European LeukemiaNet

Treatment Policy

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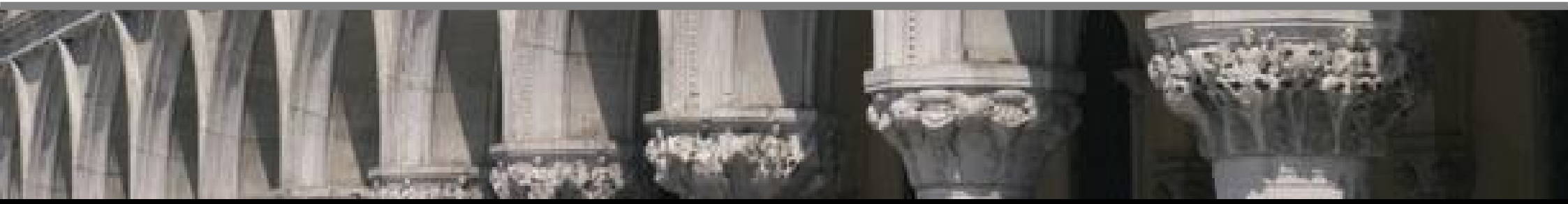
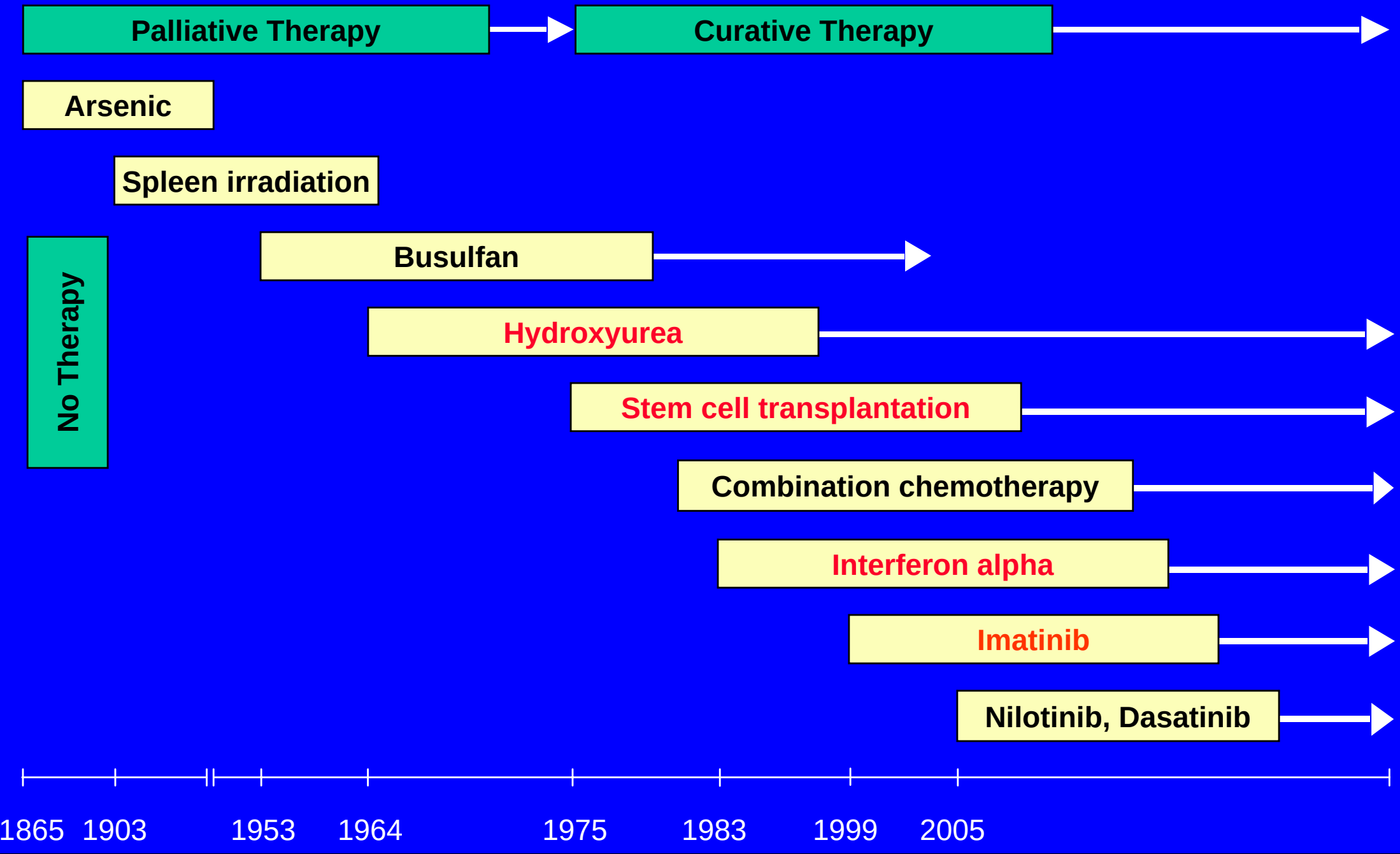


