 103) as presented to the FDA Oncology Drugs Advisory Committee

Adverse event	All grades (%)	Grades 3/4 (%)
Somnolence	23	0
Hypoesthesia	17	2
Paresthesia	15	2
Peripheral neuropathy (sensory)	13	0
Peripheral neuropathy (motor)	7	1
Peripheral neuropathy (unspecified)	5	1
Ataxia	9	2
Depressed level of consciousness	6	1
Tremor	5	0
Neuropathy	4	0
Amnesia	3	0
Dysgeusia	3	0
Balance disorder	2	0
Sensory loss	2	0

in children*: 38% total, 22% °3-4

Table 3 Nelarabine neurological toxicity data in pediatric patients (n = 84) as presented to the FDA Oncology Drugs Advisory Committee

Adverse event	All grades (%)	Grades 3/4 (%)
Headache	17	6
Somnolence	7	2
Hypoesthesia	6	4
Peripheral neuropathy (sensory)	6	6
Peripheral neuropathy (motor)	4	2
Peripheral neuropathy (unspecified)	6	2
Convulsion	4	4
Motor dysfunction	4	1
Nervous system disorder	4	0
Paresthesia	4	1
Tremor	4	0
Ataxia	2	1

* Toxicity at recommended dose and schedule

reviewed by Cohen et al., 2008; and Cooper-TM, 2007

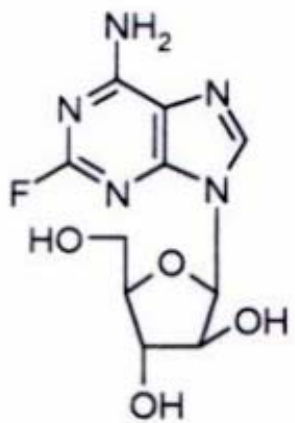
Nelarabine - neurotoxicity is dose-limiting

Other toxicities*:	adults	children
• hematologic	70% **°3-4**	90% (62% **°4** neutropenia)
• infection	frequent	17% **°3-4**
• laboratory:		4 – 9% **°3-4** (Bili, ALT; Alb, K^+)
• GI	1%	none at **°3-4**

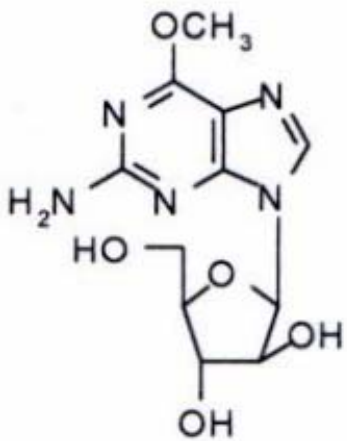
***** Toxicity at recommended dose and schedule

reviewed by Cohen et al., 2008; and Cooper-TM, 2007

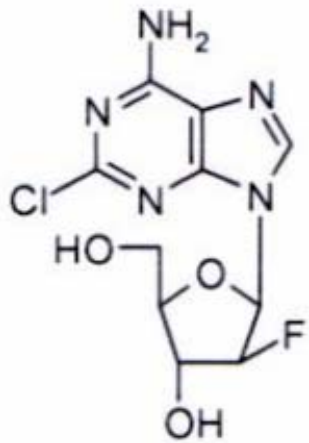
Forodesine - Another Purine Nucleoside Analog?



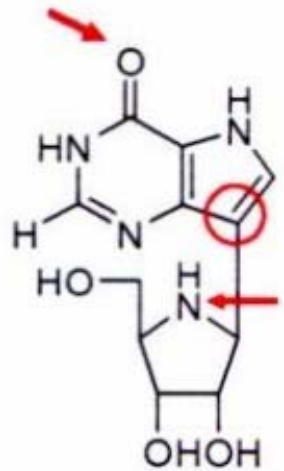
Fludarabine



Nelarabine

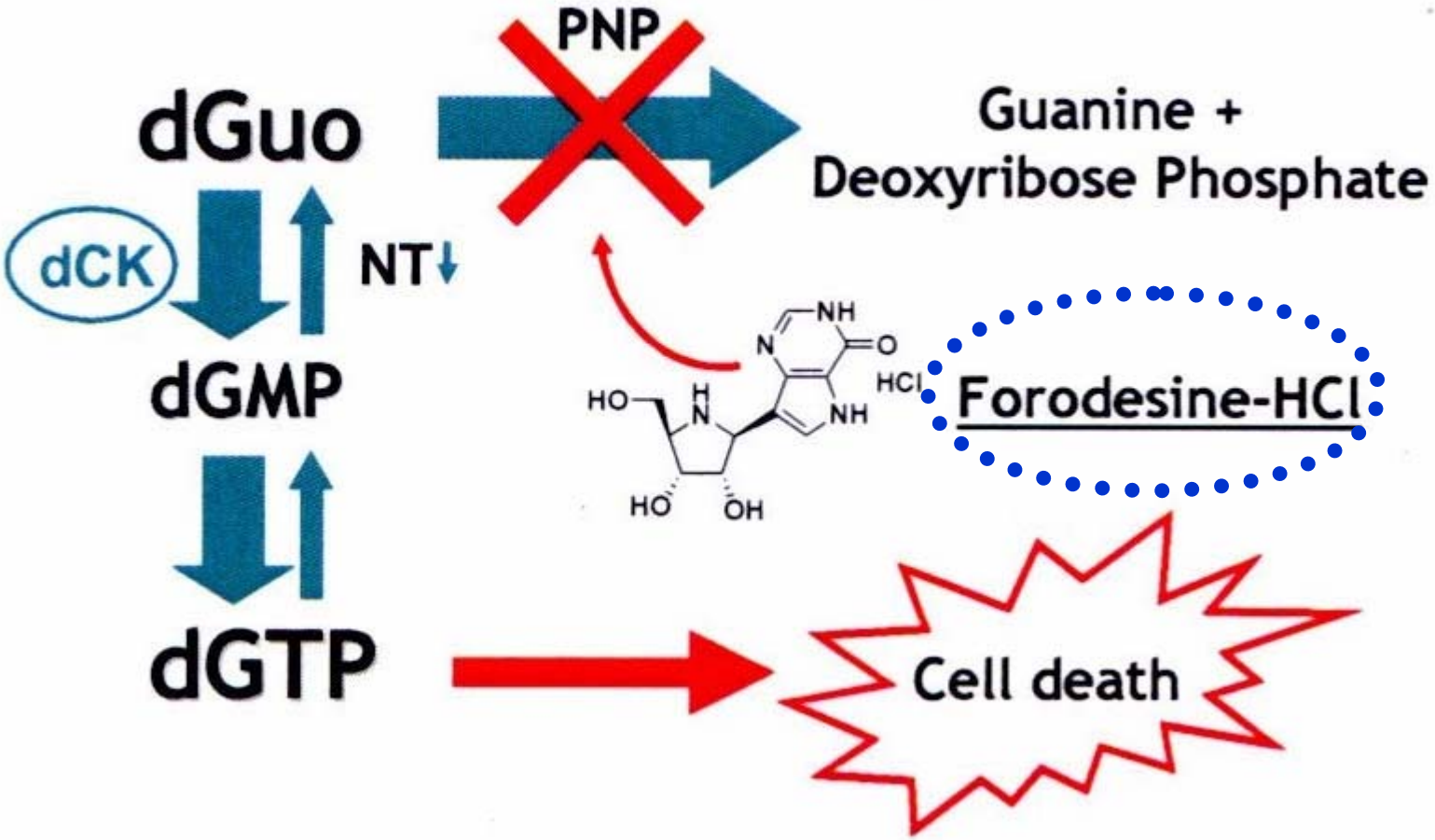


Clofarabine



Forodesine

Purine Nucleoside Phosphorylase (PNP) Inhibition Leads to Apoptosis



Forodesine - first selective PNP inhibitor:

What makes it different?

	conventional antimetabolites	forodesine
DNA damage	yes	no
mutagenicity	yes	no
MTD	low	not reached
hematotoxicity	yes	minor
systemic toxicity	yes	low
oral administration	mostly no	yes

Rationale to Use Forodesine in ALL

- Intracellular dGTP accumulation and apoptosis *in vitro* in T- and B-ALL primary cells / cell lines
- Synergistic or additive activity *in vitro* with DNA damaging agents (oxaliplatin, doxorubicin, vincristin)
- *In vivo* efficacy demonstrated in Phase I/II studies

Forodesine - Clinical Experience

Study	Indication	Route	Responses No	%	
103	Refractory/relapsed CTCL	IV	4/13	31	ORR [1]
105	Refractory/relapsed CTCL	oral	16/56	28	ORR [1]
			14/36	39	ORR [2]
106	Refractory/relapsed pre-B-ALL	IV	2/28	7	CR [3]
201	Refractory/relapsed T-ALL	IV / oral	9/75	12	CR [3]

Phase IIa Study BCX1777-201: Complete Remission in Advanced Relapsed or Refractory T-ALL Patients

Pat. No.	No. of Pre-Treat-ments	Age/ Sex	Relapsed/ Refractory	Wks of the-rapy	Time to CR (wks)	Time to Pro-gression (days)	Overall Survival (days)
1 #	9	23/M	Relapsed	9	2	77	77
2	1	60/M	Relapsed	31	6	238	238+
3 *	4	28/F	Relapsed	10	2	119	459+
4 ‡	2	3/F	Relapsed	51	2	398+	398+
5 §	2	20/F	Refractory	7	6	207	224
6	2	76/M	Refractory	12	2	91	91+
7 §	3	27/M	Refractory	6	2	180+	180+

Pediatric case: 3-year old girl with T-ALL

- T-ALL, initial treatment failure after 2 induction therapies, 1st remission after HD AraC / L-asp. / HD MTX
- allogeneic HSCT (unrelated donor, 6/6 HLA matched)
- relapse 6 month after allo. HSCT, start with forodesine treatment
- **2 weeks forodesine treatment: complete remission** with complete donor chimerism (BM)
- 3 weeks of forodesine treatment: **new onset of hepatic GvHD**, interruption of forodesine treatment, GvHD treatment with prednisone and subsequently cyclosporine A for 4 months
- restart of forodesine treatment (twice weekly for 1 year)
- **actual follow-up (>2.5 years): alive & well in CR, no GvHD**

New purine nucleoside analogs

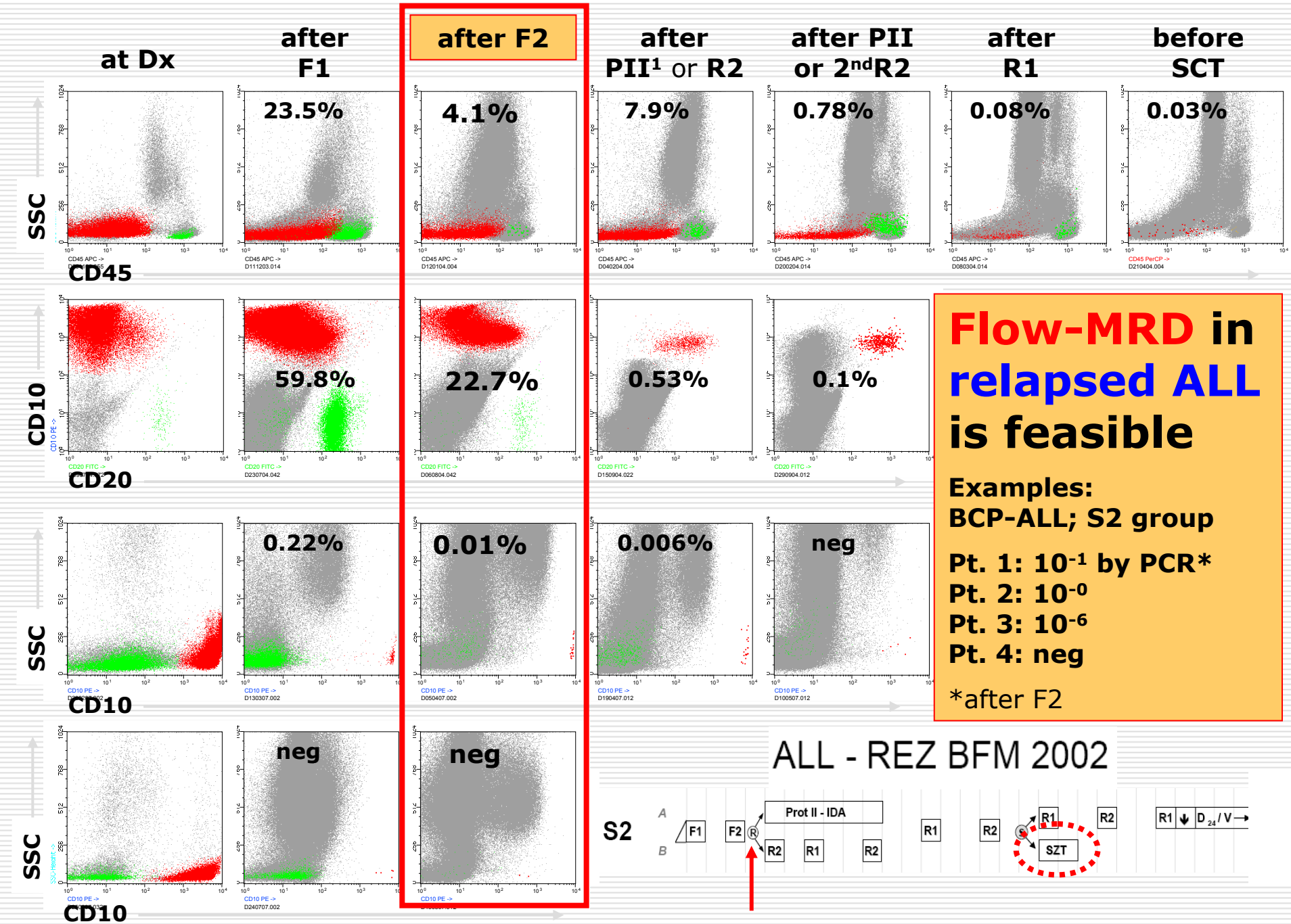
Clinical studies registered at ***ClinicalTrials.gov*** as per 09-2008

	total/active	**pediatric**/active
• **Clofarabine***	60/40	19/19
• **Nelarabine**	14/3	11/2
• **Forodesine**	12/4	4/1

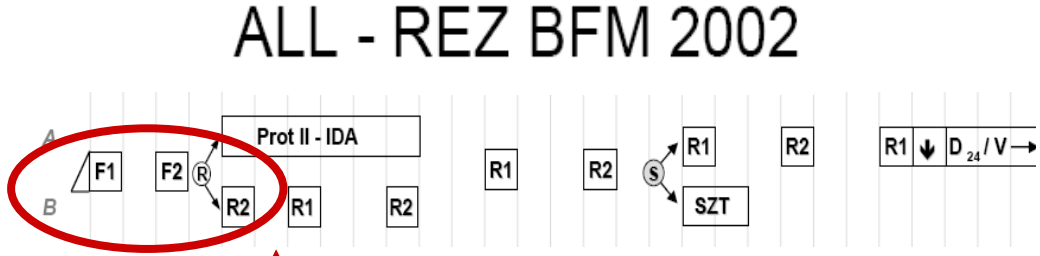
* many on SCT-regimens

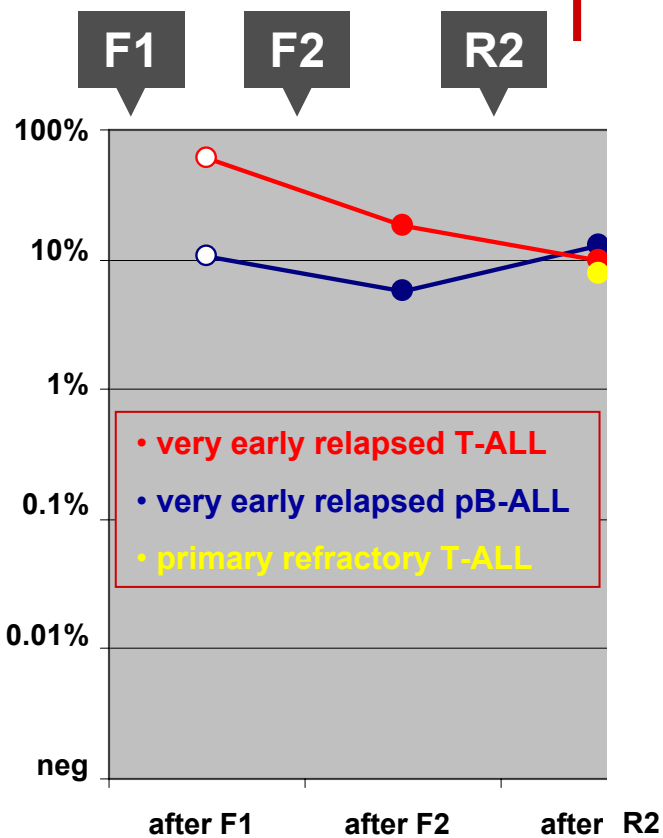
New therapeutic options in refractory or relapsed acute leukemia

