Drug-drug interaction studies in oncology –
A regulatory perspective

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This presentation reflects my personal opinion as a scientist.
It does not necessarily represent the official view of the BfArM.
Topics

• Regulatory basis
• Assessment during Clinical Trial Application
• Oncology patient factors
• Drug examples and assessment for approval
• Conclusions
Regulatory basis

- Guideline on the evaluation of anticancer medicinal products in man, Draft (EMA/CHMP/205/95/rev. 4)


- Guideline on Summary of Product Characteristics - SmPC (September 2009)
Anticancer guideline (1)

- No explicit guidance on DDI studies in oncologic patients foreseen in the current draft guideline
- Recommendations for combination therapy studies
- **4. Pharmacokinetics**
  - Due to importance ... for understanding the clinical pharmacology of the investigational drug, including DDI assessment, mass-balance studies are strongly recommended.
  - Studies in patients with impaired organ function should mainly be selected based on prior information on the elimination route and formation/elimination of potential pharmacologically active metabolites.
  - Recommended to collect sparse samples in phase III trials for evaluation of intrinsic factors through popPK modelling and understanding the exposure-response relationships for the drug
Anticancer guideline (2)

6.3.1 Combination therapy studies of cytotoxic compounds

→ While the degree of efficacy for a new combination relies on assumptions, it is often possible to predict toxicity, based on the toxicities of the individual drugs.

→ Factors influencing toxicity (organ dysfunction, concomitant therapy) should be explored as appropriate.

→ As the sequence of administration may be of importance with respect to potential PK interactions and anti-tumour activity, this has to be accounted for in the design of the studies.

→ If relevant PK interactions can be excluded, dose-finding studies may be initiated at about half the recommended mono-therapy dose, e.g. to start at the full recommended mono-therapy dose for one of the compounds and reduced dose (<50%) for the other compound.
6.2 Non-cytotoxic compounds

→ Based on preclinical findings, early trials may sometimes be conducted in healthy volunteers.

→ In accordance with the guidance for cytotoxic compounds, availability of established therapies should be regarded as an exclusion criterion for phase I.

→ Eligibility criteria and number of patients should be defined according to the objectives of the study, taking into account variability in PK and PD

6.3.2 Combinations involving a non-cytotoxic drug

→ Selected chemotherapy regimen combined with the new non-cytotoxic drug should normally be “best available”, except strong pharmacological arguments against

→ Research aiming at understanding the mechanisms and prerequisites for the add-on effects is encouraged
DDI guideline (1)

- Interaction studies are usually performed in healthy adults although in some cases, e.g. tolerability, patients could be included.
- Consider interactions at the level of absorption, distribution and elimination.
- Potential for PK interactions should both be investigated for effects of other drugs on the investigational drug and vice versa.
- If an altered metabolite exposure may result in an altered efficacy or safety, investigate risk of clinically relevant PK interactions by metabolites
4.2 **Effects of other drugs on the investigational drug**

- If *in vitro* data indicate a possible clinically relevant interaction with a drug that cannot be excluded from the phase II or III studies, it is recommended to perform *in vivo* interaction studies with these drugs prior to phase II or III.

4.7.3 **Effects of the investigational drug on other drugs**

- Mainly intended to evaluate extent of inhibition or induction of an enzyme or transporter.

- Based on the interaction studies with probe drugs, the results are used to predict interactions with other drugs which are substrates for the same enzyme/transporter and which are likely affected in a clinically relevant manner to provide adequate treatment recommendations for the other drugs.
4.2.3 Metabolism

- For enzymes in metabolic pathways - CYP and non-CYP enzymes - contributing to ≥ 25% of drug or active metabolite elimination, quantify the in vivo contribution.

