Ablauf, Risiken und ethische Vertretbarkeit von Phase-I-Studien

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Rank	Status	Study
1	Not yet recruiting	Intrathecal Pertuzumab and Trastuzumab in Patients With New Untreated Asymptomatic or Low Symptomatic Brain Metastasis in HER2 Positive Breast Cancer **Conditions:** HER2 Positive Untreated Metastatic Breast Cancer; Asymptomatic or Low Symptomatic Brain Metastasis in Breast Cancer **Interventions:** Drug: Pertuzumab; Drug: Trastuzumab
2	Not yet recruiting	Food Effect Study PF-04136309 **Condition:** Healthy **Intervention:** Drug: PF-04136309
3	Not yet recruiting	Seasonal Trivalent Inactivated Split Virion Influenza Vaccine Clinical Trial (IVACFLU-S) **Condition:** Influenza, Human **Interventions:** Biological: Trivalent Seasonal Influenza Vaccine; Biological: Placebo Comparator
4	Not yet recruiting	A Study of the Safety of Toca 511, a Retroviral Replicating Vector, Combined With Toca FC in Subjects With Newly Diagnosed High Grade Glioma Receiving Standard of Care **Condition:** Newly Diagnosed HGG **Interventions:** Biological: Toca 511; Drug: Toca FC
5	Recruiting	Metabolism and Pharmacokinetics of [14C]-BI 409306 After Administration as Oral Solution in Healthy Male Volunteers **Condition:** Healthy **Intervention:** Drug: 14C-BI 409306
6	Recruiting	Drug-Drug Interaction Study of Glucokinase Activator HMS5552 and Metformin in T2DM **Condition:** Type 2 Diabetes Mellitus **Interventions:** Drug: Metformin; Drug: HMS5552

Charakteristika Phase I Studien

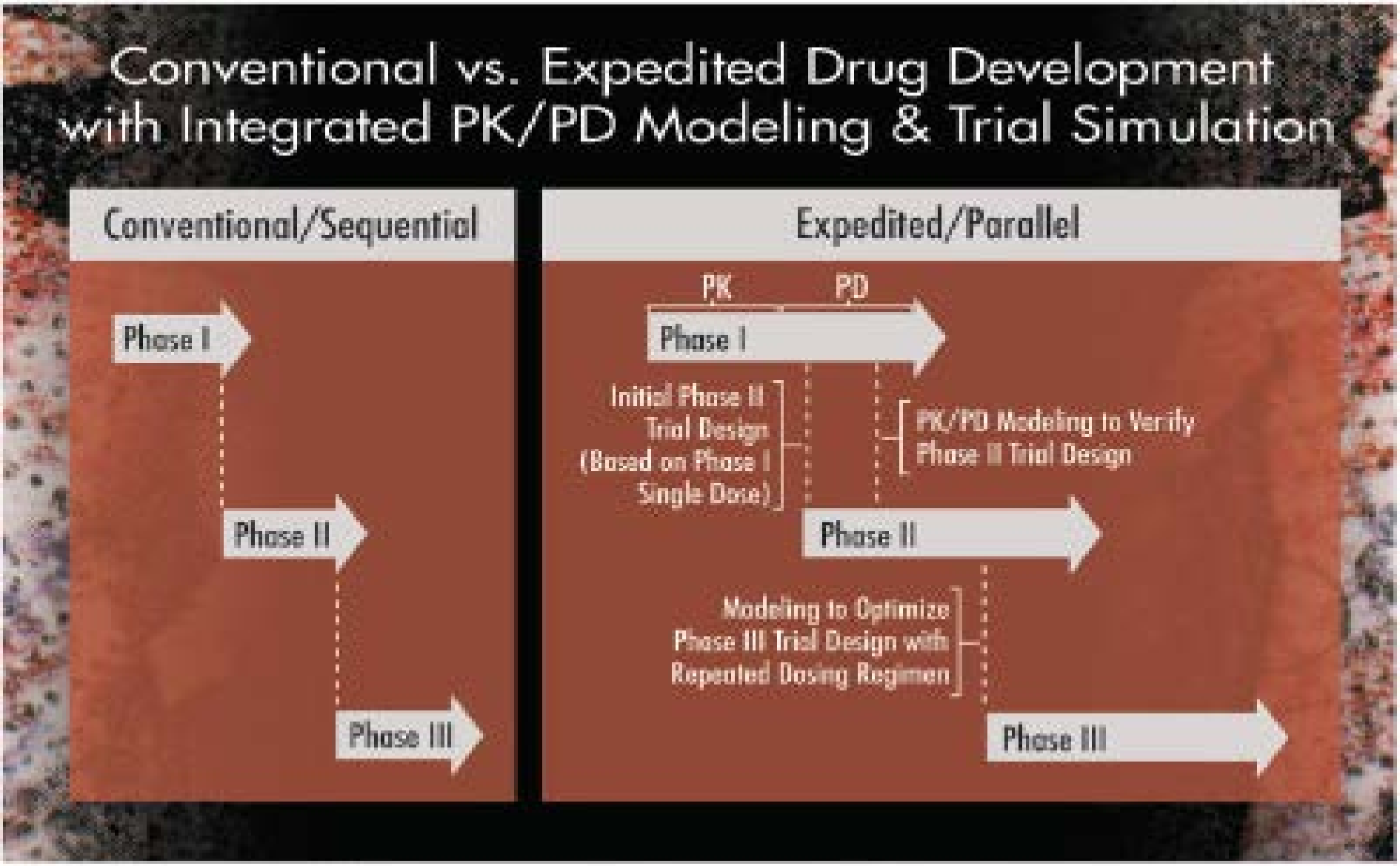
Zielstellung: Planung der Phase II und III, „Label“

