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We make it work

BE and ADME studies in oncological patient populations

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EU-Guideline on anticancer drugs

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Covers completely different types of drugs

- *cytotoxic:* irreversible lethal lesion e.g. via DNA replication
- *non – cytotoxic:* anticancer but not belonging to class of cytotoxics
- *cytostatic:* inhibit cell division without direct effect on tumour cells
- *chemosensitizer:* increases activity of anticancer drugs
- *chemoprotectant:* counteracts activity of anti – tumour drugs on normal tissues

Guideline on the evaluation of anticancer medicinal products in man/EMEA/CPMP/EWP/205/95/Rev.3/Corr.2, 2005: 9

Anticancer Medicinal Products

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Cytotoxic drugs

- alkylating agents
- antimetabolites
- anthracyclines
- (plant) alkaloids
- topoisomerase inhibitors

affect cell division / DNA synthesis

Cytotoxic drugs

- monoclonal antibodies
- tyrosine kinase inhibitors

targeted therapy

Early trials with cytotoxic drugs

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Primary focus for conventional cytotoxic drugs

- toxicity (Maximum Tolerated Dose, Dose Limiting Toxicity)
- tumour response
- eventually: tumour stabilisation

"The basic assumption governing the design of these (early phase-I) studies is that for dose finding purposes, toxicity is an acceptable endpoint."

For non-cytotoxic drugs, toxicity may not serve as suitable marker (case-by-case)

Guideline on the evaluation of anticancer medicinal products in man/EMEA/CPMP/EWP/205/95/Rev.3/Corr.2, 2005: 9

EU-Guideline on anticancer drugs

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"In most cases, patients with advanced disease and no available established treatment options constitute the target population for these trials.

Use of an experimental compound in patients with available treatment options may be appropriate when there is prior evidence of activity in patients failing the available treatment option. However, there are complex medical and ethical issues to be addressed when including these patients into Phase II trials.

If appropriately justified from the patient's perspective, window of opportunity studies may be acceptable."

Guideline on the evaluation of anticancer medicinal products in man/EMEA/CPMP/EWP/205/95/Rev.3/Corr.2, 2005: 9

EU-Guideline on anticancer drugs

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"Recruitment should be conducted according to a predefined plan that allows the objectives to be achieved with the smallest possible number of patients.

Frequently it is appropriate to apply predefined stopping rules for activity which is deemed too low and toxicity if deemed too high and to power the study to obtain a sufficiently precise estimate of anti - tumour activity to decide whether further studies are indicated."

Guideline on the evaluation of anticancer medicinal products in man/EMEA/CPMP/EWP/205/95/Rev.3/Corr.2, 2005: 9

Irinotecan (Camptosar®, Campto®)

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Drug characteristics

- topoisomerase-1-inhibitor with classical cytotoxic properties affecting all types of cells with high division rate
- derivative of camptothecin (plant alkaloid), 1960
- pro-drug with broad anti tumour activity
- first approved by Pharmacia & Upjohn in 1998 (US/ full approval)

Irinotecan (Camptosar®, Campto®)