- New nucleoside analoga
- **MRD-based treatment tailoring**
- **FLAMSA**
- Antibodies
- Signal transduction inhibition


at Dx
after F1
after F2
after PII¹ or R2
after PII or 2ndR2
after R1
before SCT
SSC
CD45
CD10
CD20
SSC
CD10
SSC
CD10
23.5%
4.1%
7.9%
0.78%
0.08%
0.03%
59.8%
22.7%
0.53%
0.1%
0.22%
0.01%
0.006%
neg
neg
neg
Flow-MRD in relapsed ALL is feasible
Examples:
BCP-ALL; S2 group
Pt. 1: 10-1 by PCR*
Pt. 2: 10-0
Pt. 3: 10-6
Pt. 4: neg
*after F2
ALL - REZ BFM 2002
S2
A
B
F1
F2
R
Prot II - IDA
R2
R1
R2
R1
R2
S
R1
SZT
R2
R1
D 24 / V

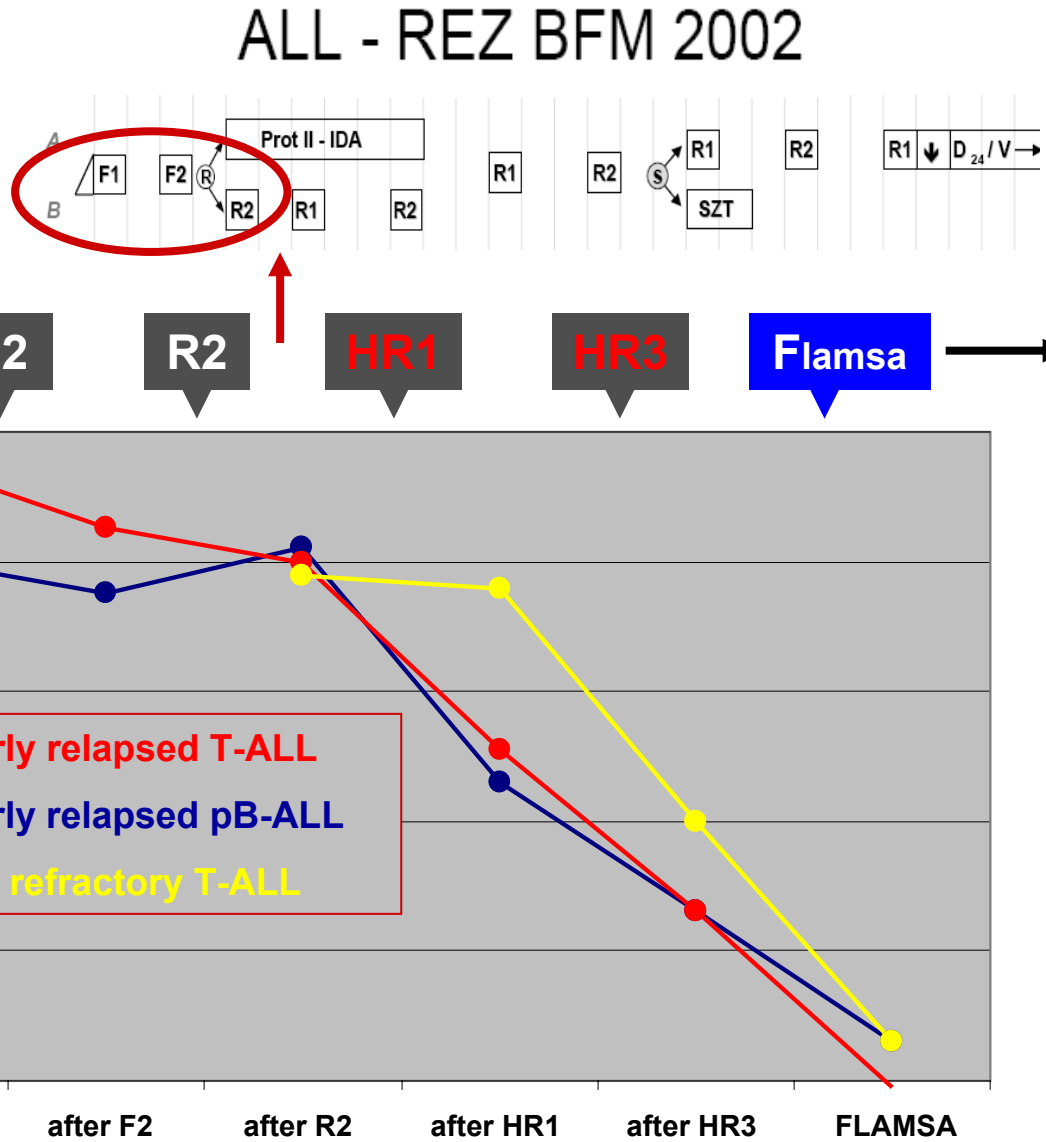
Treatment options and tailoring in resistant ALL: MRD-based



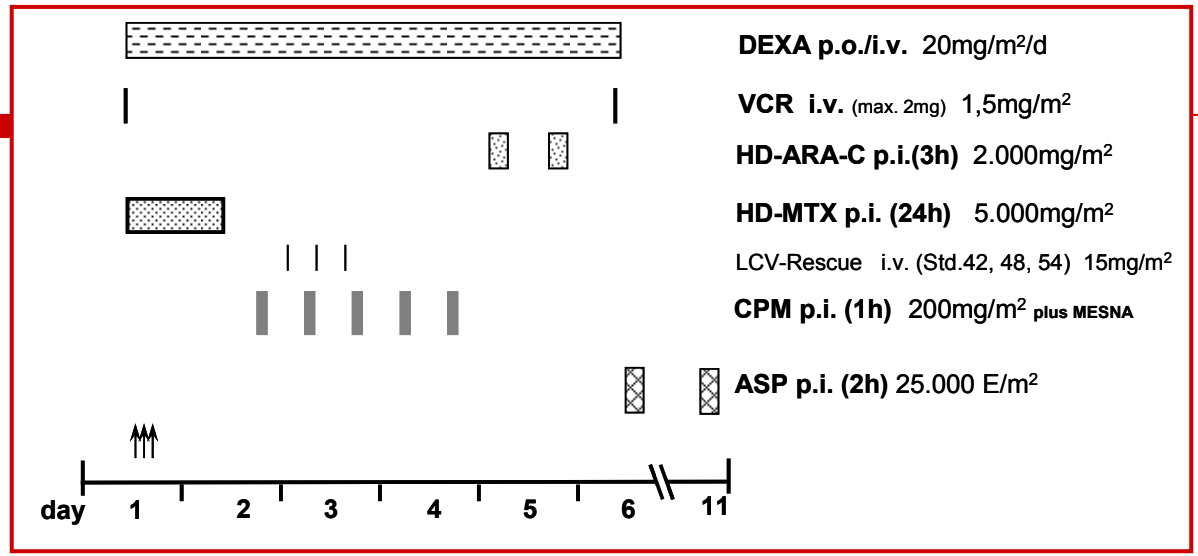


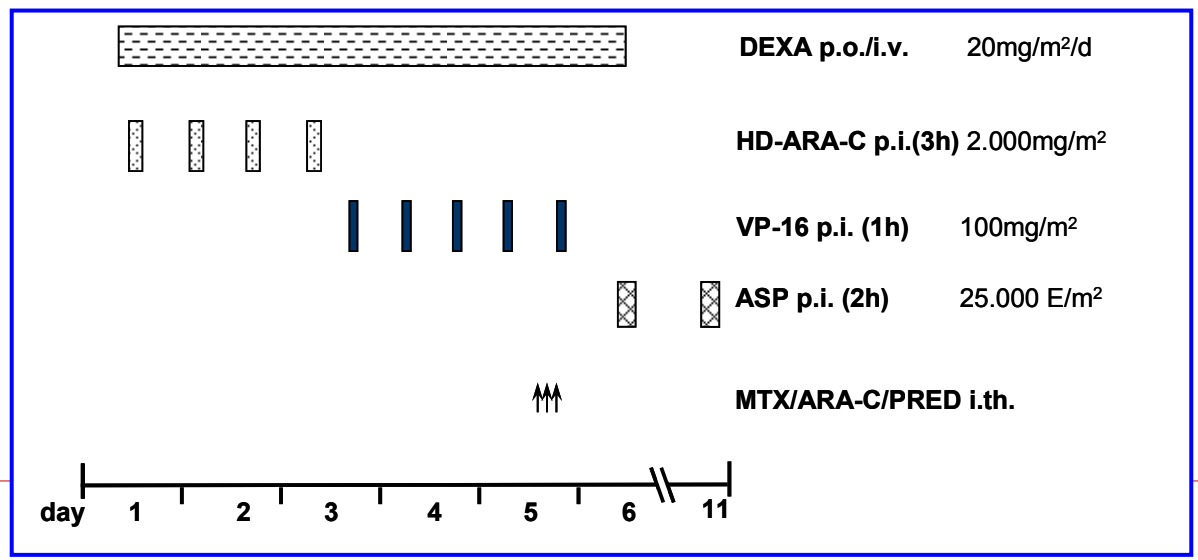
conventional options?

Treatment options and tailoring in resistant ALL: MRD-based



ALL-BFM 2000: courses HR-1 and HR-3





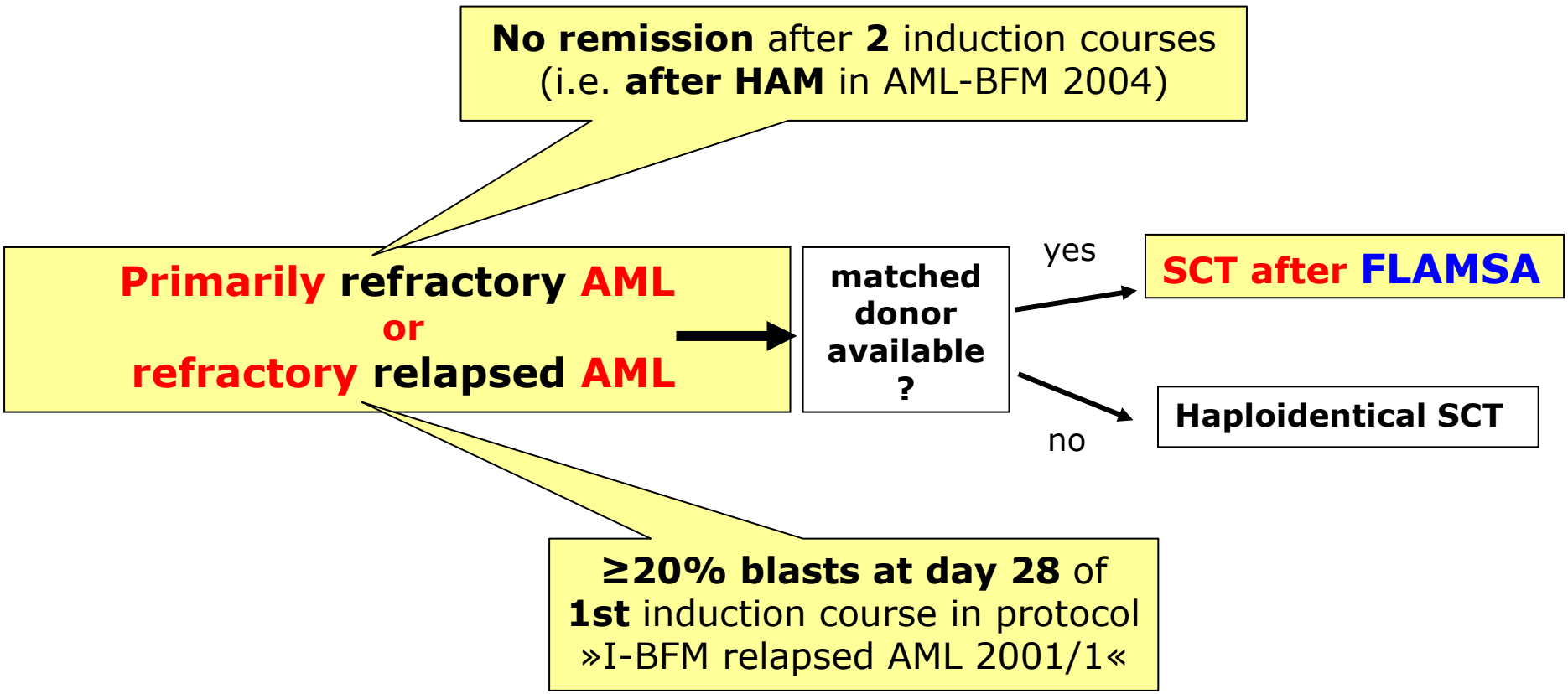
Chemotherapy course „FLAMSA“

Schmid and Kolb et al, JCO 2005

Amsacrine*	**1x 100mg/m2** BSA over 1h **day 1 – 4**
Fludarabine	**1x 30mg/m2** BSA over 30min **day 1 – 4**
Cytarabine	**1x 2g/m2** BSA over 2h **day 1 – 4** **(start 4 hours after Flu)**

an old drug´s revival

Refractory AML and FLAMSA-RIC SCT



Synopsis „FLAMSA-RIC“ results

Schmid and Kolb et al, Blood 2006

N=103 refractory/relapsed adult AML patients (median age 52y)

- **Primary induction failure (PIF) n=37 (after 2 courses)**
- **Early relapse (< 6 months of CR1) n=53**
- **Refractory (n=8) or ≥2nd relapsed AML (n=5)**

OS: 54%, 40%, 32% after 1, 2, and 4 years

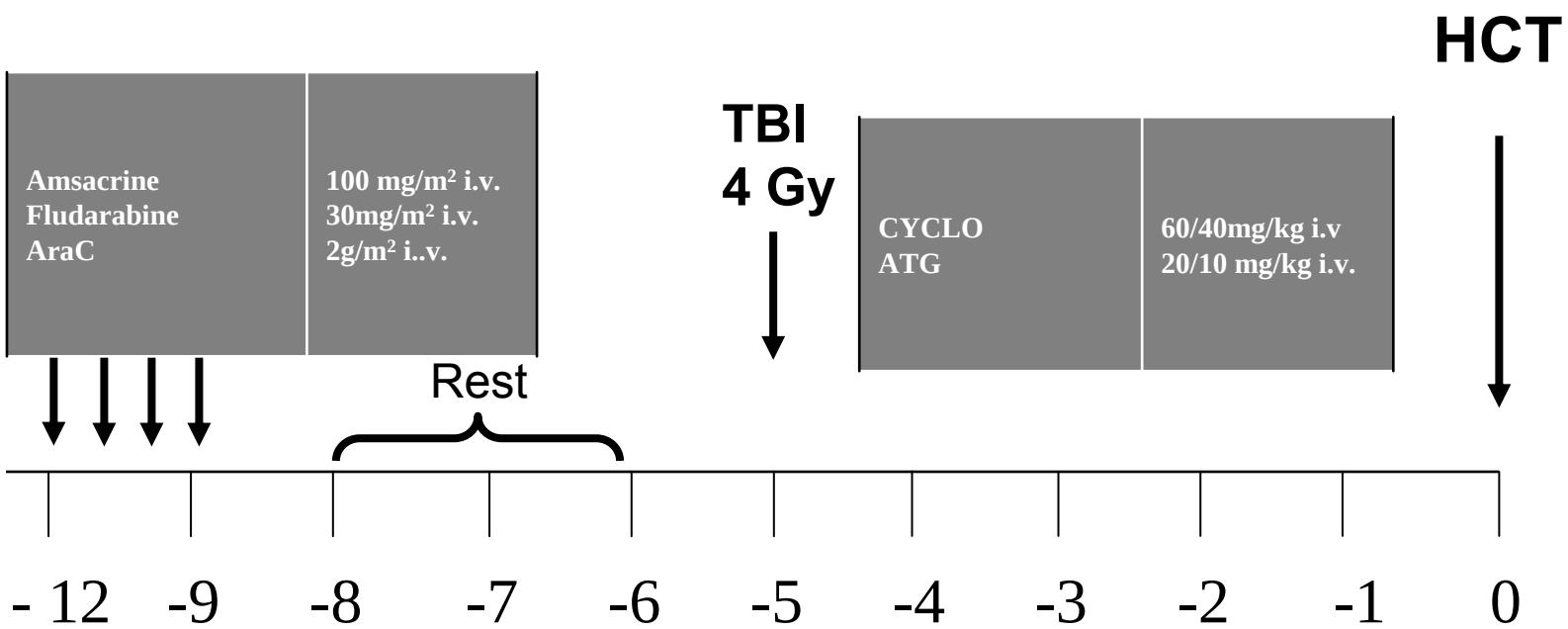
OS in PIF: 63% after 2 years

OS in +pDLT (day +120): 87% (n=17; if no GVHD)