- First in Human – Sicherheit und Verträglichkeit, Pharmakokinetik und ggf. auch Pharmakodynamik
  - gesunder Proband
  - Patient (i.d. Regel bei zytotoxischen o.ä. Substanzen)
- PK-PD bei Probanden (auch nach Zulassung, z.B. Interaktionen, Biopharmazie,…)
- PK-PD bei besonderen Patientenpopulationen (auch nach Zulassung, z.B. bei Leber- oder Nierenfunktionseinschränkung, Alter)

Behandlungsdauer: Einmaldosis oder kurzzeitige (5-7 Tage) Dauergabe (steady state)

- **„Proof of Concept“ kann Phase I oder auch frühe Phase II sein!**

“Faster Time to Market”



First in Human: Startdosis

1. No Observed Adverse Effect Level NOAEL:
   - < 1/10 der Menge, die im Tierversuch zu einer Nebenwirkung geführt hat
2. Bei MoAb u.a. Biologika auch Minimum Anticipated Biological Effect Level MABEL:
   - 1 - 3% der Menge, die eine Sättigung der Rezeptoroccupancy oder der Hemmung des Targetproteins in vitro entspricht

European Medicines Agency

London, 19 July 2007
Doc. Ref.EMEA/CHMP/SWP/28367/07

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

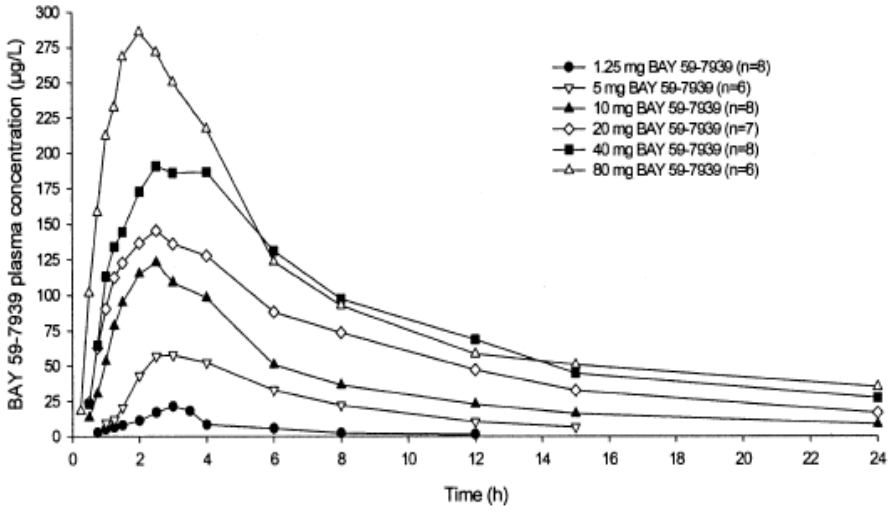
DRAFT AGREED BY CHMP EXPERT GROUP	6 March 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	22 March 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	23 May 2007
AGREED BY CHMP EXPERT GROUP	4 July 2007
ADOPTION BY CHMP	19 July 2007
DATE FOR COMING INTO EFFECT	1 September 2007

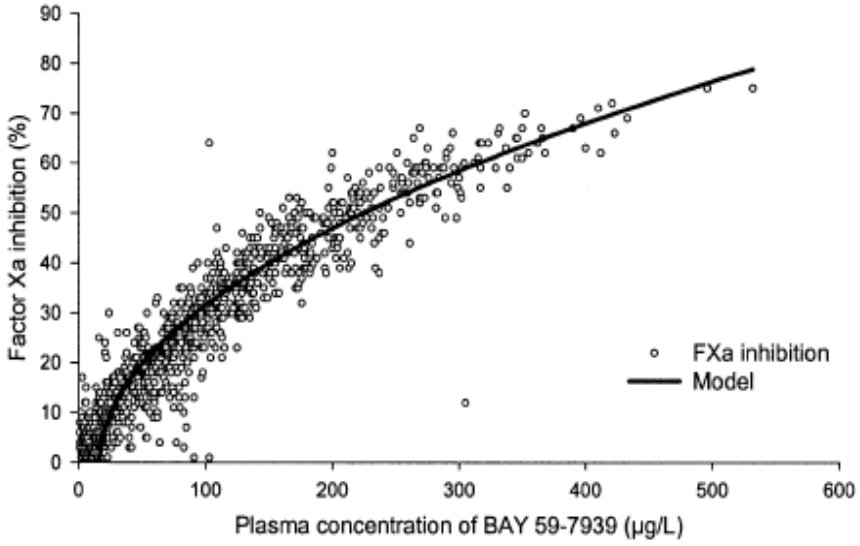
Beispiel Rivaroxaban: Dosisbereich FIH-Studie

