Modern drug development in oncology – How to successfully design the early phase trials?

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Evolving landscape of compound classes

	Chemotherapy	Small molelcules / TKI	Immunotherapy / CPI
Relative treatment duration	Short, defined cycle number	Long (until PD and tox)	Long (tbd)
Occurrence of toxicity	Short term	Short and long term	Long term
Characteristics of toxicity	Non –target, proliferating cells	Off-target, target based	Auto-immune tox
Onset of tumour response	rapid	Rapid to later	Rather later, pseudoprogression possible
administration	i.v.	Oral	i.v. / s.c.

Requires adapted trial designs and measures during compound development

I. ADAPTIVE TRIAL DESIGN

Adaptive design

We learn as we go !

a flexible and effective way to conduct clinical trials ? Goals :

-improving the study power

-reducing sample size and total cost

-treating more patients with more effective treatments

-identifying efficacious drugs for specific subgroups of patients based on their biomarker profiles

-shortening the time for drug development

TABLE 1. CURRENT ONCOLOGY TRIALS: PERFORMANCE MEASURES

Average Time: 7.6 years (Phase I to Approval; 2005-2009)[7]

Average Cost per Patient:

Oncology vs. All Rx categories (2011)[8]

Phase II: $73,000 (vs. $36,000)
Phase IIIa: $57,000 (vs. $47,500)
Phase IIIb: $66,000 (vs. $47,000)

Overall Success Rates (1993-2004)[1]

7.1% of Phase I oncology entries were approved
19.0% of Phase I entries in all Rx categories were approved

Phase III Success Rates (2003-2010)[5]

34% of oncology trials achieved statistical significance in primary endpoints

TABLE 2. MOST COMMON TYPES OF ADAPTIVE SETTINGS IN MODERN CLINICAL TRIALS

- Stopping early (or late, i.e. extending accrual) with a conclusion of superiority or futility
- Adaptively assigning doses to more efficiently asses the dose-outcome relationship
- Dropping arms or doses
- Seamless phases of drug development within a single trial
- Changing the proportion of patients randomized to each arm
- Adaptively homing in on an indication or responder population
- Adding arms or doses
- Changing accrual rate

Adaptive design

Many, but not all adaptive designs are formulated under the **Bayesian framework**. Bayesian methods model the parameter of interest by

(I) obtaining the prior distribution;

(II) collecting data to calculate the data likelihood; and then

(III) computing the posterior distribution using Bayes theorem.

The Bayesian method is adaptive in nature and provides an ideal statistical framework for adaptive trial designs

CAVE software !!

Biomarker guided adaptive design

targeted therapies

- **requires the identification of biomarkers that can be used to identify patients who are likely to be sensitive to the targeted therapy**

START EARLY !!! BEFORE WE DO THE PIVOTAL IN VIVO TRIALS – PRECLINICAL WORK – INTEGRATED TEAM

Adaptive design

Questions :

Your experience with adaptive design ?

What points in adaptive seem most important?

What points in adaptive design seem realistic to you?

II. PATIENT SELECTION

Patient selection

- The primary aim : to identify the maximum-tolerated dose (MTD)
- Recommended phase II dose (RP2D) needed.

- **For cytotoxic drugs**
- **For targeted drugs** **DIFFERENT !!!!**
- **For immunotherapy**

QUESTIONS

- Can we do studies with anti cancer compounds in a healthy population ?

Who has done this already ?

Which type of study?

Selection of patients

- A key component, in particular for phase I trials, but probably true for all phases of drug development, is the assessment of an individual patients **prognosis**.
- CAVE : **progressive metastatic disease -** through all standard lines of treatment :

  a limited life expectancy.

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Prediction of early death among patients enrolled in phase I trials.

Sufficient life expectancy for phase I trials needed= challenging

Most protocols : at least 90 days life expectancy

-not ethical to expose a very frail patient to new drugs

-form research perspective : CAVE jeopardising the study and subsequent drug development in case of early death