- If interaction with strong inhibitor results in marked effect on exposure of the drug - potentially leading to dose adjustments, contraindications or other specific recommendations - → recommended to perform additional study with a moderate enzyme inhibitor

- Appendices VI - VIII list
  → examples of strong enzyme inhibitors
  → probe drugs
  → Classification of inhibitors
    - strong: >5-fold ↑ in AUC or >80% ↓ of oral clearance
    - moderate: >2-fold ↑ in AUC or 50 - ≤80% ↓ of oral clearance
    - mild: 1.25 - 2-fold ↑ in AUC or ≤50% ↓ of oral clearance
4.4.7 Population PK analysis

- If conventional DDI studies with rich sampling cannot be performed, potential for interactions may be investigated in a well performed population PK analysis on high quality data from sparse samples (i.e. phase II/III data).
- Mainly appropriate when interaction study is performed in patients
- To detect unexpected interactions
- To investigate the effects of other drugs on the investigational drug
- Information obtained in the popPK analysis may be used in the product information but need to be worded properly, e.g.

  “a population PK analysis based on phase III data, indicated that concomitant treatment with drug X at a dose range y-z mg reduced the systemic exposure by on average w% (range).”
**DDI and SmPC guideline**

**Translation into treatment recommendations**
- Treatment recommendations should ensure that patients receive effective and safe treatment.
- “Caution is advised” to be avoided in favour of a recommendation on proposed actions.
- Detailed information about drug interactions in the SmPC section 4.5 cross-referring to the sections 4.2, 4.3 or 4.4 if relevant.
  - 1. Interactions affecting the investigational drug.
  - 2. Interactions resulting in effects on other drugs.
    Inside these subsections,
    - contraindicated combinations,
    - those where concomitant use is not recommended,
    - others.
- Clinical manifestations, effects on exposure, duration on discontinuation.
- If limited therapeutic alternatives exist due to DDI with most drugs of the same class, examples of less interacting drugs could be given.
CTA: Clinical assessment (1)

- If drug can be administered to healthy volunteers, no patient must be harmed
- Ethical considerations \(\rightarrow\) Declaration of Helsinki:
  - 31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects
- Important to maintain gold standard therapy for the respective population
- Not acceptable to withdraw concomitant or supportive care medication for study reasons
CTA: Clinical assessment (2)

- **For approved drugs:**
  - Do patients need this therapy?
    A benefit is to be expected in these patients

- **For drugs under development:**
  - Dependent on current knowledge, e.g. animal models or tumour models, decide on the patient population:
    e.g. patients with no further treatment options

- **B/R evaluated for every drug substance under development**
CTA: Clinical assessment (3)

Possible Designs:

- "Classic" DDI study as sub-study:
  - e.g. 1 week of run-in DDI study, thereafter investigational drug and/or standard or combination with therapeutic intention
  - Therapy should not be postponed for too long, e.g. 4 weeks not acceptable

- Add-On therapy:
  - DDI/PK often investigated as secondary parameter during dose finding, primary parameter is clinical safety as of DLT/MTD.
  - Cytotoxic drug might reduce tolerability of standard therapy: dose reduction for beneficial dose of therapeutic standard not acceptable
Cancer patient factors (1)

- **Advantages:**
  - Clinical real-life situation
  - Possibly higher sensitivity
  - Allows studying PD effects

- **Disadvantages:**
  - Concurrent conditions
  - Concomitant medications
  - High inter- and intra-subject variability
  - Wash-out of concomitant treatment impossible
  - Placebo unethical
  - Often only sparse blood sampling
Cancer patient factors (2)

- **Conditions, e.g.:**
  - Elderly patients
  - Renal impairment
  - Hepatic impairment
  - Myelosuppression
  - Infections, mucositis
  - Low performance status
  - Cardiac diseases
  - Tumour pain
  - Ability to swallow drugs
  - Refractory nausea/vomiting
  - Malabsorption
Cancer patient factors (3)

- Treatment factors, e.g:
  - Previous chemotherapy → renal impairment, myelosuppression, cardiac toxicities, hepatic impairment
  - Concomitant and supportive care →
    Aprepitant: substrate of CYP3A4, mild inhibitor/inducer of CYP2C9, 3A4
    Antidepressants (SSRI): inhibitors of 2C9, 2D6
    Phenprocoumon: substrate of 2A6, 2C9, 3A4
    Dexamethasone: strong inducer of CYP2C9, 3A4/5 and Pgp
    Tramadol: substrate/activation by polymorph 2D6
    Cotrimoxazole: active renal secretion, CYP2C9 inhibitor
    Aciclovir: active renal secretion
    Metoclopramide: ↑ GI motility; 2D6 inhibitor
    Omeprazole: ↑ GI pH; 2C19 inhibitor, 3A4 inducer
Examples: Pazopanib (1)