- Plasma IC_{50} Fxa-Hemmung: (Tiermodell)
  9 ng/ml = (Toxicokinetic Upscaling) = 0.25 g/kg
  $\rightarrow$ Dosis = ca. 15 mg Einzeldosis
- NOAEL (Ratte): ~ 0.6 mg/kg
  = ca.40 mg Einzeldosis

z.B. Rivaroxaban: Pharmakokinetik/Dynamik First Dose in Human

- Single-Dose
- Niedrigste Dosis 1.25 mg = 1/30 der NOAEL
- Höchste Dosis nach Prüfplan 80mg = 2*NOAEL, hierbei erwartet ca. 80% Fxa-Hemmung
- Start der ersten Kohorte mit der niedrigsten Dosis
- Jeder Proband nimmt nur an einer Dosierung teil





Rivaroxaban: Safety + Tolerability Phase I (multiple dose)

Table 1 The incidence (*n*) of drug-related, treatment-emergent adverse events (TEAEs) after administration of BAY 59-7939 and placebo; includes events occurring in more than one subject (*ALT* alanine aminotransferase, *GLDH* glutamate dehydrogenase)

Disorder	Placebo (*n*=21)	BAY 59-7939					
		5 mg od (*n*=7)	5 mg bid (*n*=7)	5 mg tid (*n*=7)	10 mg bid (*n*=7)	20 mg bid (*n*=7)	30 mg bid (*n*=8)
Any drug-related TEAE	6	3	0	4	0	3	4
Headache	4	2	–	2	–	3	2
Diarrhea	2	–	–	1	–	–	1
Fatigue	2	–	–	2	–	–	–
Dyspepsia	–	–	–	1	–	–	1
Flatulence	1	1	–	–	–	–	–
Increase in ALT and GLDH more than three times upper limit of normal	–	–	–	–	–	–	1
Dizziness	–	–	–	–	–	–	1
Altered taste	–	–	–	–	–	–	1
Exanthema	1	–	–	–	–	–	–
Feeling hot	–	–	–	–	–	–	1
Hyperacidity	–	1	–	–	–	–	–
Pressure in ear/tinnitus	–	–	–	1	–	–	–

Time and Events Schedule (Schedule of Procedures) for a Single Ascending Dose, First-time-in-human (FTIH), IND-enabling Phase 1/Phase I Clinical Study Protocol (Clinical Pharmacology Study Protocol)

	Screen Day –28 to –1	CRU Admission (Baseline)	Day 1			Day X to X	Prior to Discharge (Day X)	Follow-up ≥3 days and ≤5 days after Discharge
			Pre-dose	Dosing	Post-dose	Post-dose		
Informed Consent Form Signed	X							
Eligibility Review and Confirmation	X	X	X					
Medical History	X							
Physical Examination	X	X					X	X
Height Assessment	X							
Weight Assessment	X	X	X				X	
Urine Drug Test	X	X						
HIV & Viral Hepatitis Screen	X							
Vital Signs	X	X	X		X	X	X	X
12-lead ECG	X	X	X		X	X	X	
Clinical Laboratory (Blood) and Urinalysis	X	X	X		X	X	X	
Prior Medication Assessment	X	X	X					
Serum Pregnancy Test	X							X
Urine Pregnancy Test		X						
CRU Admission		X						
Randomization			X					
Administer Study Drug				X				
Pharmacokinetic Sampling (Blood)			X		X	X	X	
Pharmacokinetic Sampling (Urine)			X		X	X	X	
Treatment-Emergent Adverse Events				X	X	X	X	X
Concomitant Medication Assessment				X	X	X	X	X
CRU Discharge							X	X

Phase I Proband oder Patient?

- **CPMP/EWP/205/95:** The CPMP Guideline on the evaluation of **anticancer medicinal products** distinguishes between **cytotoxic** compounds, for those early phase studies should be undertaken in patients without established therapeutic alternatives, and **non-cytotoxic** compounds where early trials may sometimes be conducted in healthy volunteers.
- **EMEA/CHPM/SWP/28367/07:** The EMA guideline on strategies to identify and mitigate risks illustrates some factors to be considered for this **case-by-case** decision, e.g. relative presence of the target in healthy subjects or risks of immediate toxicity.

EMEA/CHPM/SWP/28367/07 GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN -HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

The choice of the study population, i.e. healthy subjects or patients, …. should be fully **justified by the sponsor on a case-by-case basis**.

Several factors should be considered, such as:

(a) the risks inherent in the type of medicinal product - it is important that those risks (and uncertainty about them) be quantified and justified;

(b) its molecular target,

(c) immediate and potential long term toxicity;

(d) the lack of a relevant animal model;

(e) the relative presence of the target in healthy subjects or in patients; e.g. cancer patients;

(f) the possible higher variability in patients;

(g) the ability of healthy volunteers to tolerate any potential side effects;

(h) the potential pharmacogenomic difference between the targeted patient group and healthy subjects;

(i) the patients' ability to benefit from other products or interventions; and

(j) the predicted therapeutic window of the IMP.

Wensing G et al. The safety of 1 n trials - an analysis of studies cond 000 to 2005. Int J Clin Ph

- 5 Severe AE
- 2 Drug Related: Hypotension after CNS-active drug (symptomatic treatment)
- 1 Procedure-related: Syncope after venous cathederisation

quency of greater eers.

