EU Clinical Trials Directive:
Freuden und Leiden eines Studienleiters in der Pädiatrischen Onkologie

Martin Schrappe

Univ.-Kinderklinik Kiel

Pediatric Oncology in Europe
Background (1)

- 15 000 new cases each year in Europe
- 3000 will die each year but the majority can be cured.
- 1 out of 1000 adults aged 18 to 40 is a pediatric cancer survivor.
- Cancer is not one disease – it comprises a large number of different diseases from newborns to teenagers (60 or more, if biomarkers are considered even more!)
- Many cancers in children are unique and not present in adults.

Pediatric Oncology in Europe
Background (2)

- Specific medicines for children with cancer are not available.
- Available treatments would be considered obsolete in all other areas of Pediatrics due to toxicity.
- Non- commercial, mostly population-based, investigator driven clinical trials (IDCTs) created "Standards of Care and Treatment " in the past decades.
- Treatment success is based on *off-label* medication but IDCTs are considered the best available, high level quality assurance for patient safety and treatment.

Epidemiology of childhood cancer: Survival

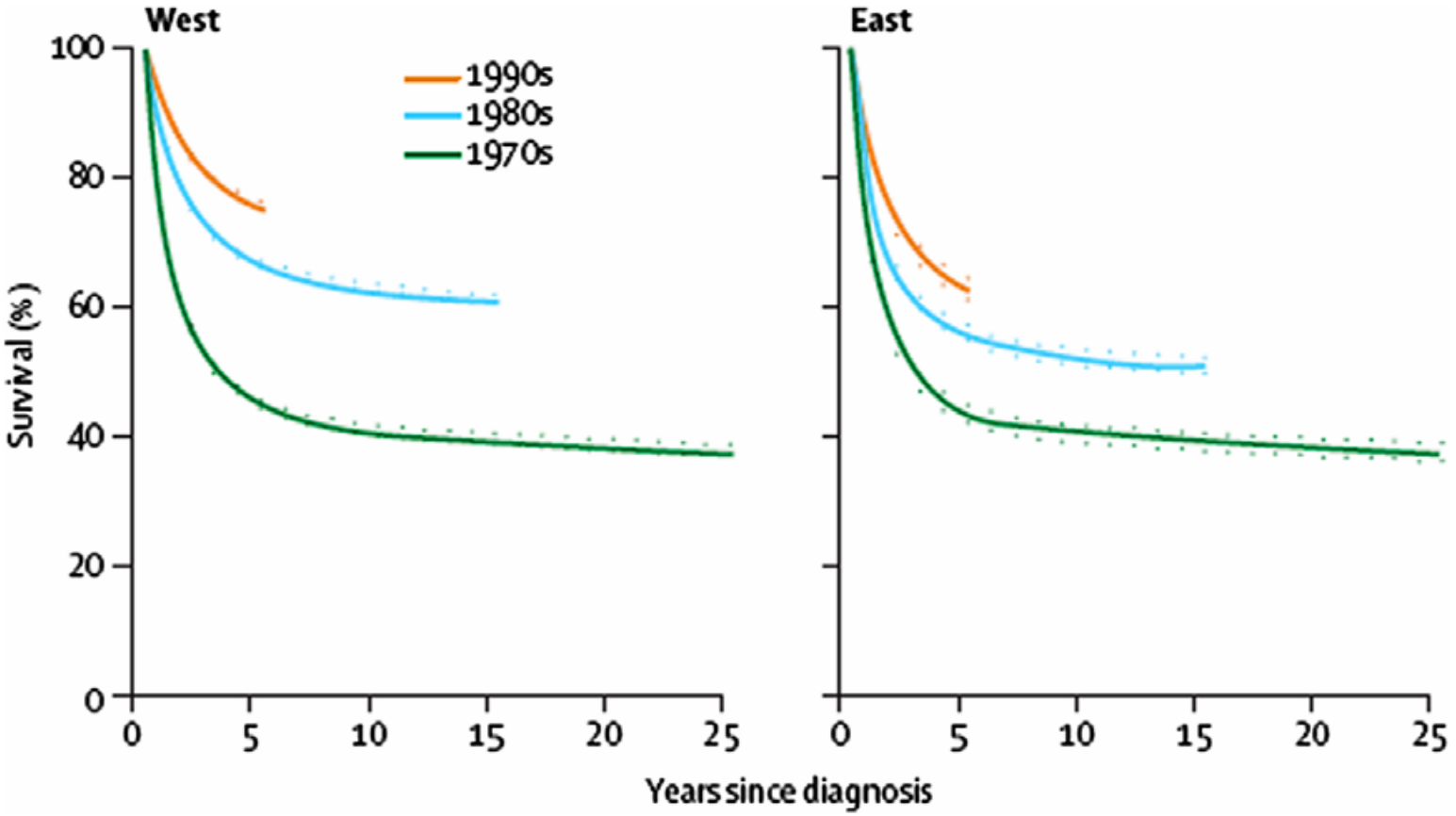
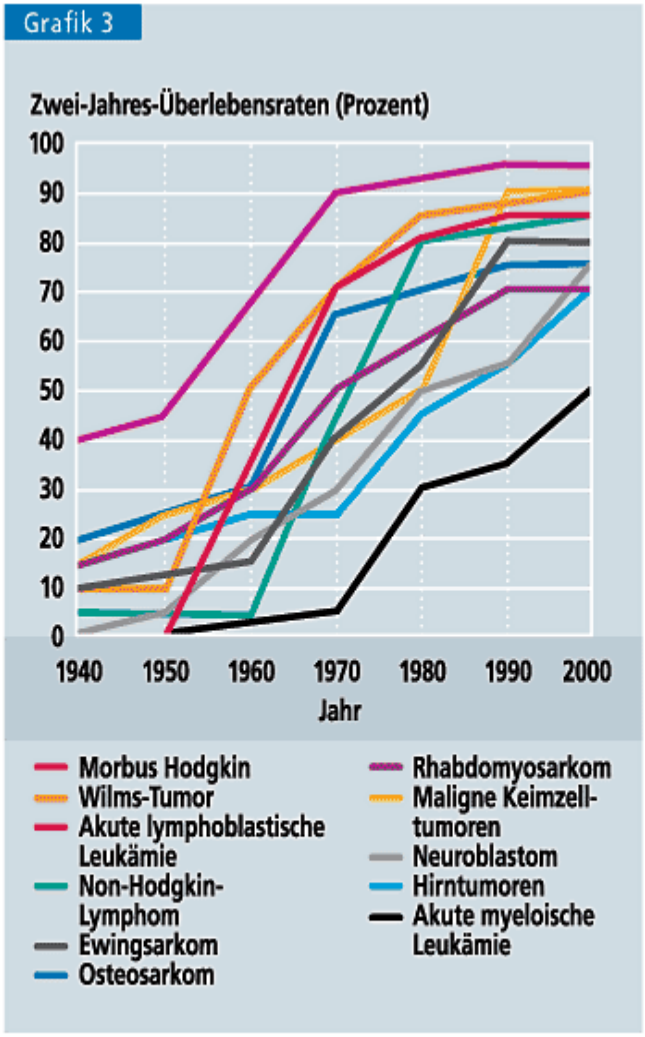


Fig. 3. Survival rates by decade of diagnosis for childhood cancer (age 0–14) for East and West Europe. *Source:* ACCIS (1970–1999). Reprint from Ref. [24] (ACCIS, European Automated Childhood Cancer Information System).

Kaatsch, Cancer Treatment Reviews 2010, 36, 277–285, Epidemiology of childhood cancer

Situation in Deutschland

Grafik 3



Anstieg der Überlebensraten von Kindern und Jugendlichen mit bösartigen Erkrankungen seit 1940 (es wird nur eine 2-Jahres-Überlebensrate angegeben, da es aus der Zeit vor 1970 keine längeren Verlaufsdaten gibt).

Tabelle

5-Jahres-Überlebenswahrscheinlichkeit für ausgewählte Diagnosen im 5-Jahres-Abschnitt (1991–1995)

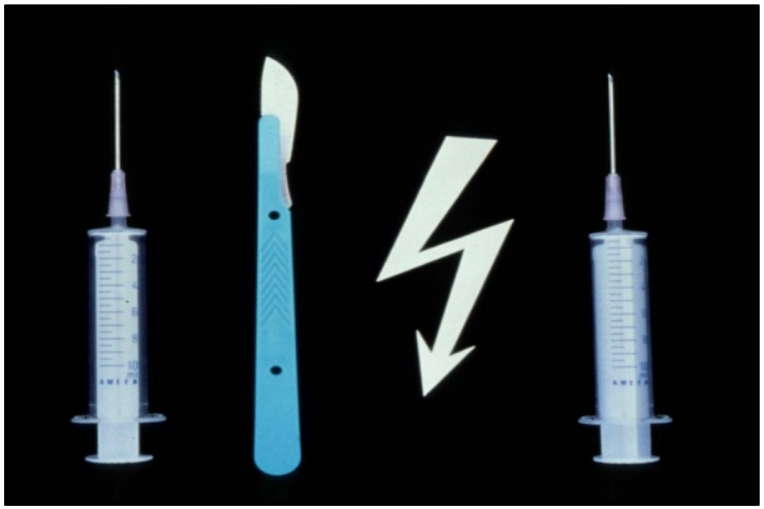
Diagnose	Patienten-zahl (n)	5-Jahres-Überlebens-wahrscheinlichkeit (Prozent) und 95%-Kofidenzintervalle
Retinoblastom	192	100
Morbus Hodgkin	458	96 (95–98)
Non-Hodgkin-Lymphom	594	89 (86–91)
Nephroblastom	561	88 (85–91)
Keimzelltumoren	307	87 (83–91)
Akute lymphoblastische Leukämie (ALL)	2 444	85 (84–87)
Hirntumor	1 683	68 (66–71)
Ewingsarkom	179	67 (60–73)
Osteosarkom	217	66 (60–73)
Neuroblastom	677	65 (61–68)
Rhabdomyosarkom	331	65 (60–70)
Periphere neuroektodermale Tumoren	452	57 (52–62)
Akute myeloische Leukämie (AML)	433	50 (45–55)
Alle Erkrankungen*	8 642*	77 (76–78)

*inklusive weiterer seltener Diagnosen
aus dem Jahresbericht 2000 des Deutschen Kinderkrebsregisters

Krebserkrankungen bei Kindern

Erfolg durch einheitliche Therapiekonzepte seit 25 Jahren

Ursula Creutzig[1], Günter Henze[2], Stefan Bielack[1], Ralf Herold[2], Peter Kaatsch[3], Jan-Henning Klussmann[1], Norbert Graf[4], Dirk Reinhardt[1], Martin Schrappe[5], Martin Zimmermann[5], Heribert Jürgens[1]



Textkasten

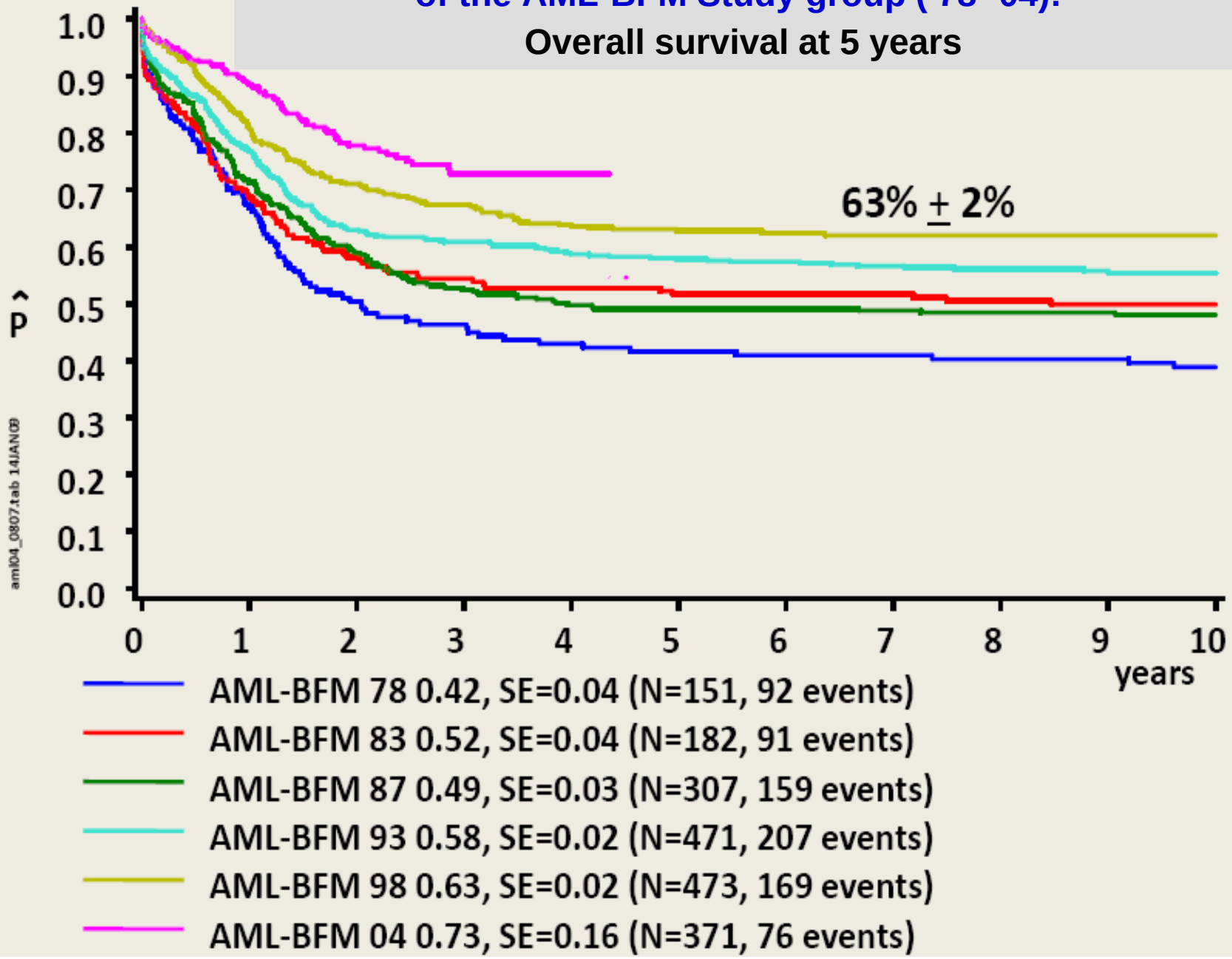
Projekte und die entsprechenden Studienbezeichnungen der Gesellschaft für Pädiatrische Onkologie und Hämatologie

- Akute lymphoblastische Leukämie: ALL-BFM 2000
- Akute lymphoblastische Leukämie: CoALL-06-97
- Akute lymphoblastische Leukämie: Rezidive – ALL-REZ BFM 96
- Akute myeloische Leukämie: AML-BFM 98
- Schwere aplastische Anämie: SAA94
- Chronische myeloische Leukämie bei Kindern: CML-päd 95/96
- Ewingsarkom: European Ewing Tumour Working Initiative of National Groups – EURO-E.W.I.N.G. - 99
- Hepatoblastom: HB 94
- Hirntumoren Medulloblastome: HIT MED
- Kraniopharyngeom: HIT-ENDO
- Hochmaligne Gliome: HIT-GBM
- Niedrigmaligne Gliome: HIT-LGG
- Morbus Hodgkin: GPOH HD-2002 (in Planung)
- Maligne nichttestikuläre Keimzelltumoren: MAKEI 96
- Testikuläre Keimzelltumoren: MAHO 98
- Maligne endokrine Tumoren – MET 97
- Myelodysplastische Syndrome (einschließlich CMML) -98: EWOG-MDS 98
- Nephroblastom (Wilms-Tumor) Nephroblastom-Studie: SIOP 2002/GPOH
- Non-Hodgkin-Lymphom: NHL-BFM 95
- Neuroblastom: NB 97
- Osteosarkom: COSS 96
- Weichteilsarkome: CWS-96
- Nasopharynxkarzinom: 98