• Indication: Advanced renal cell carcinoma
• Substance class: TKI of VEGFR, PDGFR and c-KIT
• Recommended dose: 800 mg pazopanib od
• Metabolism: primarily CYP3A4, minor 1A2 and 2C8
  Substrate for P-gp and BCRP
• Rationale for DDI: Conditional approval with follow-up measure to examine DDI with ketoconazole
• Design:
  Repeat-dose, single sequence, in patients with solid tumours
  – Period I: 400 mg pazopanib od for at least 7 consecutive doses.
    PK sampling over 24h at the end of Period I
  – Period II: 400 mg pazopanib and 400 mg ketoconazole od for 5 consecutive doses. PK sampling over 24h at the end of Period II
  – After DDI completion, eligible patients could have transitioned to follow-up study or ended their study participation.
Examples: Pazopanib (2)

- **Results:**
  - AUC $\uparrow$ 66%
  - $C_{\text{max}} \uparrow$ 45%

- **Assessment:**
  - Pazopanib dose reduction required to achieve systemic exposure similar 800 mg od without CYP3A4 inhibition

- **SmPC section 4.5:**
  1. detailed description of study treatments and results
  2. Warning of likely significantly higher exposure in combination:
     “Concomitant use of pazopanib with a strong CYP3A4 inhibitor should be avoided.
     If no medically acceptable alternative to a strong CYP34A inhibitor is available, the dose of pazopanib should be reduced to 400 mg daily during concomitant administration (see section 4.4).
     In such case attention to adverse drug reaction should be intensified, and further dose reduction may be considered if possible drug-related adverse events are observed.”
Examples: Bortezomib (1)

- **Indication:** Multiple Myeloma
- **Substance class:** Proteasome inhibitor
- **Metabolism:** weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 3A4
- **Rationale for DDI:** Addition of bortezomib to standard melphalane-prednisone treatment
- **Design:** PK-substudy of pivotal phase III study
  Full concentration-time profiles at c1/d25 and c2/d4 during first 2 treatment cycles of 21 evaluable (of 27) patients
- **Recommended dose:**

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Examples: Bortezomib (2)

- **In/Ex Criteria:**
  $\geq 65$ years, Platelets $\geq 100 \times 10^9$/L, Hb $\geq 8$g/dL, ANC $\geq 1 \times 10^9$/L, AST/ALT $\leq 2.5 \times \text{ULN}$, Bili $\leq 1.5 \times \text{UL}$; uncontrolled CV/other disease likely to interfere

- **ConMed:** like total study population

- **Result:**
  AUC $\uparrow$ by 17%
  Cmax $\downarrow$ by 9%
  CIs beyond reg. ranges due to high variability

- **Assessment:** Supportive clinical data showed no changes in dose intensities of melphalane and bortezomib

- **SmPC section 4.5:**
  “A drug-drug interaction study assessing the effect of melphalan-prednisone on bortezomib showed a 17% increase in mean bortezomib AUC based on data from 21 patients. This is not considered clinically relevant.”
Examples: Vemurafenib (1)

- **Indication:** BRAF V600 mutation-positive unresectable or metastatic melanoma
- **Substance class:** Inhibitor of BRAF serine-threonine kinase
- **Recommended dose:** 960 mg bid
- **Metabolism:** low; inhibits 2C9 and 2C19, other isoenzymes to lesser extent; 3A4 inducer
- **Rationale for DDI:** Effect on PK of cocktail of 5 CYP substrates (1A2-Caffeine, 2C9-warfarin, 2C19-omeprazole, 2D6-dextromethorphan, 3A4-midazolam)
- **Design:** 20 V600E+ melanoma patients
  - d1 single doses of substrates, PK d1-5
  - from d6 ongoing vemurafenib at RD, PK d19
  - d20 coadministration with substrates, PK d20-25
  - After DDI part, continuing study treatment
Examples: Vemurafenib (2)