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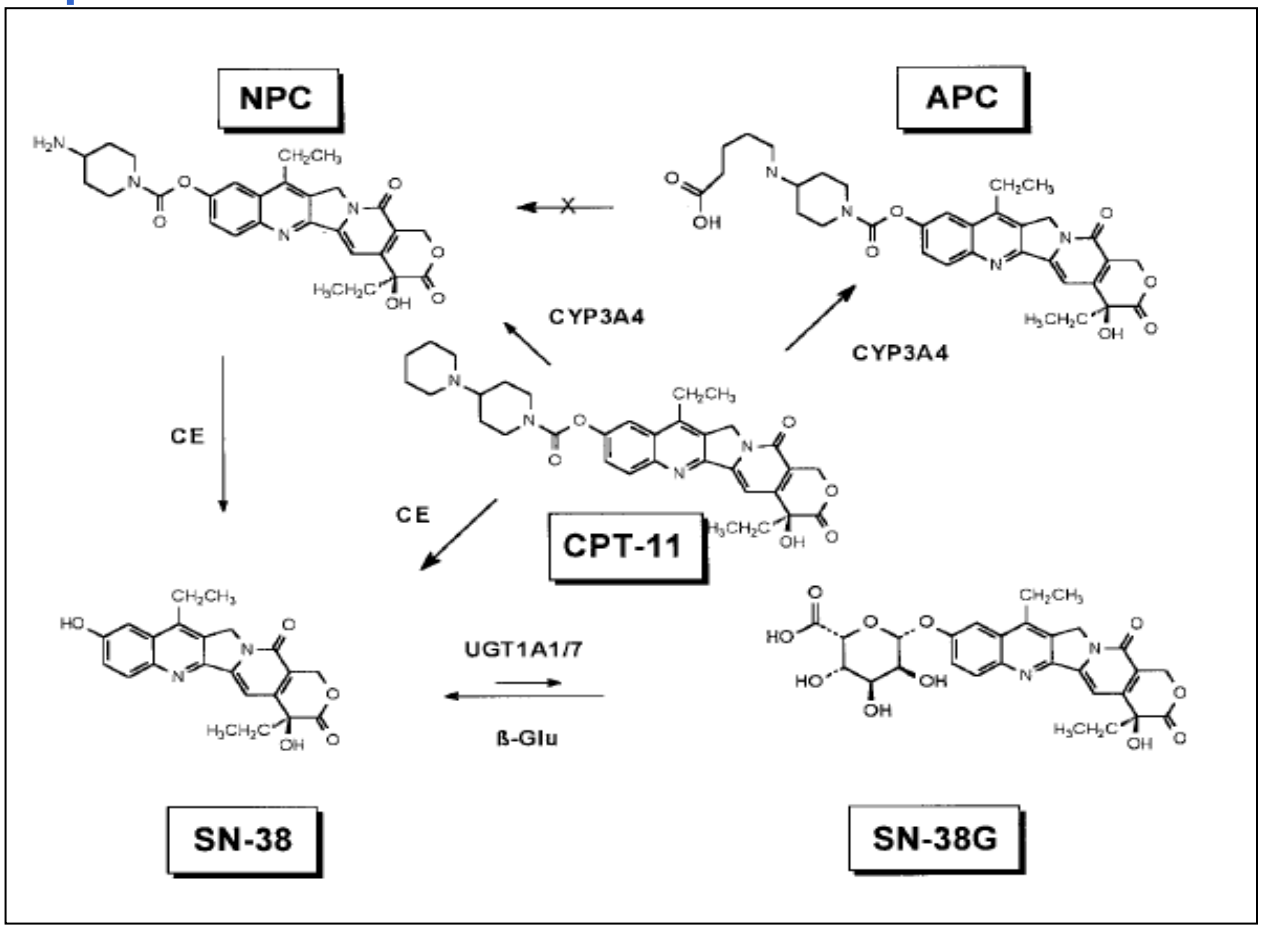
Complex pharmacokinetics



Mathijssen et al., Clinical Cancer Research, 2001: 7

Irinotecan (Camptosar®, Campto®)

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Basic properties and characteristics

- pro-drug of the active SN-38; activation by enzymatic cleavage of the bulky side-chain
- irinotecan is subject to extensive metabolic conversion with two different activation pathways
- final elimination as glucuronide (urinary and biliary secretion)
- contribution of esterases, UGT1A1, CYP3A4, p-glycoprotein, organic anion transporting proteins (high CV%)
- local activation in tumour cells is assumed

Extremely complex pharmacokinetic and pharmacological profile

Irinotecan: i.v. vs. oral

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Potential advantages of oral therapy

- activity of topoisomerase-1 inhibitors is schedule-dependent: low dose protracted favourable against intense short schedule (presence during active DNA-synthesis)
- high concentrations of tissue carboxylesterases in liver and GI-tract promotes presystemic conversion of irinotecan to SN-38
- low pH in stomach favours active lactone more than inactive carboxylate form
- conversion in the liver could result in higher concentration at the site of action for liver metastases

Chronic oral dosing might be advantageous with good cytotoxic effect and fewer side effect

Irinotecan – oral administration

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Phase-I-study: MTD, DLT, PK and food effect

- study participants
  - histologically confirmed diagnosis of malignant tumour
  - either refractory to conventional chemotherapy
  - or for whom no effective therapy existed
- subjects classified and selected based on performance scores commonly applied in oncology