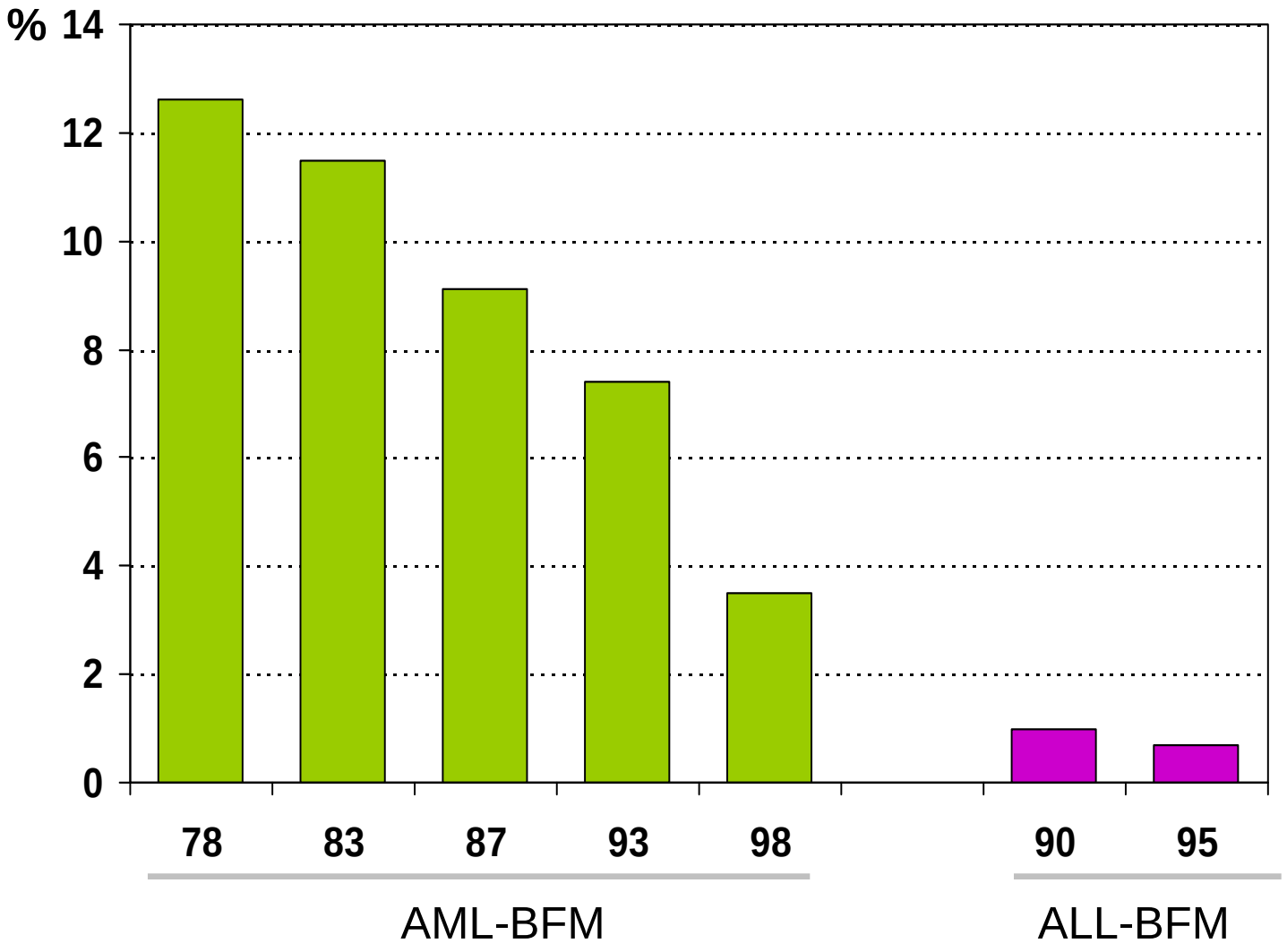
Zentrale Einrichtungen und Projekte: Deutsches Kinderkrebsregister und das Projekt Spätfolgen (LESS)
Cooperatives Pädiatrisches Stammzelltransplantations-Register

Treatment results in pediatric AML in six consecutive trials of the AML-BFM Study group ('78-'04):

Overall survival at 5 years



Early death rate in AML- and ALL-BFM-Studies

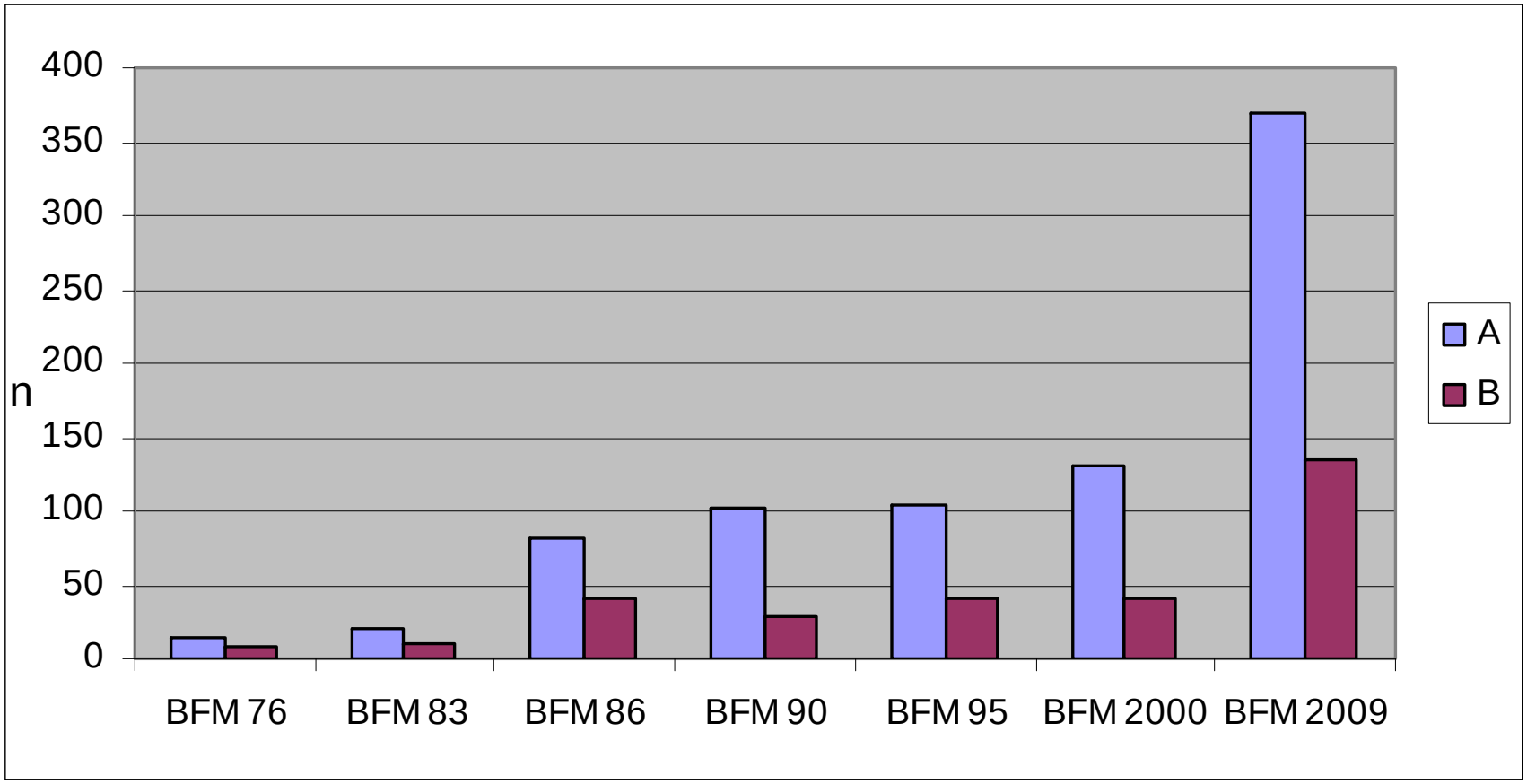


Creutzig et al. (2005) JCO; Schrappe et al. (2000) BLOOD; Möricke et al. (2008) BLOOD

Die Serie der ALL-Studien der BFM Studiengruppe

Studie ALL-BFM	Periode	Länder
70	1970-1976	Berlin - Frankfurt - Münster
76	1975-1980	Deutschland
79	1979-1981	Deutschland
81	1981-1983	Deutschland
83	1983-1986	Deutschland
86	1986-1990	Deutschland/Österreich
90	1990-1995	Deutschland/Österreich
95	1995-2001	Deutschland/Österreich/Schweiz
2000	2000-2009	“Go Europe“
2009	2010-2015	“International“

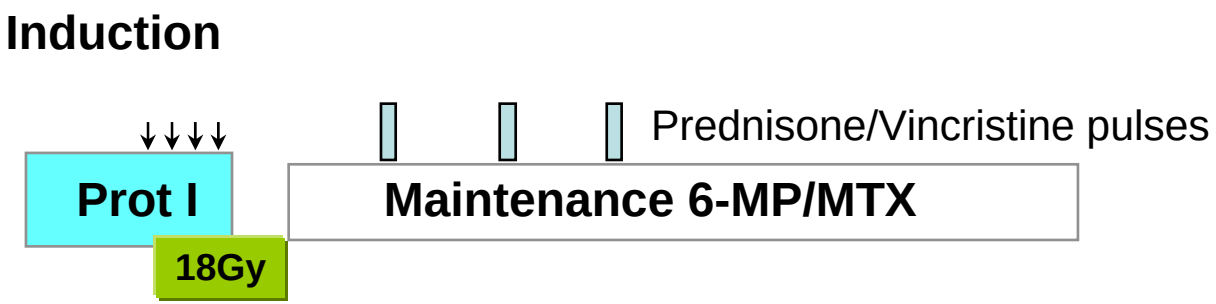
ALL-Studien der BFM Studiengruppe



Was ist A, was ist B?

Was ist „n“?

“Berlin Protocol“ (ALL-BFM 70)



The west-berlin therapy study of acute lymphoblastic leukemia in childhood--report after 6 years

Riehm H, Gadner H, Welte K. Klin Pädiatr. 1977 Jan;189(8):89-102

The Berlin childhood acute lymphoblastic leukemia therapy study.

Riehm H, H Gadner, G Henze, E Odenwald: Am J Pediatr Hematol Oncol 2:299-306, 1980

“Berlin Protocol“

4-drug induction **4-drug consolidation**

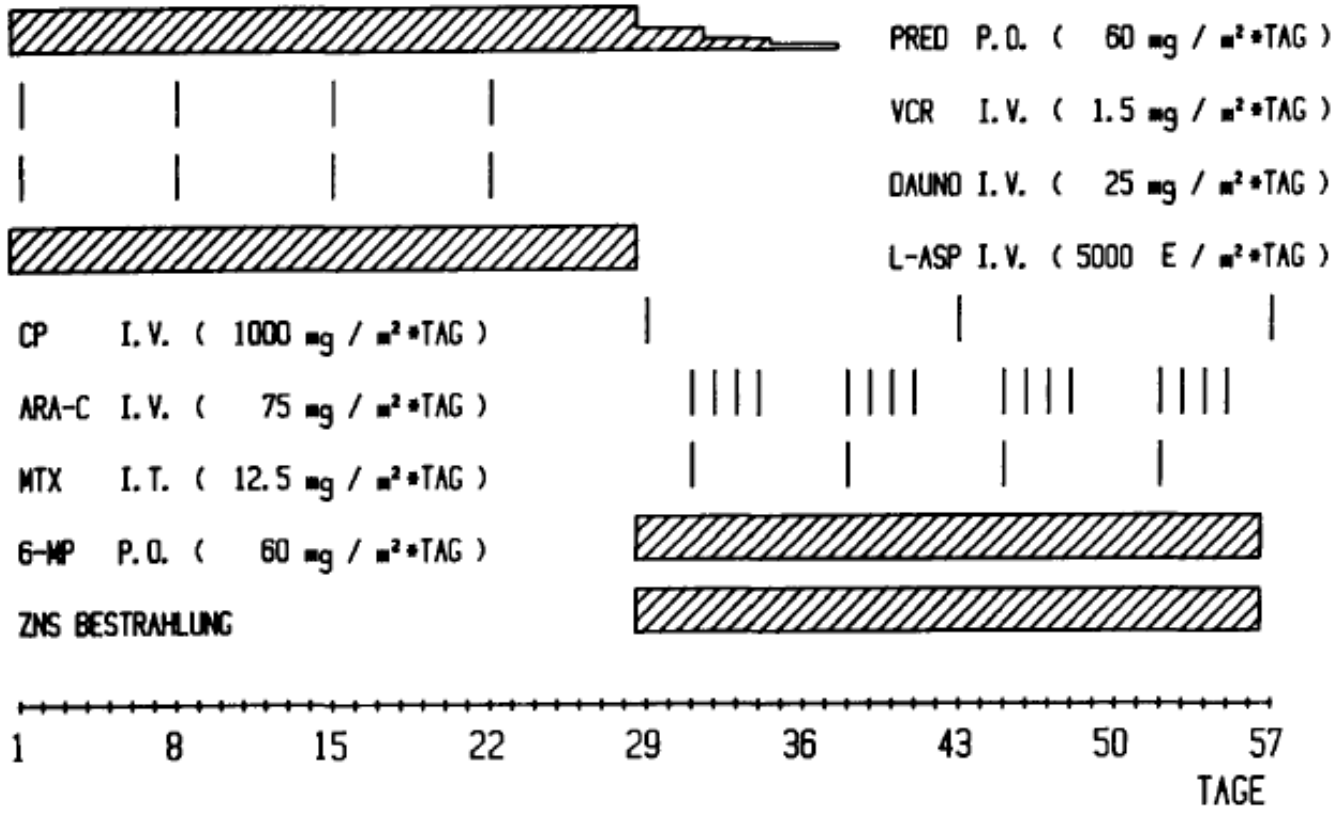
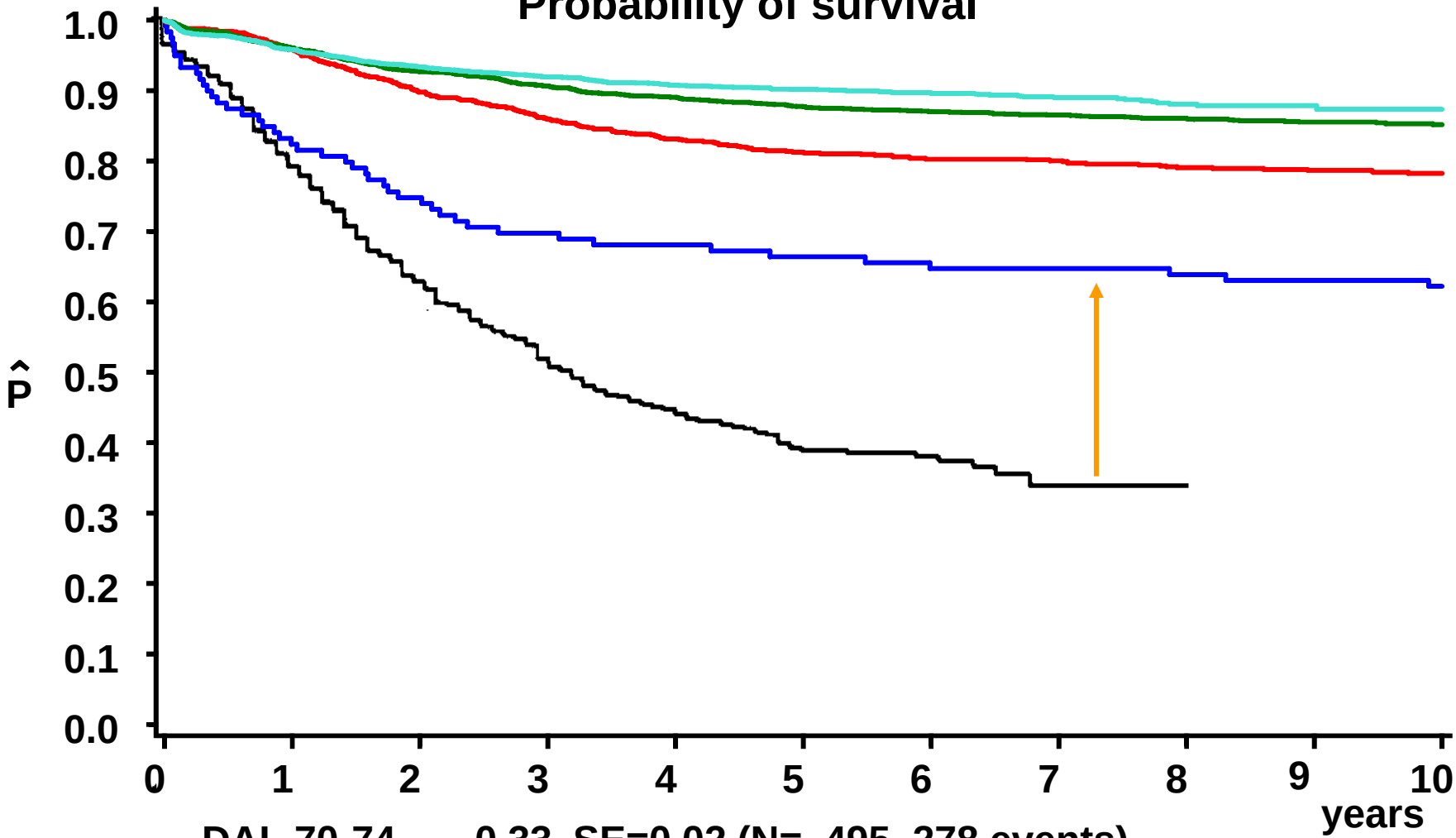


Abb. 2 Induktionstherapie (Protokoll I). PRED: Prednison; VCR: Vincristin; DAUNO: Daunorubicin; L-ASP: L-Asparaginase; CP: Cyclophosphamid; ARA-C: Cytosin-Arabinosid; MTX: Methotrexat; 6-MP: 6-Mercaptopurin