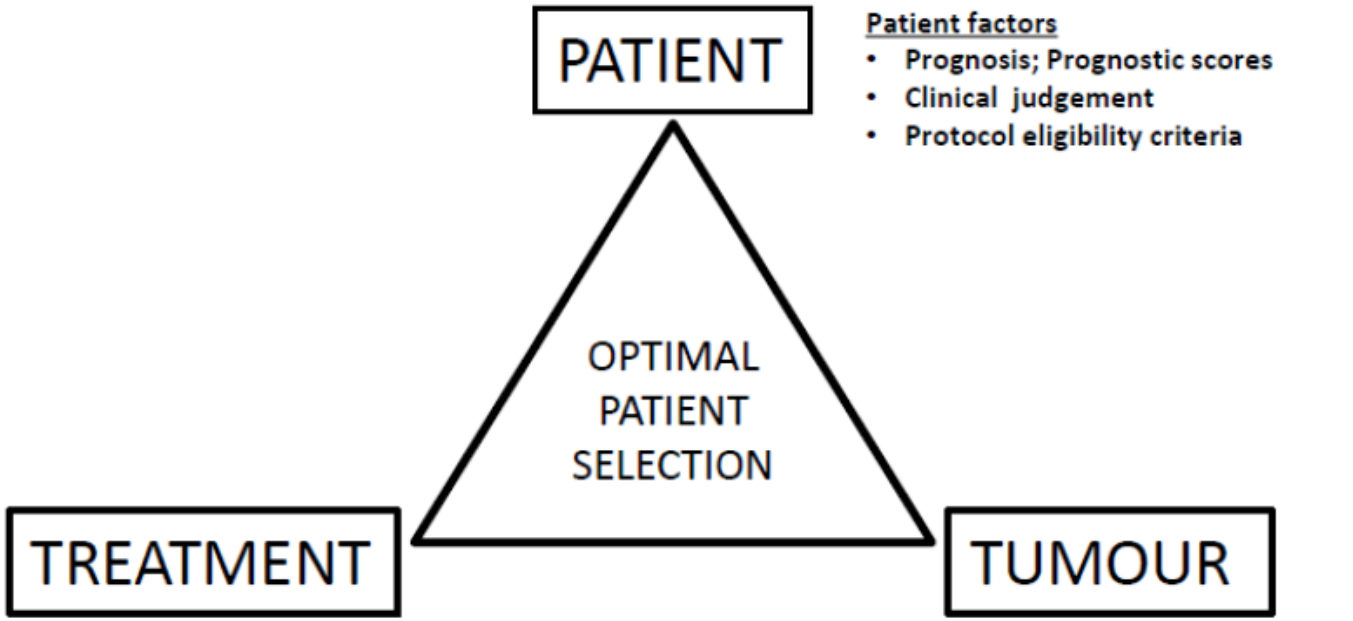
British Journal of Cancer 2012 Ploquin et al.

Patient selection

- Estimating prognosis is inherently challenging for a clinician and estimates are ***often made based on intuition and experience rather than in a scientific or an evidence-based manner***.

Performance Status	Definition
0	No symptoms; normal activity level
1	Symptomatic, but able to carry out normal daily activities
2	Symptomatic; in bed less than half of the day; needs some assistance with daily activities
3	Symptomatic; in bed more than half of the day
4	Bedridden

It has been shown that an ECOG PS of 3 indicates a prognosis of less than 3 months and a PS of 4 of less than 1 month.



Renal function
Bone marrow
Pancreatic cancer

Score	Prospective validation	Parameters	Overall Survival (weeks)	P-value	HR
Royal Marsden Hospital Score [36] Arkenau 2008	Yes	LDH (>ULN) = 1 Albumin (<35 g/L) = 1 > 2 sites of metastases = 1	Score 0-1: 33.0 Score 2-3: 15.7	0.036	1.4
Hammersmith Score [37] Stavraka 2014	No	LDH >450 IU/dL = 1 Albumin <35 g/dL = 1 Sodium <135 mmol/dL = 1	Score 0-1: 31.2 Score 2-3: 8.9	<0.001	
Princess Margaret Hospital Index [39] Chau 2011	No	High LDH >2 metastatic sites ECOG PS > 0			
European Model B [42] Olmos 2012	No	Albumin <35 g/dL = 1 LDH (>ULN) = 1 ≥ 3 sites of metastases = 1 Low TPTi (<24 weeks/treatment) = 1 Increased ALP (>ULN) = 1 Low lymphocyte count (<18%) = 1 High WBC (>10,500/uL)	Score 0: 141 Score 1: 61 Score 2: 54 Score 3: 37 Score 4: 29 Score 5: 21 Score 6: 11 Score 7: 10	0.036 (log-rank)	- 2.00 2.54 3.24 4.57 6.20 14.1 14.1