Historic Development of CML Therapy



Rationale for CML "guidelines"

- TKIs: paradigm shift in CML
- 1998 ASH guideline on CML Tx does not cover TKIs
- 2006
  - too early for evidence-based analysis of IM effects
  - Not too early to review available data

ELN review of CML therapy

- Review panel: 19 expert members of ELN
- Scope
  - Review of literature after 1998
  - Panel meetings
  - Discussion limited to early chronic phase (ECP)
    - More advanced phases more difficult to generalize
    - Importance of 1st line Tx strategy
- Requirements
  - Definition of phase, remission
  - Definition of risk of progression / death

Summary of ELN expert panel "guidelines"

- Confirm value in CML Tx of
  - IM 400 mg/d
  - Allogeneic SCT
- Recommend
  - initial Tx decision to be based on established risk factors
  - For patients initially on IM
    - with Tx failure: increase dose or change Tx
    - with suboptimal response: consider increase in dose or change of Tx
  - Regular monitoring at expert centers

Review findings

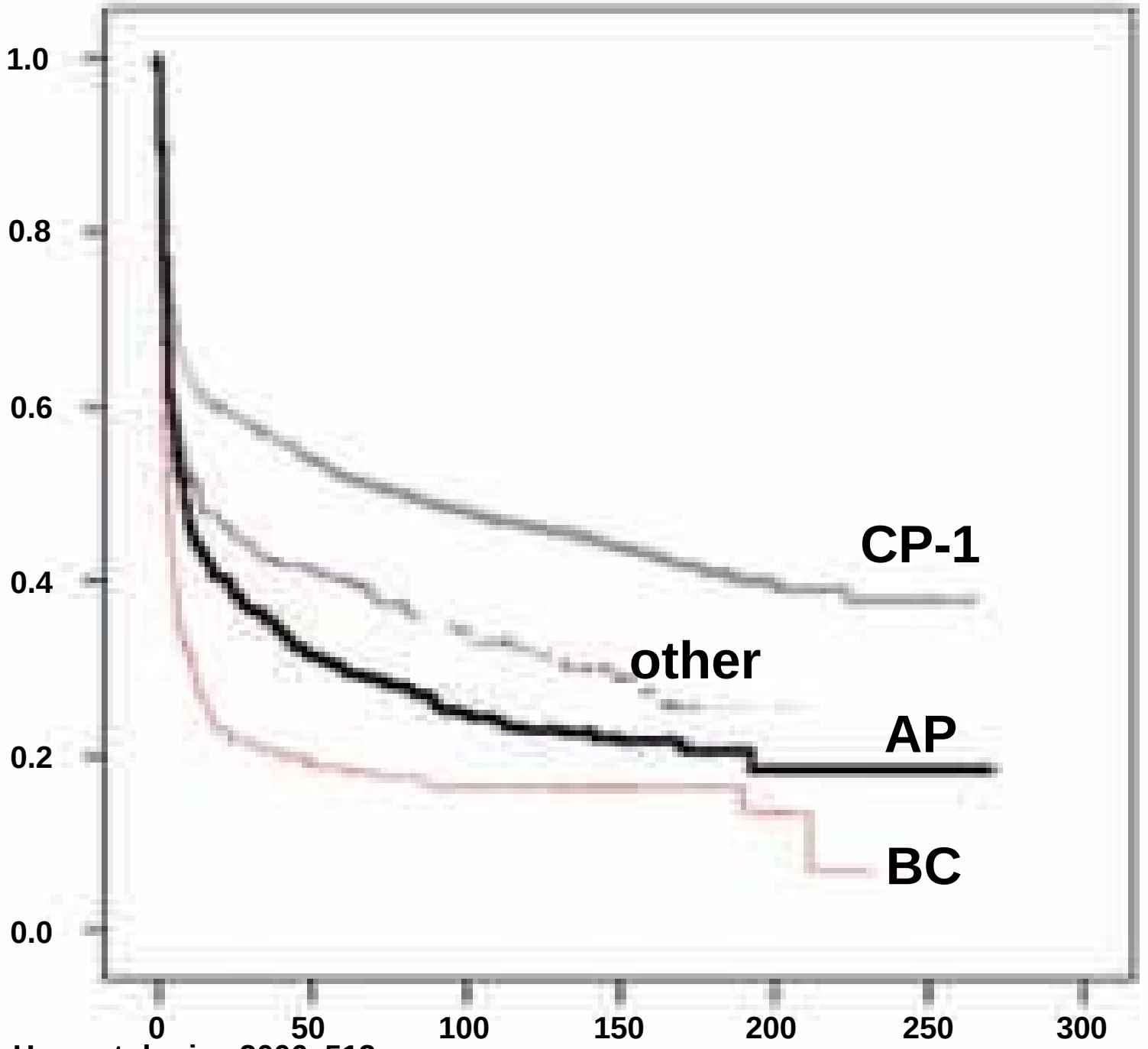
Summary and update of recombinant IFNα

- rIFNa superior to conventional CT
- rIFNa + ara-C vs. rIFNa: higher CR, equal OS
- Low dose (3 MIU 3x/wk) as effective as high dose (5 MIU/m2/d) but better tolerated
- 9-10-year OS for rIFNα: 27%-53%
- 10-year OS for complete cytogenetic responders (n=317)
  - 90% (low Sokal risk)
  - 40% (high Sokal risk)

Summary and update of allogeneic SCT (1/2)

- allo SCT in first CP
  - 10-yr OS 60%, 10-yr EFS 50%
  - 10-yr OS 47%, 15-yr EFS 52%