Riehm H. et al, Klin Pädiatr 1977

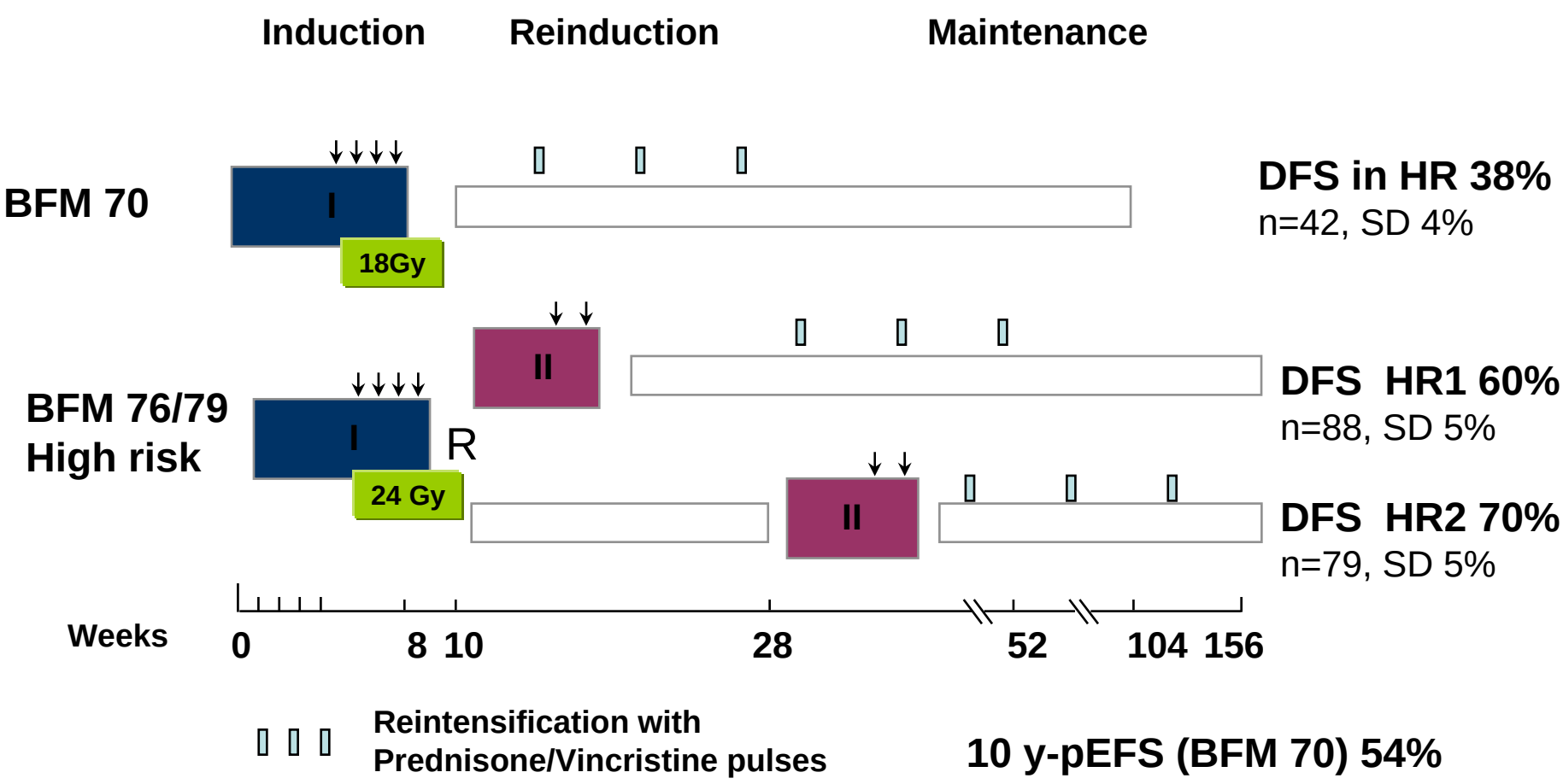
Results in childhood ALL in Germany from 1970 until 2009



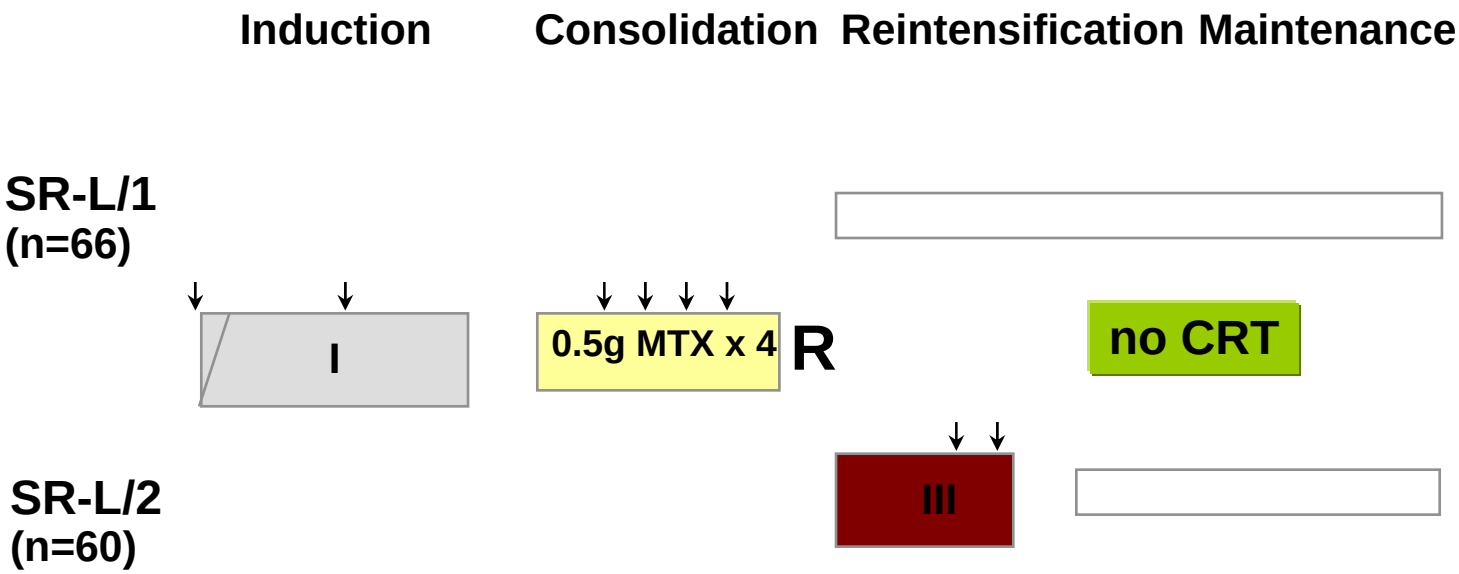
Essential treatment elements and principles

- Intensive induction plus consolidation
- Delayed intensification (= reinduction) for HR and LR pts
- Maintenance therapy
- Preventive CNS-directed therapy

Introduction of delayed intensification (ALL-BFM 76)



Randomized evaluation of delayed intensification in low-risk patients of study ALL-BFM 83*



* ALL-BFM 83: Low-risk ALL (SR-L) comprised 30% of all pts

Reinduction: ‘Protocol III‘

DEXA ***po/iv*** 10 mg/m²/d

VCR ***iv*** 1.5 mg/m² /d

DOX ***pi*** **(1h)** 30 mg/m² /d

L-ASP ***pi*** **(1h)** 10,000 U/m² /d
(E.coli Bayer / Erwin.)

ARA-C ***iv*** **75 mg/m²/d**

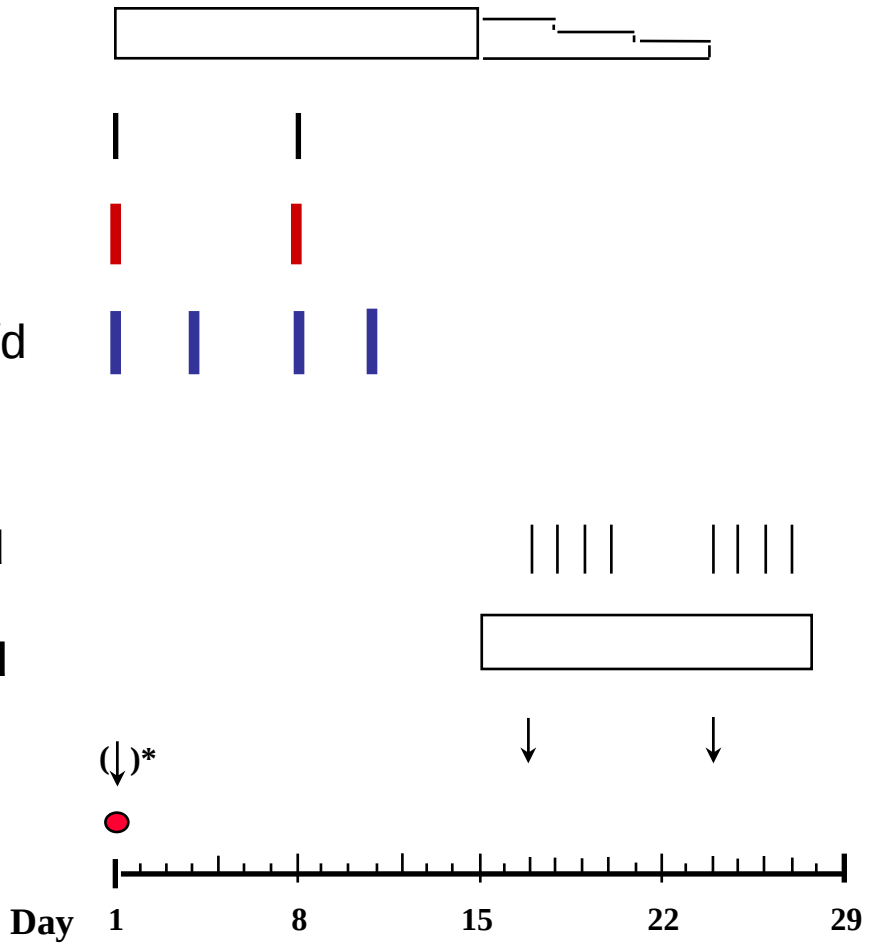
TG ***po*** **(14 d)** **60 mg/m²/d**

MTX ***IT***

Dose age-adapted:

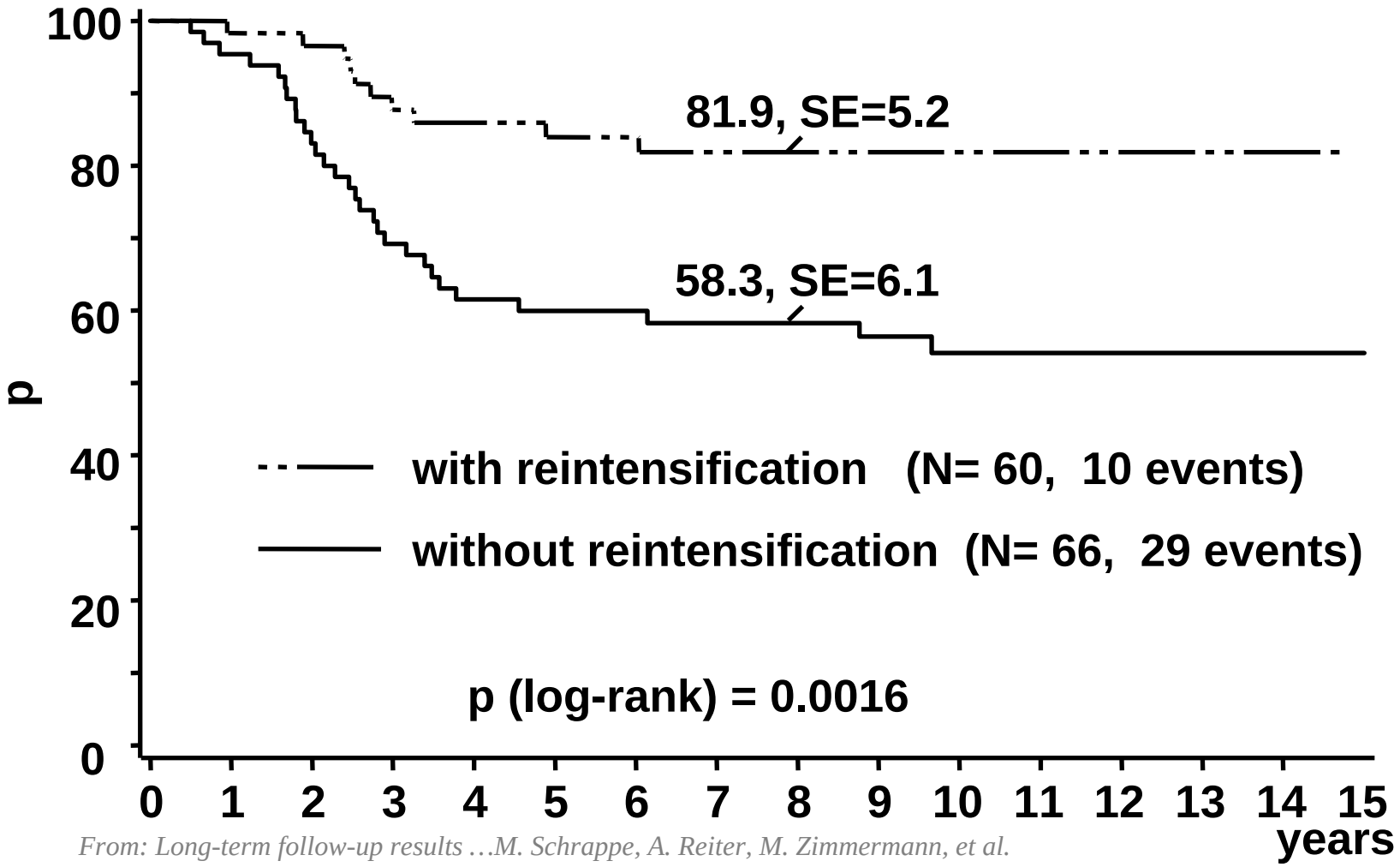
	<1J	1J	2J	≥3J
MTX IT	6mg	8mg	10mg	12mg

*** if CNS positive: additional MTX** ***IT:*** **d 1**



Impact of early intensive reinduction therapy on event-free survival in children with low-risk acute lymphoblastic leukemia.

Henze G, Fengler R, Reiter A, Ritter J, Riehm H.
Haematol Blood Transfus. 1990;33:483-8.



From: Long-term follow-up results …M. Schrappe, A. Reiter, M. Zimmermann, et al. Leukemia 14 (2000): 2205-2222

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Internationale klinische Studien

Beispiele

INTERFANT-99, -06

ESPhALL

AIEOP-BFM ALL 2000/-2009

Klinische Studien bei seltenen Entitäten

- Infant ALL (< 1 J.): INTERFANT Studien
- Ph+ ALL: ESPhALL

Interfant-06
Recruitment (1)

	AIEOP	BFM-A	BFM-G/COALL	CPH	DCOG	EORTC CLG	FRALLE	UK CCLG	NOPHO	PPLSG	*total*
Expected pts./year	10	1	BFM-G 10 COALL 4	2	5	7	7	11	5	4	66
Protocol opening	11/06^	06/08	10/08	01/06	05/06	01/08^	2009^	06/08	05/06*	01/06	
Date of first recruited	11/06	05/09	11/08	07/06	05/06	02/08	10/09	12/08	07/06	03/06	
Diagnosed pts. since 2006	50	9	72	14	19	17§	38	27§	49	29	324
Diagnosed before official opening	*23*	*7*	BFM-G *29* COALL *10*	*0*	*0*	*NK*	*30#*	*NK*	*34*	*0*	*133*
Not eligible	1	0	0	0	0	1	0	2	0	0	4
Not evaluable	0	0	0	0	0	0	0	1	1	0	2
Eligible pts.	26	2	33	14	19	16	8	24	14	29	185
Did not enter	0	0	0	0	0	0	0	0	0	2	2
On study patients	26	2	33	14	19	16	8	24	14	27	183
On study pts./year	5	1	16	3	5	5		9	3	6	