Soepenberg O. Et al. Clin Cancer Res. 11, 2005

Irinotecan – oral administration

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Phase-I-study: selection of subjects

- performance Scores
  - ECOG (Eastern Cooperative Oncology Group), very similar to WHO score
  - southwest Oncology Group Performance Score
  - Karnofsky scoring (developed by David Karnofsky and Joseph Burchenal in 1949)
  - for children the Lansky Score is commonly applied with a more observational approach referring to typical childish behaviour

Soepenberg O. Et al. Clin Cancer Res. 11, 2005

Oral irinotecan: Patient selection

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ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

Oral irinotecan: Patient selection

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Karnofsky scoring

100	normal, no complaints, no signs of disease
90	capable of normal activity, few symptoms or signs of disease
80	normal activity with some difficulty, some symptoms or signs
70	caring for self, not capable of normal activity or work
60	requiring some help, can take care of most personal requirements
50	requires help often, requires frequent medical care
40	disabled, requires special care and help
30	severely disabled, hospital admission indicated but no risk of death
20	very ill, urgently requiring admission, requires supportive measures or treatment
10	moribund, rapidly progressive fatal disease processes
0	death

Patient selection: Children

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Lansky Score

100	fully active, normal
90	minor restrictions in strenuous physical activity
80	active, but tired more quickly
70	greater restriction of play *and* less time spent in play activity
60	up and around, but active play minimal; keeps busy by being involved in quieter activities
50	lying around much of the day, but gets dressed; no active playing participates in all quiet play and activities
40	mainly in bed; participates in quiet activities
30	bedbound; needing assistance even for quiet play
20	sleeping often; play entirely limited to very passive activities
10	doesn't play; does not get out of bed
0	unresponsive

Oral irinotecan: Phase-I-study

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Characteristics of the study participants – eligibility criteria

- southwest Oncology Group Performance Status 0-2
- limits for neutrophils, hemoglobin, platelets
- creatinine clearance ≥ 60 ml/min
- bilirubin level ≤ 2 ml/dl
- AST/ALT < 3 x normal range
- chemotherapy: 3 to 6 weeks washout
- radiation therapy: 4 weeks ago acceptable

Oral irinotecan: Phase-I-study

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Planned co-medication

- prophylactic antiemetics
- loperamide

High probability of interference with absorption process/ GI-transit must be accepted for medical reasons

DLT and MTD: Irinotecan Study

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Dose-limiting toxicity (Nat. Cancer Inst. Tox. Crit.)

- grade 4 neutropenia lasting for ≥ 5 days
- neutropenic fever (grade 4 ≥ 38,5°C) & infection (≥ grade 3)
- thrombocytopenia < 25 x 10^9 cells/L
- ≥ grade 3 diarrhea despite maximal loperamide support
- ≥ grade 2 nausea and vomiting failing maximal oral antiemetic therapy or leading to discontinuation for ≥ 3 days
- other ≥ grade 3 nonhematologic toxiaties (except alopecia)
- treatment delay due to drug-attributed toxicities > 2 weeks

Maximum tolerated dose (MTD)

- one dose level below the dose that induced DLT

Soepenberg et al., Clinical Cancer Research, 2005

Oral irinotecan: Phase-I-study

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Results after administration of irinotecan mixed in CranGrapeJuice®

- delayed diarrhea was the DLT-factor of this trial (direct effect of SN-38 on intestinal mucosa)
- for patients <65 years MTD was 66mg/m^2/d and DLT was 80 mg/m^2/d
- for patients ≥ 65 years MTD was 50 mg/m^2/d and DLT was 66 mg/m^2/d

Drengler et al. J Clin Onc

Oral irinotecan: Phase-I-study

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Results after administration of irinotecan mixed in CranGrapeJuice®

- virtually not hematologic toxicity was observed from 20 to 50 mg/m²/d
- partial remission of tumour: 1 patient
  stable disease: 17 patients
  progressive disease: 5 patients