  - 10-yr OS 63%, 15-yr EFS 65% (meta-analysis, n=316)
- CIBMTR (n=4513)
  - 18-yr OS 50% (first CP), 37% (others)
  - 18-yr cum. incidence of relapse 25% (CP), 37% (others)
- EBMT (n=2628)
  - 20-yr OS 34%
    - 41% for first CP, HLA-identical sibling
    - 49% for EBMT risk score 0-1

Survival Probability of Transplantation



Gratwohl et al., Haematologica 2006, 513

Summary and update of allogeneic SCT (2/2)

- EBMT (n=3142, any phase, any donor):
  - OS 72%-11% depending on risk (70%-25% for ECP)
- Improved results today due to better
  - allele matching
  - management of infections and supportive care
  - Immunosuppression
- PB stem cells not better than BM stem cells
- RIC-alloHSCT under evaluation; may permit SCT also in older patients

Summary and update of autologous SCT

- Treatment intensification with autoHSCT to achieve more remissions and prolong OS
- Meta-analysis of 6 randomized studies did not show advantage for autoHSCT

Summary and update of Imatinib (ECP)

- IM superior to rIFNa and LDAC (IRIS)
- 2 independent retrospective analyses con-firmed superiority to other non-transplant Tx
- Current survival outcome in ECP better than for any other reported Tx
  - Annual rate of progression to AP/BC during 1st 4 years of Tx fairly constant (1.5%, 2.8%, 1.6%, 0.9%)

Summary Treatment Criteria

- Phase of disease
- Risk profile at diagnosis
- Transplantation risk
- Time to remission, remission quality
- Mode of resistance (Clonal evolution, IC_{50} of mutants, NB: P-loop-mutants [aa 248-256] and T315I)
- Additional chromosomal abnormalities?