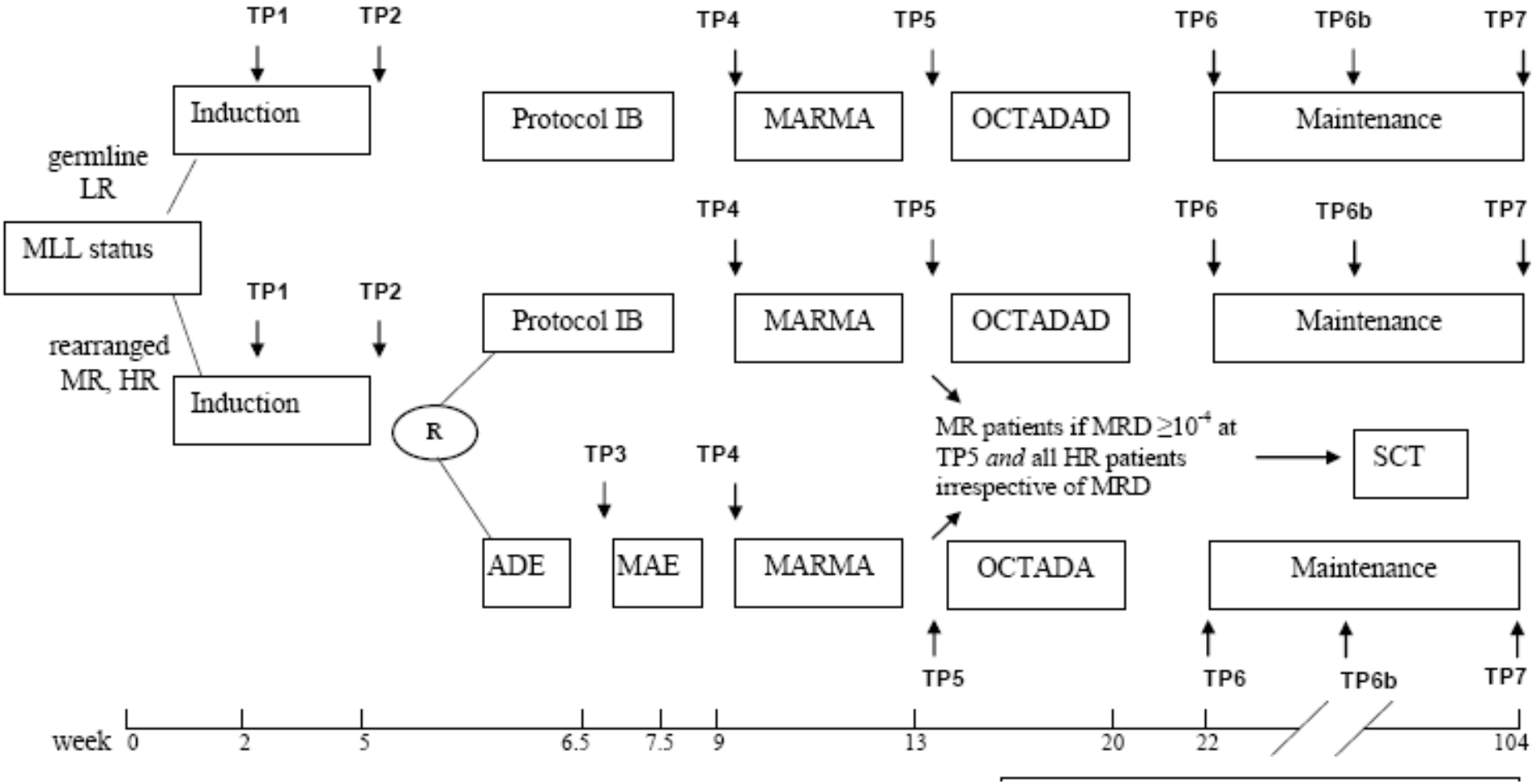
^in selected centers *in Finland, only §includes only pts. since official opening #includes all diagnoses in France

Interfant-06
Recruitment (2)

	Argentina*	DFCI	HONG-KONG	MD Anderson	PINDA	ANZCHOG	Seattle	SJCRH§	*total*
Expected pts./year	**7**	**3**	**1**	**3**	**2**	**1**	**3**	**3**	**23**
Date of official opening	06/06	01/06	01/06	-	01/06	02/06	09/06	11/06	
Date of first recruited	10/06	12/06	03/06	-	02/06	02/06	01/07	02/07	
Diagnosed pts. since 2006	**36**	**12**	**12**		**22**	**12**	**4**	**3**	**101**
Diagnosed before official opening	***1***	***0***	***1***		***1***	***0***	***0***	***0***	***3***
Not eligibile	**0**	**1**	**1**		**1**	**0**	**0**	**0**	**3**
Not evaluble	**1**	**0**	**0**		**0**	**0**	**0**	**0**	**1**
Eligible pts.	**35**	**11**	**10**		**20**	**12**	**4**	**3**	**94**
Did not enter	**0**	**0**	**0**		**0**	**0**	**0**	**0**	**0**
On study patients	**35**	**11**	**10**		**20**	**12**	**4**	**3**	**94**
On study patients/year	**7**	**2**	**2**		**4**	**2**	**1**	**-**	

* trial temporarily closed in May 2009
§ SJCH closed trial on 13 November 2007

Interfant-06



Klinische Studien bei seltenen Entitäten

- Infant ALL (< 1 J.): INTERFANT Studie
  - Deutschland: 16 Pat./J.
  - Österreich: 1 Pat./J.
  - **International: 90 Pat./J. (15 study groups)**

Klinische Studien bei seltenen Entitäten

- Infant ALL (< 1 J.): INTERFANT Studie
  - Deutschland: 16 Pat./J.
  - Österreich: 1 Pat./J.
  - **International: 90 Pat./J. (15 study groups)**
- Ph+ ALL

EsPhALL
Recruitment
(within December 31st, 2009)

	AIEOP	BFM-A	BFM-G	COALL	CPH	DCOG	FRALLE	MRC	NOPHO	Hong-Kong	PINDA	*total*
Expected pts. /year	8	1	10	3	1	3	4	9	4	2	4	49
Date of opening	01/04	05/04	04/05	05/05	01/04	02/04	12/05	05/04	03/04	10/07	09/08	
Date of first registered	01/04	06/04	05/05	05/05	01/04	02/04	12/05	05/04	03/04	01/08	11/08	
Registered pts.	50	4	51	7	9	16	20	40	23°	3	6	229
Not evaluable for eligibility	0	0	0	0	0	0	3	0	1	0	0	4
Not eligible pts.	5	0	3	0	0	2	1	0	1	0	0	12
Not entered pts.	18	3	7	0	0	2	1	1	0	0	0	32
On study patients	27	1	41	7	9	12	15	39	21	3	6	181

° 1 more patient diagnosed in 2007 (no consent to collection of any data)

- After 2005, authorization in BFM-A was withdrawn
- Enlargement to groups participating in the ALLIC protocol was decided in May 2007 in Brugge. As of April 2010, Hong-Kong and PINDA (Chile) have activated the protocol. In Serbia and Hungary agreement with Novartis for Imatinib supply was not reached.

Following tables refer to 181 on-study patients.

Klinische Studien bei seltenen Entitäten

- Infant ALL (< 1 J.): INTERFANT Studie
  - Deutschland: 16 Pat./J.
  - Österreich: 1 Pat./J.
  - **International: 90 Pat./J.**
- Ph+ ALL: ESPhALL Studie
  - Deutschland: 13 Pat./J.
  - Österreich: 1 Pat./J.
  - **International: 50 Pat./J. (11 study groups)**

Klinische Studien bei seltenen Entitäten

Infant ALL / Ph+ ALL

- Bei je ca. 15 Pat./J. sind (randomisierte) nationale Studien zur geprüften Therapieoptimierung für diese Entitäten NICHT möglich.
- Ergebnisverbesserung durch Einschluß in internationale Studien?
- Alternative: Einschluß in ALL Gesamtstudie (BFM: Praxis für Infant-ALL bis 1999 bzw. für Ph+ ALL bis 2005)

Klinische Studien in Gesamtentitäten

- **AIEOP-BFM ALL 2000 (vor EU CTD 2001 bzw. rev. AMG 2004)**
  - zwei getrennte Protokolle jeweils in Landessprache (Deutsch/italienisch)
  - gleiche Stratifizierung
  - (fast) identische Therapie
  - Vorbereitungszeit: 2 Jahre (z. T. überbrückt durch „Pilotphase ALL-BFM 1999“)

Klinische Studien in Gesamtentitäten

- **AIEOP-BFM ALL 2000 (D/Ö/CH/I)**
  - **4741 Pat. (1.7.2000-31.7.2006, ohne Ph+) (= ca. 800/J.)**
  - **127 Teilnehmerkliniken**
- Vorteile:
  - Internationale Sichtbarkeit hoch
  - 4 randomisierte Fragen möglich in 5 Jahren (verlängert auf 6 Jahre)
  - Umfangreiche Analysen in Subgruppen machbar
  - Wissenschaftliches Begleitprogramm dank langjähriger Kooperation hocheffektiv (Proben-/ Datenaustausch; Validierung neuer Marker etc)
- Nachteile:
  - Hoher organisatorischer Aufwand/Abstimmungsbedarf
  - Diagnostik nicht einheitlich (Beispiel Zytogenetik)
  - Toxizitätserfassung/SAE nicht einheitlich
  - Therapieergebnisse heterogen

Klinische Studien in Gesamtentitäten

- **AIEOP-BFM ALL 2009** (lt. EU-CTD2001/ neues AMG)
  - Geplante Rekrutierung: **990 Pat./J.**
  - 3 randomisierte Studienfragen
  - Internationaler Sponsor (Kiel), 7 nationale Koordinatoren
  - Studienkliniken in 7 Ländern (D/A/CH/I/CZ/INS/AUS)
  - 2 Datenbanken (Kiel, Mailand)

International structure of trial AIEOP-BFM ALL 2009

Collaborative groups: National Coordinators / represented by

- AIEOP: AIEOP Bologna / V. Conter, Monza, Italy
- BFM-A: St. Anna Children‘s Hospital, Vienna / G. Mann, Vienna, Austria
- BFM-G: UK S-H Kiel / M. Schrappe, Kiel, Germany
- BFM-CH: Univ. Children‘s Hosp. Zürich / F. Niggli, Zürich, Switzerland
- CPH: Univ. Hosp. Prague / J. Stary, Prague, Czech Republic
- INS: Tel Aviv / B. Stark, Tel Aviv, Israel
- AUS: Sydney / L. D‘Pozza, Sydney, Australia

International Sponsor: UKSH (Kiel)
Coordinating Principal Investigator: M. Schrappe

DSMC

Trial Steering Committee (TSC)
Each group repr. by nat. coordinator

Trial Data Analysis Com.
M.-G. Valsecchi, Monza, Italy
M. Zimmermann, Hannover, Germany

Trial Research Committee (TRC)
J.P. Bourquin, G. Cazzaniga, S. Izraeli, R. Panzer, *M. Stanulla*, R. Sutton, J. Trka

Trial Diagnostics Committee (TDC)
(Coordinators below)

Pharmacology of ASP‘ase
C. Rizzari, J. Boos

PCR-MRD (QC in ESG-MRD)
through ESG network

Cyto- and molecular genetics
J. Harbott

Immunphenotyping and FCM-MRD
M. Dworzak

Klinische Studien in Gesamtentitäten

AIEOP-BFM ALL 2009 (lt. EU CTD/ neues AMG)

- Vorteile:
  - Große internationale Sichtbarkeit
  - Einheitliches Studienprotokoll (englisch; auch Fassungen auf Deutsch und Italienisch)
  - Hohe Patientenzahl erlaubt randomisierte Fragen
  - Koordinierte Begleitforschung

- Nachteile:
  - Lange Vorlaufzeit wegen
    - Abstimmung mit Partnern,
    - zur Abarbeitung aller Formalien,
    - zur Erstellung einer international nutzbaren Datenbank
    - Klärung zur Patientenversicherung (uneinheitlich)
    - Verträge zw. Sponsor und Studiengruppen uneinheitlich und in der Vorbereitung/Abstimmung sehr zeitaufwändig
  - Verzögerter Studienstart aufgrund der organisat. Anforderungen

AIEOP-BFM ALL 2009: Patient recruitment by group

(patients included with date of diagnosis until 31.10.2011)

	start patient recruitment	patients recruited	*expected* recruitment per year	*actual* recruitment per year*
AIEOP (Italy)	01.10.10	182	340	168
ANZCHOG (Australia)	01.12.11	-	(70)	n.a.
BFM-A (Austria)	01.12.10	56	50	62
BFM-G (Germany)	01.06.10	503	370	355
BFM-CH (Switzerland)	01.12.10	20	30	22
CPH (Czech Republic)	01.12.10	67	60	73
INS (Israel)	01.04.11	13	70	22
all		841	920 (990)	702

*as extrapolated on the basis of the patients recruited since start of the study

Good Clinical Practice ?

EU-Clinical Trials Directive EC 2001/20

L 121/34 EN Official Journal of the European Communities 1.5.2001

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 4 April 2001

on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

Non-commercial clinical trials
(Investigator initiated trials (IIT), research-lead trials)

- Definition according to the EU draft guidance on the specific modalities of „non-commercial clinical trials“ (2005):

  “Non-commercial clinical trials” are clinical trials conducted by researchers without the participation of the pharmaceutical industry...

- *“Non-commercial sponsors commonly study the “effectiveness” of a medicinal product compared to alternatives …*”

EU Clinical Trials Directive
Official Goals

- Improve protection of patients and reliabilty of research reporting
- Harmonise and increase the competitiveness of European clinical research

→ **Changes concern non-commercial as well as pharmaceutical industry clinical trials**

- If investigational medicinal products (IMPs) with marketing authorisation are used, some simplifications were realized for non-commercial clinical trials regarding
  - access to the IMPs
  - IMP-related data (SmPC instead of IMP Dossier)
  - labelling of the IMPs
  - documentation

Clinical Trials Directive slows registration of paediatric studies

For more information on the **EURAMOS1 trial** see http://www.euramos.org

Registration of new non-commercial paediatric trials in Europe essential for optimising paediatric treatments—has fallen since the Clinical Trials Directive 2001/20/EC was implemented, according to sarcoma experts meeting in Stuttgart, Germany (Nov 30–Dec 2, 2006). "Before implementation, 10–20 studies were opened per year in the UK, but this has now fallen to just a handful", says Kathy Pritchard-Jones (Royal Marsden Hospital, London, UK). "Treatment within a trial is associated with definite survival advantage and, with fewer trials available, we must fear cure rates in Europe will decline as a direct consequence of legislation which was originally intended to protect patients", Stefan Bielack (Olgahospital, Stuttgart, Germany) told *The Lancet Oncology* (*TLO*).

For more information on the **European Science Foundation** see http://www.esf.org

Because the 2001 legislation was a directive it became mandatory for European Union member states to adopt the legislation by May 2004. The directive's aim was to simplify and harmonise administrative procedures governing trials and to provide patient protection by setting pan-European legal standards. However, although stakeholders were slow to react initially, there has been growing concern about how this legislation might hamper the running of non-commercial academic trials, particularly those in children. "Trials in children are particularly disadvantaged because these cancers are often complex heterogenous diseases requiring complex multimodal treatments, and are rare diseases requiring wider international collaboration", says Jeremy Whelan (University College Hospital, London, UK). Many trials in children try to optimise treatment rather than test new drugs. Bielack notes: "these treatments for children are not lucrative and nobody is willing to finance the extra costs or to assist in managing the exponentially increased bureaucratic workload". According to Herbert Jürgens, from the University Children's Hospital in Muenster, Germany, the Commission Directive 2005/28/EC set-out guidelines for good clinical practice and addressed some of these initial concerns, but this later directive did not exempt trials optimising treatments from full compliance with the 2001 directive. Another issue Bielack told delegates at the Stuttgart meeting that the directive requires a single sponsor to take overall responsibility for initiating and managing the trial, including all of the legal, ethical, and financial aspects, thereby taking on all the liability for no commercial benefit. Furthermore, Jürgens told *TLO* that: 50–90% of medicines have never been evaluated in children and are classified as investigational medicinal products (IMPs) because they are often used outside their marketing indications. "The need for trials in children to develop paediatric medicines is gaining global recognition to avoid such off-label use, with its associated potential for inappropriate dosing and unforeseen adverse drug reactions".

Money is not available for trials in children

In any trial, the sponsor has to report suspected unexpected serious adverse reactions (SUSARs) associated with IMPs to the competent authority, to the ethics committee, and to all investigators within 15 days of knowledge of a non-fatal event. But in Germany, Bielack commented, another level of bureaucracy has been added: "the same reporting requirements are mandatory for SUSARs from other studies investigating the same IMP". He cites as an example the use of interferon in the EURAMOS1 trial—a multinational collaborative study in children with osteosarcoma, launched under the new directive, of which he is the co-ordinator. "Interferon is used in a multitude of completely unrelated diseases and in adults [including] elderly patients with significant comorbidity. From the experience of the first 10 months of our trial, we have extrapolated that 180 000 pages of often irrelevant information on SUSARs will be distributed throughout Germany. This is like a polymerase chain reaction for waste paper and is bound to lead to a desensitisation for any real toxic-effects data."

Nonetheless, those at the Stuttgart meeting acknowledged the directive has resulted in a better structuring of multinational trials, and they highlighted the success of EURAMOS1. According to Mariana Resnicoff (co-ordinator of the European Science Foundation's European Collaborative Research Programme on pan-European Clinical Trials that provided funding for EURAMOS), "the experience gathered by the EURAMOS investigators could serve to pave the way for future pan-European academic clinical trials". Bielack agrees: "the EURAMOS group has developed strategies to deal with issues such as sponsorship and pharmacovigilance that might be applied to other trials and a single European safety desk for paediatric oncology trials should be considered".

To help future trials in Europe, the European Medical Research Councils are participating in a consultation initiated by the European Commission–Directorate General Enterprise and Industry on a paper *Draft guidance on specific modalities for non-commercial trials*, which is due to be released for comment in June 2006.