Table 5. Adverse events coded by MedDRA Term with a frequency of greater than 1% in First-in-M Phase I trials in healthy male volunteers in relatin to the number of dose steps administered.

Studies		Treatment periods	Adverse events (any event)	Distribution of severity of AE		
				mild	moderate	severe
Total	24	1,160	323 (27.84%)	289 (89.47%)	29 (8.98%)	5 (1.55%
Placebo	24	368	8 (22.28%)	74 (90.24%)	8 (9.75%)	
Verum						
DS 1	24	152	34 (22.37%)	33 (97.06%)	1 (2.94%)	
DS 2	21	136	37 (27.21%)	32 (86.49%)	5 (13.51%)	
DS 3	20	139	38 (27.34%)	36 (94.74%)	2 (5.26%)	
DS 4	17	134	41 (30.60%)	37 (90.24%)	3 (7.32%)	1 (2.44%)
DS 5	14	115	53 (46.09%)	42 (79.25%)	8 (15.09%)	3 (5.66%)
DS 6	8	60	17 (28.33%)	17 (100.00%)		
DS 7	3	23	5 (21.74%)	5 (100.00%)		
DS 8	3	22	8 (36.36%)	5 (62.50%)	2 (25.00%)	1 (12.50%)
DS 9	2	11	8 (72.73%)	8 (100.00%)		

		ber	(%)
			100.00
	dache	100	17.06
	asopharyngitis	43	7.34
	Flushing	41	7.00
	Feeling hot	32	5.45
5	Nausea	24	4.10
6	Nasal congestion	23	3.92
7	Dizziness	20	3.41
8	Diarrhoea	19	3.24
9	Alanine aminotransferase increased	15	2.56
10	Orthostatic hypotension	14	2.39
11	Hypotension	11	1.88
12	Paresthesia	11	1.88
13	Fatigue	10	1.71
14	Blood creatine phosphokinase increased	9	1.54
15	Vomiting	9	1.54
16	Dysgeusia	8	1.37
17	Feeling cold	8	1.37
18	Pharyngolaryngeal pain	8	1.37
19	Back pain	6	1.02
20	Malaise	6	1.02

Emanuel EJ, et al. Quantifying the risks of non-oncology phase I research in healthy volunteers: meta-analysis of phase I studies. BMJ 2015

Phase I Studien (nicht nur FIH) zwischen 2004 und 2011 an Pfizer- Phase I Units

- 11,028 participants who received the study drug in 394 distinct non-oncology phase I studies*
- 7028 participants (63.7%) experienced 24,643 adverse events.
- **85 % mild**
- **14 % moderate**
- **1.0% (n=255) severe**
- **34 (0.31%) serious adverse events SAE occurred**
  - **no deaths or life threatening events**
  - 11 were related to the study drug
  - 7 were related to study procedures (e.g. Lumbar Puncture)
  - 16 were unrelated to a study drug or procedure, including four that occurred when the participant was receiving a placebo.
- 24 % of adverse events were deemed to be unrelated to the study drug.
- 10 % of adverse events occurred among participants receiving placebo.
- The most common adverse events were headache (12.2%), drowsiness (9.8%), and diarrhea (6.9%).