Principle of CML-Management

Weigh

- disease risk (phase, risk profile)
- against therapy risk (adverse effects, transplantation risk)
- Consider response

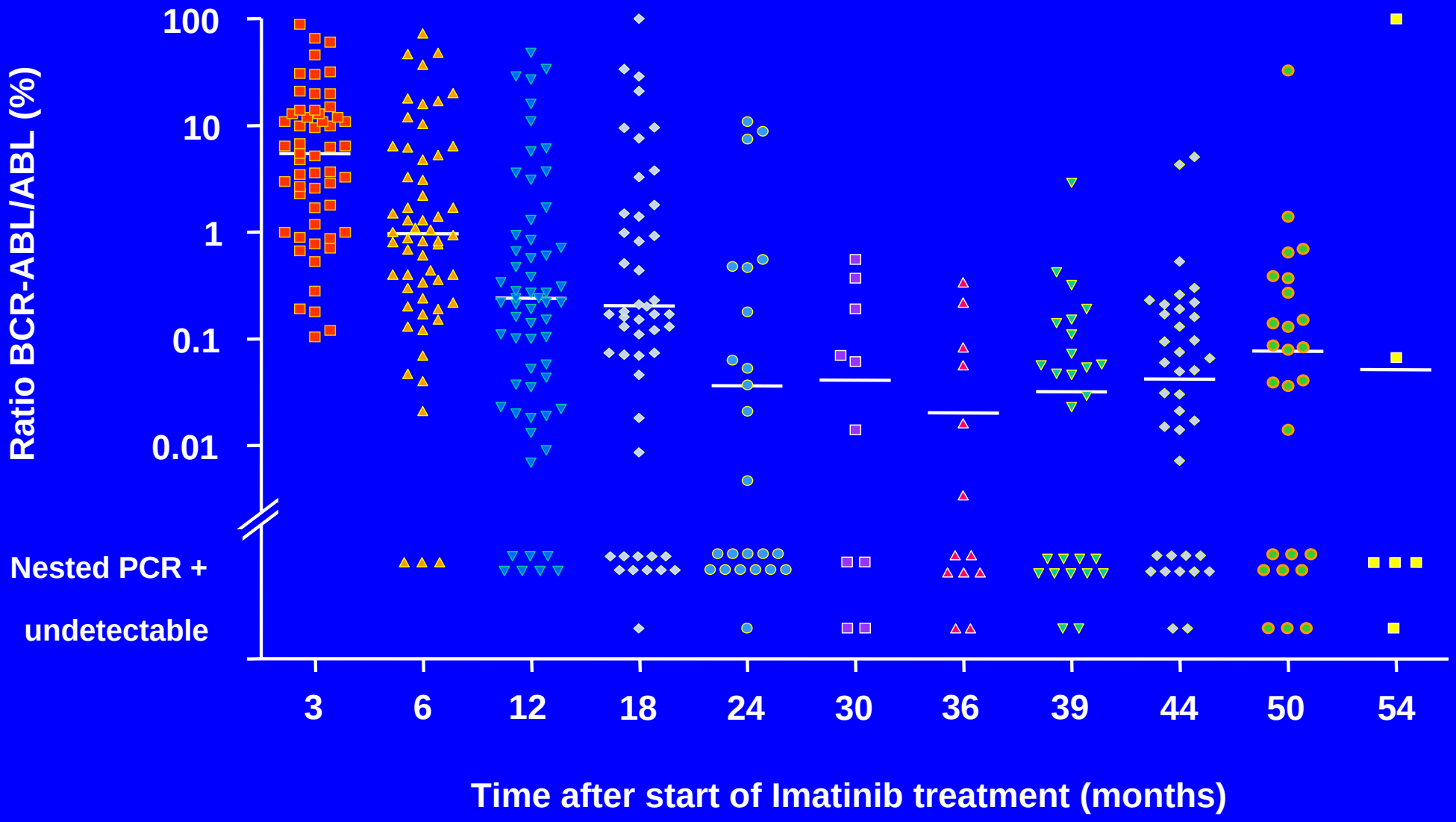
The Importance of Response Monitoring

- Hematologic (q 2 weeks until CHR)
- Cytogenetic (q 6 months until CCR)
- Molecular (q 3 months after CCR)