CHAID method :
high risk patients,
decision tree

CHAID
Chi-squared Automatic Interaction Detection

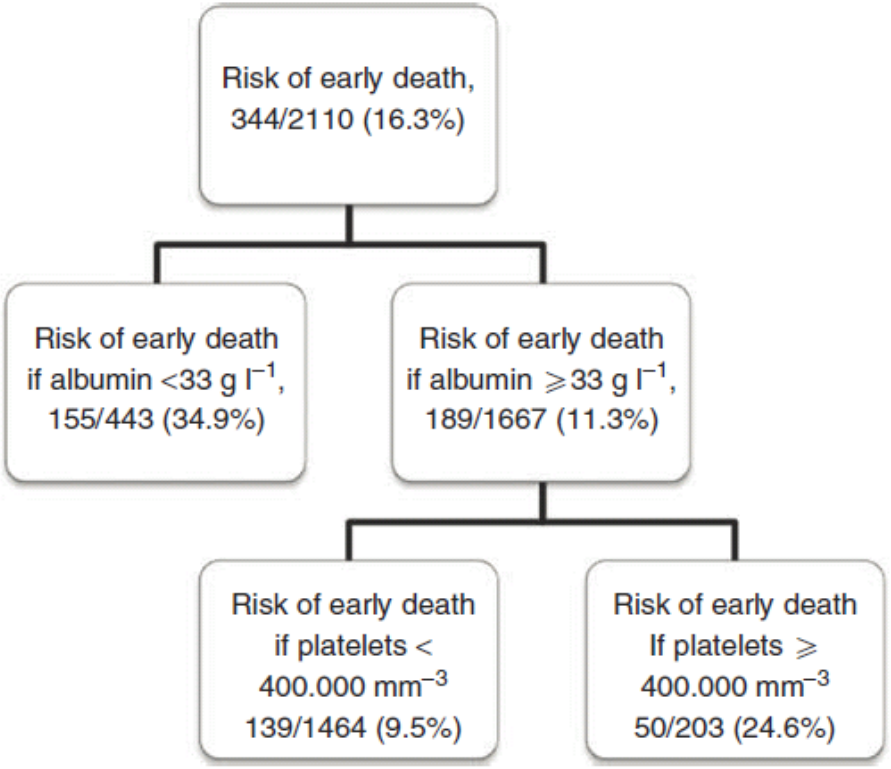


Figure 1 Decision tree generated by the CHAID analysis in the training data set.

British Journal of Cancer 2012 Ploquin et al.

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Prediction of early death among patients enrolled in phase I trials.

Low level of serum albumin :

- marker of cancer related **malnutrition**
- known prognostic marker in cancer patients

High number of platelets :

- poor prognosis
- marker of **inflammation** induced by cancer
- can increase risk of **thrombosis** – early mortality
- activator of tumor **angiogenesis**

British Journal of Cancer 2012 Ploquin et al.

How to deal with preselection based on biomarkers?

Prescreening?

How to deal with interval in between ICD and first dosing ?

f.i. *met* trials / *braf* trials

PRECISION projects

III. Safety

Safety

Dose limiting toxicities – defined as those that are related to IMPs and deemed unaccaptable, leading to restriction of further dose escalation

DLT definition:

- standardised sets?
- Definition depending on drug characteristics, and treatment duration, schedule?
- DLT assessment period? Cycle 1 , cycle 2,..
- Severity of events: grade 3 and higher, grade 2
- Duration of grade 2 events to become a DLT?

Grading of AEs according to CTCAE

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Example « blood and lymphatic system disorders »

Blood and lymphatic system disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C	Life-threatening consequences; urgent intervention indicated	Death

DLT definition

standardised sets?

- All hematological events ≥ grade 3, with the exception of non-febrile neutropenia < 7days, …
- All non-hematological events ≥ grade 3 with the exception of hair loss, nausea and vomiting > x days

Definition depending on drug characteristics, and treatment duration, schedule?

- e.g.targeted therapy: ≥ grade 3 febrile neutropenia, ≥ grade 3 events depending on target expression, eg LFT increase, hypertension

Duration of DLT reporting

- Dilon et al 2016: 15% of patient experienced highest grade dermatologic event at cycle 2 or later
- Paoletti et al 2014, DLT-TARGETT: 85% of participants in favour of considering severe side effects after cycle 1 as DLT

Severity of toxicity to meet DLT definition by NCI CTCAE grade

Table 3 – Minimum NCI CTCAE grade used to meet DLT definition for the 825 toxicity items described in the 155 trials.