*** Nur 3% der Teilnehmer bekamen ein “Biological”**

“Cytokine Storm” TGN1412 (A monoclonal, activating AB [Target CD28] London 2006

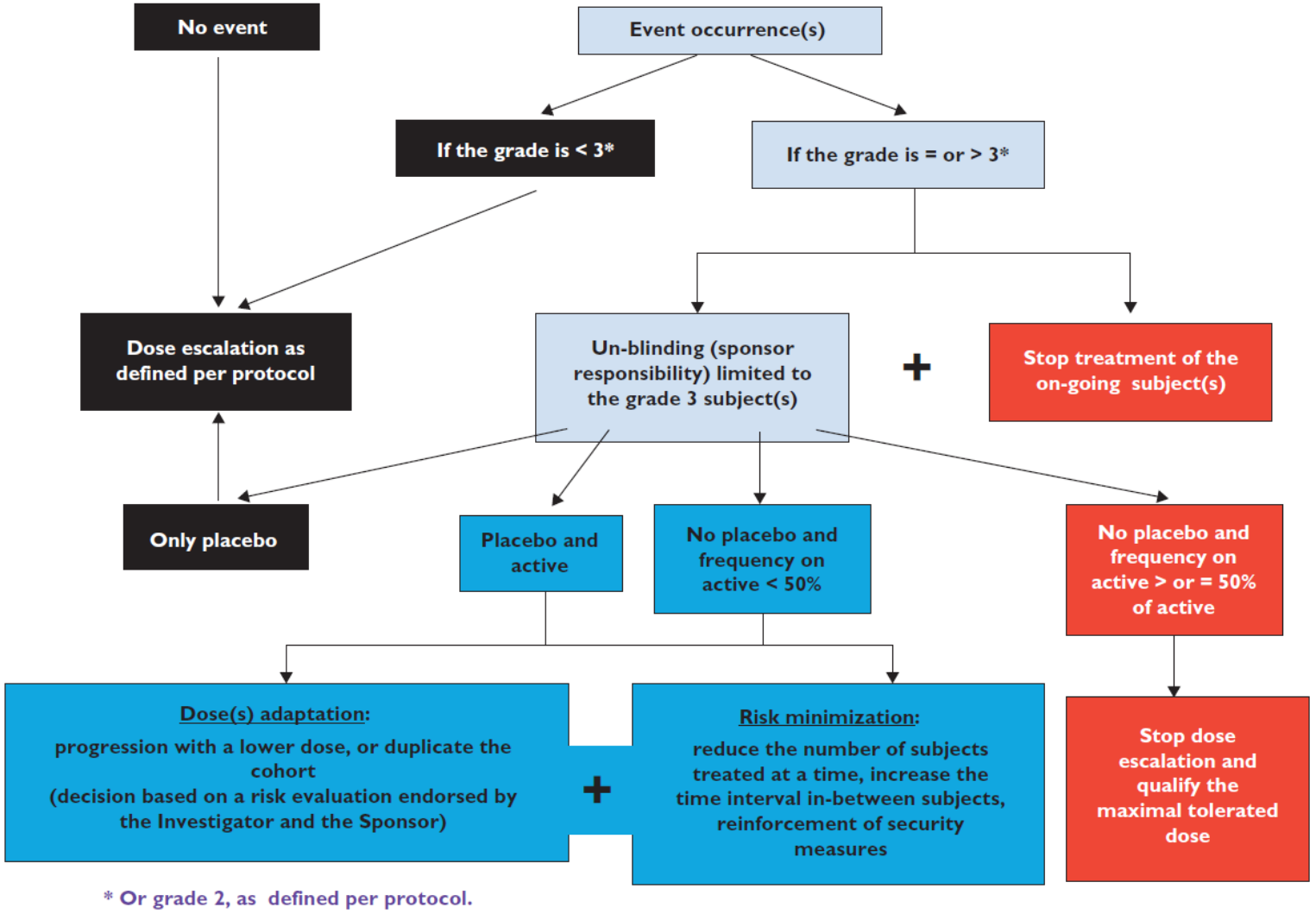
Patientenstudie, z.B. Phase I Dacetuzumab: Cytokin-Release-Syndrom

A phase I multidose study of dacetuzumab (SGN-40; humanized anti-CD40 monoclonal antibody) in patients with multiple myeloma

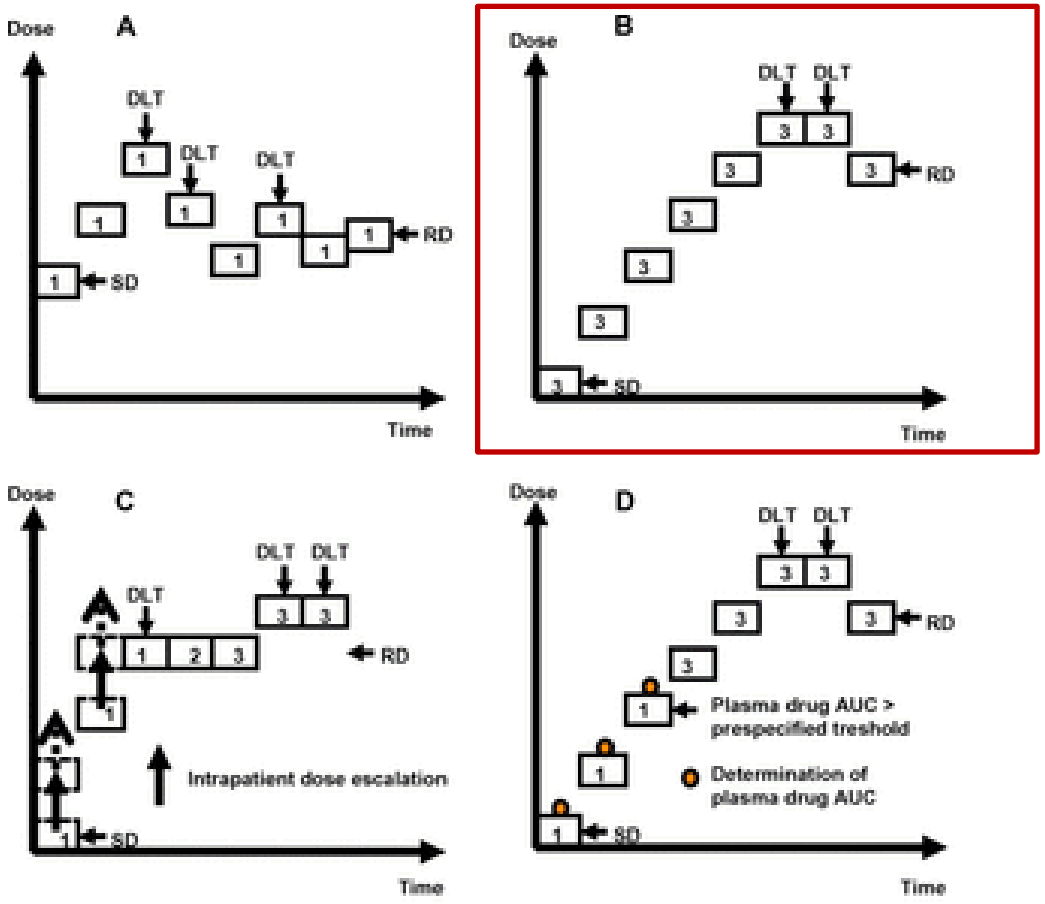
Table 2. Patients with symptoms of cytokine release syndrome[1] within one day of dacetuzumab dose.