Drengler et al. J Clin Onc

Oral irinotecan: PK-outcome

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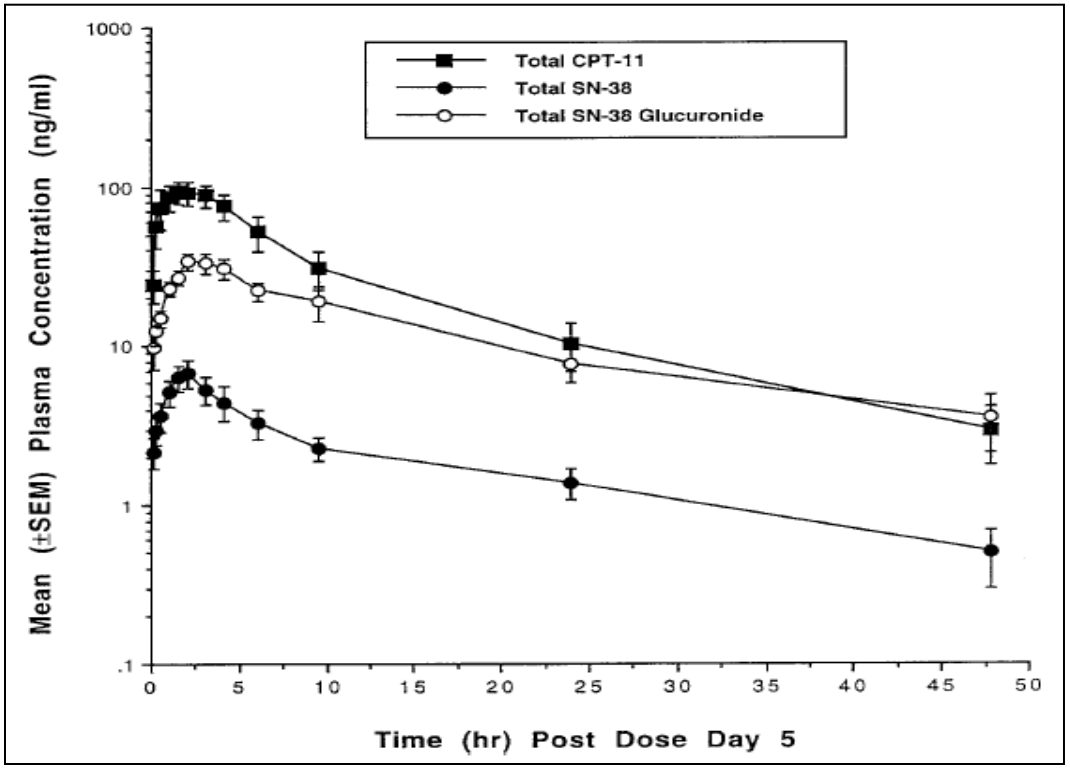
Major results



Drengler R. Letal., J Clin Oncol., 1999, 17

Irinotecan: i.v. vs. oral

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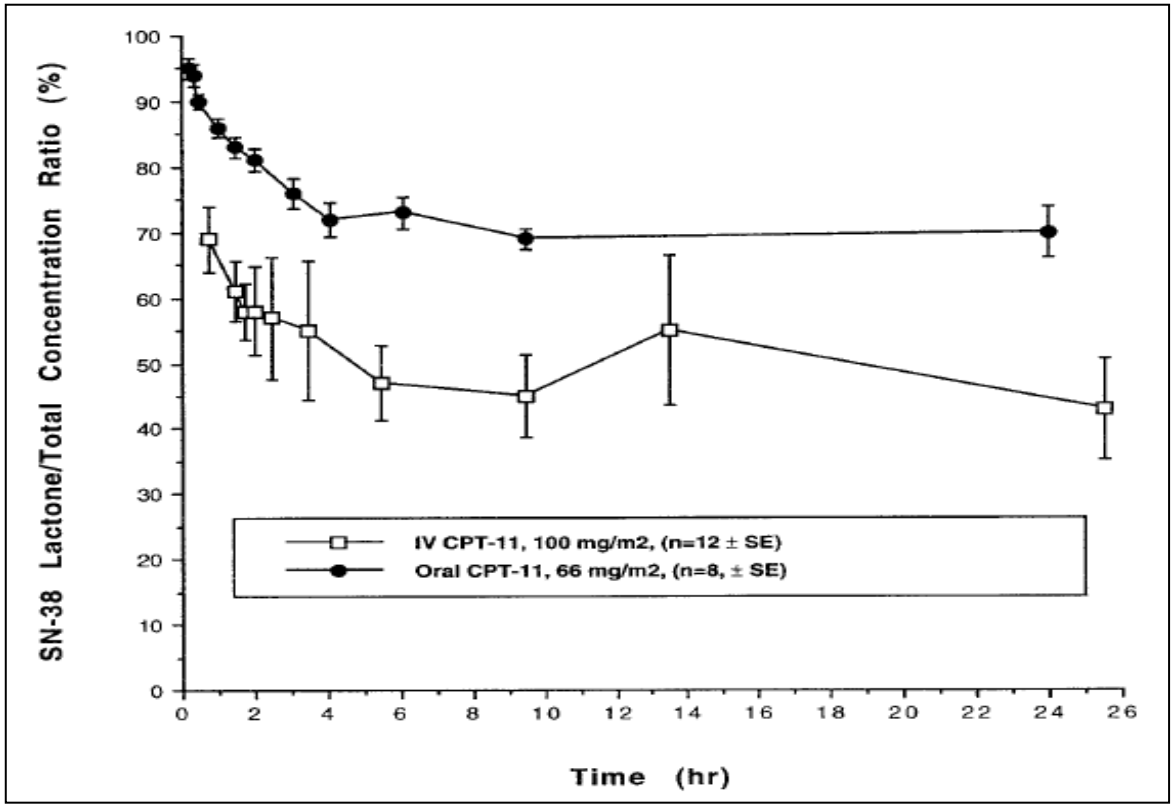