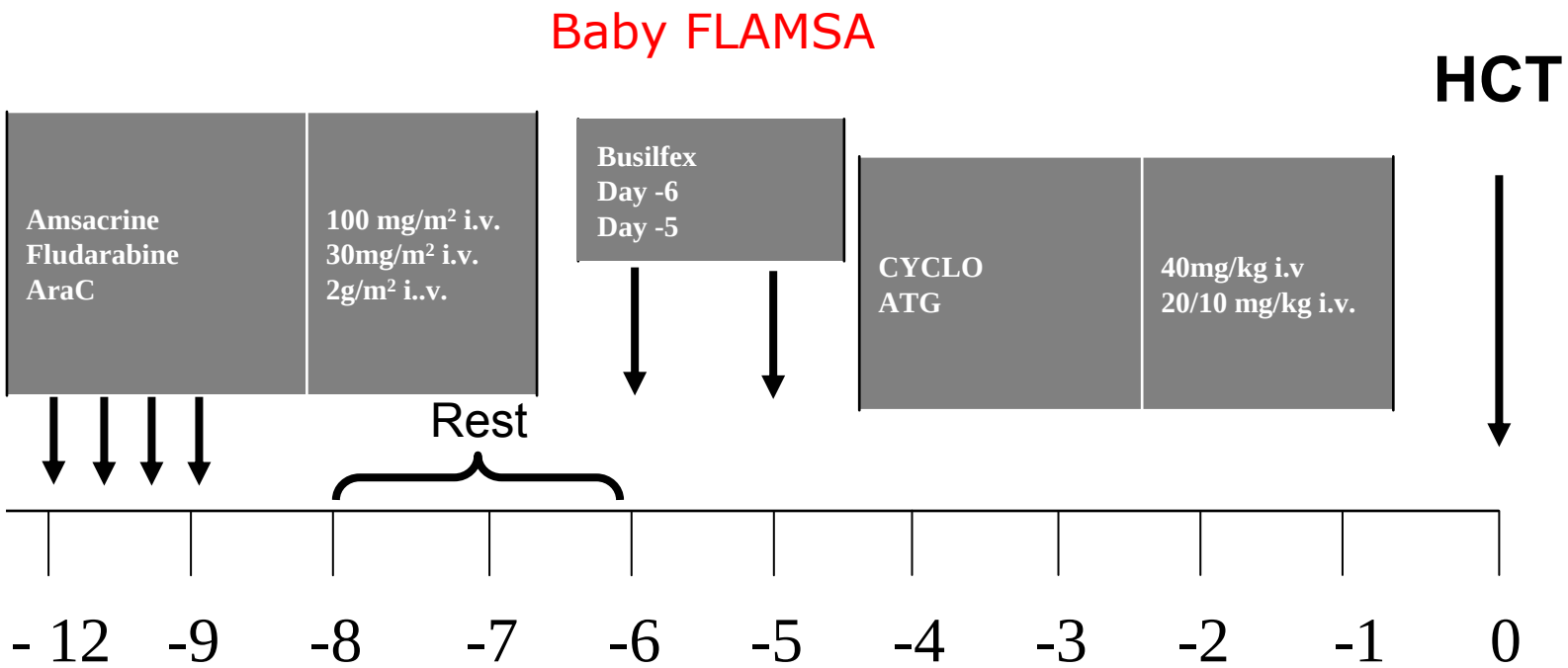
EFS: 47%, 37%, 30% after 1, 2, and 4 years

Non-relapse mortality after one year:	17%
Relapse mortality after one year:	29%
Acute GVHD grade II-IV:	28%
Chronic GVHD:	33%

Preparative regimen „FLAMSA-RIC adult“



„FLAMSA-RIC pediatric“ in study AML-BFM-SCT 2007



New therapeutic options in refractory or relapsed acute leukemia

- New nucleoside analoga
- MRD-based treatment tailoring
- FLAMSA
- **Antibodies**
- **Signal transduction inhibition**

New (chemo-)**therapeutics** for ***targeted therapy***

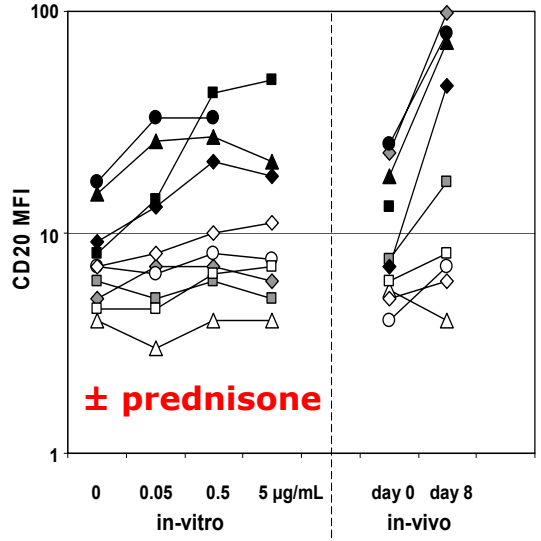
- **Immunotherapeutics:** *xxx**mab***

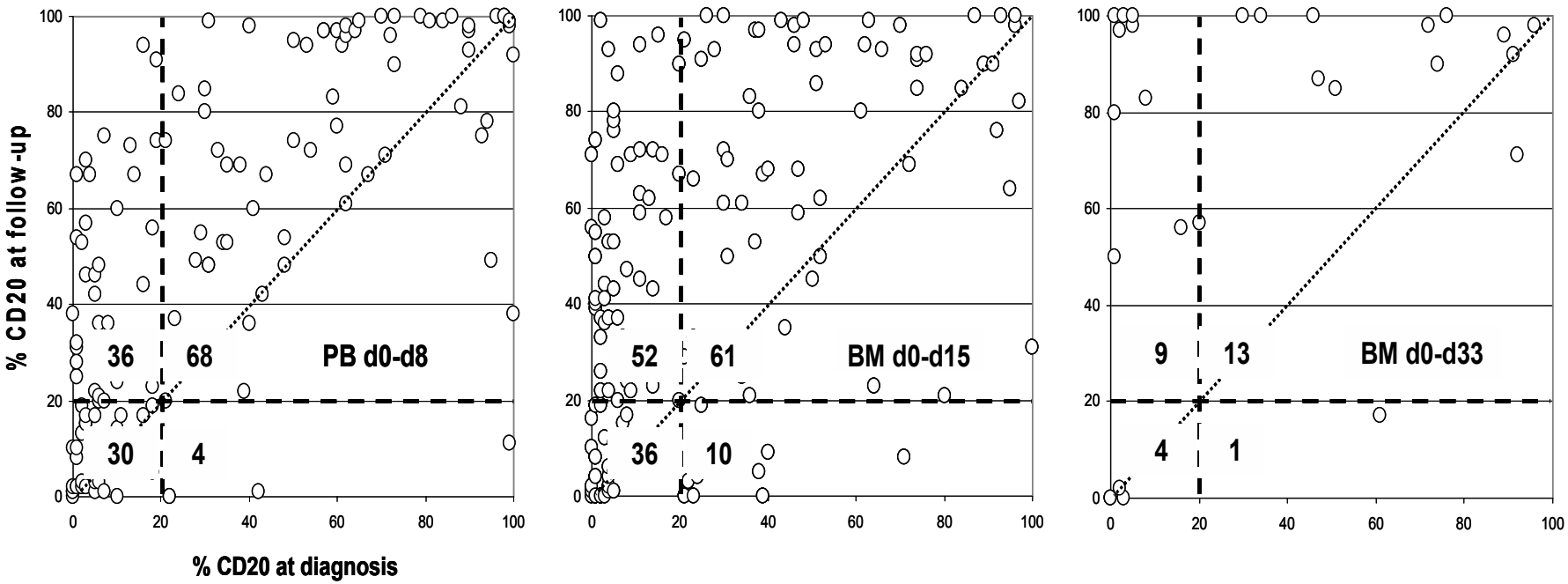
  - **complement- or cell-mediated cytolysis**
    Rituxi*mab* (MabThera®) = anti-CD20
    Alemtuzu*mab* (Campath-H1) = anti-CD52

  - **targeted release of cytostatic drugs**
    Gemtuzu*mab*-Ozogamicin (Mylotarg™) = anti-CD33

  - **direct apoptosis induction**
    Rituxi*mab*

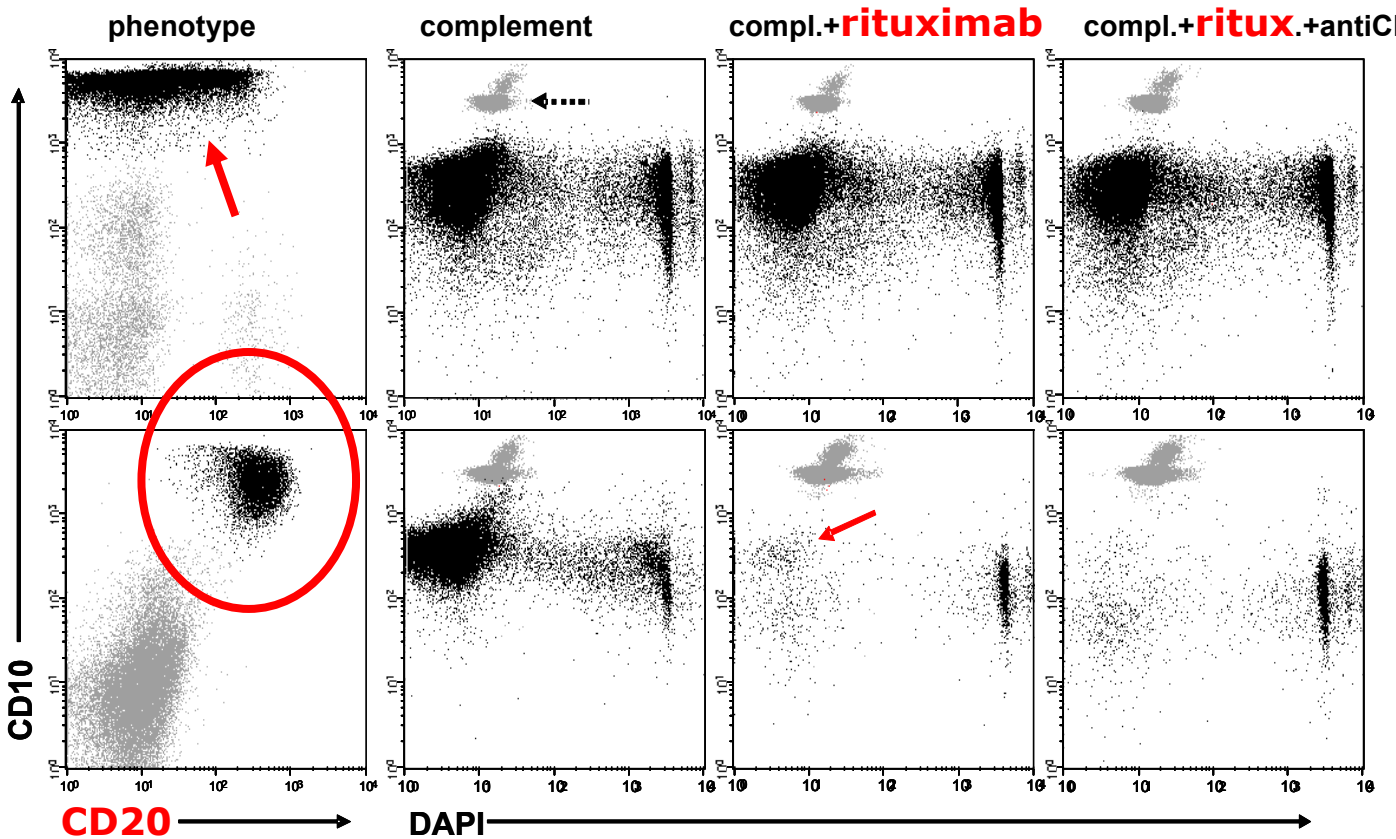
Steroid-induced CD20 up-regulation in-vivo





Dworzak et al., BLOOD published online 2008

Steroid-induced CD20 up-regulation in-vivo translates into higher rituximab sensitivity



diagnosis

end- induction

Dworzak et al., BLOOD published online 2008

Synopsis „Mylotarg“ in pediatrics

- single agent: 7.5 mg/m^2 BSA on days 0 and 15

  BFM-experience (Reinhardt et al., Onkologie 2004)
  PR in 5/12, 0/12 CR directly after GO in **AML**
  SCT in n=5: 1/5 in CR at 8 months after SCT
  SAE: anaphylactic infusion-reaction, 1 **VOD** after SCT

  Arceci et al., Blood 2005
  6–9 mg/m2 BSA on days 0 and 15
  CR in 8/29 (28%) overall in refractory/relapsed **AML**
  SCT in 13/29 possible (6 **VODs**)
  toxicities: myelosupression, sepsis (24%)
  liver (ALT/AST 21%, Bili 7%, VOD 1 case)
  mucositis °3/4 in 3%
  conclusion: 6 mg/m^2 BSA is well tolerated

Synopsis „Mylotarg“ in pediatrics

- combinations: usually (2)-3 mg/m^2 BSA plus chemo

Aplenc et al., JCO 2008 (COG phase 2)
combined with Ara-C/mitox or Ara-C/Asparaginase

Brethon et al., BJH 2008 (phase 2)
fractionated 3 mg/m2 BSA days 1, 4, 7 plus LD-Ara-C
CR/CRp in 9/17 (53%; refractory/relapsed AML)
SCT in 8 pts.; alive 3/8; VOD: none

Roman et al., CCR 2005 (phase 1)
GO (4.5 - 69mg/m^2) >day 60 after RIC (Flu/Bu) SCT

COG, MRC AML trials; I-BFM relapsed AML study…

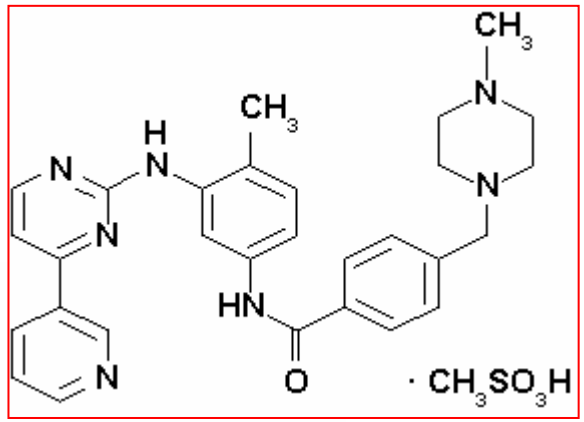
New (chemo-)**therapeutics** for ***targeted therapy***

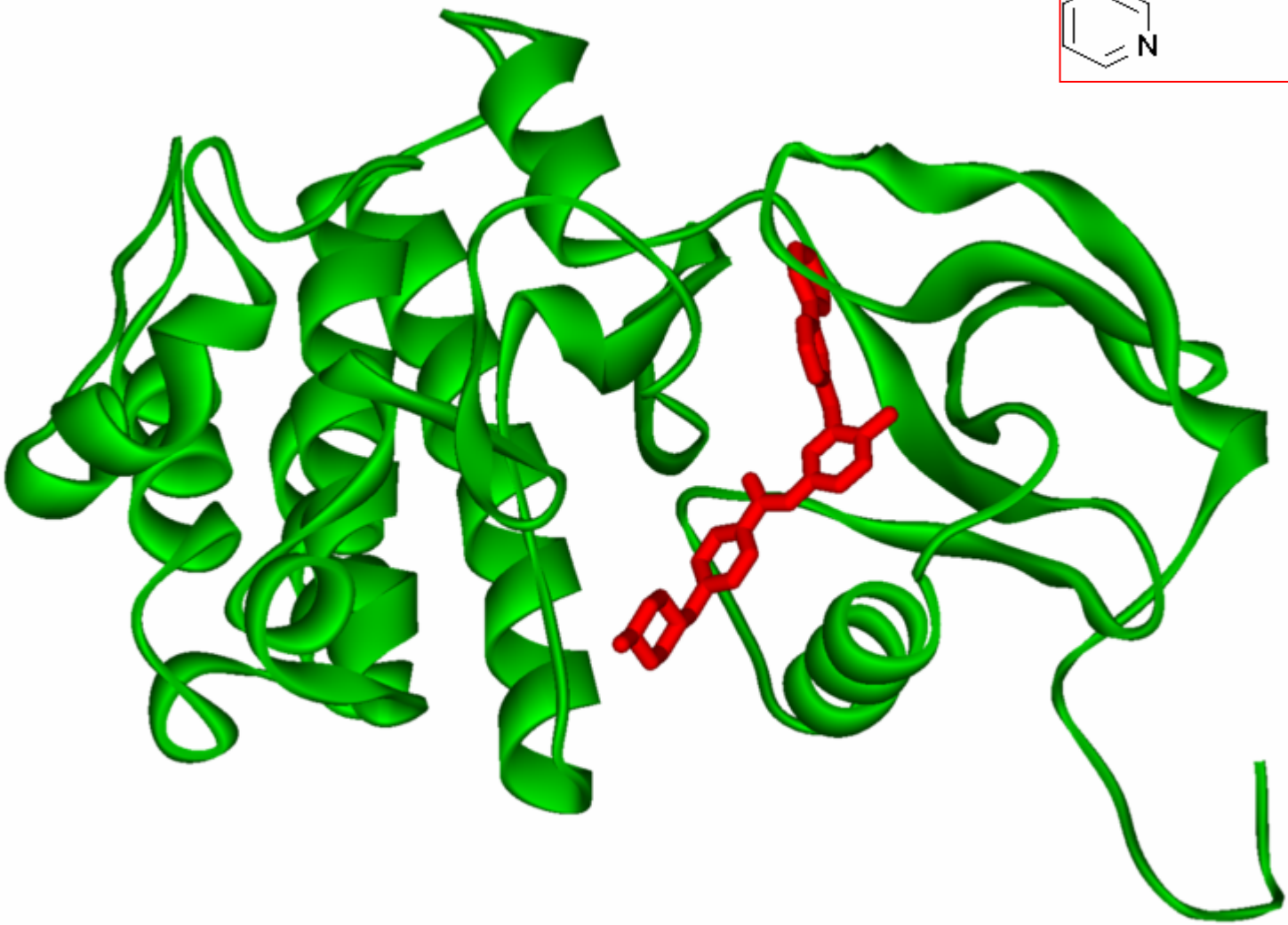
- **Protein-inhibitors:** *xxx**nib***
  = *Small Molecule Inhibitors*