Emma Cannell

Tied up in red tape, European trials shut down

TRIAL AND ERROR

The European Clinical Trials Directive has created bureaucratic nightmares and is shutting down trials. Since the directive's launch:

Increase in the cost of academic cancer trials in the UK	200%
Drop in academic drug trials in Finland	75%
Drop in academic trial submissions in Ireland	70%
Increase in the cost of trials supported by EORTC	85%
New trials supported in 2004 by the group	19
New trials supported in 2005 by the group	7

Sources: Cancer Research UK; *Brit. Med. J.*; EORTC

Beispiel *INTERFANT-06*

Internationale Studie zur Behandlung der ALL bei Säuglingen (< 1 Jahr)

EU Clinical Trials Directive
Consequences

- More requirements regarding
  - procedure of approval by authorities and ethical committees
  - trial insurance
  - quality assurance and quality control
  - pharmacovigilance
  - validation of data acquisition systems
  - data archiving

→ resulting in higher administrative efforts and costs

Initiation procedure of INTERFANT 06 in Germany

Preparation of submission to authorities and ethics committees

- Finalisation of the German protocol part
  → size of the complete final protocol version: 317 pages (including SmPCs) (INTERFANT 99: 150 pages)
- Patient information: 18 pages (INTERFANT 99: 4 pages)
- Collection of the qualification documents of study clinics (n=47) and investigators (n=150); documents complete about one year later → ~1000 pages
- [Application to the Deutsche Krebshilfe for funding (~9 months)]
- Attempt to conclude the trial insurance using the inexpensive master policy of the German Cancer Association failed because SCT is included in the protocol (although all pts. undergoing SCT (estimated no. per year: 2-3) will in fact enter trial ALL-SZT BFM 2003).
  → **Costs for 65 patients: 27.887,- € (instead of 1980,- €)**

Initiation procedure of INTERFANT 06 in Germany

Submission to the authorities

- Submission of the protocol to the authorities (15.01.08):
  - authority primarily concerned: Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
  - Paul-Ehrlich-Institut (competent authority for clinical trials with sera, blood products...) also involved (hematopoietic stem cells, ATG)
- <u>Submitted documents:</u>
  - Application form *Module 1* (315 pages)
  - Trial protocol (317 pages)
  - some other documents

  } x 4

  → **Submission of ~2560 pages**
- all administered drugs (supportive therapy excluded) were regarded as investigational medicinal products (IMPs)
  → **28 IMPs** (considering different pharmaceutical forms)

Initiation procedure of INTERFANT 06 in Germany

Submission to the Ethics Committees

- Submission of the protocol to the ethics committees (EC) (15.01.08):
  - EC in charge (Kiel)
  - 35 involved EC

  } → for 47 trial sites
- Charges by the involved EC: 0,- to 1300,- € → ~ 6000,- €
- <u>Submitted documents:</u>
  - Application form *Module 1* (315 pages)
  - Application form *Module 2* (8 pages)
  - Trial protocol (317 pages)
  - some other documents (18 pages)

  } x 79
  - investigator/trial site qualification docs (3000 pages)

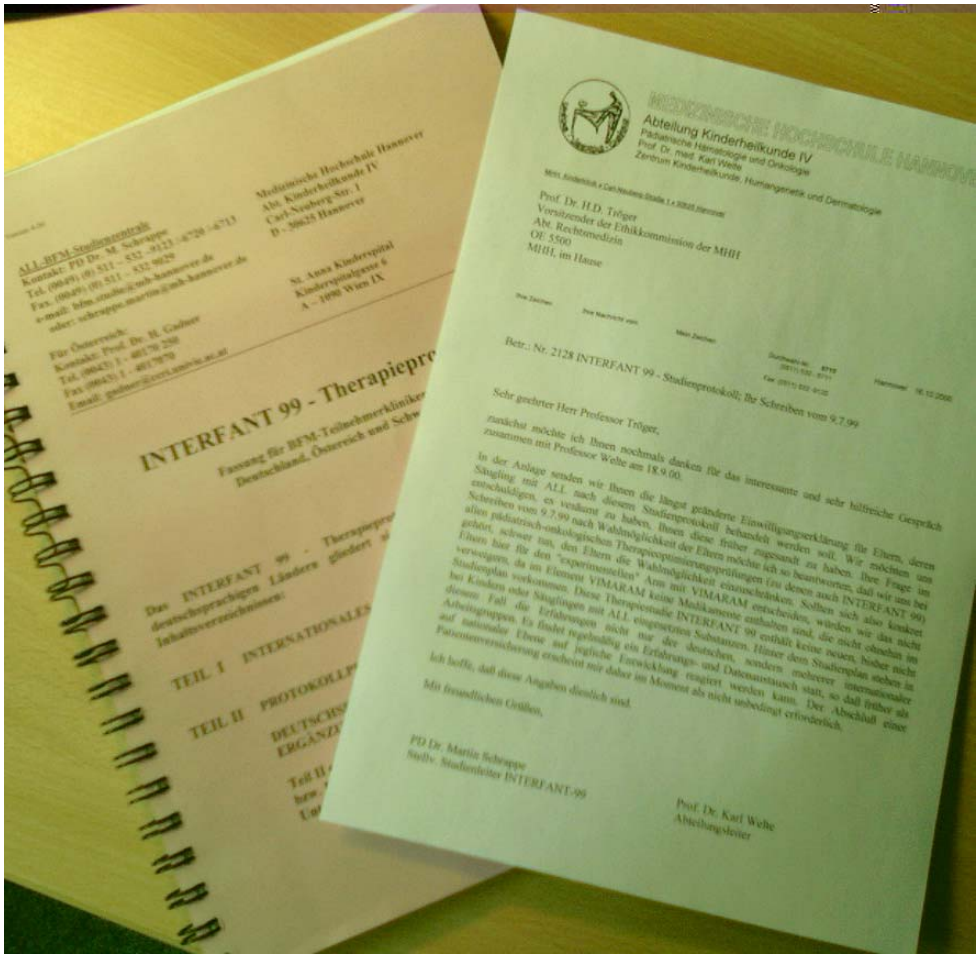
  → **~ 55,000 pages**
- + 36 CD-ROMs (1 per EC)

INTERFANT-06
Patientenzahl

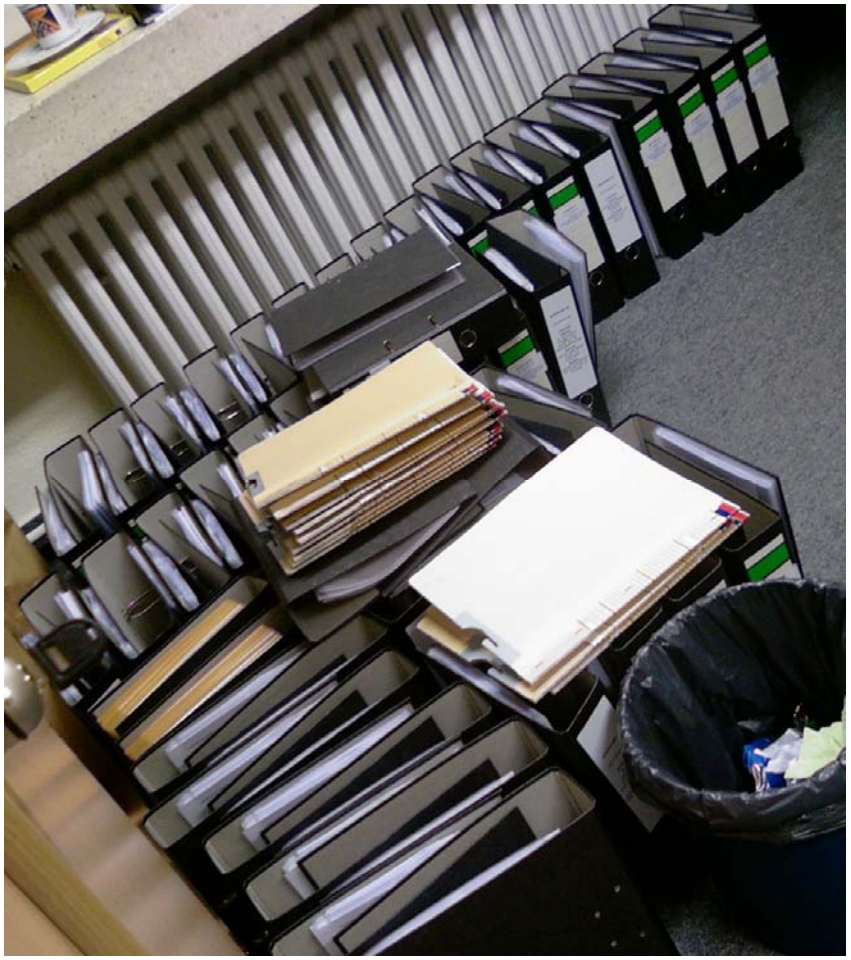
89 p.a.

Submission of an IDCT to the Ethics Committees (INTERFANT trial)

1999



2008

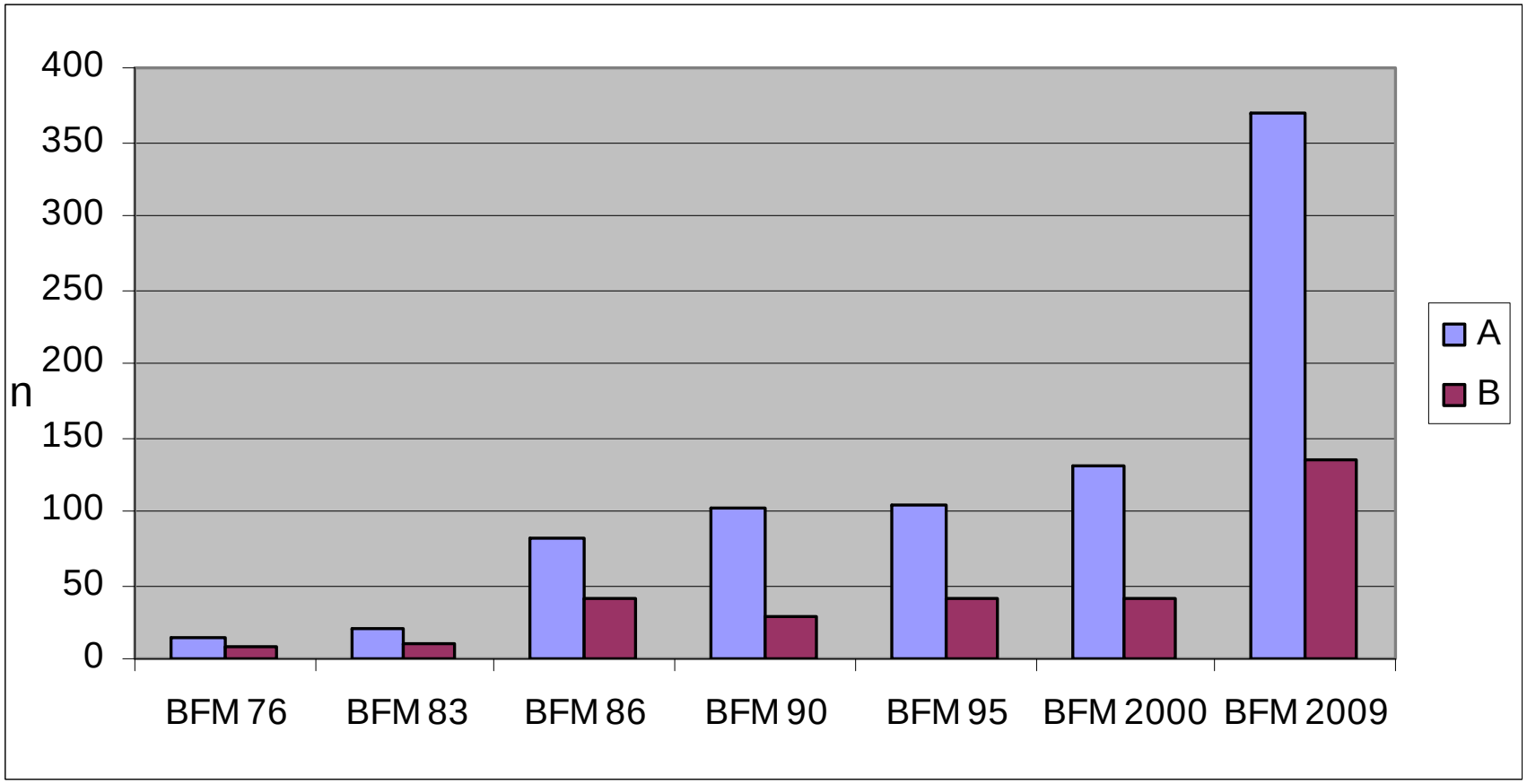


Initiation procedure of INTERFANT 06 in Germany

Remarks by the BfArM (and PEI)

- Initial formal complaints (corrected by 18.02.08):
  - *„Complete documents have to be submitted regarding production and application of the stem cells.“*
  - *„A statement is required, why the study shall recruit underage patients.“* (According to the AMG the conduction of a clinical trial in underage patients is only allowed if sufficient results can not be expected when conducting the trial in adult patients ...)
  - German label for the drug *Erwinase* was required.

ALL-Studien der BFM Studiengruppe



Was ist A, was ist B?

What is „n“?

Regulatory Approval

Sponsor

Regulatory Approval

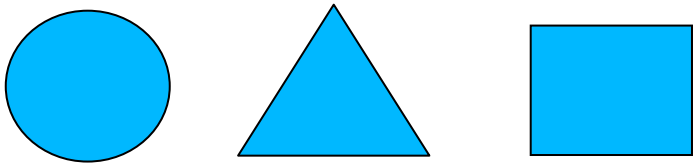
Sponsor

Sponsor

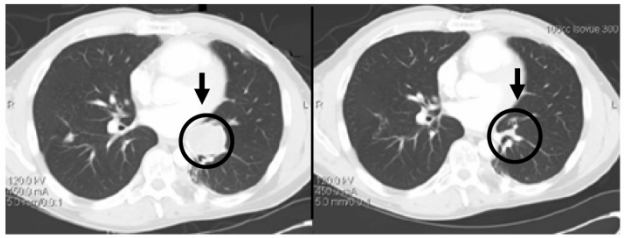
National Regulatory Approval

National Regulatory Approval

Standard Tumor Therapy

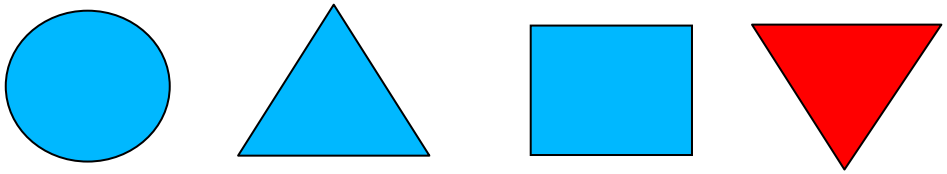


Promising Drug

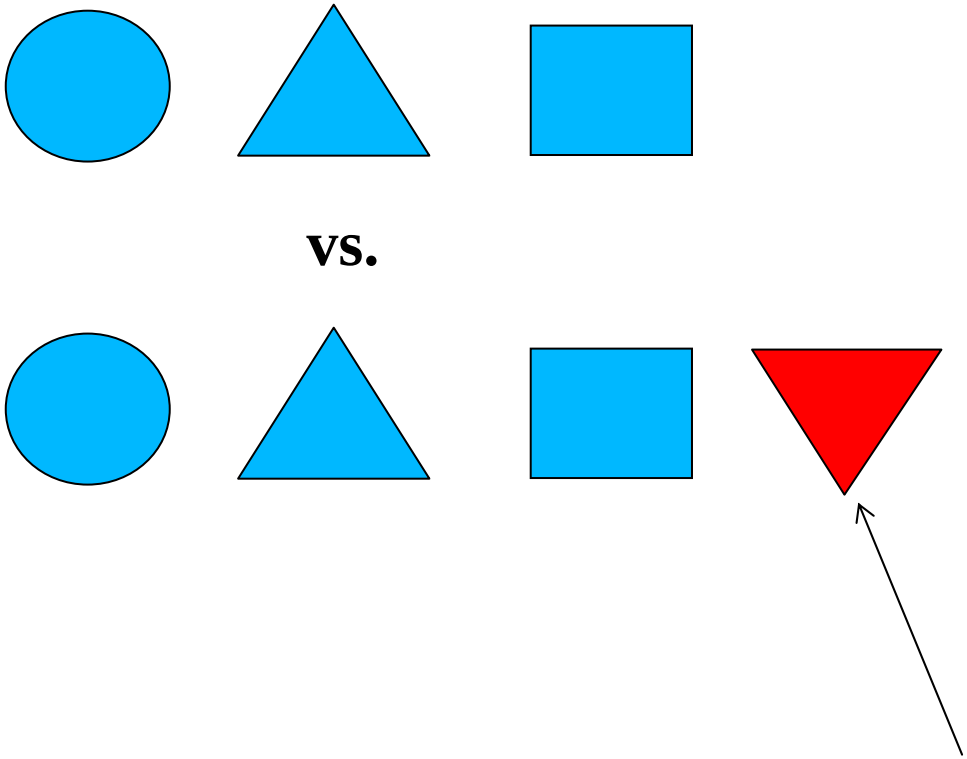


IMP
=
Investigational Medical Product

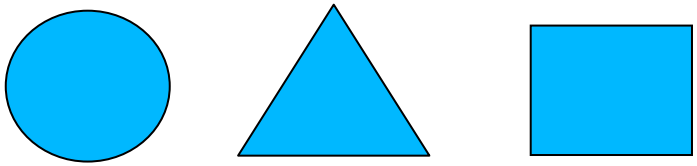
New Combination Regimen



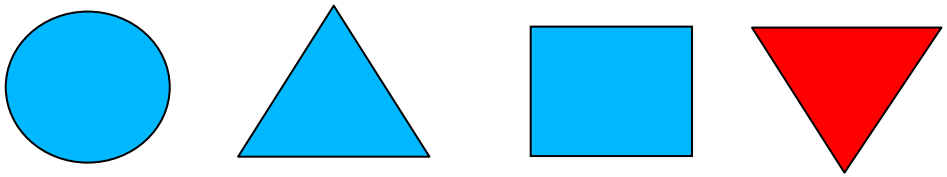
Randomized Trial

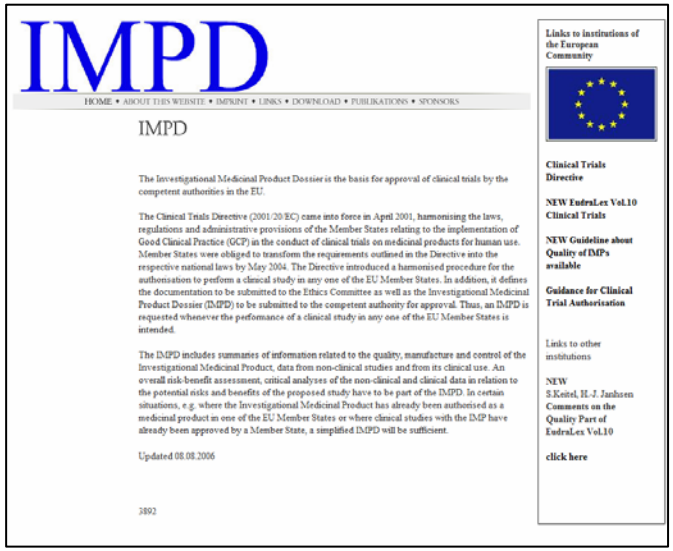


Randomized Trial



vs.