Ratio of SN-38 lactone concentration to SN-38 total concentration versus time. Data from the current study and from Sasaki et al.

Drengler R. Letal., J Clin Oncol., 1999, 17

Oral irinotecan: PK-outcome

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Major results

- relative ratio of total SN-38 to irinotecan about threefold higher compared with i.v.
- no relevant accumulation over 5 days of treatment
- no relevant food effect
- mean absolute bioavailability: 25 %

Phase-II-study with oral irinotecan have been started

BIBF 1120 - angiokinase inhibitor

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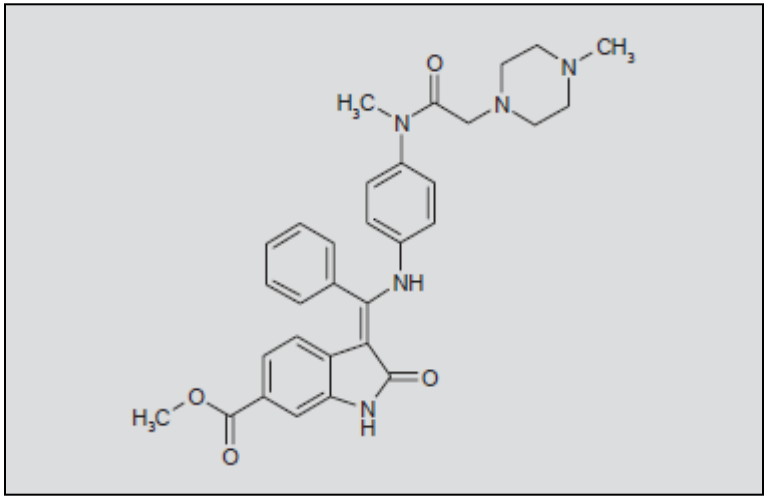
BIBF 1120 acts on three key receptor families

- vascular endothelial growth factor receptors (VEGFRs)
- platelet-derived growth factor receptors (PDGFRs)
- fibroblast growth factor receptors (FGFRs)



BIBF 1120 - angiokinase inhibitor

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Angiogenesis

- formation of new blood vessels
- fundamental to tumour growth and metastasis
- controlled by complex balance of different regulators
- antiangionetic drugs often develop resistance
- multitargeting tyrosine kinase inhibitors have been developed to circumvent resistance development

BIBF 1120 - development program

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Phase-I-studies

- monotherapy in advanced cancer patients (dose escalation for identification of MTD and DLT)
- combined phase-I-studies for identification of MTD and DLT in combination with
  - paclitaxel and carboplatin (gynaecology)
  - paclitaxel and carboplatin (lung cancer)
  - docetaxel (prostate cancer)
- PK-studies in healthy volunteers are acceptable due to the safety profile of the drug