- **cell surface receptor inhibition**
- **inhibition of intracellular signal transduction**

Example of small-molecule interaction with its protein-target:

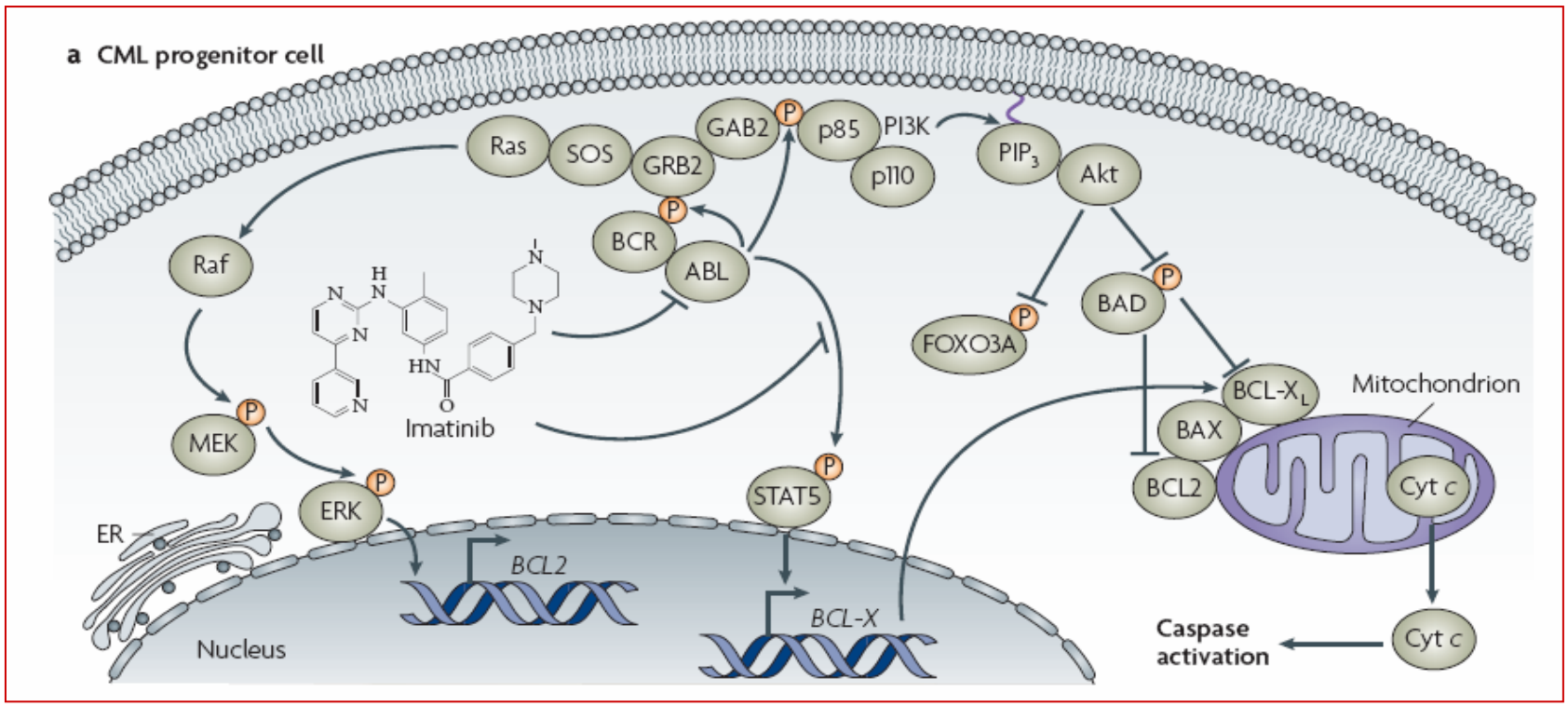
Imatinib (red) and BCR-ABL (green)





Imatinib (STI571 bzw. **Glivec™**)

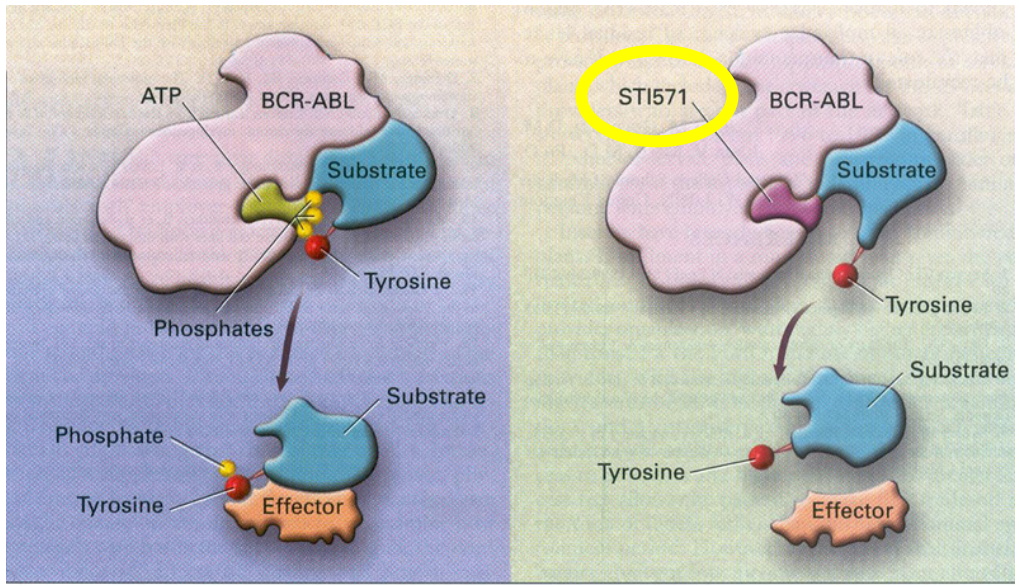
action:
blocks intracellular signaltransduction



Δ to usual chemotherapeutic drugs:
no direct interference with DNA or cell division

Imatinib (STI571 bzw. **Glivec™**)

mechanism and clinical development



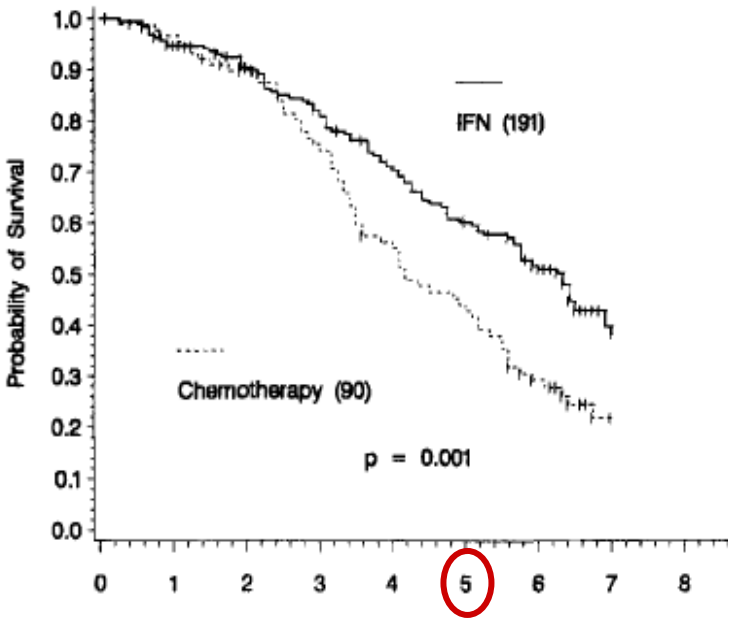
1998 **Clinical trials started**

2001 **FDA approval for CML**

2003 **FDA approval as first-line therapy of CML**

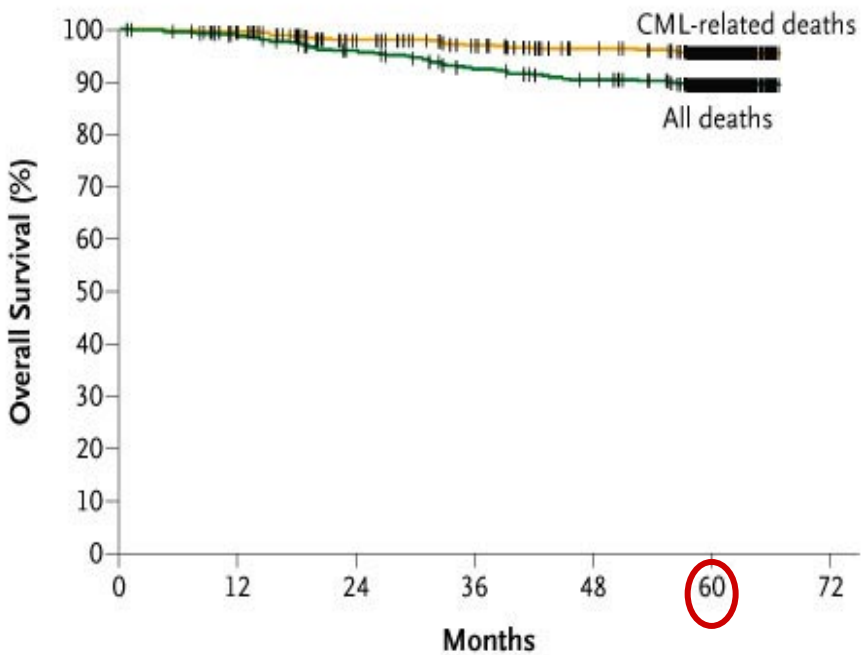
Treatment results in CML

chemotherapy vs. IFN



Hasford et al., Blood 1996

and Imatinib



Druker et al., N Engl J Med 2006

Response to imatinib mesylate therapy according to the stage of the disease at inclusion.

in children !

	Complete hematologic response	Complete cytogenetic response or FISH negativity	Molecular response (bcr-abl/abl < 10^{-4} or undetectable transcript)
Status at inclusion (number of pts)			
Chronic phase (**22**)	8 /10[a] (80 %)	12/20[b] (60 %)	11 / 22 (50%)
Accelerated phase (**5**)	4 / 5 (80 %)	2 / 5 (40 %)	0 / 5
Blastic crisis (**3**)	2 / 3 (67 %)	0 / 3	0 / 3