Reduction in BCR-ABL transcripts on IM therapy

- High frequency of CCR on IM Tx calls for measurement of MRD
- 3-log reduction from a standard baseline (MMolR) in 50% of patients in ECP (70% of pts in CCR)
- BCR-ABL transcripts undetectable in 4%-34%
- Rate of further reduction in BCR-ABL decreases over time γ
  stem cells less sensitive to IM?
- Cure uncertain γ Tx not to be discontinued

Imatinib: *BCR-ABL* Transcript Levels After CCR in Chronic Phase



Müller et al., Leukemia 2003, update Hochhaus

Relevance of Molecular Monitoring (RQ-PCR)

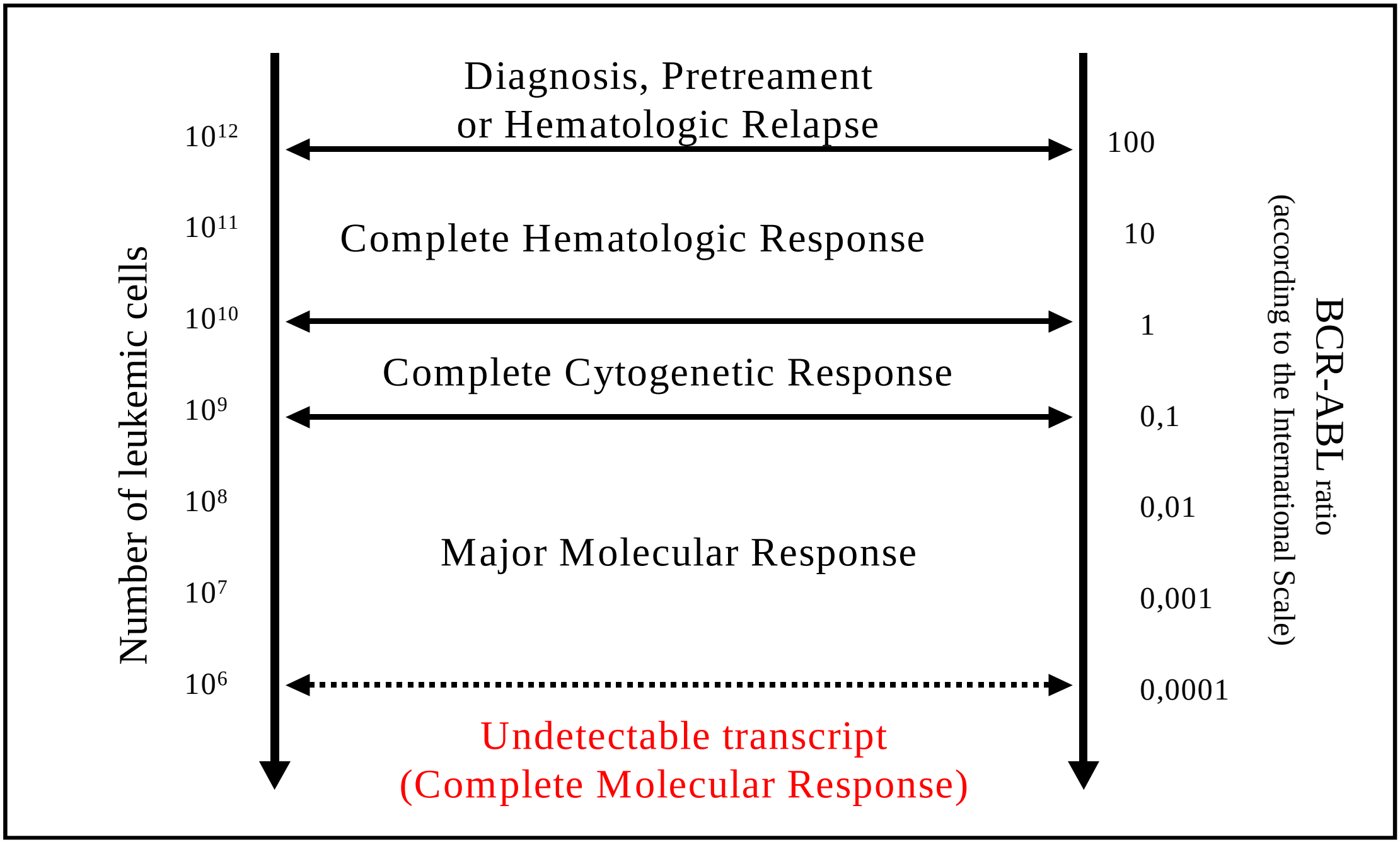
- Only method to measure residual disease after CCR
- The degree of transcript reduction has prognostic relevance (Hughes et al., NEJM 2003)