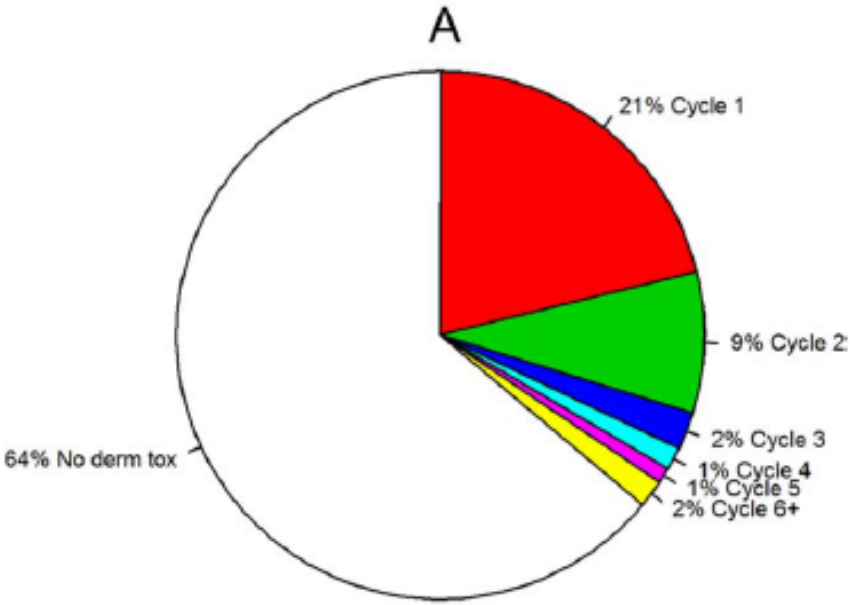
Toxicity categories	Number of items							
	⩾G4	⩾G3	⩾G2	⩾G1	Other	Not specified	Not a DLT	All
Haematologic toxicity, nos	42	42	1	0	0	0	0	85
Neutropenia	65	4	0	0	0	0	0	69
Thrombocytopenia	39	18	0	0	11	0	0	68
Febrile neutropenia	17	17	2	0	0	10	0	46
anaemia	11	5	0	0	0	0	3	19
Thrombocytopenia with bleeding	2	11	0	0	0	3	0	16
Coagulation abnormality	0	2	0	0	2	0	0	4
Lymphopenia	0	0	0	0	0	0	1	1
Haemorrhage	0	0	1	0	0	0	0	1
Haematologic toxicity (all)	176	99	4	0	13	13	4	309
Non-haematologic toxicity, nos	2	135	10	0	1	0	0	148
Gastro-intestinal symptoms								
Nausea	3	51	4	0	7	0	12	77
Vomiting	6	53	4	0	7	0	7	77
Diarrhoea	2	27	4	0	3	0	0	36
Constipation	0	1	0	0	0	0	1	2
Hepatic toxicity								
AST elevation	1	8	0	0	5	0	0	14
ALT elevation	1	8	0	0	4	0	0	13
ALP elevation	1	0	0	0	1	0	4	6
Bilirubin elevation	2	0	1	0	3	0	0	6
GGT elevation	1	0	0	0	1	0	1	3
Hepatic, nos	0	1	1	0	0	0	0	2
Renal toxicity								
Creatinine elevation	0	2	2	0	6	0	0	10
Proteinuria	0	2	2	0	0	0	0	4
Haematuria	0	0	2	0	0	0	0	2