Millot et al., Leukemia 2006

external signals

SCF

FL

IL3

GCSF

GMCSF

TPO

SDF-1

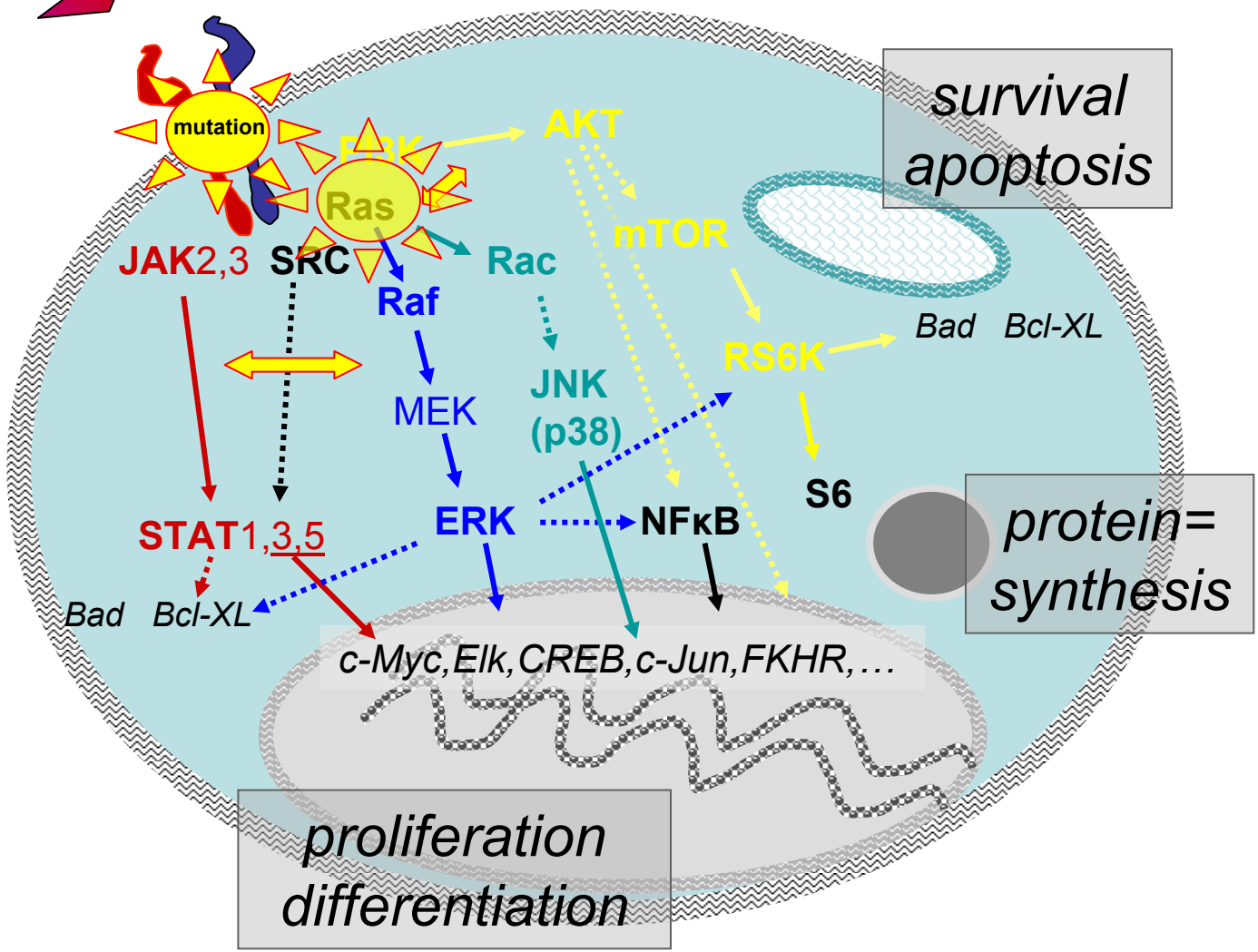
IL6

VEGF

PDGF

TGFβ

IFNγ



external signal factor

SCF

FL

IL3

GCSF

GMCSF

TPO

SDF-1

IL6

VEGF

PDGF

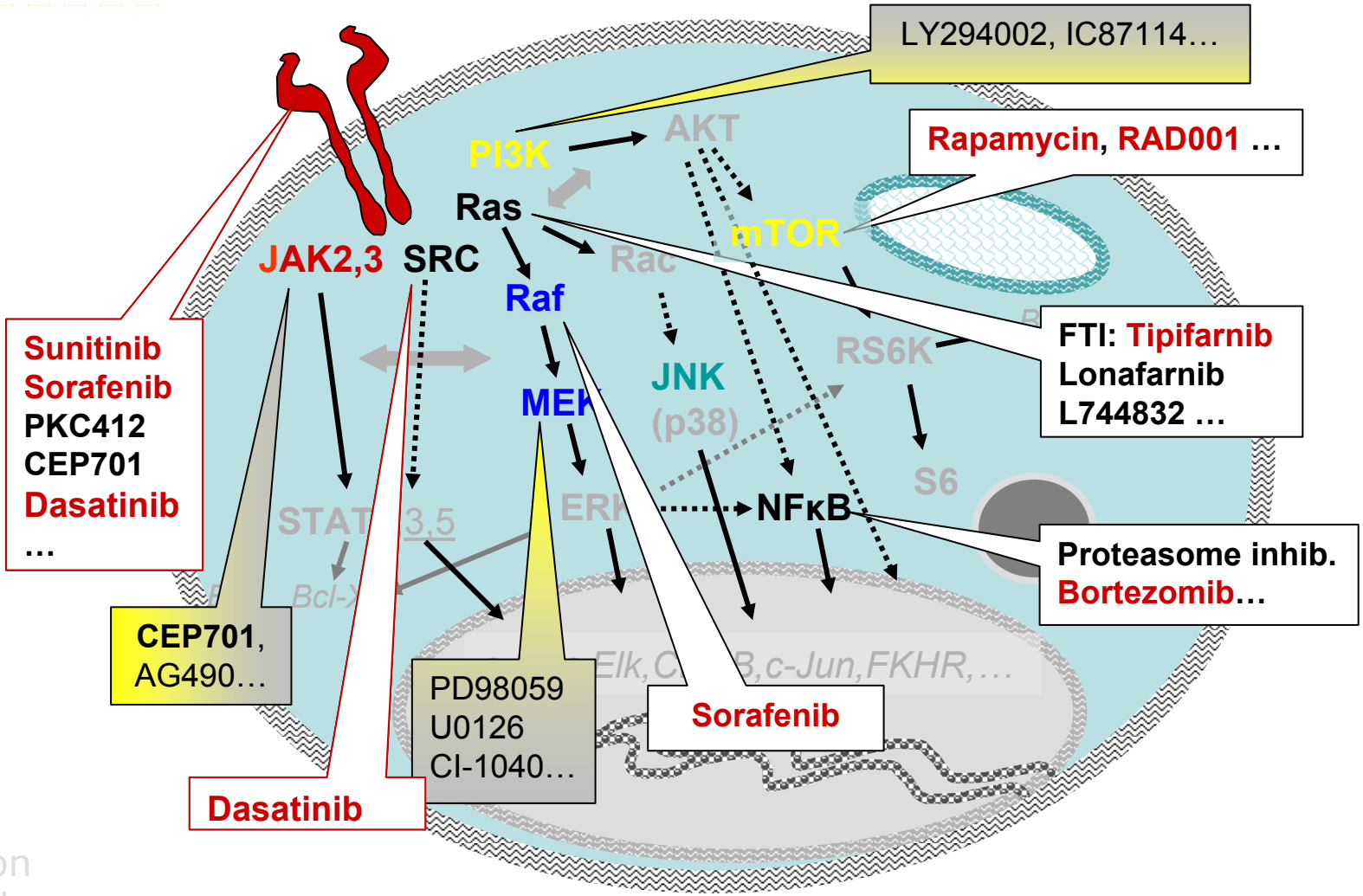
TGFβ

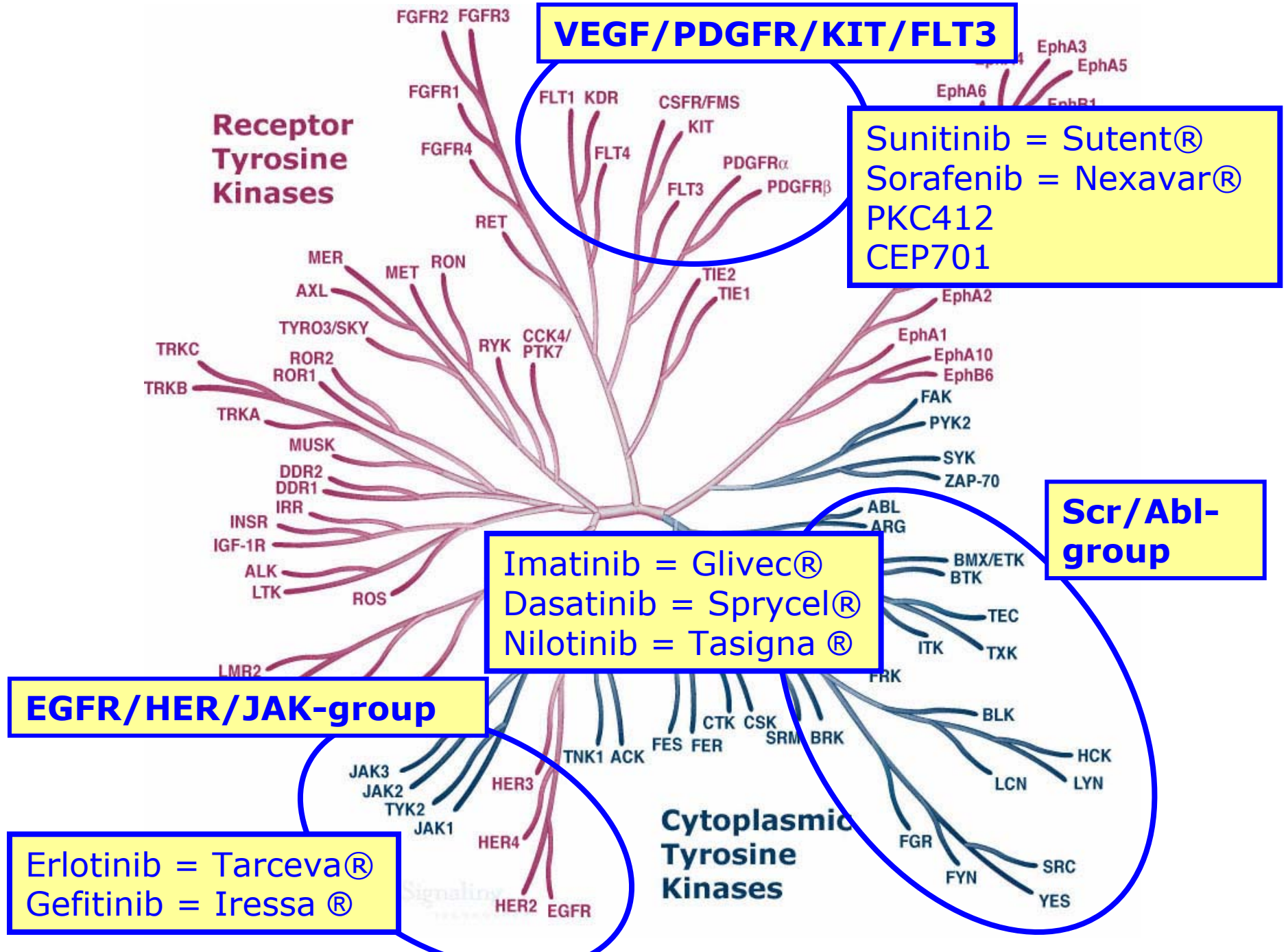
IFNγ

adhesion molecules

cytokine-R

RTKs, eg. **FLT3, KIT**, PDGFRb, VEGFR




VEGF/PDGFR/KIT/FLT3
Sunitinib = Sutent®
Sorafenib = Nexavar®
PKC412
CEP701
Receptor Tyrosine Kinases
FGFR2 FGFR3
FGFR1
FGFR4
RET
FLT1 KDR
FLT4
CSFR/FMS
KIT
FLT3
PDGFRα
PDGFRβ
TIE2
TIE1
EphA3
EphA5
EphA6
EphA2
EphA1
EphA10
EphB6
FAK
PYK2
SYK
ZAP-70
MER
MET
RON
AXL
TYRO3/SKY
RYK
CCK4/ PTK7
TRKC
TRKB
TRKA
ROR2
ROR1
MUSK
DDR2
DDR1
IRR
INSR
IGF-1R
ALK
LTK
ROS
LMR2
Scr/Abl-group
Imatinib = Glivec®
Dasatinib = Sprycel®
Nilotinib = Tasigna ®
ABL
ARG
BMX/ETK
BTK
TEC
ITK
TXK
FRK
BLK
HCK
LCN
LYN
FGR
FYN
SRC
YES
CTK
CSK
SRM
BRK
FES
FER
TNK1
ACK
EGFR/HER/JAK-group
JAK3
JAK2
TYK2
JAK1
HER3
HER4
HER2
EGFR
Erlotinib = Tarceva®
Gefitinib = Iressa ®
Cytoplasmic Tyrosine Kinases

Specific patterns of signal pathway activation cause the different clinical potentials of the various SMI

- between different types of malignancies
- within certain types of malignancies (inter-individual differences)

Specific patterns of signal pathway activation
cause
the different clinical potentials of the various SMI

- between different types of malignancies

- within certain types of malignancies
(inter-individual differences)

Applications and possible target cancers

CML, Ph+ALL (ABL): Imatinib, Nilotinib, Dasatinib

AML FLT3mut: PKC412, Sunitinib, Sorafenib, CEP701
AML KITmut: Dasatinib, PKC412, (Sorafenib, Imatinib)

Mastocytosis (KIT): Imatinib, PKC412, Dasatinib,

GIST (KIT): Imatinib, Sunitinib, Dasatinib, Nilotinib, PKC412

Renal cell-Ca (VEGFR): Sunitinib, Sorafenib

HCC (VEGFR): Sorafenib, Sunitinib

In adults further carcinomas:
mammary, NSCLC, pankreatic (HER/EGFR): Nilotinib, Gefitinib

Specific patterns of signal pathway activation
cause
the different clinical potentials of the various SMI

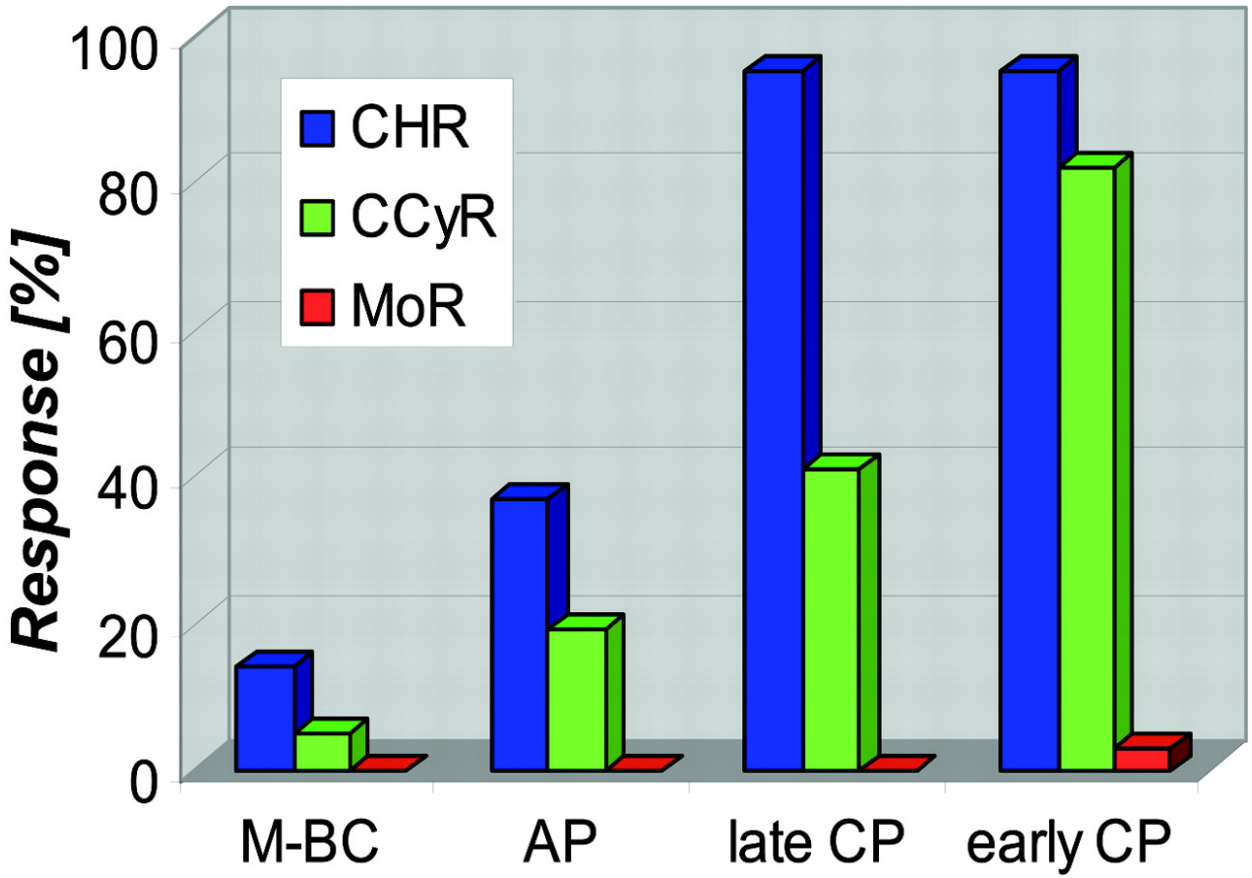
- between different types of malignancies

- within certain types of malignancies
(inter-individual differences)

1) resistance conferring mutations
2) other targets
3) additional signal pathways activated