BIBF 1120 – complex PK properties

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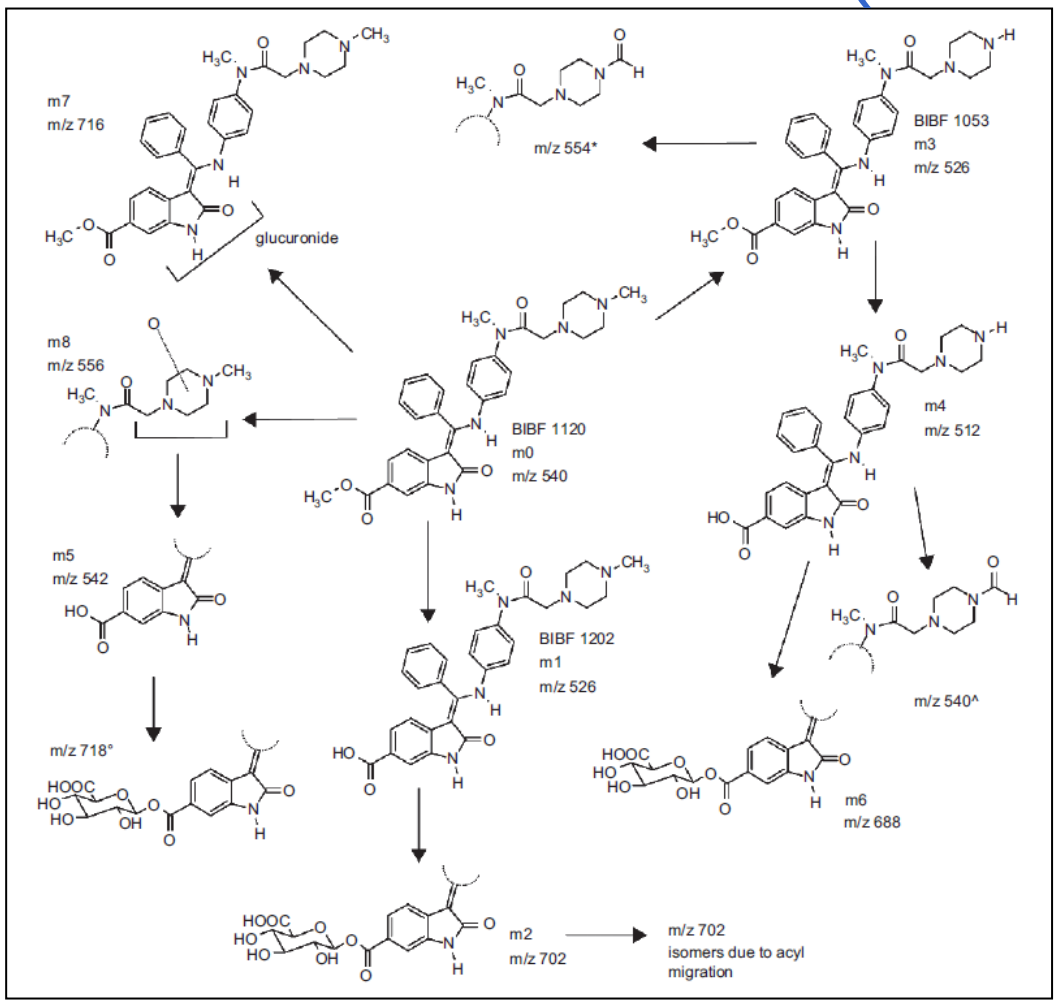
Metabolism of BIBF 1120 (PK in healthy subjects)



P. Stopfer et al, „Pharmacokinetics and metabolism of BIBF 1120 after oral dosing to healthy male volunteers“, 2011, 206

Bioequivalence trials in oncology

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When may BE (BA) studies become necessary?

- scale up
- post-approval changes / formulation development
- generic development

For which types of formulations?