Molecular Response Definition

- Complete — Transcripts undetectable
- Major — BCR-ABL/ABL ratio $\leq$0.1

Check every 3 months, search for mutation in case of failure, suboptimal response or rising transcript level

Relationship of Response to Tumor Load



Initial Treatment Options CP

- Standard dose imatinib (400 mg)

Alternatives:

- Interferon combined with HU and/or low dose AraC
  (ECP, standard risk only)
- High dose imatinib (experimental)
- Allografting (on patients' request)

Criteria for Alternative Treatments

- Imatinib failure
- Suboptimal response
- Clonal evolution to AP/BC
- Resistant mutant

Imatinib IC_{50} for BCR-ABL Mutants

Mutant	Biochemical	Cellular
Wild-type	300	260-500
M244V	380	2000
L248V	n.a.	1500
G250E	1000	1350-3900
Q252H	n.a.	1200-2800
Y253F	>5000	3475
Y253H*	>5000	>10000
E255K	2800	4400-8400
E255V	>5000	>5000
D276G	n.a.	1500
T277A	n.a.	n.a.
F311L	775	480
F311I	n.a.	n.a.
T315I*	>5000	>10000
F317L*	900	810-1500
M343T	n.a.	n.a.
M351T	820	930
M351V	n.a.	n.a.
E355D	n.a.	n.a.
E355G	n.a.	400
F359V*	4700	1200
V379I	800	1630
A380T*	340	2450
F382L	n.a.	n.a.
L387M	1500	1000
L387F	n.a.	1100
H396P	340-800	850-4200
H396R	1950	1750
S417Y	n.a.	n.a.
E459K	n.a.	n.a.
F486S	1230	2800

Alternative Treatment Options

- Increase of imatinib dose (600-800 mg)
- New tyrosine kinase inhibitors (dasatinib, nilotinib)
- HU, AraC, (IFN)
- Combination chemotherapy
- Allografting

IM dose issues

- 600 mg/d more effective than 400 mg/d in AP/BC
- 800 mg/d can benefit some subgroups of patients
- Unclear whether higher doses will increase overall number of CCR and MMolR
- Prospective studies on high-dose IM in progress
- Lower doses not explored:
  - subtherapeutic doses may lead to resistance
  - 400 mg are well tolerated

Combination Tx

- IM 400 mg/d + pegylated rIFNα2b (50-150µg/wk) (n=77)
  - Limited compliance, high discontinuation rate with IFN
- IM 400 mg/d + LDAC (n=30)
  - CCR 70% at 1 year,
    grade 3-4 hematological toxicity 53%
- Ongoing prospective randomized studies
  - IM alone vs IM + rIFNα / LDAC / HD AC
- Synergies with IM or overcoming of IM resistance seen with several drugs (preliminary results)

IM and SCT

- IM prior to alloHSCT did not increase TRM or morbidity
- IM can control leukemia in patients relapsing after alloHSCT, molecular negativity 15/18 cases
- Synergy of IM with donor lymphocyte infusion suggested

Resistance and mutations

- Multifactorial
  - **BCR-ABL mutations of kinase domain** (42%-90%)
  - BCR-ABL amplification or overexpression
  - **clonal evolution**
  - decreased IM bioavailability or cell exposure
- Mutant subclones may not be consistently associated with subsequent relapse
- Ph+ primitive cells can harbour BCR-ABL mutations prior to IM exposure and can develop rapidly under IM pressure
- Some mutations can be overcome by dose increase or are functionally irrelevant γ interpret within clinical context!