Le Tourneau et al 2011

Onset of the worst grade of dermatologic adverse events

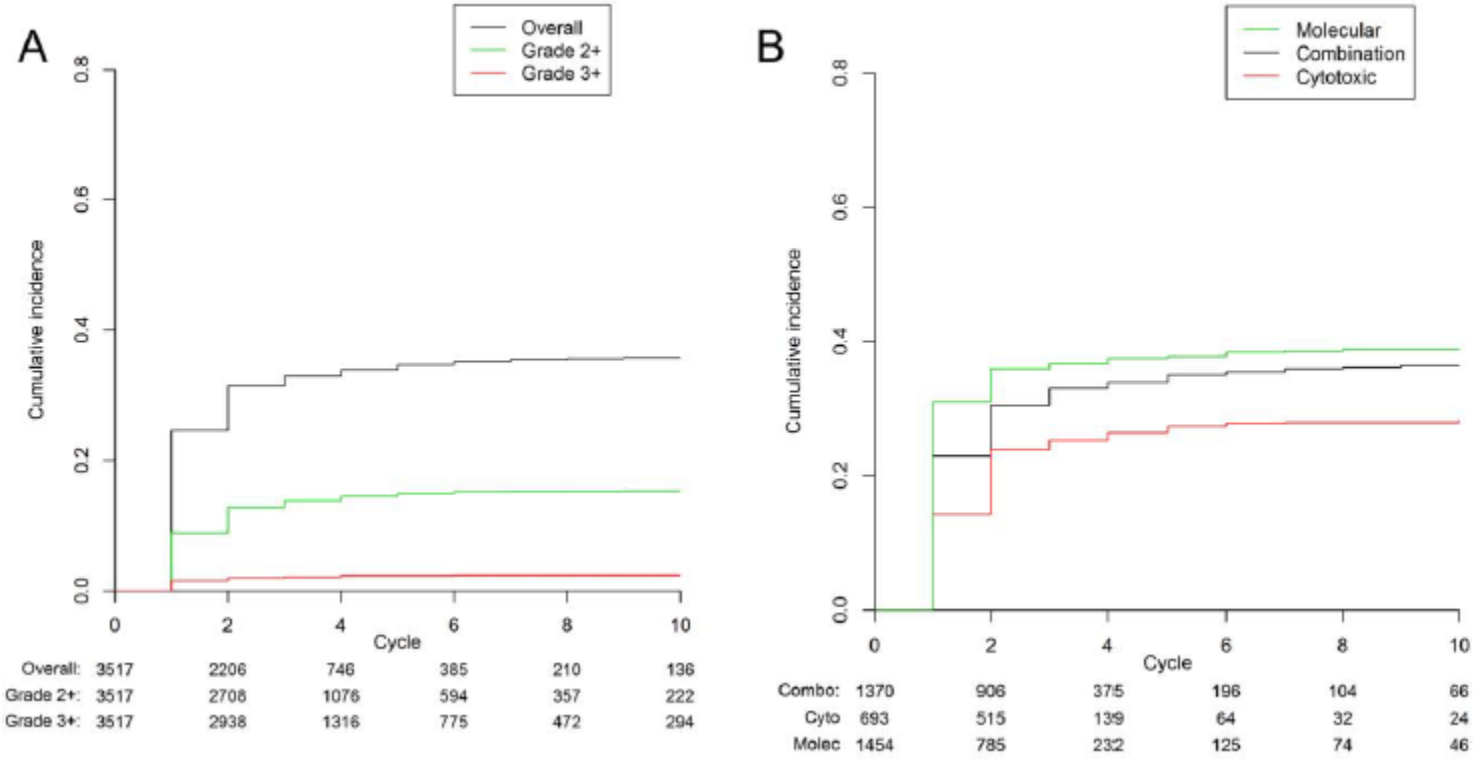
Dilon 2016

Cycle at which worst grade of treatment-related dermatologic adverse event occurred	Number of patients	% of patients	% of patients on trial at start of this cycle
1	743	21.1%	100%
2	303	8.6%	84.9%
3 or later	224	6.4%	58.5%
Experienced no treatment-related dermatologic adverse event on trial	2247	63.9%	---
Total	**3517**	**100%**	**---**



Analysis of 3517 patients with solid tumours from clinical trials with MTA, cytotoxic treatment or combination of both