- solid oral dosage forms (IR/ MR)
- liposomal formulations
- general: dosage form characteristics influencing systemic exposure of active moiety

Examples of relevance for BE-studies:

- capecitabine (Xeloda®)
- doxorubicin (Doxil®)

FDA-Guidances have been published

Example: capecitabine

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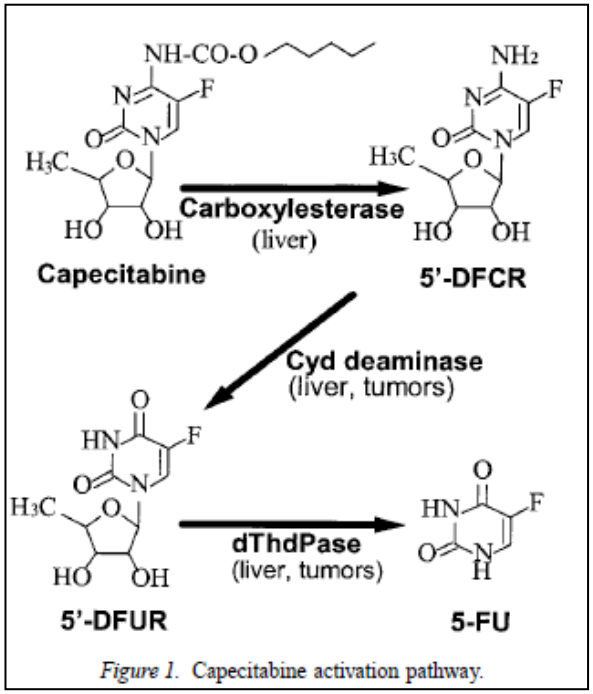

Figure 1. Capecitabine activation pathway.

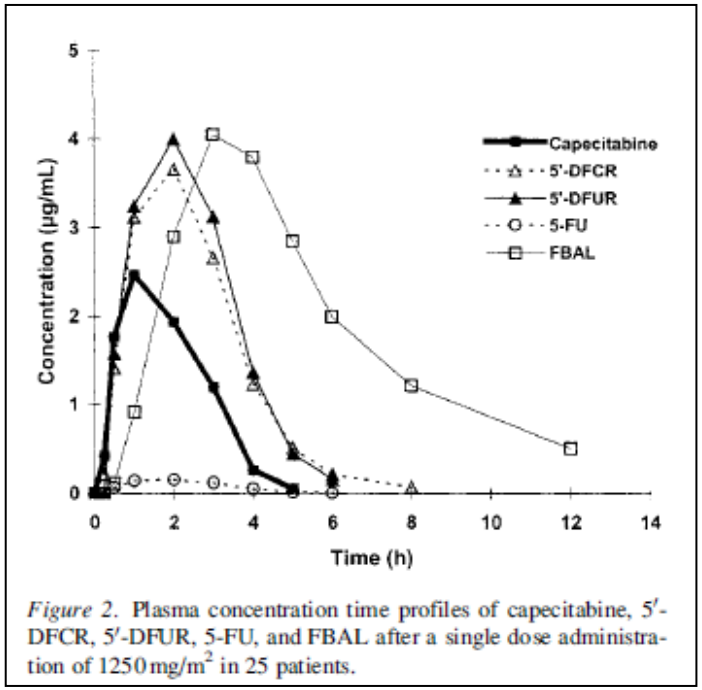

Figure 2. Plasma concentration time profiles of capecitabine, 5′-DFCR, 5′-DFUR, 5-FU, and FBAL after a single dose administration of 1250 mg/m^2 in 25 patients.

Pharmacokinetic properties

- complex metabolic pathway
- active metabolite (5-FU) with low systemic concentrations

Ian R. Judson, „A human capecitabine excretion balance and pharmacokinetic study after administration of a single oral dose of C-labelled drug“ in „Investigational New Drugs 17, 1999, 50
Karen S. Blesch, „Clinical pharmacokinetic/ pharmacodynamic and physiologically based pharmacokinetic modeling in new drug development: The capecitabine experience“ in „Investigational New Drugs 21, 2003, 197

Capecitabine BE-studies

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Challenges for study realisation

- administration to oncologic patients only
- highly-variable drug with regard to Cmax ...
- ... requires very high sample sizes for adequate power
- Xeloda® is administered with food according to SmPC

FDA-requirements for BE-studies

- type of study: fed (high-fat American breakfast)
- design: single-dose, two-way crossover
- strength: 500 mg
- subjects: cancer patients already receiving a stable twice-daily dosing regimen as prescribed

Draft Guidance on capecitabine, US-FDA

US-FDA requirements

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"The patients shall receive their own established capecitabine dosing regimen during the study as multiples of the 500 mg tablet. The dose administered to each patient should be the same between the two study periods. …dose should be included in the statistical model.
Due to the short half life of capecitabine and its metabolites (< 1 hour), the test and reference products may be dosed on two consecutive days.