Additional chromosome abnormalities (ACA) in Ph+ cells and other chromosome abormalities in Ph- cells (OCA)

- ACA (clonal evolution) rare in ECP but more frequent with disease progression
- Negative relationship of ACA with IM response
- OCA in app. 5% of pts in IM-induced CCR
- Many of these in LCP, with IFN pretreatment
  - Trisomy 8 ± other abnormalities
  - del7
  - Association with MDS (particularly in del7 and/or other complex abnormalities)
- OCA may be transient; often does not end CCR

Failure and suboptimal response: operational definition (ECP CML on IM 400 mg/d)

Time	Failure	Subopt Resp	Warnings
Dx	-	-	High risk Del9q+ ACA in Ph+ cells
3 mos	No HR	< CHR	
6 mos	< CHR No CR	< PCR	
12 mos	< PCR	< CCR	< MMolR
18 mos	< CCR	< MMolR	
Anytime	Loss of CHR Loss of CCR Mutation (IM-insensit.)	ACA in Ph+ cells Loss of MMolR Mutation (IM-insensit.)	Any # transcr level OCA in Ph- cells

Failure and suboptimal response ('anytime' events)

Time	Failure	Subopt Resp	Warnings
Anytime	Loss of CHR [1] Loss of CCR [2] Mutation [3]	ACA in Ph+ cells [4] Loss of MMolR [4] Mutation [5]	Any # transcr level OCA in Ph- cells

1) confirmed on 2 occasions, unless progression to AP/BC
2) confirmed on 2 occasions, unless CHR loss or progr. to AP/BC
3) High level of insensitivity to IM
4) confirmed on 2 occasions, unless loss of CHR or CCR
5) Low level of insensitivity to IM

Failure and suboptimal response due to mutation

- Mutant subclones may not be consistently associated with subsequent relapse
- Mutations
  - can be overcome by dose increase
  - can be functionally irrelevant
- γ interpret within clinical context!

Treatment policy: recommendations

ECP initial standard Tx

- Standard dose imatinib, 400 mg/d
- Alternatives
  - IFN + HU and/or low-dose Ara-C (standard risk only)
  - High dose imatinib (experimental)
  - Allografting (on patients' request)

Preferred Tx in high-risk disease, low transplantation risk

- Trial with IM first
- Discuss choice between IM and alloHSCT with patient
- Little reason to deny IM trial,
  as early response to IM can reinforce
  or weaken indication for alloHSCT

Preferred Tx other than IM 400 mg/d

Intolerance	SCT or IFN ± LD Ara-C vs. New agents	Shared decision-making
Toxicity		
Failure	SCT or IM 600 or 800 mg/d	Check compliance! Rule out highly resistant mutation
Suboptimal response	IM 600 or 800 mg/d (SCT if low SCT risk and high disease risk)	
'Warnings'	Continue IM 400 mg/d	Observe! Check compliance!

Treatment Choices

In case of intolerance or toxicity:

- **Allografting**
- **IFN± LD AraC**
- **investigational agents (shared decision making)**

Treatment Choices

In case of failure/resistance (check compliance!, rule out highly resistant mutation)

- **Trial with imatinib 600 or 800 mg (if mildly resistant mutation)**
- **Trial with dasatinib or nilotinib (if available)**
- **Allografting**
- **Hydroxyurea**

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Treatment Choices

In case of suboptimal response:

- **Imatinib 600 or 800 mg**
- **Allografting, if low transplantation risk and high disease risk**

Treatment Choices

In case of warnings:

- **Continue imatinib 400 mg**
- **Observe**

Check compliance!

Other scenarios

- Patient requires IM dose reduction or frequent interruption
  - Advise pt to adhere to 400 mg/d as far as possible
  - Provide appropriate supportive care
  - Monitor response frequently
  - Monitor IM blood level in case of failure, co-medication of drugs interfering with Cyt. p450, or drug-related SAE
- Pt with no other Tx options
  - Continue IM if CHR maintained; otherwise resort to HU