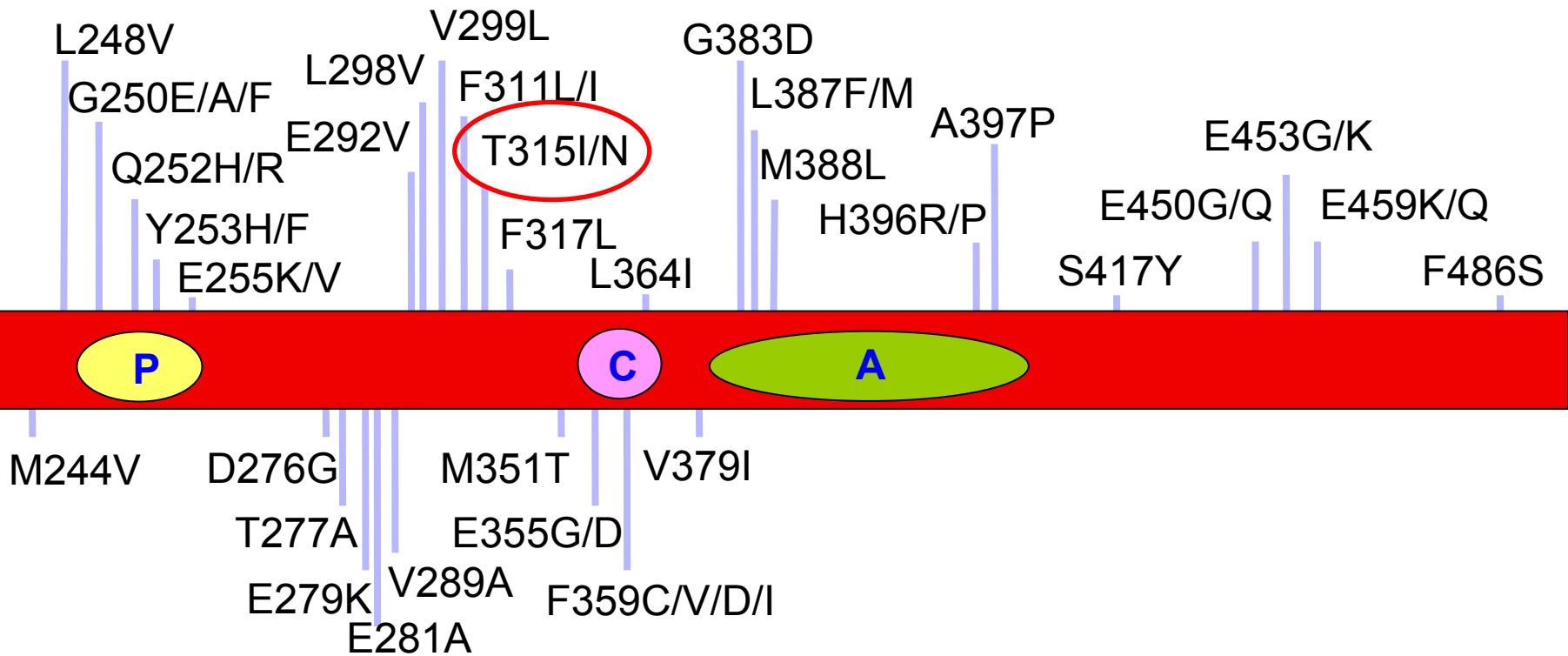
Target mutations and SMI-resistance

example: CML



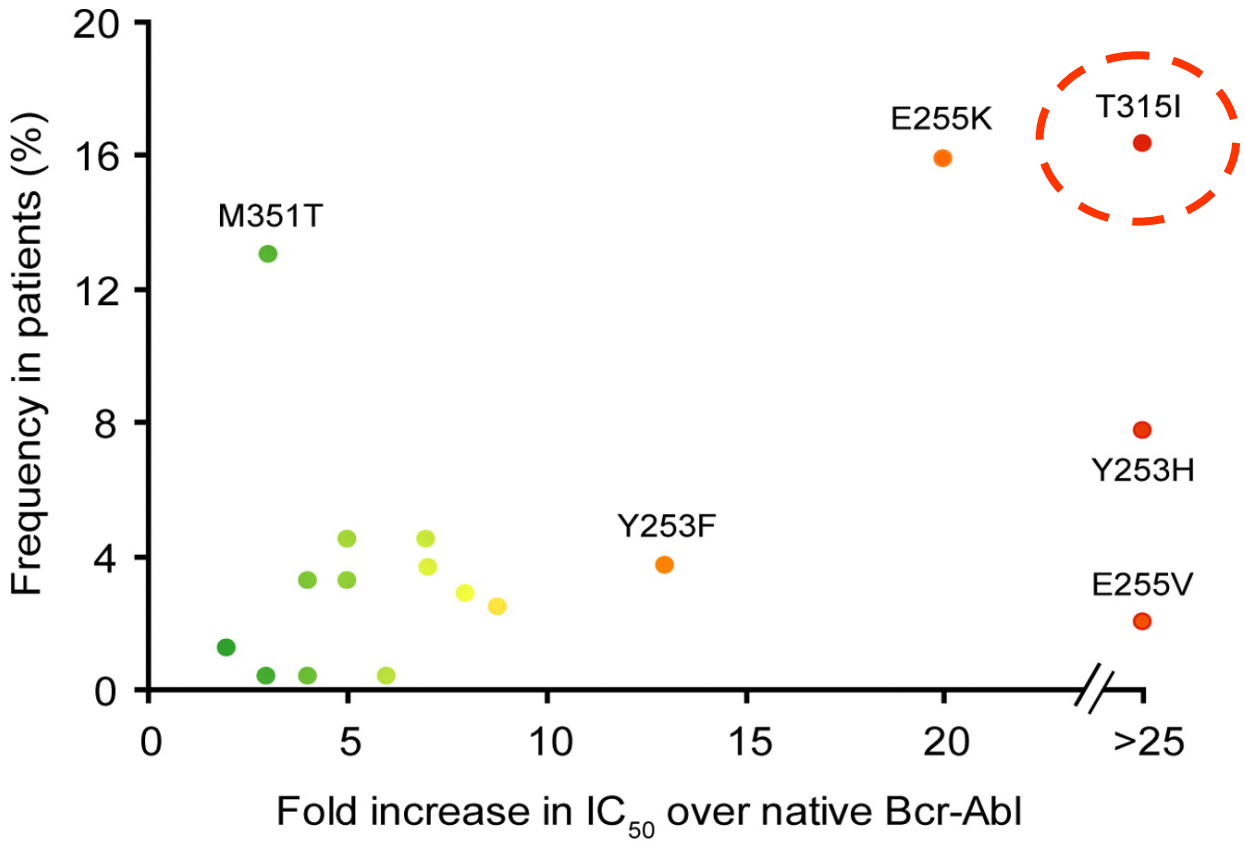
Deininger et al., Blood 2005

CML: BCR-ABL mutations
associated with clinical **Imatinib-resistance**



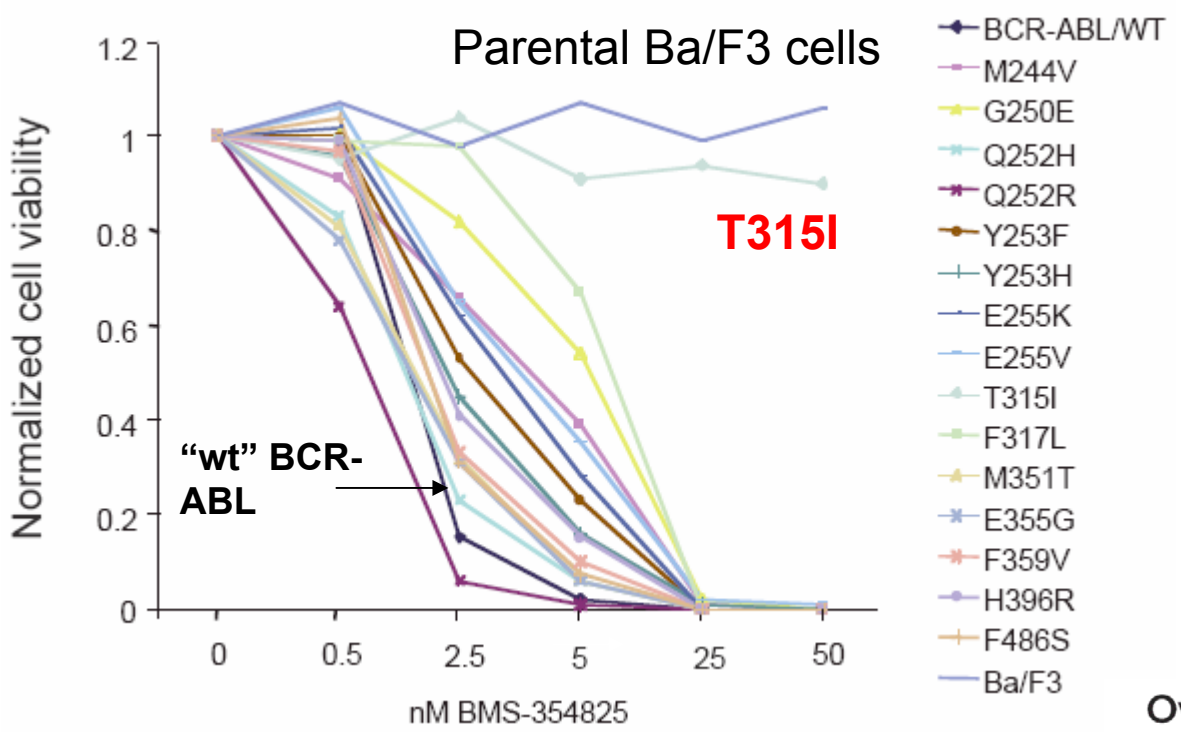
Frequency:

BCR-ABL mutations versus **Imatinib-resistance**



O'Hare et al., Blood 2007

Dasatinib is active against most **mutations** which confer Imatinib-resistance



SCIENCE VOL 305 16 JULY 2004

Overriding Imatinib Resistance with a Novel ABL Kinase Inhibitor

Neil P. Shah,[1] Chris Tran,[1,2] Francis Y. Lee,[3] Ping Chen,[3] Derek Norris,[3] Charles L. Sawyers[1,2]*

CML-paed-II = Imatinib for kids, too

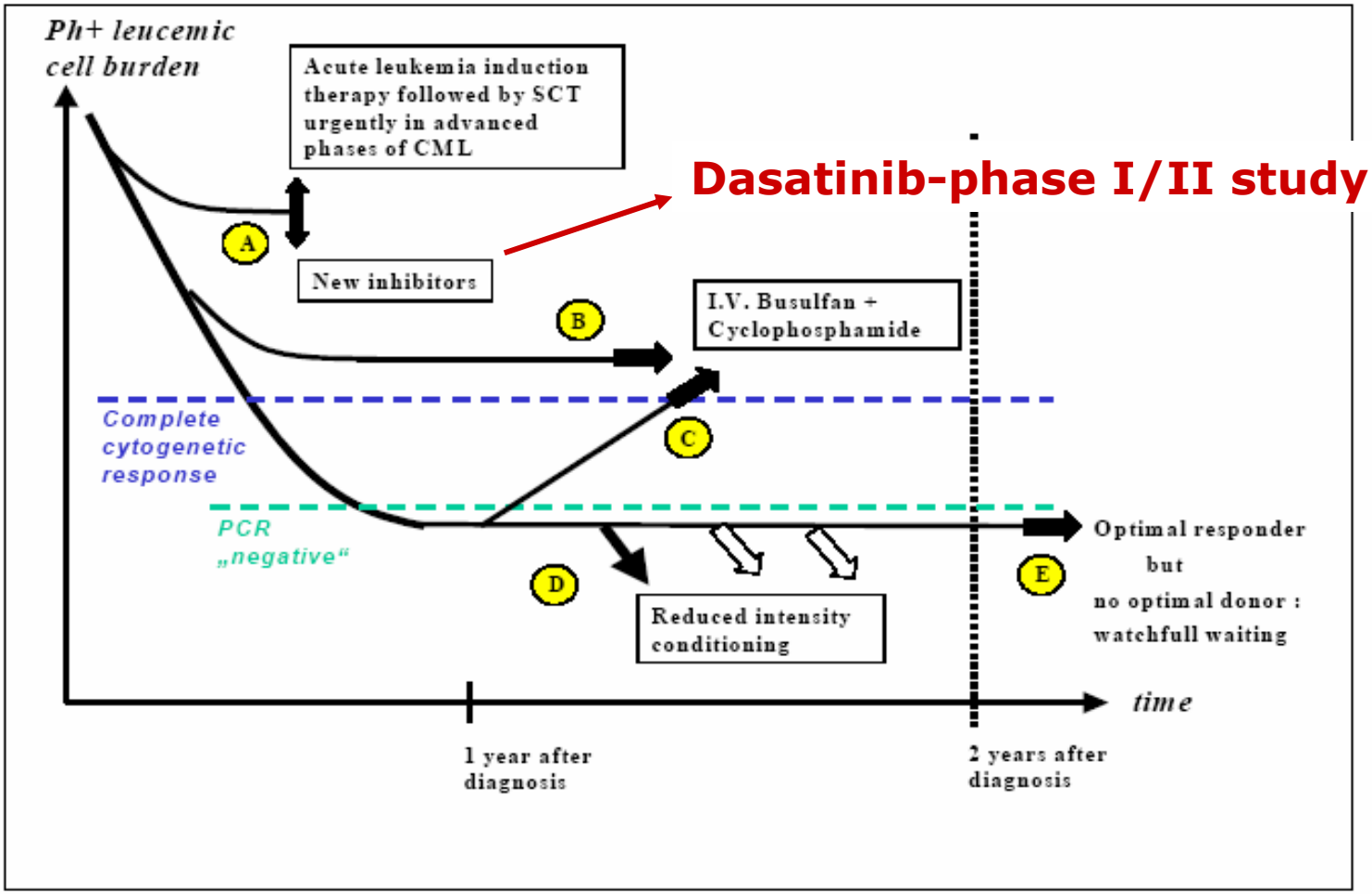


Fig 13: Algorithsms for selection of a conditioning regimen for hematopoietic stem cell transplantation depending on the treatment response to imatinib

Centers pediatric dasatinib study

BMS CA180018 protocol ITCC05

In collaboration with the International BFM Study Group

Innovative Therapies for Children with Cancer

ITCC

European consortium

Berlin – A von Stackelberg

Bristol – P Kearns

Frankfurt – T Lehrnbecher

Hannover – D Reinhardt

London – D. Lancaster

Manchester – E Estlin

Monza – C. Rizzari

Nantes – F Mechinaud

Paris – A Baruchel

Paris – J Landman-Parker

Rotterdam – M Zwaan

Vienna – M Dworzak, A Attarbaschi

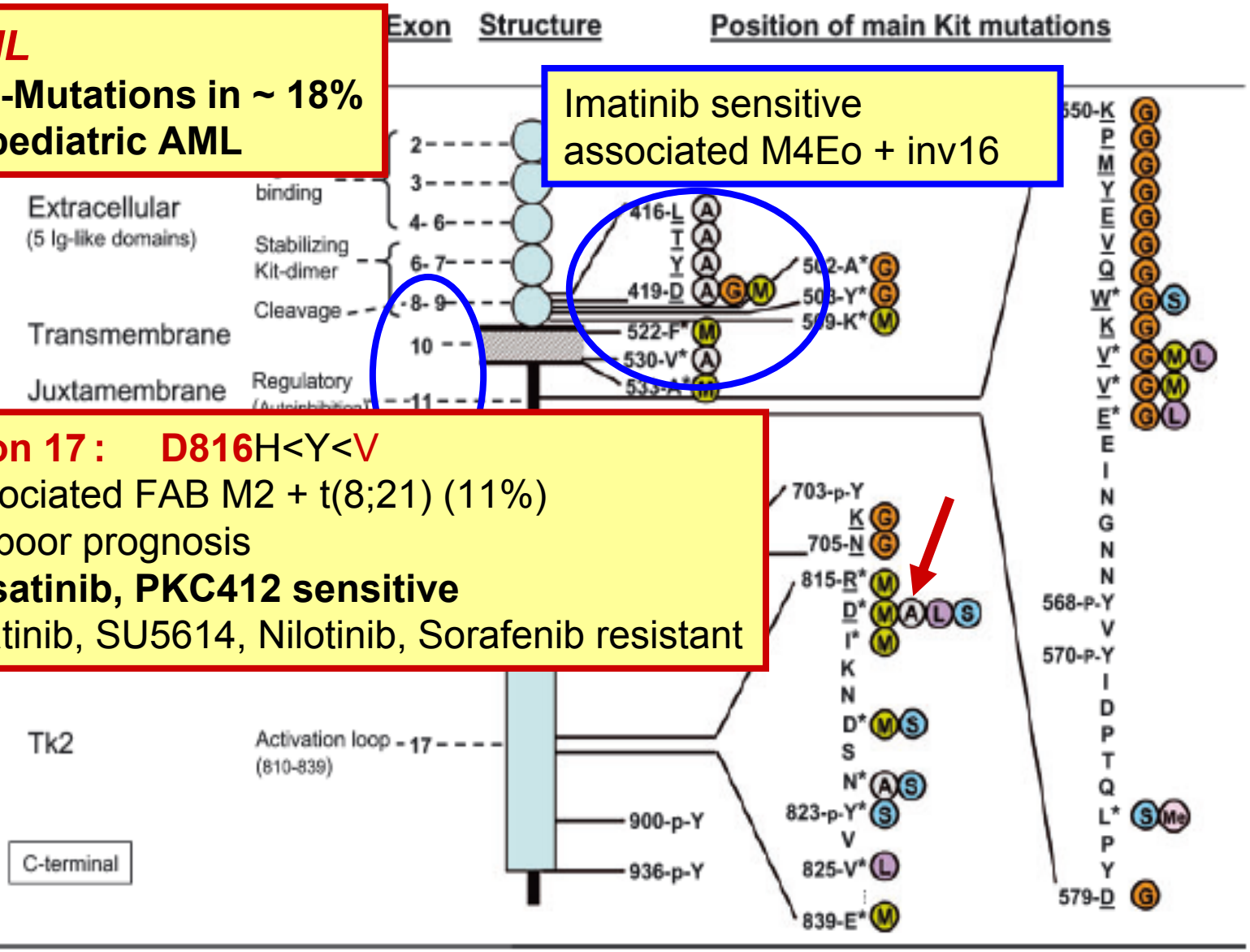
KIT mutations

in GIST (G), AML (A), und Mastozytose (M)

AML

KIT-Mutations in ~ 18% of pediatric AML

Imatinib sensitive
associated M4Eo + inv16



Exon 17 : D816H<Y<V
associated FAB M2 + t(8;21) (11%)
>> poor prognosis
Dasatinib, PKC412 sensitive
Imatinib, SU5614, Nilotinib, Sorafenib resistant

Genetic alterations in AML – additional signal pathways

"targeted therapy" is necessary

Translocations / mutations	FAB association	Incidence adults	Incidence children	Comment
t(8;21); AML1/ETO	M2	6-12%	12%	favorable if no c-KIT D816 mutation
inv(16); CBFβ/MYH11	M4Eo	7%	8%	frequent mutations in NRAS, c-KIT; favorable
t(15;17); PML/RARα	M3	7%	6%	associated with FLT3-ITD and –TKD; favorable if treated with retinoic acid
MLL break-apart t(9;11) and others	M5	5%	8-10%	frequent in infants
MLL-PTD	all types	6%	<1%	associated with normal karyotype; unfavorable
FLT3-ITD	M1-M5	25-30%	12%	associated with normal karyotype; unfavorable
FLT3-TKD (D835)	M1-M5	7%	3-7%	no prognostic impact
c-KIT D816 (Exon 17)	M2	6%	7.3%	associated with t(8;21); unfavorable; imatinib/PKC412/sorafenib-resistant
c-KIT Exon 8 mutations	M2/M4Eo	3%	4%	associated with inv(16); imatinib-sensitive
c-KIT-ITD (Exon 11/12)	M2/M4	1%	7%	imatinib-sensitive
NRAS mutations	M4Eo	10.3%	18%	associated with inv(16); favorable; Ras blockade
NPM1 mutations	M4/M5	27.5%	6.5%	associated with normal karyotype; favorable if no FLT3-ITD
C/EBPα mutations	M1/M2	7-15%	n.a.	associated with normal karyotype; favorable
PTPN11 mutations	M5	3.5%	4%	typical for JMML; hypersensitivity to GM-CSF; Ras hyperactivation
JAK2 V617F mutation	all types	2.7%	n.a.	associated with CBF-AML and secondary AML; unfavorable