	Group A[2] N=16 n/N (%)	Group B[2] (Cohorts I – IV) N=16 n/N (%)	Group B[2] (Cohorts V – VII) N=12 n/N (%)	All patients N=44 n/N (%)
Dosing Day 1	7/16 (44)	9/16 (56)	2/12 (17)	18/44 (41)
Dosing Day 8	5/14 (36)	4/15 (27)	1/12 (8)	10/41 (24)
Dosing Day 15	4/14 (29)	5/15 (33)	3/10 (30)	12/39 (31)
Dosing Day 22	3/11 (27)	0/15 (0)	1/9 (11)	4/35 (11)

Sibille et al. A safety grading scale to support dose escalation and define stopping rules for **healthy subject** first-entry-into-man studies.
Br J Clin Pharmacol 2010



Dosissteigerung bei onkologischen Phase-1-Studien



Koyfman SA et al. Risks and benefits associated with novel phase 1 oncology trial designs. Cancer 2007; 110:1115-24

Of 955 phase 1 oncology articles initially identified, 149 studies, comprising 4532 patients, were analyzed.

Aggressive dose escalations were associated with increased rates of both hematologic (17% vs 10%) and nonhematologic (17% vs 13%) toxicity with similar response rates.

Ethische Aspekte bei Phase-I-Studien an (gesunden) Probanden

- Gabe des AM bei Personen, die keine Indikation für eine Behandlung haben
- Fremdnützige Forschung

➢ Probanden könnten immunisiert werden

➢ Probanden könnten „genötigt“ werden

➢ Probanden könnten durch das Design gefährdet werden (v.a. akademische Studien)

Apseloff G et al. **Credibility and comprehension of healthy volunteers in lengthy inpatient drug studies.** Am J Ther. 2013

- A large percentage of subjects **trial failed to comprehend** a variety of basic concepts related to the consent form and their participation in the drug study.
- The chart review demonstrated that subjects **who are paid larger stipends may not be more likely to report** abnormalities on their medical history.

Ethische Aspekte bei Phase-I-Studien an Patienten

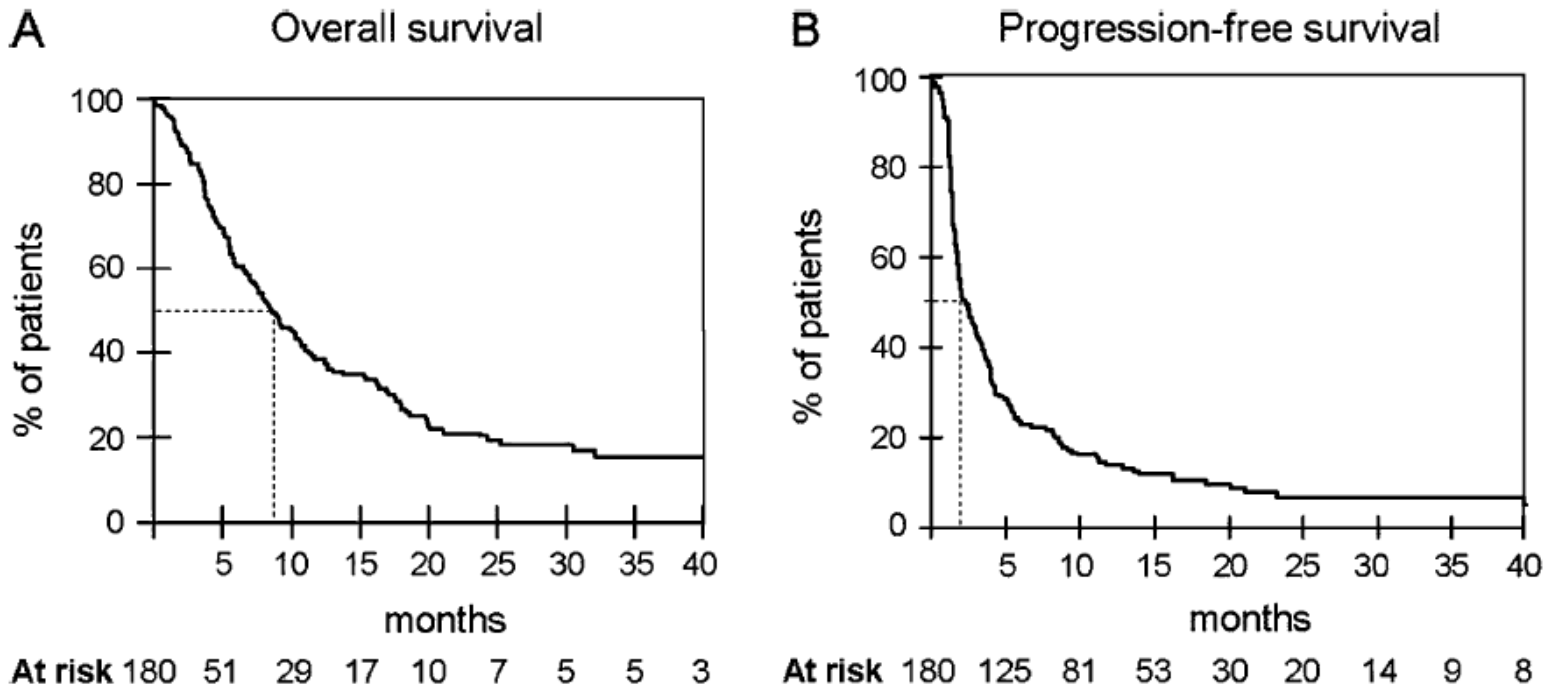
- Gabe des AM bei Erkrankten, die aber (höchstwahrscheinlich) keinen Nutzen haben werden
- Hohe “Dichte” an Begleitinterventionen (Bildgebung, PK-Daten, Biomaterial,…)
- Der Gruppennutzen ist mitunter nur mittelbar