Applicants may consider using a reference-scaled average bioequivalence approach, available evidence suggests that this is a highly variable drug substance/ product. As capecitabine is rapidly absorbed and the parent drug and its metabolites have very short half-lives, pharmacokinetic blood samples should be collected at appropriate intervals to assure accurate estimation of the pharmacokinetic parameters. Due to evidence of ex-vivo metabolism of 5´-DFCR to 5´-DFUR, please take adequate measures during blood collection to inhibit cytidine deaminase activity in blood and prevent ex-vivo metabolism of 5´-DFCR to 5´-DFUR."

Draft Guidance on capecitabine, US-FDA

US-FDA requirements

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"Cancer patients with mono-therapy are generally recommended for the BE studies. However, cancer patients receiving concomitant drug(s) are allowed to participate, provided:

- *The concomitant medication is the same for both study days and clearly documented.*
- *The subjects should follow the same dosing regimen for the concurrent medications for both periods of the BE study. Each concurrent medication should be well documented and clearly stated in the protocol.*
- *The concurrent medications do not interfere with the assay for measuring the drug or metabolite in plasma. Please should ensure that analytical interferences are ruled out during bioanalytical method validation"*

Draft Guidance on capecitabine, US-FDA

BE studies with capecitabine

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Challenges

- recruitment of a high number of oncologic patients with on-going Xeloda® therapy requires adapted infrastructure different to classical phase-I-studies in oncology
- comprehensive standardisation of study conditions with frequent blood samples and quick sample work-up is difficult to achieve in hospital surrounding
- high-fat American breakfast with up to 1.000 kcal is considered as *(unnecessary?)* burden for the seriously ill study participants

Short elimination half-life facilitates practical performance of the trial

Liposome-encapsulated doxorubicin

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Challenges

- biopharmaceutical characteristics of the liposomes require very long PK-characterisation
- guidance requires separate quantitation of free and encapsulated doxorubicin (validation of separation necessary)
- free doxorubicin is highly variable with regard to AUC & Cmax
- significant interference of the new formulation with the patient's therapy and thus ...
- ... significant risk of efficacy/safety related disadvantages in case of insufficient formulation characteristics (τ=4 weeks)

Request: In-vitro characterisation of the dosage form should *(nearly)* allow to omit the study !

Conclusion

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Early phase studies in oncology

- cytotoxics: patients with advanced disease / no available established treatment options
- non-cyctotoxics: patients or healthy subjects on a case-by-case decision basis

Later scale-up / post-approval changes / BE-studies

- cytotoxics: patients under standard therapy provided that interference with therapy is little and/or *in-vitro* data minimise the risk
- non-cyctotoxics: patients or healthy subjects on a case-by-case decision basis

Many thanks to ...

SocraTec R&D

... for comprehensive scientific and medical discussion

- Prof. Dr. Henning Blume
- Dr. Ralf-Steven Wedemeyer
- Dr. Frank Donath
- Dr. Ramon Villalobos-Hernandez

... for excellent technical support

- Marina Breit

Relevant Guidance's (EU)

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- Note for guidance on the pre-clinical evaluation of anticancer medical products (CPMP/ SWP/ 997/96)
- Guideline on the evaluation of anticancer medicinal products in man (CPMP/ EWP/ 205/ 95)
- Points to Consider on application with
  - meta-analyses
  - one pivotal study (CPMP/ EWP/ 2330/ 99)
- Concept Paper on the development of a CPMP note for guidance on the clinical pharmacokinetic investigation of the pharmacokinetics of peptides and proteins (CPMP/ EWP/ 226/ 02)

Relevant Guidance's (EU)

SocraTec R&D

- Reflection Paper on the regulatory guidance for the use of Health-Related Quality of Life (HRQL) measures in the evaluation of medicinal products (CPMP/ EWP/ 139391/ 04)
- Draft Guideline on clinical trials in small populations (CPMP/ EWP/ 83561/ 2005)
- Note for Guidance on evaluation of anticancer medicinal products in man: Addendum on Paediatric Oncology (CPMP/ EWP/ 569/ 02)
- Points to Consider of diagnostic agents (CPMP/ EWP/ 1119/ 98)