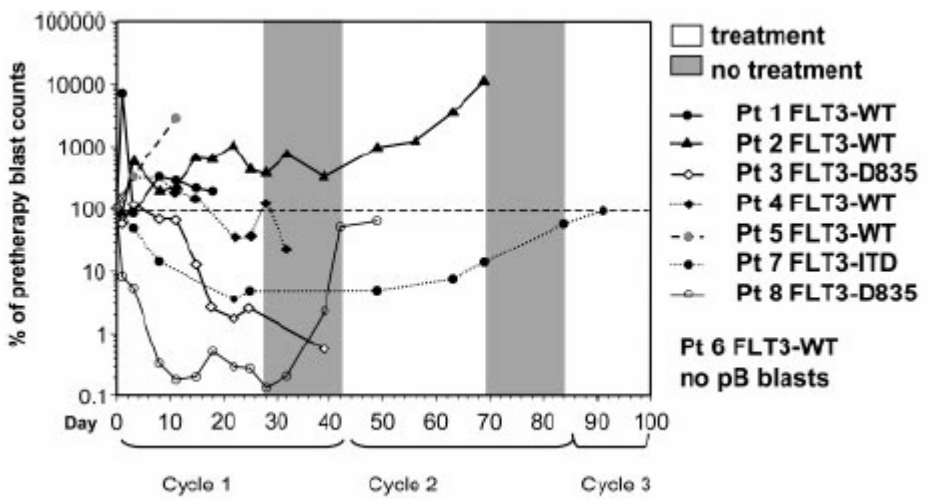
"Small Molecule" inhibitors in AML

Compound	Target	Age group	Phase	Dosing	Response	Plasma levels	Reference
sunitinib	VEGF,FLT3, cKIT	>50y	1	50mg/d orally	6/14	≤100ng/ml	Fiedler et al. 2005
SU 5614	VEGF,FLT3, cKIT	>27y, mean 65y	2	190mg/m2/w i.v.	8/43	n.d.	Fiedler et al. 2003
sorafenib	Raf,VEGF, FLT3,cKIT	>50y, median 70	1	100 – 400mg bid orally	n.a.	5 µg/ml*	ongoing
tipifarnib	Ras	>24y, median 65	1	100 – 1200mg bid orally	10/34	1 µg/ml	Karp et al. 2001
		>34y, median 74	2	600mg bid orally	37/158	n.d.	Lancet et al. 2006
CEP 701	FLT3	>18y, median 61	1/2	60mg bid orally	5/14	1µg/ml	Smith et al. 2004
		>67y, median 73	2	40 – 80mg bid orally	8/27	n.d.	Knapper et al. 2006
PKC412	FLT3,cKIT	>29y, median 62	1/2	75mg tid orally	14/20	>1µg/ml	Stone et al. 2005
rapamycin	mTOR	>55y, median 72	1/2	2mg/d orally	4/9	≤30ng/ml	Recher et al. 2005
RAD001	mTOR	>18y, median 64	1/2	5 – 10mg qd orally	0/9	15ng/ml*	Yee et al. 2006
dasatinib	Scr/Abl	1 – 21y	1/2	60 – 150mg/m2/qd orally	n.a.	15ng/ml*	ongoing
imatinib	Abl,cKIT	>23y, median 70	2	400mg qd orally	0/10	n.d.	Cortes et al. 2003
		>21y, median 66	2	600mg qd orally	5/21	n.d.	Kindler et al. 2004

In vivo STI-mono-therapy in AML

First results are (somewhat) disillusioning …

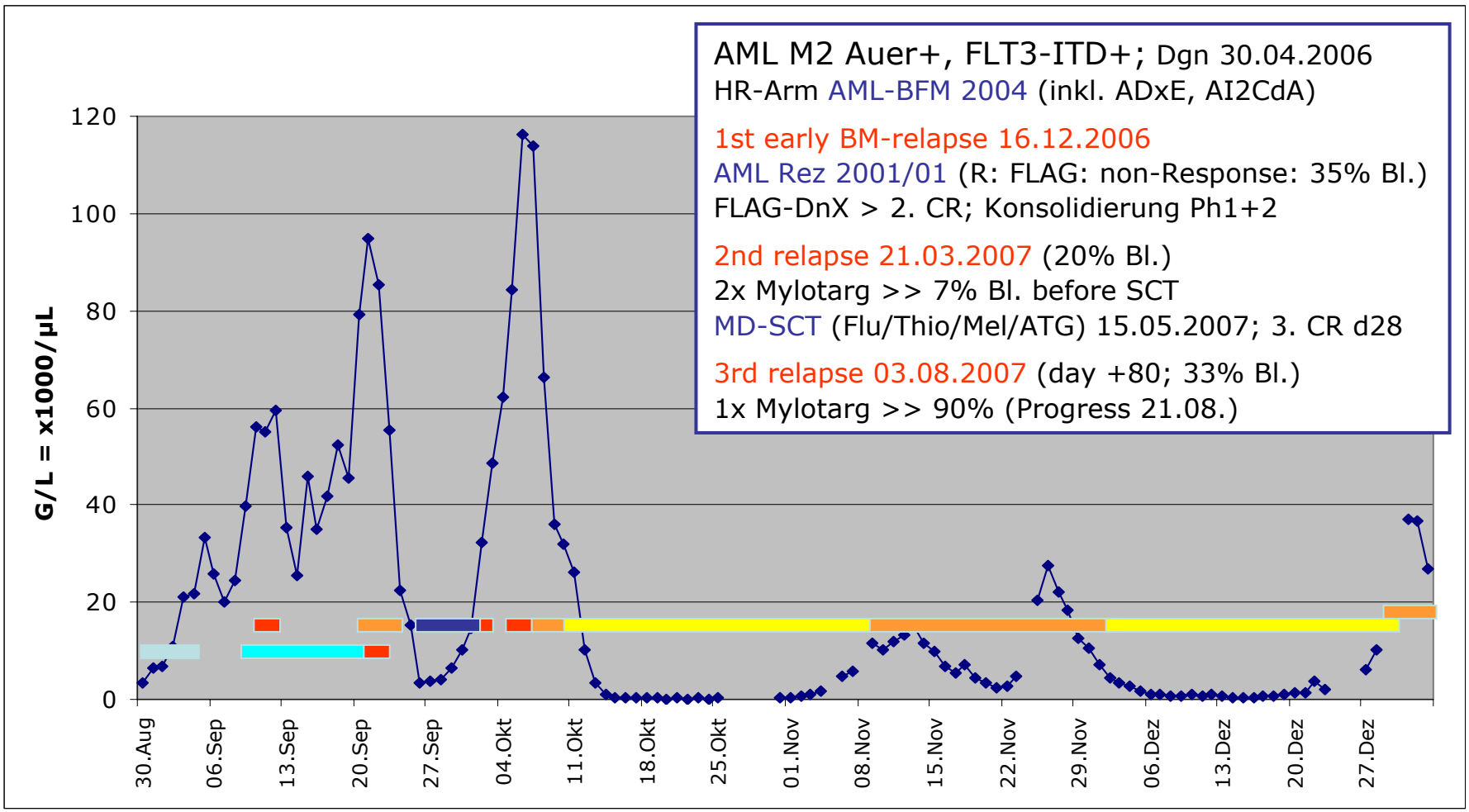
- **only short-term activity – rapid emergence of resistance**
- **no exclusive correlation with certain mutational subtypes**
  - **additional mutations**
  - **other signal pathways activated**



SU11248 = Sunitinib (Sutent®)
FLT3-Inhibition of AML in vivo

FIEDLER et al BLOOD, 01 FEBRUARY 2005

	= dasatinib 120mg/m2	30.08. – 04.09.
	= dasatinib 100mg/m2	09.09. – 20.09.
	= cytarabine 100mg/m2/day contin.	10./11.+21./22.09., 02.+05./06.10.
	= hydroxyurea 3 x 500mg/day	20. – 24.09., 07. – 10.10., 10.11. – 02.12., 29.12. cont.
	= everolimus 2 x 1,5mg/day	26.09. – 01.10.
	= sunitinib 1 x 25mg/day	11.10. – 09.11.; 03. – 30.12.



Future perspectives of SMI

1) Combination therapies

- together with conventional chemotherapy

- together with other SMI

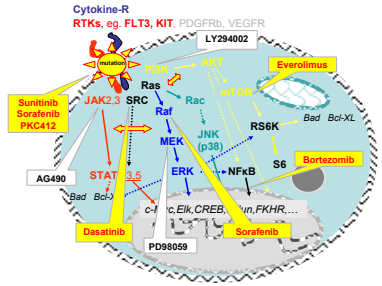
„change from fatal to chronic disease“

- together with immunotherapy

2) „Targeted“ therapy

„biology-driven“ = rational usage = cost-efficient usage

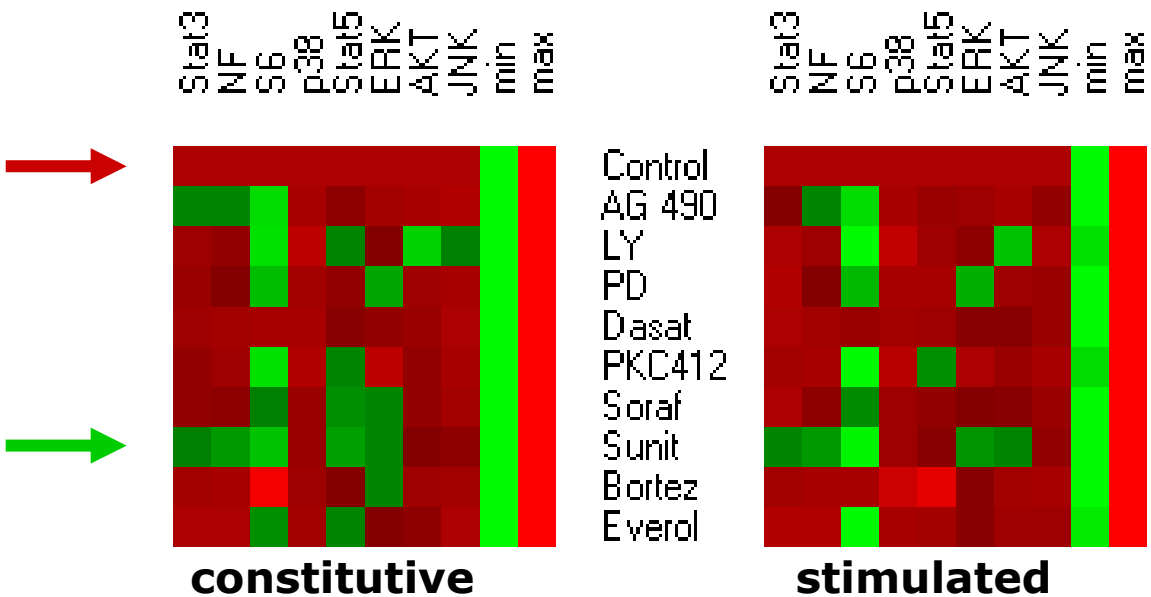
PhosphoSignal-FLOW in AML



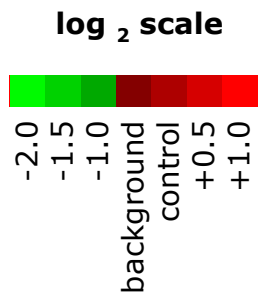
signal inhibition by STIs: in vitro

example:

AML t(9;11) MLL/AF9

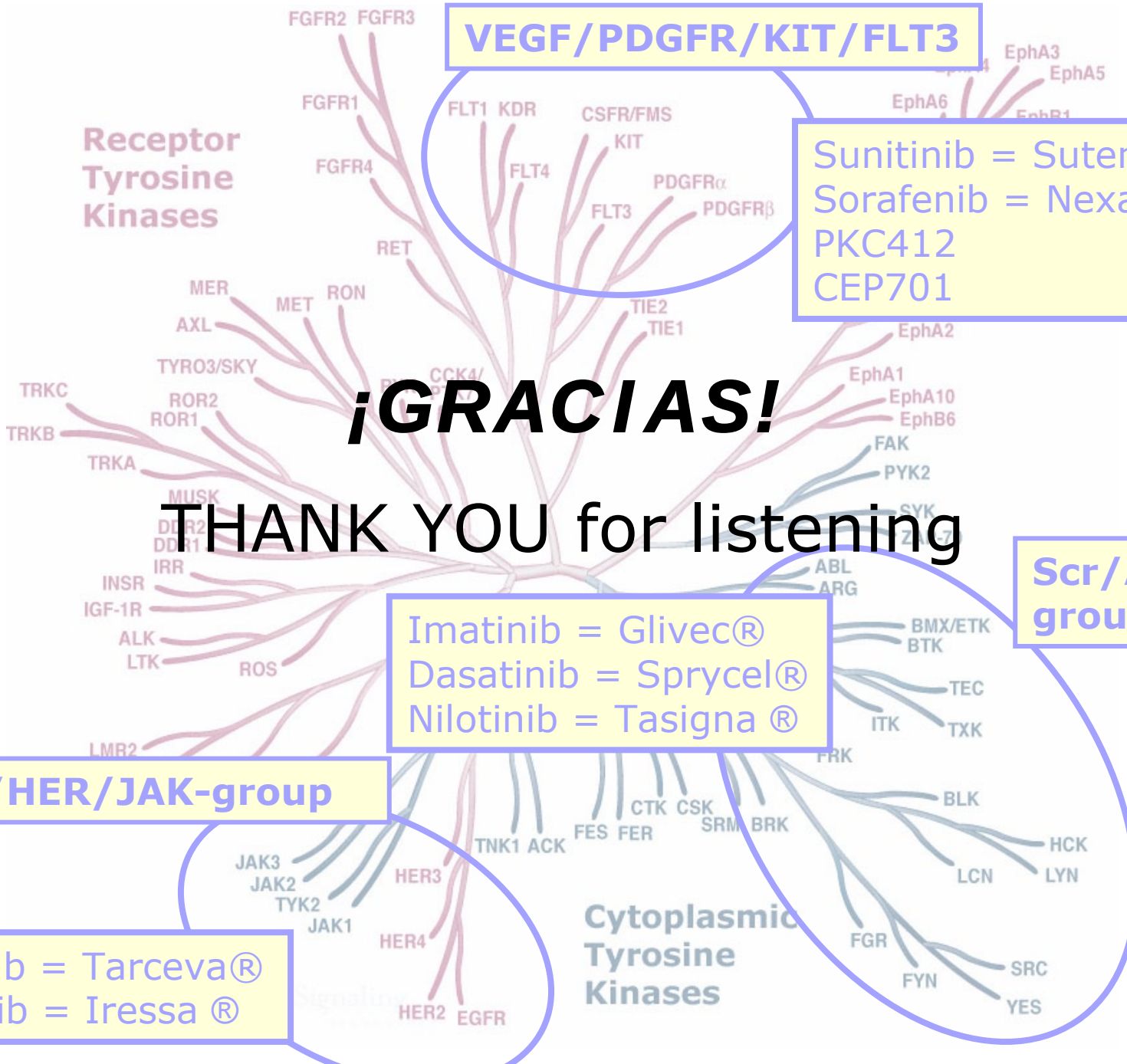


constitutive **stimulated**



New therapeutic options in refractory and relapsed leukemia

- **New nucleoside analoga** (2^{nd} or 3^{rd} generation)
- **MRD-based treatment tailoring**
- **FLAMSA**
- **Antibodies**
- **Signal transduction inhibition**


VEGF/PDGFR/KIT/FLT3
Sunitinib = Sutent®
Sorafenib = Nexavar®
PKC412
CEP701
¡GRACIAS!
THANK YOU for listening
Imatinib = Glivec®
Dasatinib = Sprycel®
Nilotinib = Tasigna ®
Scr/Abl-group
EGFR/HER/JAK-group
Erlotinib = Tarceva®
Gefitinib = Iressa ®
Receptor Tyrosine Kinases
Cytoplasmic Tyrosine Kinases
FGFR2
FGFR3
FGFR1
FGFR4
RET
FLT1
KDR
CSFR/FMS
KIT
FLT4
FLT3
PDGFRα
PDGFRβ
TIE2
TIE1
EphA3
EphA5
EphA6
EphA2
EphA1
EphA10
EphB6
MER
MET
RON
AXL
TYRO3/SKY
TRKC
TRKB
TRKA
ROR2
ROR1
MUSK
DDR2
DDR1
IRR
INSR
IGF-1R
ALK
LTK
ROS
LMR2
FAK
PYK2
SYK
ABL
ARG
BMX/ETK
BTK
TEC
ITK
TXK
FRK
BLK
HCK
LCN
LYN
FGR
FYN
SRC
YES
CTK
CSK
SRM
BRK
FES
FER
TNK1
ACK
JAK3
JAK2
TYK2
JAK1
HER3
HER4
HER2
EGFR

Imatinib toxicity (children)

Table 2.: Adverse events (NCI toxicity scale) notified in 30 pediatric patients.