➢ Wirklich Patienten ohne weitere Therapieoption?

➢ Therapeutic Misconception/Misestimation

Treatment outcome and survival in participants of phase I oncology trials carried out from 2003 to 2005.

(A. Italiano et al. Annals of Oncology 19: 787–792, 2008)



Kaplan–Meier curve for overall survival (A) and progression-free survival (B) for all patients entered on study.

Signs of Efficacy in Phase I patient studies (Ferte C et al. PLoS One 2011)

- Konventionelle “Zytostatika”
  - Maximum Tolerated Dose MTD bei 76% erreicht (im Median bei 5. Dosiskohorte)
  - (Irgendeine) Wirkung bei 82 %
  - Erste Zeichen einer Wirkung bei 1.Dosiskohorte: 52%
- “Targeted agents”
  - MTD bei 51% erreicht (im Median bei 5. Dosiskohorte)
  - (Irgendeine) Wirkung bei 78 %
  - Erste Zeichen einer Wirkung bei 1.Dosiskohorte: 25%

Therapeutic Misestimation

Table 3. Comparisons of Respondents' Personal and Population Estimates of Risk and Benefit

Frequency (percent)	Higher Personal Benefit Than Population Benefit: No. of Respondents (%)	
	Yes	No
Lower Personal Risk Than Population Risk		
Yes	42 (54.6)	15 (20)
No	14 (16.7)	5 (6.7)

Pentz RD et al. **Therapeutic misconception**, misestimation, and optimism in participants enrolled in phase 1 trials. Cancer 2012; 118: 4571

Therapeutic Misconception

Main Purpose: (1) Give me a personal chance of response [Eigennutzen], or (2) give knowledge to the researcher [Gruppen, Fremdnutzen]

Table 1. Answers to Therapeutic Misconception Questions

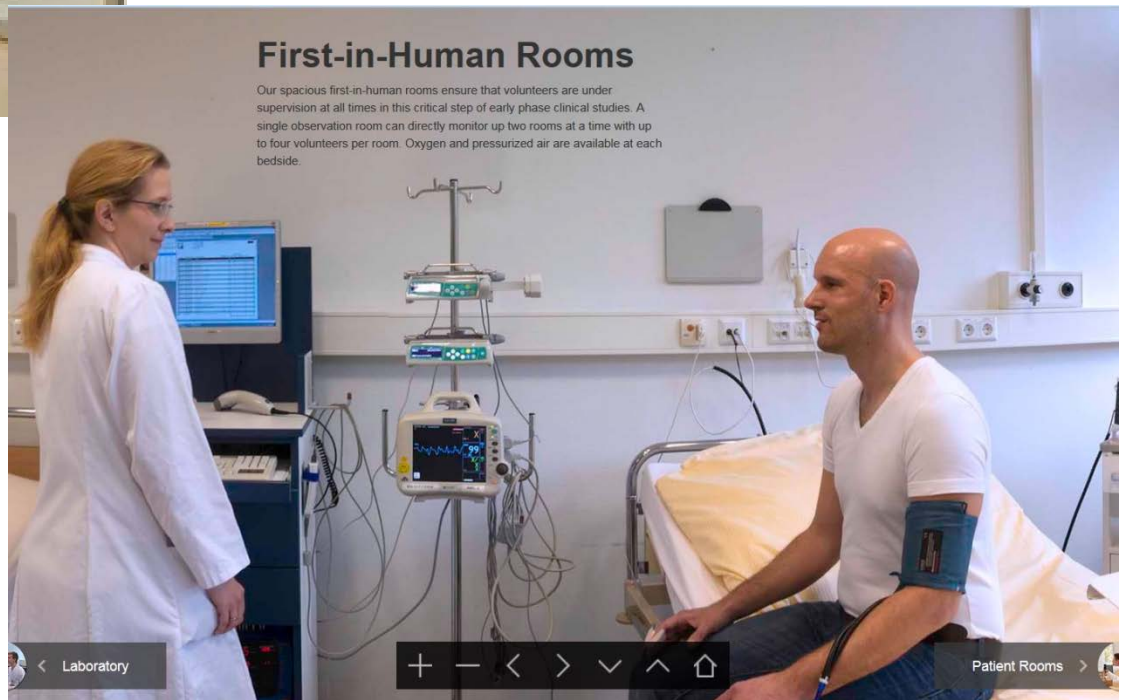
(n = 95)	Question 1: Main Purpose? No. of Respondents (%)		
Question 2: Treatment Is Decided By?	Correct	Incorrect	DNK/Blank
Correct	31 (32.6)[a]	22 (23.2)	—
Incorrect	18 (18.9)	9 (9.5)	1 (1)
DNK/blank	8 (8.4)	6 (6.3)	—