IMP
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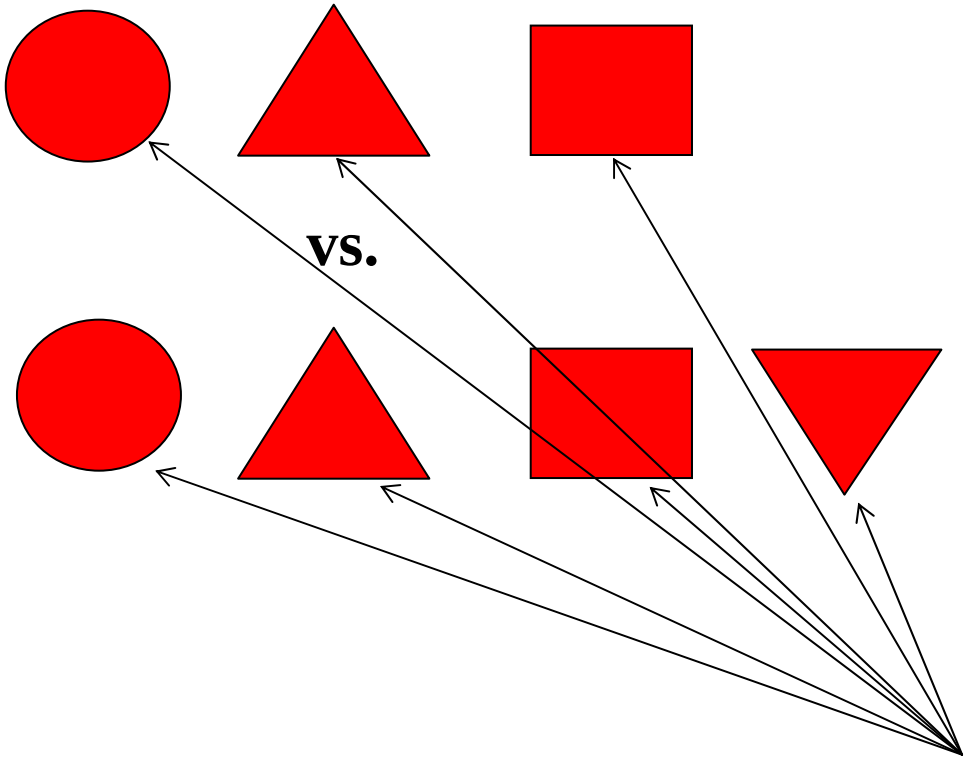
Investigational Medical Product

Randomized Trial



IMP
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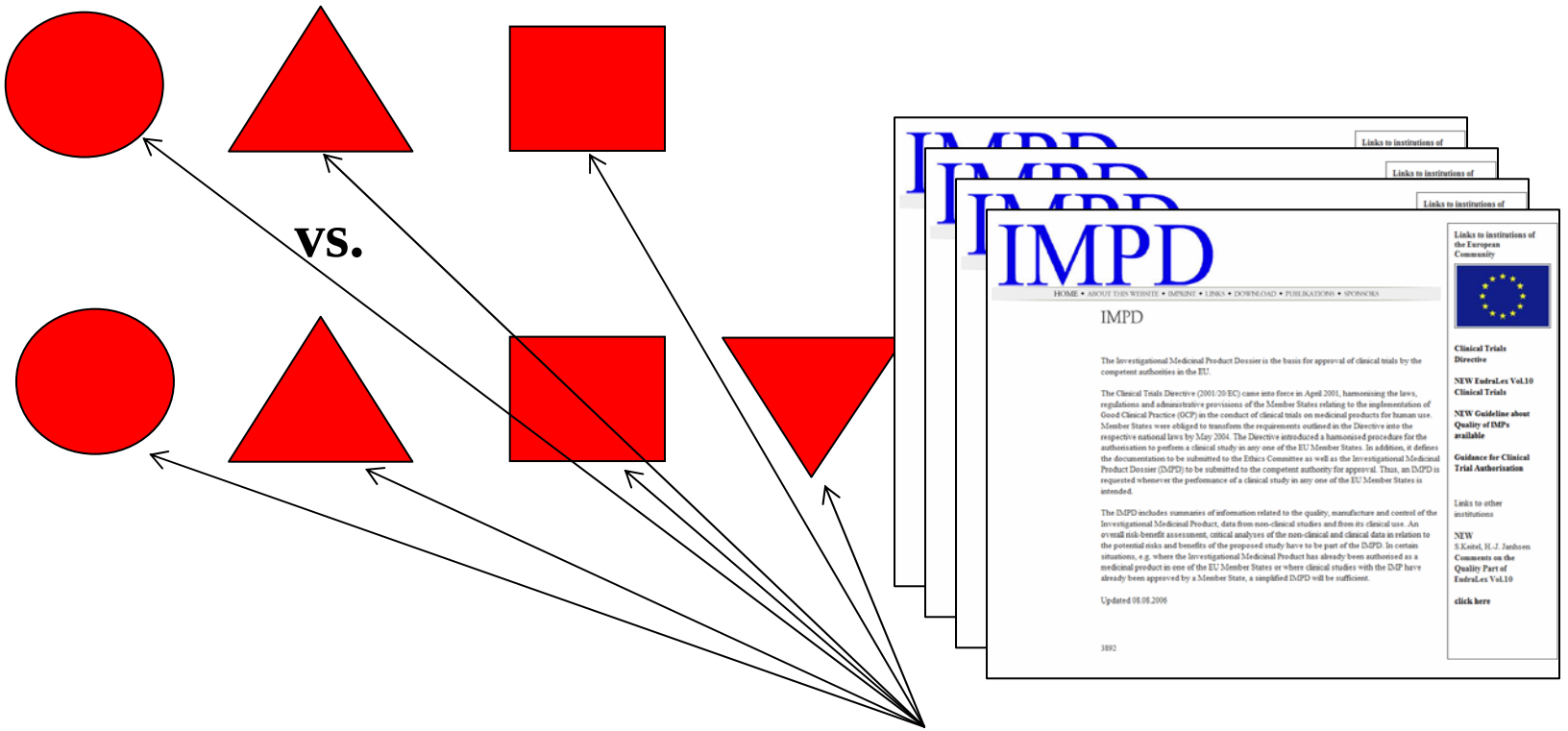
Investigational Medical Product

Randomized Trial



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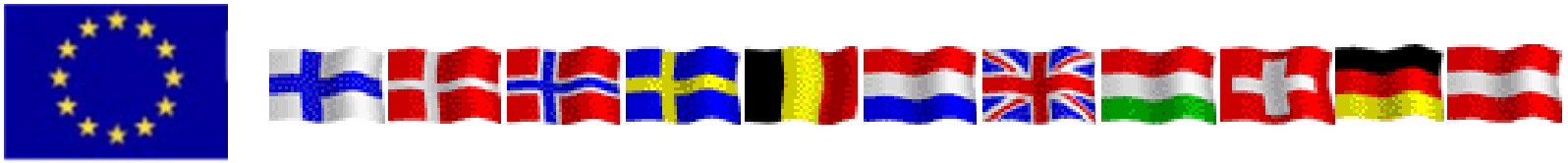
Investigational Medical Product

National Regulatory Approval

National Regulatory Approval



- ***Multiple submissions & re-submissions***
- ***“Worst” national interpretation applicable for all***

Ethics approval

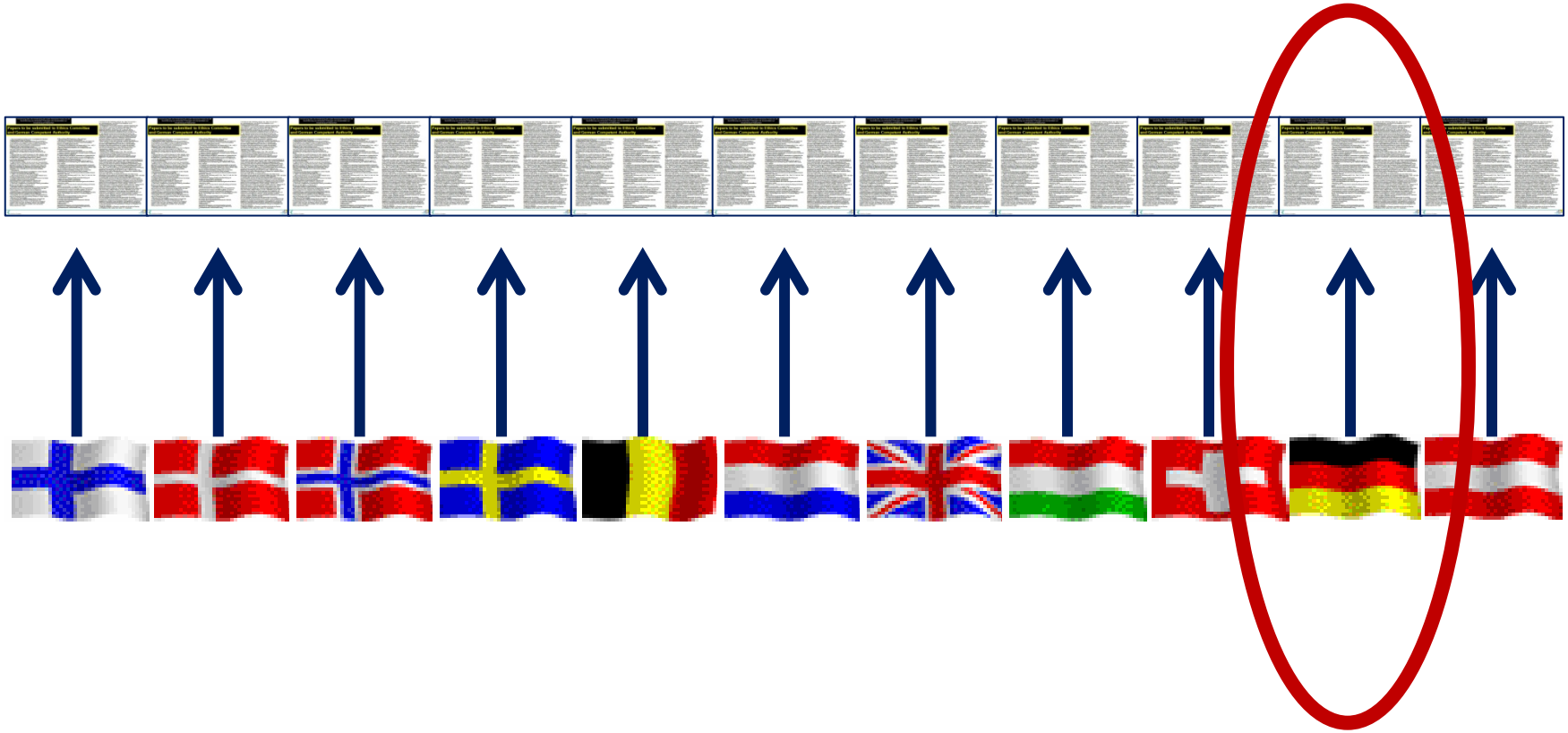
“single opinion per member state”

ethical interpretations vary

participation of children in trials:
very heterogeneous requirements

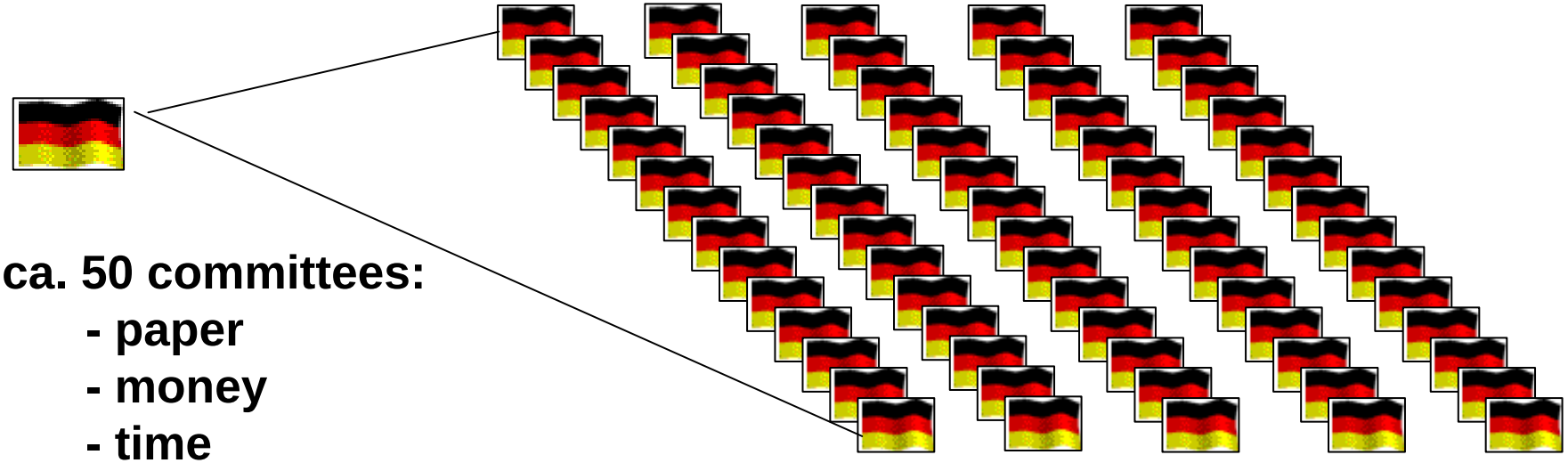
Ethics Approval

“single opinion per member state”



Ethics Approval

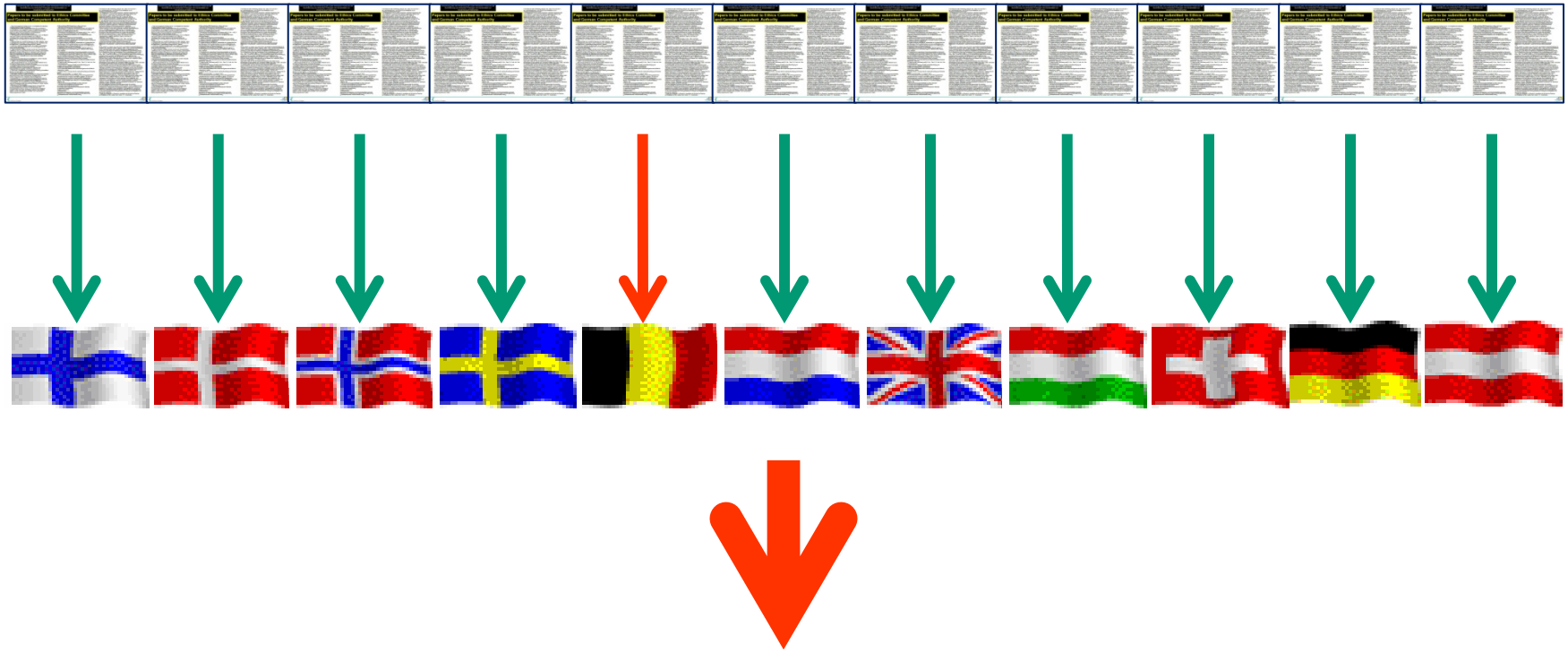
“single opinion per member state”



ca. 50 committees:

- **paper**
- **money**
- **time**
- **nerves**

Ethics Appoval

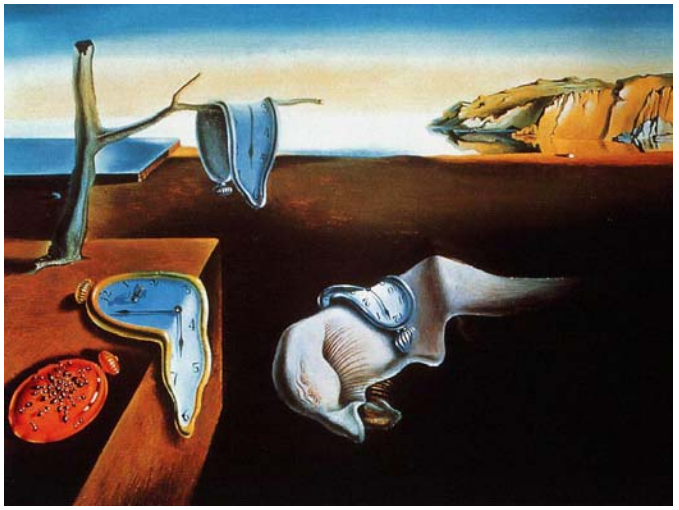


Trial Approval

- National Competent Authorities
- Ethics Committees

- Regional Competent Authorities
- Science Funders
- Insurance Companies
- Learned Societies
- Drug evaluation bodies
- ……
- ……

Trial Approval



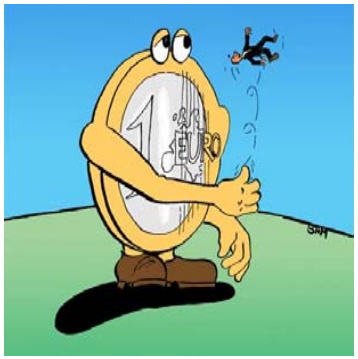
multiple submissions
resubmissions
re-resubmissions
re-re-resubmissions

of redundant, “unnecessary” information

in multiple, semi-similar formats **(templates, languages, paper or electronic)**

to multiple, semi-useful institutions

with multiple, semi-compatible interests



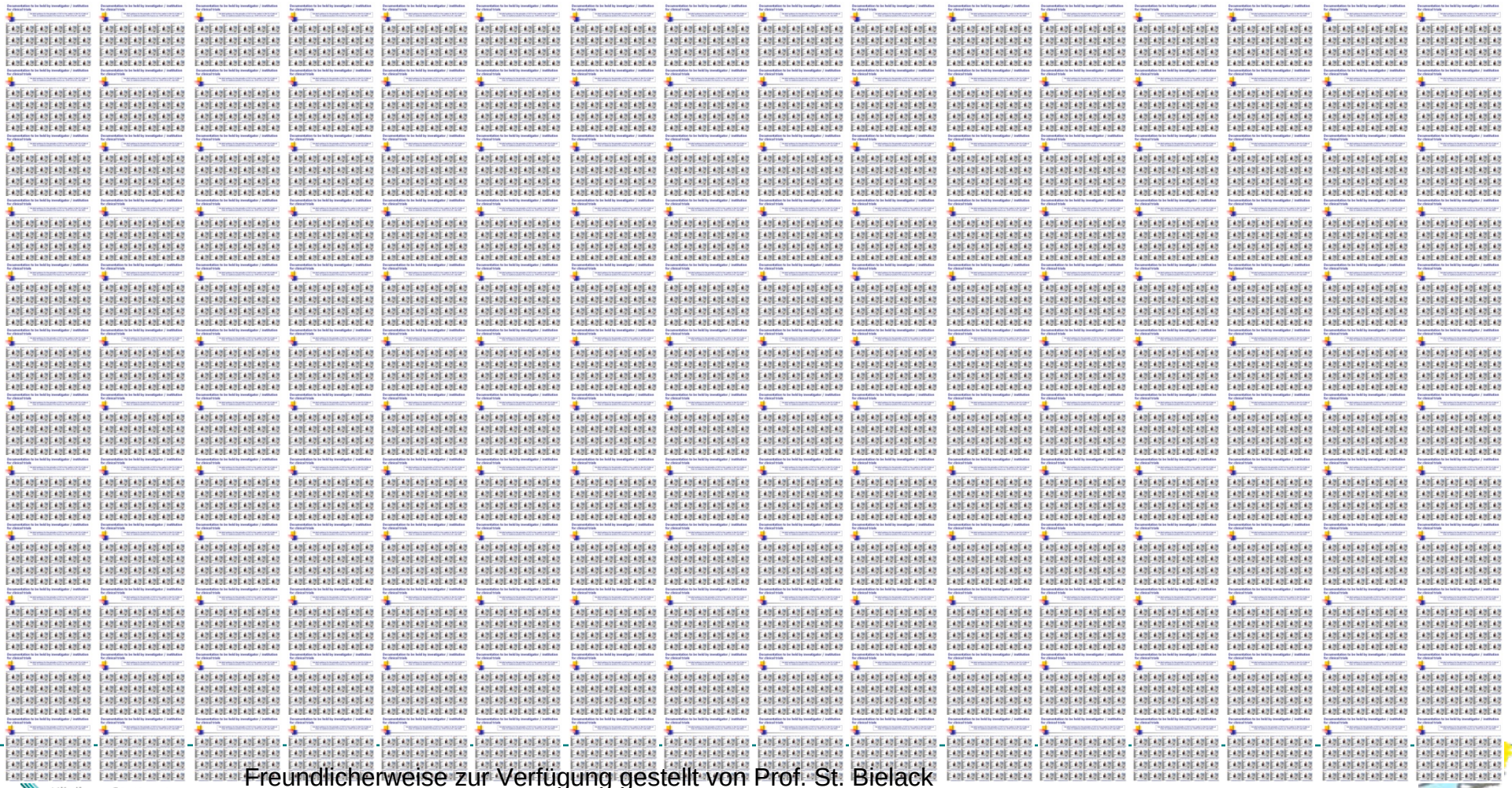
Documentation to be held by investigator / institution for clinical trials

Detailed guidance for the principles of GCP in the conduct in the EU of clinical trials on medicinal products for human use. ENTR/6416/01, July 2002

- Investigators brochure (+ updates) or SmPC
- Protocol and amendments (signed)
- Information sheet and consent form (+ updates)
- Financial aspects
- Insurance statements
- Signed agreements between parties
- EC opinion and composition
- MRHA authorisation
- Investigators CVs
- Medical and laboratory tests, including normal ranges
- Medicine labels
- Instructions for medicine use
- Shipping records
- Certificates of analysis
- Decoding procedures
- Master randomisation list
- Monitoring reports (pre-trial, initiation, close-out etc)
- List of persons responsibilities delegated to (+ updates)
- CRFs and corrections
- SAE notifications from investigators and to EC and MRHA
- EC/MRHA annual reports and final reports
- Subject screening log
- Subject identification code list
- Subject enrolment log
- IMP accountability at site
- Record of retained tissues
- Documentation of IMP destruction
- Completed subject identification code list
- Audit certificate
- Clinical study report

Documentation to be held by investigator / institution for clinical trials

Detailed guidance for the principles of GCP in the conduct in the EU of clinical trials on medicinal products for human use. ENTR/6416/01, July 2002



Safety information, collection, reporting and review of safety information

unbelievably & unneccessarily complex

Expedited reporting

- **multiple national (re-)submissions diverse formats & procedures**

- **no check for relevance of content, too many recipients, national peculiarities**

=> too much garbage to too many recipients

VOLUME 28 · NUMBER 17 · JUNE 10 2010

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Equipoise Lost: Ethics, Costs, and the Regulation of Cancer Clinical Research

David J. Stewart, Simon N. Whitney, and Razelle Kurzrock

Table 1. Costs per Year of Life Gained by Selected Interventions

Procedure	Cost/Life-Year Saved*
Clinical trials regulations	$2,700,000
Hemodialysis[29]	$43,000-$104,000
Statins for heart disease (moderate- to high-risk patients)[30]	$19,000-$25,000
Colorectal cancer screening by colonoscopy[32]	$14,000
Adjuvant trastuzumab breast cancer[31]	$20,000
Bevacizumab advanced non–small-cell lung cancer[33]	$380,000
Paclitaxel/cisplatin for advanced ovarian cancer[34]	$26,000

*Converted to 2009 US dollars using an online inflation calculator.[35]

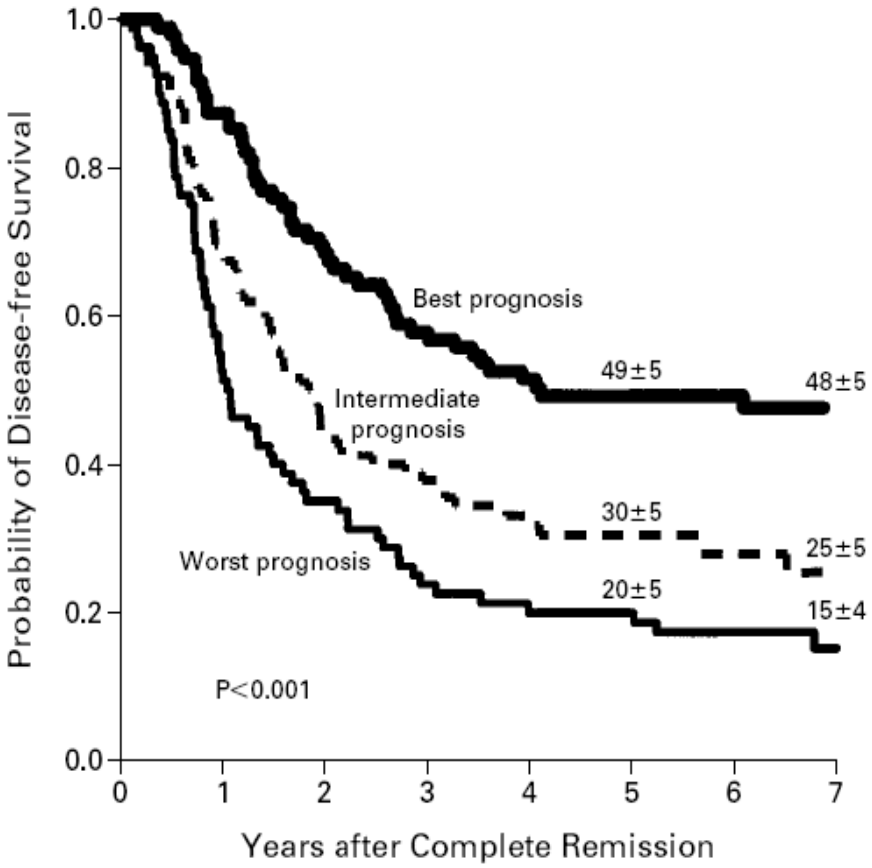
Was tun?

Klinische Forschung fortsetzen

Ziele und Inhalte definieren

OUTCOME OF TREATMENT IN CHILDREN WITH PHILADELPHIA CHROMOSOME–POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

N Engl J Med 2000;342:998-1006



PATIENTS AT RISK

Best prognosis	95	83	65	55	46	39	32	22
Intermediate prognosis	92	64	40	33	25	14	11	9
Worst prognosis	80	42	28	19	16	15	10	5

Best prognosis: age <= 10y, and WBC < 50,000
Intermediate prognosis: age >10y, or WBC 50-100,000
Worst prognosis: any age but WBC >100,000

Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia

James B. Nachman,[1] Nyla A. Heerema,[2] Harland Sather,[3] Bruce Camitta,[4] Erik Forestier,[5] Christine J. Harrison,[6] Nicole Dastugue,[7] Martin Schrappe,[8] Ching-Hon Pui,[9] Giuseppe Basso,[10] Lewis B. Silverman,[11] and Gritta E. Janka-Schaub[12]

BLOOD 110 (2007): 1112-1115

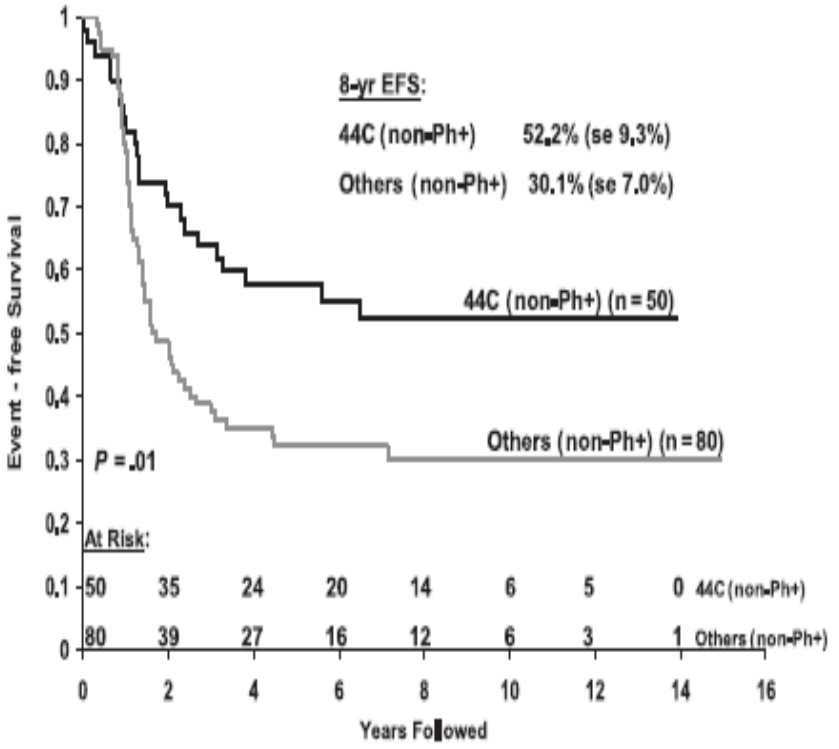


Figure 3. Comparison of EFS for non-Ph+ hypodiploid patients with 44 chromosomes or fewer than 44 chromosomes.

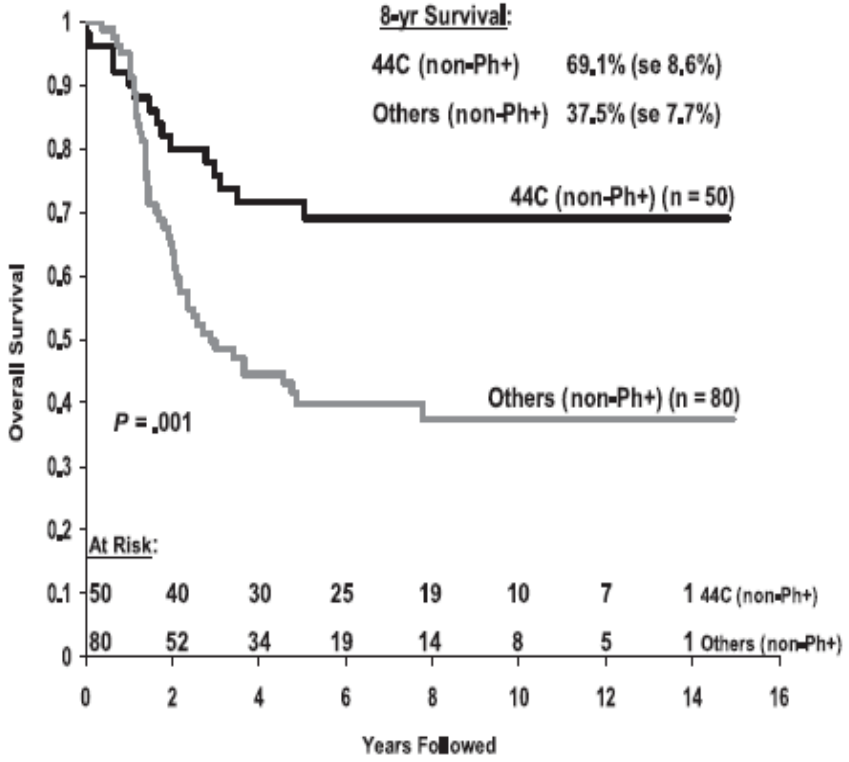


Figure 4. Comparison of survival for non-Ph+ hypodiploid patients with 44 chromosomes or fewer than 44 chromosomes.