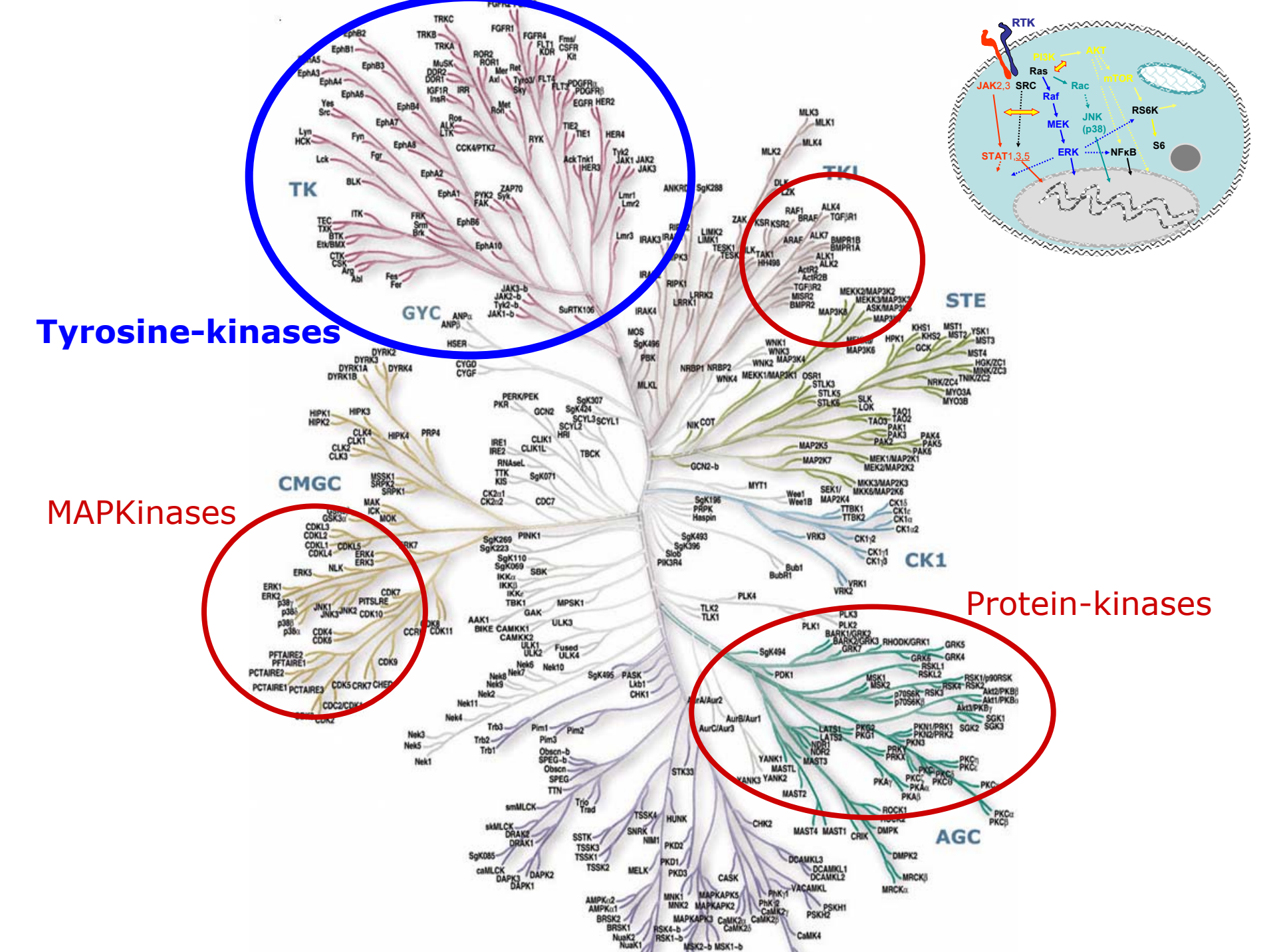
Adverse events	All grades no* (%)	Grade 3 or 4 no* (%)
Hematologic toxicity	11 (37%)	6 (20%)
Anemia	1 (3%)	0
Neutropenia	10 (33%)	5 (17%)
Thrombocytopenia	6 (20%)	3 (10%)
Non hematologic toxicity	15 (50%)	2 (7%)
Infection	5 (17%)	1 (3%)
Skin rash	4 (13%)	0
Nausea	4 (13%)	0
Vomiting	3 (10%)	0
Liver transaminase elevation	2 (7%)	1 (3%)
Diarrhea	1 (3%)	0
Edema	1 (3%)	0
Headache	1 (3%)	0

* number of patients who experienced hematological or non hematological toxicities. Some patients experienced more than one side effects.

Millot et al., Leukemia 2006

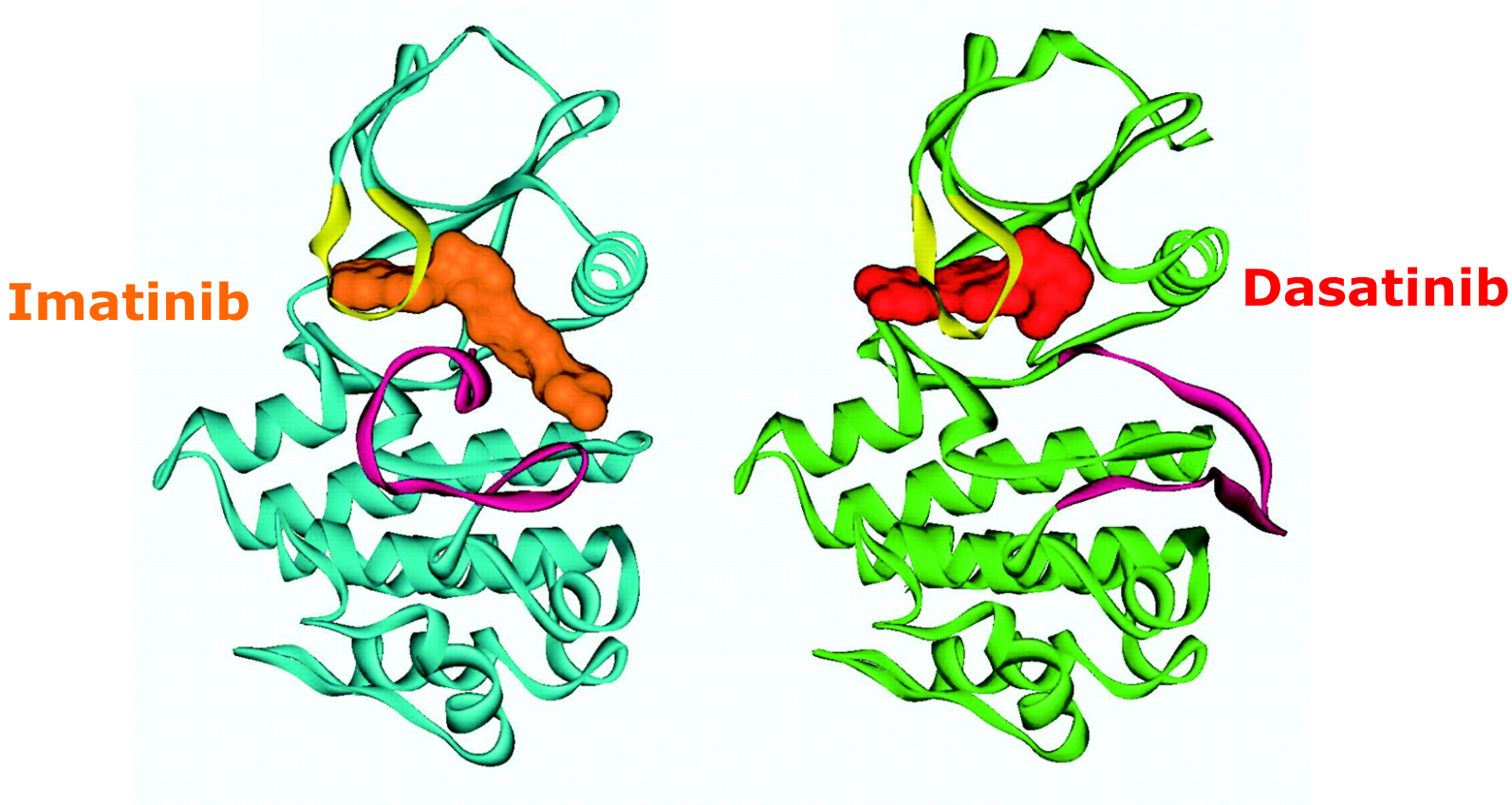
Side effect profile of SMI

Imatinib (Gleevec)	TKI	ABL1/2, PDGFRα/β, KIT	CML, Ph+ B-ALL, CMML, CEL, GIST	Oedema, nausea, myelosuppression, immunosuppression (?)
Dasatinib (Sprycel)	TKI	ABL1/2, PDGFRα/β, KIT, Src family	CML	Myelosuppression, oedema, pleural/ pericardial effusion, panniculitis, QT prolongation, bleeding
Nilotibib (Tasigna)	TKI	ABL1/2, PDGFRα/β, KIT	CML	Myelosuppression, hyperbilirubinaemia, rash, QT prolongation
Sunitinib (Sutent)	TKI	VEGFR1–3, KIT, PDGFRα/ β, RET, CSF1R, FLT3	Renal cell carcinoma, GIST	Haemorrhage, hypertension, adrenal dysfunction, hypothyroidism
Sorafenib (Nexavar)	TKI	VEGFR2, PDGFRβ, KIT, FLT3, RAF1, BRAF	Renal cell carcinoma, melanoma	Skin rash, hypertension, haemorrhage, acute coronary syndromes
Lapatinib (Tykerb)	TKI	EGFR, ERBB2	Breast cancer	Skin rash, diarrhoea
Gefitinib (Iressa)	TKI	EGFR	NSCLC	Skin rash, diarrhoea, nausea, interstitial lung disease
Erlotinib (Tarceva)	TKI	EGFR	NSCLC, pancreatic cancer	Skin rash, diarrhoea, nausea, interstitial lung disease


Tyrosine-kinases
MAPKinases
Protein-kinases
TK
GYC
TKL
STE
CMGC
CK1
AGC
RTK
PI3K
AKT
Ras
JAK2,3
SRC
Rac
mTOR
Raf
MEK
JNK
(p38)
RS6K
ERK
S6
STAT1,3,5
NFκB

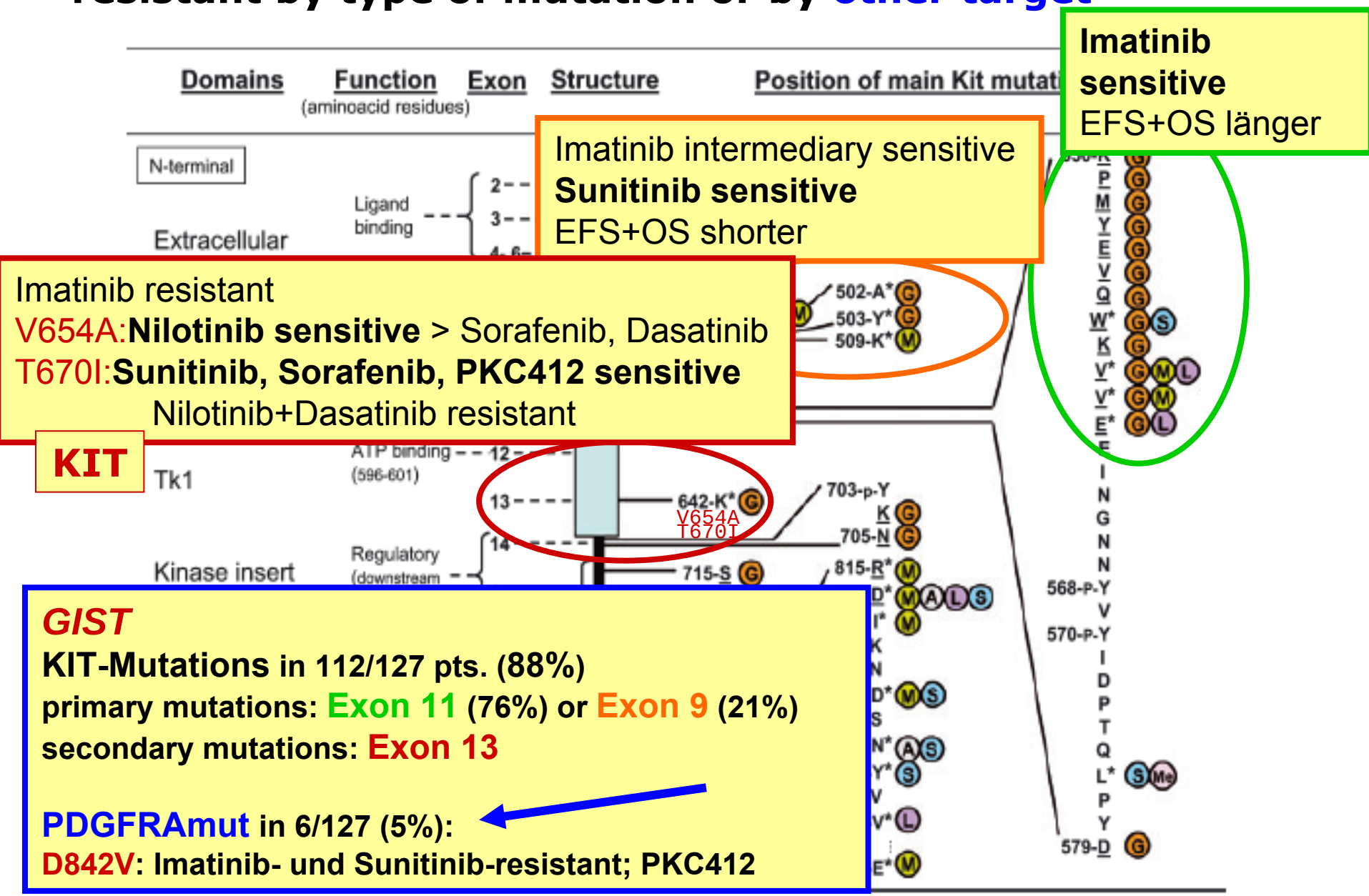
Mutation and resistance:

A story of the optimum key for a specific lock – or, one key for all ?

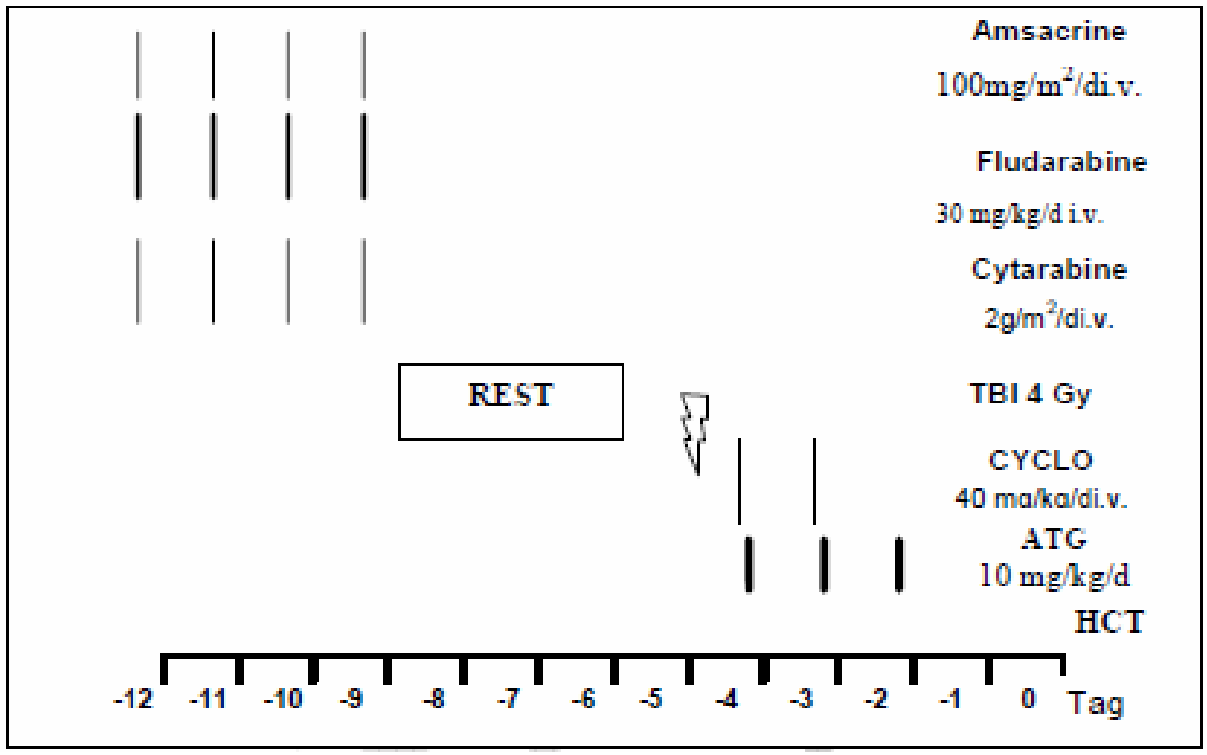


Deininger et al., Blood 2005

Same type of malignancy – example *GIST* resistant by type of mutation or by other target



Preparative regimen „FLAMSA-RIC“



Forodesine in pediatric ALL

Experience in 7 pediatric patients (≤18 years of age) with i.v. administered forodesine at a dose of 40 mg/m^2 or 80 mg/m^2 x 5 days/week for up to 6 cycles:

- 5 patients with advanced T-ALL after response failure to at least one prior treatment with standard chemotherapy (Protocol No. BCX1777-T-04-201). 1/5 CR
- 2 patients with refractory B-cell precursor ALL (Protocol No. BCX1777-Bi-04-106). 0/2 CR
  - Overall response rate: 1/7 pts (14%)
- Adverse events similar to those seen in adults.

Forodesine Dosages

Intravenous Administration

- 40-80 mg/m^2/day, 5-day on/2-day off

Oral Administration

- 200-300 mg daily (adults)
- Bioavailability:
  - 100 mg gelatin capsules: approx. 28%
  - i.v. solution: approx. 40-60%