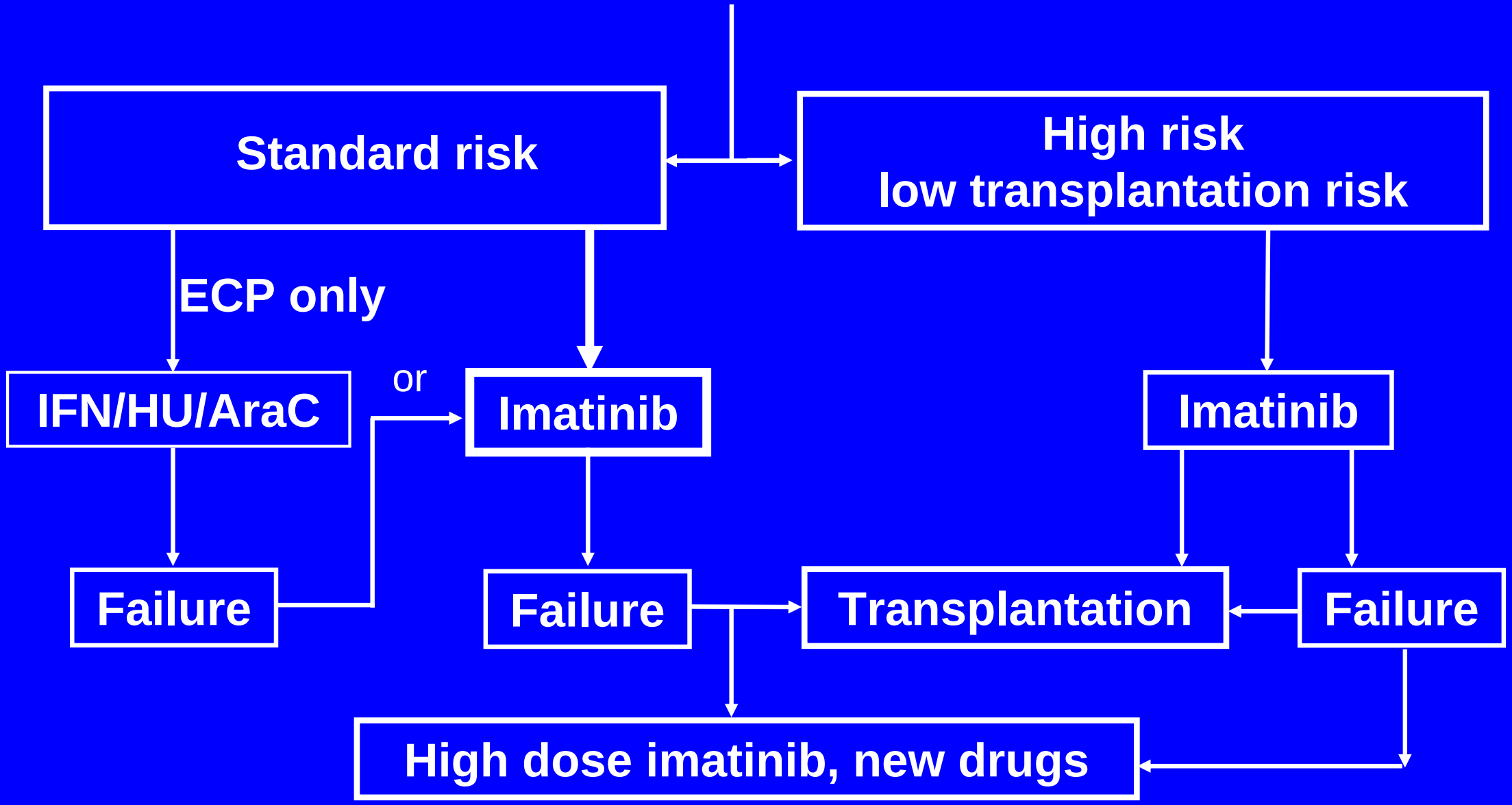
Summary and update of Imatinib (late CP, AP, BC)

- IM in late CP
  - CCR 41%-64%
  - 5-yr PFS 69%, 4-yr OS 86%-88%
  - Better OS than historical controls even when no CCR
- IM in AP
  - Best results at 600 mg/d: CHR 37%, CCR 19%, 3-yr PFS 40%
- IM in BC
  - CHR ca. 25%, some CCR, short PFS (≤10 ms median), 3-yr OS 7%

Tx in initial AP and BC

- Treatment initially with IM
- Trial of other TKI
  (based on mutational analysis)
- Then proceed to allografting

CML in chronic phase 2006



EVOLVING CONCEPTS IN THE MANAGEMENT OF CHRONIC MYELOID LEUKEMIA

RECOMMENDATIONS FROM AN EXPERT PANEL ON BEHALF OF THE EUROPEAN LEUKEMIANET

EXIT