Cumulative incidence of AEs Dilon 2016



IV. ANTI TUMOUR ACTIVITY / PD

Anti-tumour activity

- RECIST,
- iRECIST http://www.eortc.org/recist/irecist/
- PERCIST

- Tumour Growth Rate (TGR)
- Target PET scan

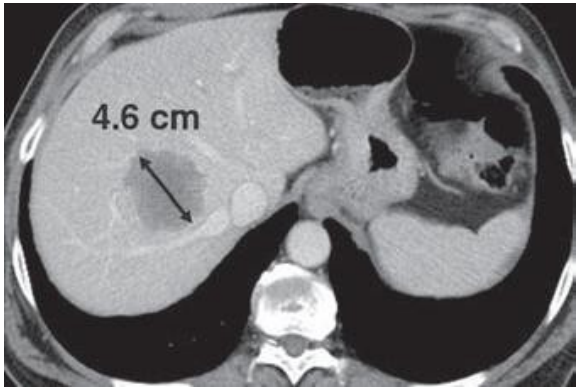
RECIST 1.1

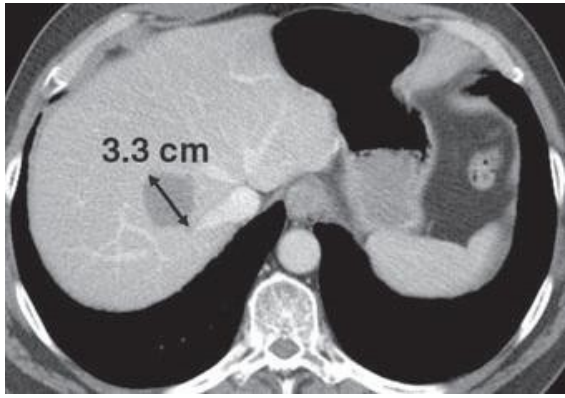
Baseline Documentation
Only patients with measurable disease at baseline should be included

Target Lesions
- maximum of five (5) target lesions in total (up to two (2) per organ)
-Select largest reproducibly measurable lesions
-If the largest lesion cannot be measured reproducibly, select the next largest lesion which can be

Non-Target Lesions
It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g. “Liver - multiple locations”)

Measurable Lesions
•Tumor ≥10 mm in longest diameter (LD)
•Lymph nodes ≥15 mm in short axis on CT (CT slice thickness recommended to be no more than 5 mm)





Target lesion (liver) BL and Follow up

RECIST 1.1: response target lesions

Response to Target Lesions	Criteria
Complete Response (CR)	• Disappearance of all target lesions. • Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm.
Partial Response (PR)	• At least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline ***sum diameters.***
Progressive Disease (PD)	• At least a 20% increase in the sum of diameters of target lesions, taking as reference ***the smallest sum on study*** (this includes the screening sum if that is the smallest on study). • In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. • The appearance of one or more new lesions is also considered progression.
Stable Disease (SD)	• Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference ***the smallest sum diameters*** while on study.
Non-Evaluable (NE)	• None of the above is possible. • State of target lesion is set to Non-evaluable.

EORTC NCI AACR 2016

iRECIST vs RECIST 1.1: Unchanged

RECIST 1.1	iRECIST
Definitions of measurable, non-measurable disease	√
Definitions of target (T) and non target (NT) lesions	√
Measurement and management of nodal disease	√
Calculation of the sum of measurement (SOM)	√
Definitions of CR, PR, SD and their duration	√
Confirmation of CR and PR	√
Definition of progression in T and NT (iRECIST terms i-unconfirmed progression (iUPD))	√

EORTC NCI AACR 2016

iRECIST vs RECIST 1.1: Changes

RECIST 1.1	iRECIST
Management of new lesions	NEW
Time point response after RECIST 1.1 progression	NEW
Confirmation of progression required	NEW
Collection of reason why progression cannot be confirmed	NEW
Inclusion and recording of clinical status	NEW

PD / Biomarker

- Tissue and liquid biopsies
- Sequential biopsies

How to realize sequential tissue biopsies?

Biomarker – Molecular Imaging

Radiolabelled antibodies, peptides, small molecules:

Target distribution, hetero - / homogeneity

Antibody distribution

Target occupancy

Tumour response evaluation

Examples: ^{89}Zr-trastuzumab, -bevacizumab, -antiPSMA, ^{18}F-5-fluoro-2'-deoxycytidine, PRRT (^{68}Ga/^{177}Lu-DotaTATE,…)

ZEPHIR Gebhart et al 2016

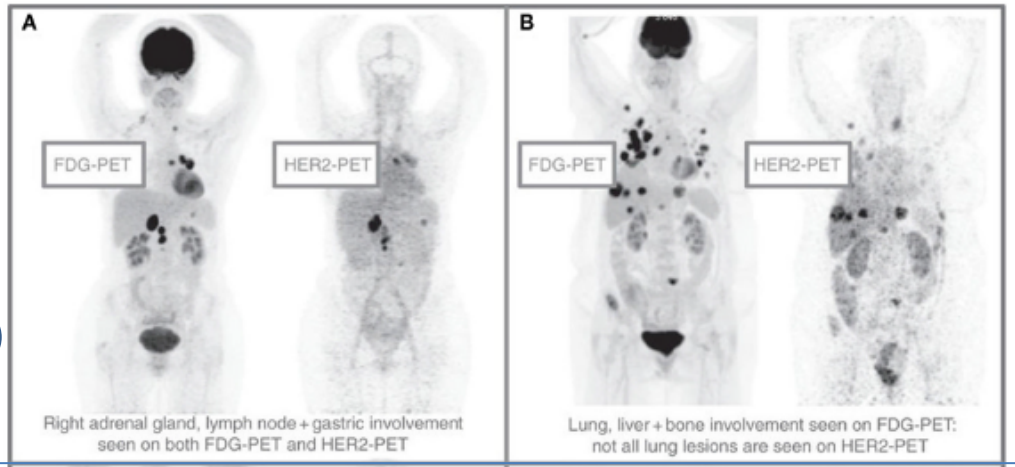
- Molecular imaging to explore intra-/interpatient heterogeneity in HER2 mapping of metastatic disease –> identify patients unlikely to benefit from ADC trastuzumab entansine T-DM1
- N=56 Patients with HER2 pos BC as per IHC3+ or FISH 2.2
- Pre-treatment imaging with HER2-PET/CET, 3 cycles of T-DM1, FDP-PET/CET before cycle 2
- CT and RECIST assessment at baseline and after 3 cycles, TTF analysis