Decided by (1) physicians preference for my benefit or (2) by study plan

Pentz RD et al. **Therapeutic misconception**, misestimation, and optimism in participants enrolled in phase 1 trials. Cancer 2012; 118: 4571-

Qualifikation Prüfer/Prüfstelle

Klassische Phase –I-Unit (mit Klinikanbindung): i.d. Regel (spätestens seit TGN) hohe GCP-Compliance

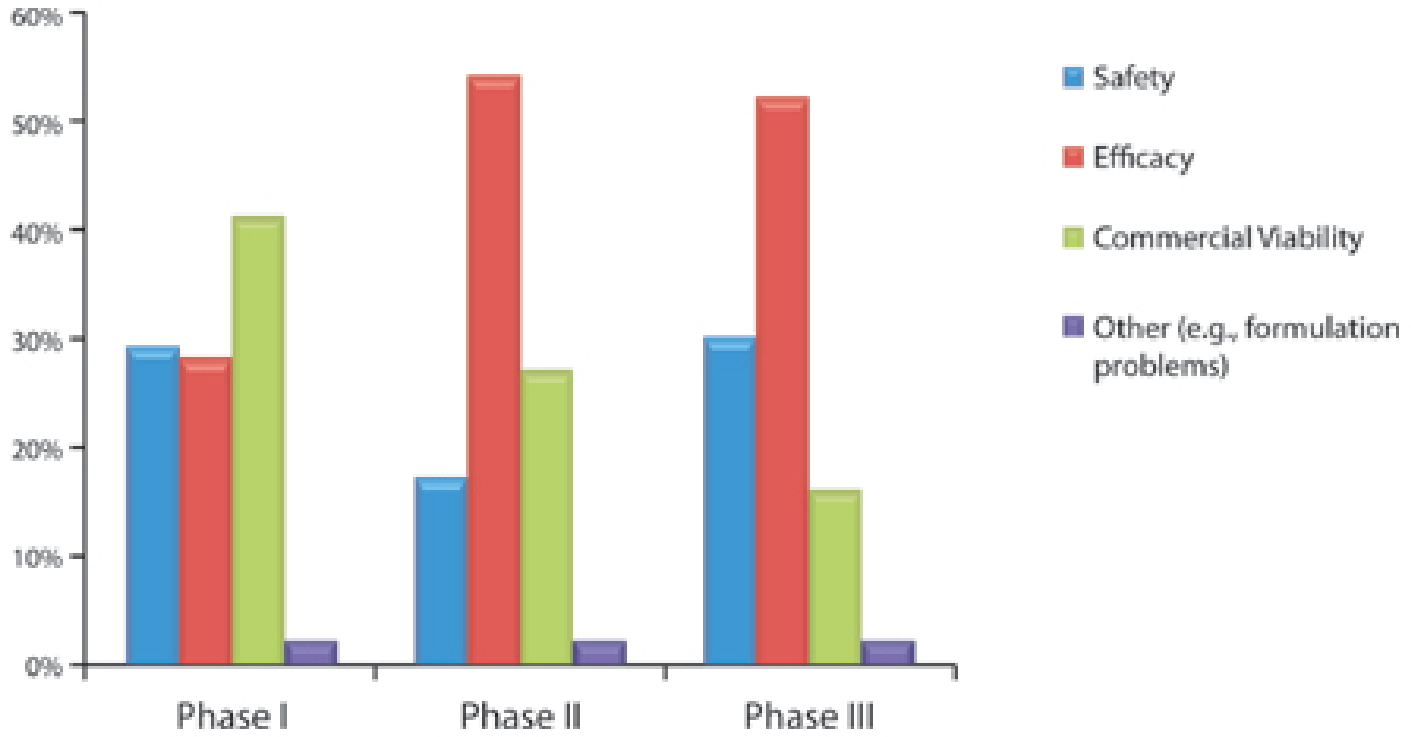


Phase –I- Studien in akademischen Einrichtungen: Voraussetzungen müssen genau geprüft werden

Zusammenfassung

- Phase I –Studien sind unverzichtbarer Bestandteil der AM-Entwicklung
- Alle Phase I-Studien benötigen einen strengen Ansatz zur Risikominimierung (u.a. DSMB)
- Für Studien an Gesunden gibt es umfängliche und regulatorisch fundierte Sicherungskonzepte, ernste Zwischenfälle sind selten (< 1%)
- Risiken sollten nicht durch überdurchschnittliche Belohnungen aufgewogen werden
- Für Studien an Patienten bestehen wesentliche Risiken und wenig Nutzen
- Hierüber muss angemessen aufgeklärt werden

Reasons for Clinical Failures by Phase



Source: Tufts CSDD

Figure 1. Commercial viability—as opposed to safety—is the leading cause of Phase I failures.

Applied Clinical Trials 2013: Volume 22, Issue 12