Studiendaten nutzen

Long-term Follow-up:

Essentiell für die Nutzen-/Risiko-bewertung päd.-onkol. Therapieprogramme

Long-term results in 53291 ALL patients enrolled in clinical trials of major pediatric study groups (LEUKEMIA Vol. 24, 2010)

Study group	Period of enrollment	Age group eligible	No. of pts	No. of studies	Event-free survival at 10y[+]
AIEOP	1982-2000	≤ 15 y *	4865	5	**71.7 ± 1.3%**
BFM	1981-2000	< 18 y	6609	5	**78 ± 1.1%**
CCG	1983-2002	< 21 y	13298	16	**72.6 ± 2.9%**
COALL	1982-2003	< 18 y	1967	5	**76.3 ± 3.0%**
CPH	1990-2002	< 18 y	730	2	**72.1 ± 2.3%**
DCOG	1984-2004	< 18 y	1734	4	**70.0 ± 2.1%**
DFCI	1985-2000	< 18 y	1457	4	**80.8 ± 2.1%**
INS	1984-2003	< 18 y	786	3	**76.5 ± 2.4%[++]**
JCCLSG	1981-1993	< 18 y	1021	4	**63.4 ± 3.3%[#]**
NOPHO	1992-2007	1 - < 15 y	2668	2	**75.0 ± 1.0%**
POG	1984-2001	1 - < 22 y	7393	12	**73.2 ± 2.1%[§]**
SJCRH	1984-1999	≤ 18 y	1011	5	**77.6 ± 2.9%**
TCCSG	1984-1995	1 - < 15 y	1846	4	**75.0 ± 1.8%**
TPOG	1997-2007	≤ 18 y	1390	2	**72.5 ± 1.3%**
UK-WPCL	1980-2002	≤ 15 y	6516	4	**74.1 ± 1.0%**

[+] listed here are the best results reported by each study group; * < 18 y in trial AIEOP-95;
[++] at 8 years; [#] at 12 years; [§] only in B-lineage (10y-EFS in T-ALL was 72.2 ± 4.7%);

AIEOP: Associazione Italiana di Ematologia ed Oncologia Pediatrica (Italy); BFM: Berlin-Frankfurt-Münster ALL Study Group (Germany, Austria, Switzerland); CCG: Children's Cancer Group (USA); COALL: Cooperative ALL Study Group (Germany); DCOG: Dutch Childhood Oncology Group (Netherlands); DFCI: Dana-Farber Cancer Institute ALL Consortium (USA); INS: Israeli National Studies of childhood ALL; JCCLSG: Japanese Childhood Cancer and Leukemia Study Group; NOPHO: Nordic Society of Pediatric Hematology and Oncology; POG: Pediatric Oncology Group (USA); SJCRH: St. Jude Children's Research Hospital (USA); TCCSG: Tokyo Children's Cancer Study Group; TPOG: Taiwan Pediatric Oncology Group; UKALL: UK Medical Research Council Working Party on Childhood Leukaemia (U.K.).

Politisch aktiv werden

Pediatric Oncology in Europe

SIOP Europe

I-BFM group

Innovative Therapies for Children with Cancer ITCC European consortium

SIOPEL

SIOP Brain Tumour Group

EIC-NHL

SIOP Renal Tumour Study Group RTSG

EURAMOS I TRIAL

SIOPEN R NET

EuroEwing

EpSSG European Paediatric Soft Tissue Sarcoma Study Group

Hodgkin's lymphoma group

Myelodysplasia Group

Rare Cancers Group

Histiocyte society

EORTC Childhood Leukemia group

- 15 EU groups on solid tumors, hematological diseases, early drug development including joint programs with adult oncology
- A track record of high ranking publications

ICCCPO

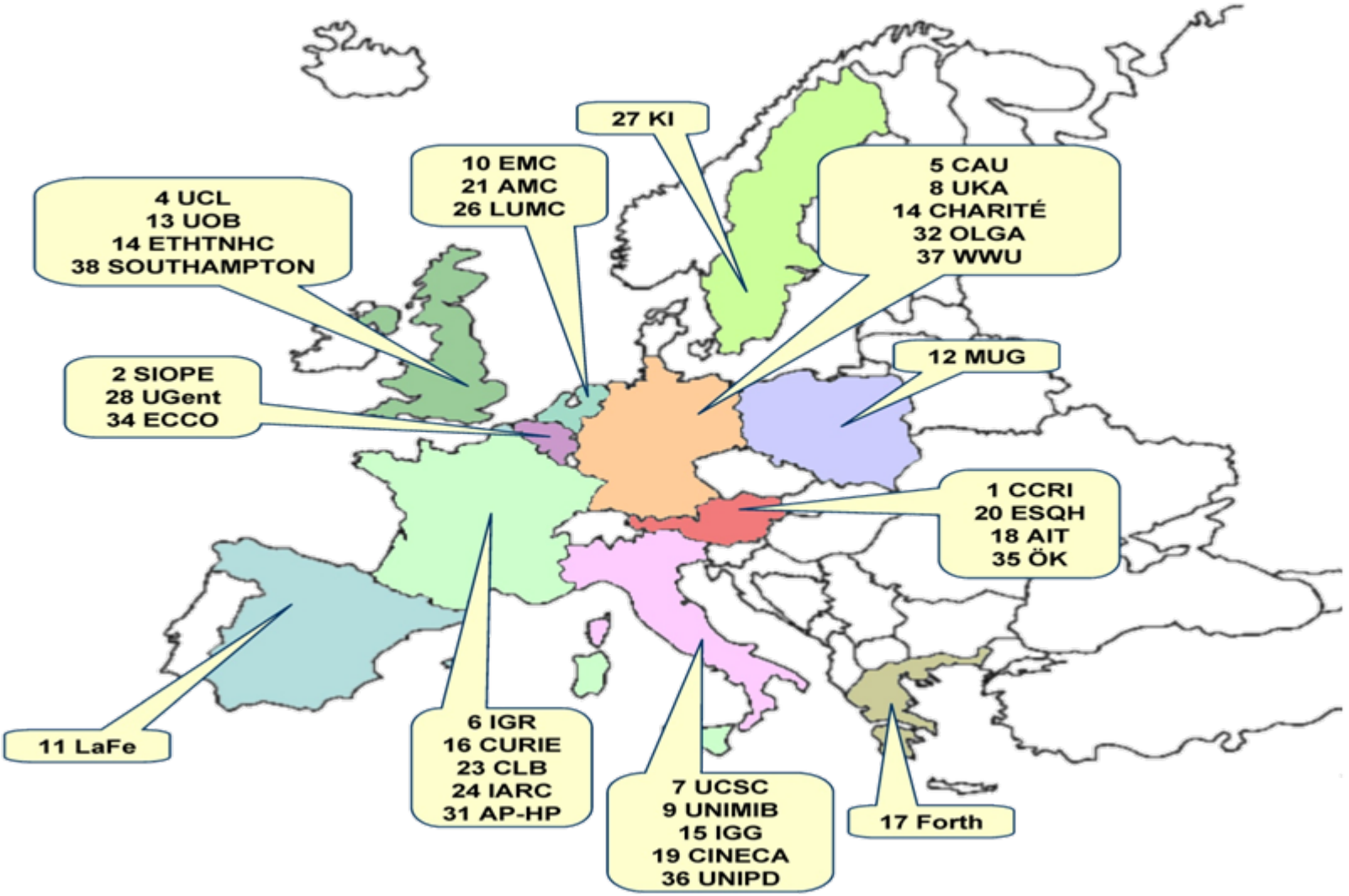
Parents Organisations

A Network of Excellence Structuring Clinical Research in Paediatric and Adolescent Oncology in Europe

HEALTH.2010.2.2.1-3

encca
European Network for Cancer research in Children and Adolescents

33 Partners -
11 European Countries-
18 WP – 80 Milestones – 82 Deliverables



The ENCCA Goals

- **To improve both cure and quality of cure of children and adolescents suffering of cancer**
- To facilitate access to
  - innovative therapies and tailored medicines
  - and standard care across Europe
- To develop biology-guided therapies
- **To propose a Virtual European Institute for Cancer Research in Children and Adolescent (sustainability)**

SEVENTH FRAMEWORK PROGRAMME

encca
European Network for Cancer research in Children and Adolescents

Joint Statement on EU-CTD

Necessary adjustments of the EU-CTD: Streamlined authorization and assessment of CTs

- Single clinical trial authorization (CTA): single EU portal for submitting all documents for multinational clinical trials
- Coordinated assessment procedure (CAP) for approval in all participating member states.
- Coordination of sponsorship
  - One sponsor – one EUDRACT number
  - Delegation of responsibilities from coordinating sponsor to international partners.
  - Liability for the trial in each national context is in the responsibility of the national partner.

Necessary adjustments of the EU-CTD: Risk adapted categories for clinical trials:

The potential risks should be balanced against the level of risk that a trial participant would be exposed to outside of the trial.

- **Type A = No higher than the risk of standard medical care ("off-label use is usually established practice and supported by published evidence or guidelines")**
- **Type B = Somewhat higher than the risk of standard medical care**
- **Type C = Markedly higher than the risk of standard medical care**
  - **Adapt insurance needs and costs accordingly**

Commissioner Dalli delivers speech on "Clinical Trials Directive – Meeting Patients' Needs"

John DALLI, European Commissioner for Health and Consumer Policy, attends a joint event organised by the European Federation of Pharmaceutical Industries and Associations and the Roche Group

Brussels, Belgium, 07 March 2012

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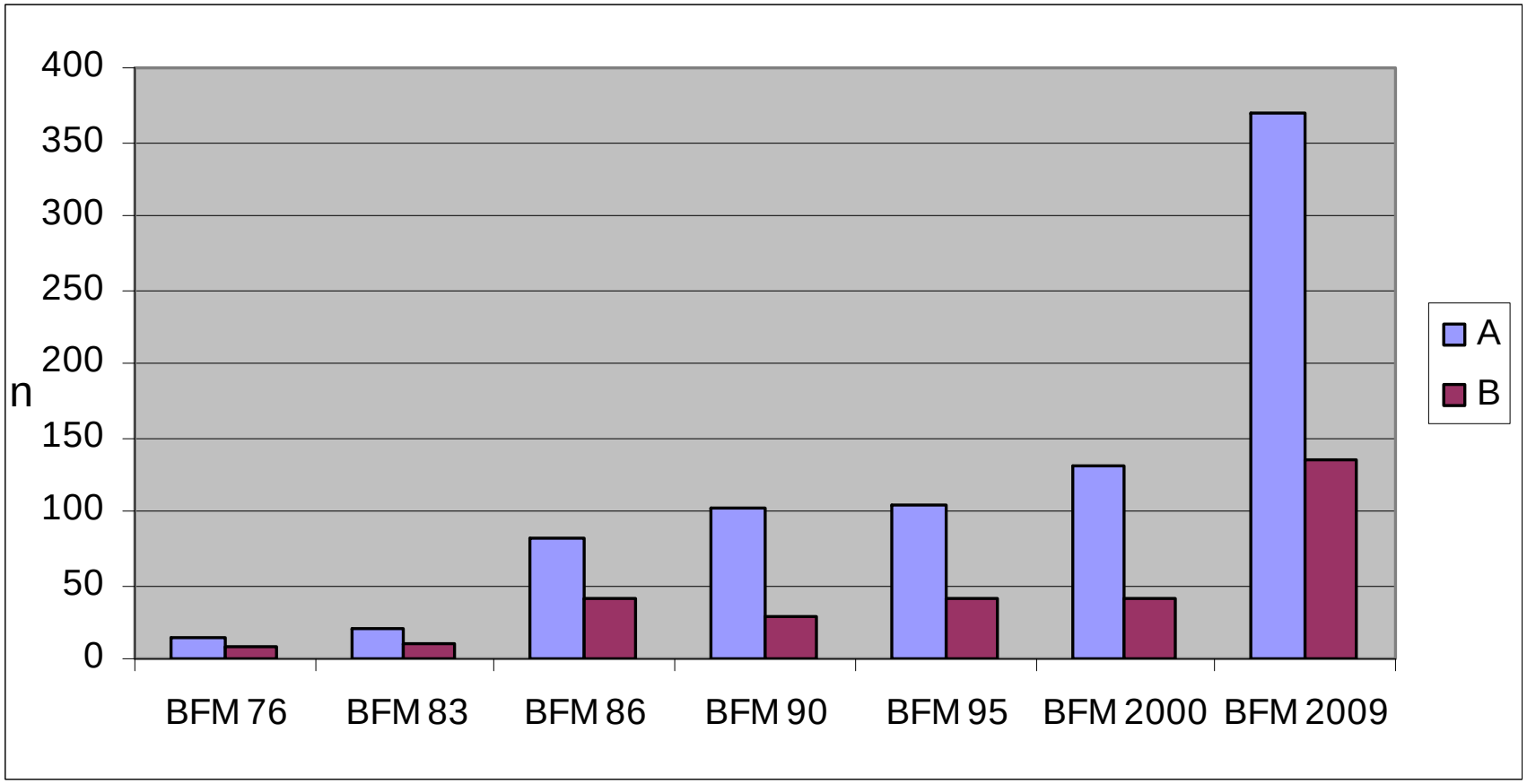

Was ist A, was ist B?

What is „n“?

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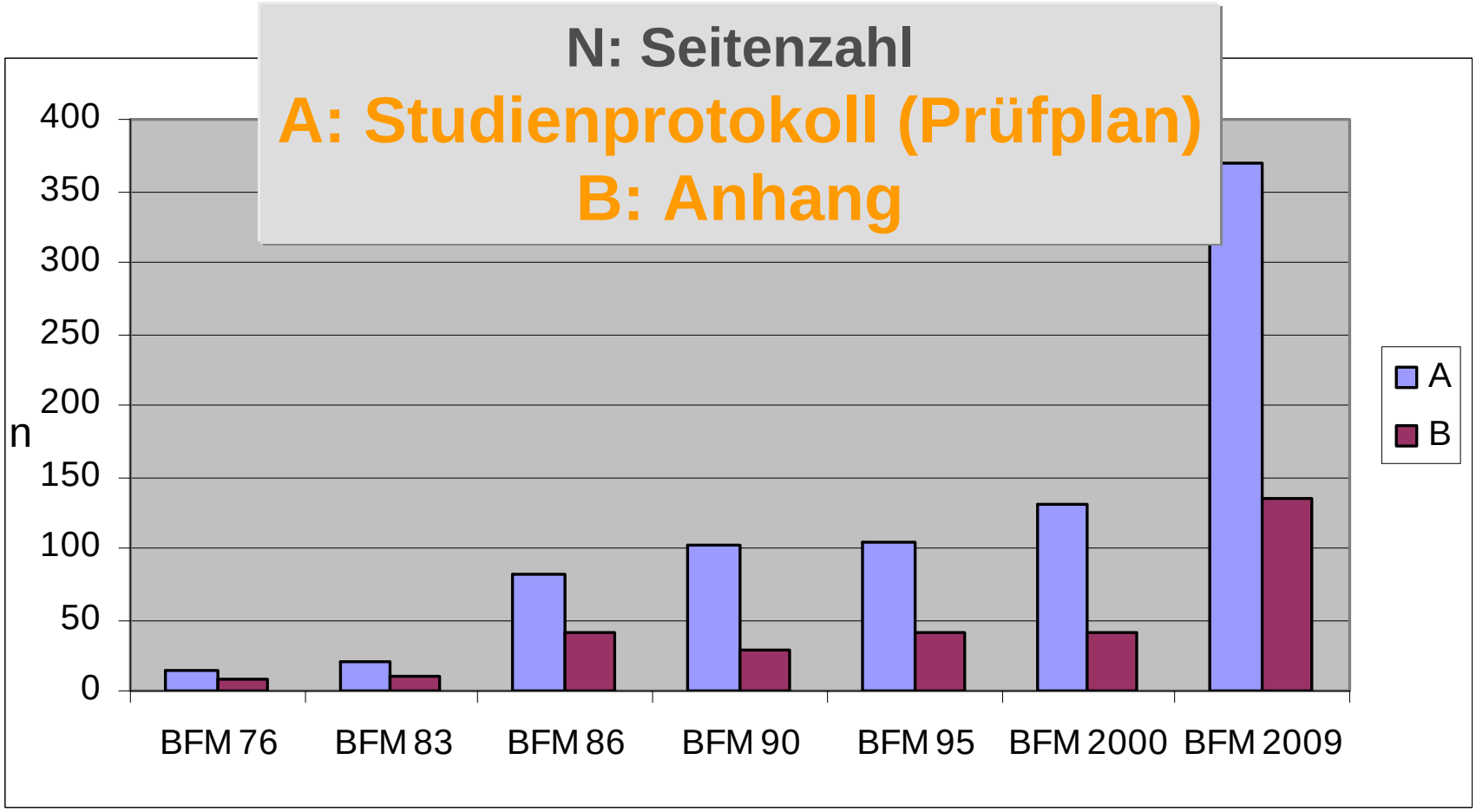

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