Jauw et al 2017, Gebhart et al 2016

Patterns of HER2-PET/CT confronted with FDG-PET/CT Gebhart et al 2016

21 patients

Positiv pattern



19 patients

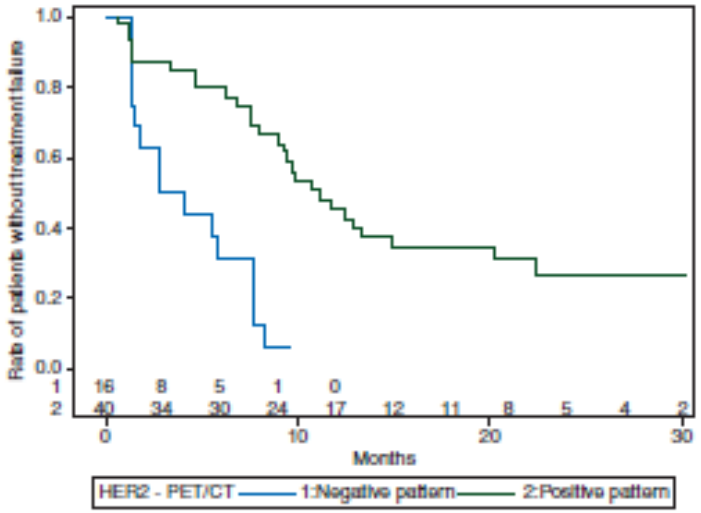
7 patients

Negativ pattern

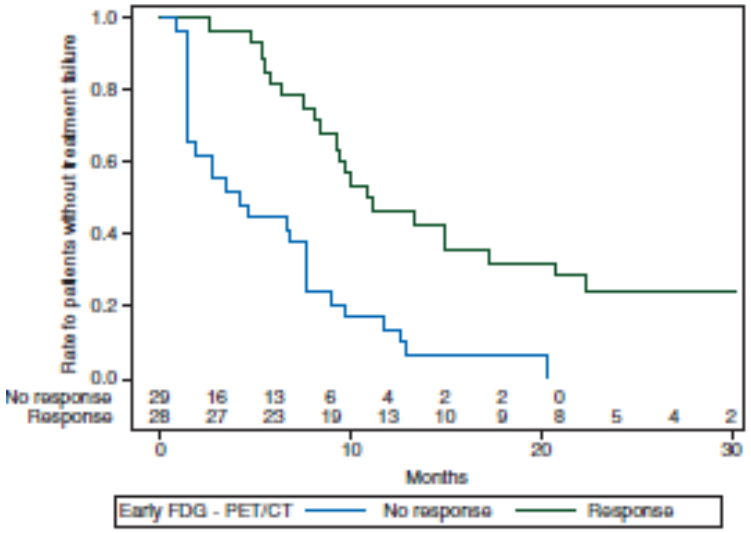
9 patients

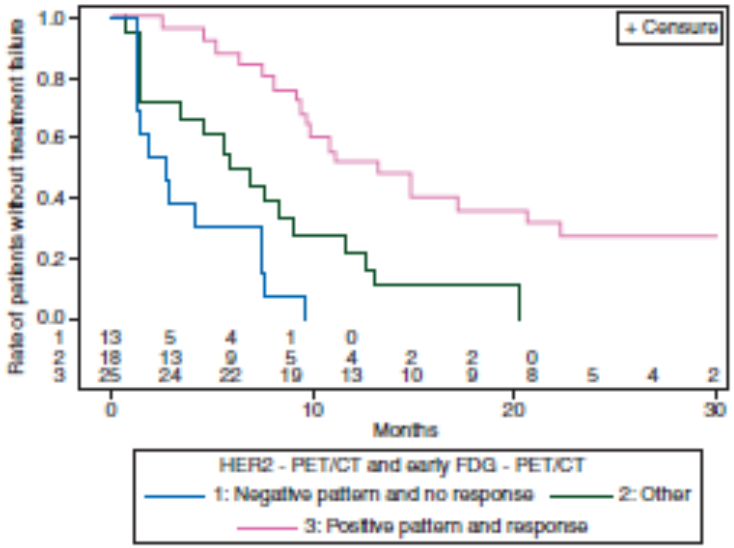
Heterogeneic tracer uptake

Time to treatment failure according to



- HER2-PET/CT alone
- Early FDG-PET/CT alone
- Combination of HER2- and FDG-PET/CT





Gebhart 2016

Discussion imaging biomarker

- Development timelines – up to 3 years non-clinical developing for imaging compound, antibody labelling with Zr up to 1 year
- Early decision
- costs

V. OUTCOME IN PHASE I

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Phase I trials in Oncology

Therapeutic misconception ?

OUTCOME

Outcome phase I trials in Oncology

Adults, all trials

2003-2006

180 patients, 10 trials

ORR 7.2 %

Disease control 48.2 %

Toxic deaths 0.5 %

38 % of the patients had al least 1 episode of grade ¾ tox

Ann Oncol 2008 Italiano et al.

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Outcome phase I trials in Oncology

Adults, all trials

PFS : 2.3 months

OS : 8.7 months

Phase I trials are safe and associated with clinical benefit in a substantial proportion of patients

Ann Oncol 2008 Italiano et al.

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Outcome phase I trials in Oncology

Rare tumors in phase I

30 patients, 2005-2009 - Median age 45 years

Adenoid cystic ca, adrenal ca, thymoma, CUP, lacrimal

63 % at least 1 prior chemo, 37 % at least 2

PR 1 patient

SD in 29 patients (97%), 80 % SD at 3 months, 43 % SD at 6 months

Journal of Clinical Oncol 2010 ASCO Abstract

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Outcome phase I trials in Oncology

Rare tumors in phase I

PFS : 5.6 months (CI95% 4.4-6.9)

OS : 23.2 months (CI95% 8.3-37)

Grade 3 tox : 5 pts (17%) (neutropenia, diarrhea)

Benefit is better than the outcome reported in an overall population included in phase I trials

Journal of Clinical Oncol 2010 ASCO Abstract

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Outcome phase I trials in Oncology

Patients with gynecologic malignancies in phase I

USA, 1 insitution, 1999-2010 : 184 patient inclusions, 120 patients / 41 trials - 30.6 % of all phase 1 trials
median age 59 years

17 DLTs (9.2 %), 1 treatment related mortality

27% grade 3 hematol tox, 24% grade 3 non-hematol tox
SD 50% (22 % > 4 mths); 6,3% with PR; 1.9 % CR :

58 % clinical benefit

Gynecol Oncol. 2013 Hou et al.

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Outcome phase I trials in Oncology

Pediatric phase I and Early phase II

Pts < 21 years, Jan 2000 – Dec 2012

235 patients (106 in phase I), median age 10.4 (0.8 – 20.7)

26 trials / 16 cytotoxic and 10 targeted agents

117 (50%) brain, 68 (29%) sarcoma

13/106 : DLT / no toxic deaths, hematologic !

Grade 3 and 4 toxicity : combination trials, cytotoxic agents, at least 1 prior treatment

J Pediatr Hematol Oncol. 2014 Bautista et al.

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Outcome phase I trials in Oncology

12 % (30 pts) : ORR

16 % (42 patients) : stable disease for > 4 months

Median OS : 9.0 months

73 % received further anticancer treatment

Phase I and II trials in children are safe and associated with clinical benefit

J Pediatr Hematol Oncol. 2014 Bautista et al.

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Outcome phase I trials – Radiation Therapy

1/3 of cancer patients receive RT at some point

Phase I/II trials involving RT published 2001-2010

2994 subjects in 98 trials

1812 acute grade 3/4 toxicity
33 treatment related deaths

Multivariate regression analysis : toxicity rates higher with chemotherapy and in trials for cancers of the head/neck

RISK of TOXICITY IS SIGNIFICANT

J Med Imaging Radiat Oncol 2013 Lawrence et al.