- **In/Ex Criteria:** Adequate hematologic, renal, liver function, no poor metabolisers
  
  no refractory nausea/vomiting precluding adequate absorption

- **ConMed:**
  
  no CYP substrates;
  inhibitors/inducers not prohibited

- **Result:**
  
  1A2 inhibition: AUC caffeine $\uparrow$ 2.5-fold
  
  3A4 induction: AUC midazolam $\downarrow$ to 32%
  
  2C9 mild induction: AUC S-warfarin $\uparrow$ by 20%
  
  no DDI for other CYPs

- **Assessment:**
  
  effects on CYP1A2 and on 3A4 clinically relevant
  
  small effect on 2C9, but warning on potential need of warfarin dose adjustment

- **SmPC sections 4.4 and 4.5:**
  
  Detailed information on warnings and interactions also from *in vitro* for Pgp
Examples: Vemurafenib (3)

4.4 Special warnings and precautions for use

Effects of vemurafenib on other medicinal products
Vemurafenib may increase the plasma exposure of medicinal products predominantly metabolized by CYP1A2 and decrease the plasma exposure of medicines predominantly metabolized by CYP3A4, including oral contraceptives. Dose adjustments for medicinal products predominantly metabolized via CYP1A2 or CYP3A4 should be considered based on their therapeutic windows before concomitantly treating with vemurafenib (see sections 4.5 and 4.6).

Exercise caution and consider additional INR (International Normalized Ratio) monitoring when vemurafenib is used concomitantly with warfarin.

Effect of other medicinal products on vemurafenib
Vemurafenib pharmacokinetics could be affected by medicines that inhibit or influence P-gp (e.g., verapamil, clarithromycin, cyclosporine, ritonavir, quinidine, dronedarone, amiodarone, itraconazole, ranolazine) (see section 4.5).

Concomitant administration of potent inducers of P-gp, glucuronidation, CYP3A4 (e.g., rifampicin, rifabutin, carbamazepine, phenytoin or St John’s Wort [hypericin]) should be avoided when possible (see section 4.5). Alternative treatment with less inducing potential should be considered to maintain the efficacy of vemurafenib.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of vemurafenib on CYP substrates
CYP1A2 inhibition was observed when a single dose of caffeine was co-administered after repeat dosing with vemurafenib for 15 days. This resulted in an average 2.5-fold increase (maximum up to 10-fold) in caffeine plasma exposure after vemurafenib treatment. Vemurafenib may increase the plasma exposure of substances predominantly metabolized by CYP1A2 and dose adjustments should be considered.

CYP3A4 induction was observed when a single dose of midazolam was co-administered after repeat dosing with vemurafenib for 15 days. This resulted in an average 32% decrease (maximum up to 80%) in midazolam plasma exposure after vemurafenib treatment. Vemurafenib may decrease the plasma exposure of substances predominantly metabolized by CYP3A4. On this basis, the efficacy of contraceptive pills metabolized by CYP3A4 used concomitantly with vemurafenib might be decreased. Dose adjustments for CYP3A4 substrates with narrow therapeutic window should be considered (see section 4.4 and 4.6).

Mild induction of CYP2B6 by vemurafenib was noted in vitro at a vemurafenib concentration of 10 μM. It is currently unknown whether vemurafenib at a plasma level of 100 μM observed in patients at steady state (approximately 50 μg/ml) may decrease plasma concentrations of concomitantly administered CYP2B6 substrates, such as bupropion.

When a single dose of warfarin was co-administered after repeat dosing with vemurafenib for 15 days, some patients exhibited increased warfarin exposure (mean 20%) (see section 4.4). Caution should be exercised when vemurafenib is co-administered with warfarin (CYP2C9) in patients with melanoma.

Due to the long half-life of vemurafenib, the full inhibitory effect of vemurafenib on a concomitant medicinal product might not be observed before 8 days of vemurafenib treatment. After cessation of vemurafenib treatment, a washout of 8 days might be necessary to avoid an interaction with a subsequent treatment.

Effects of vemurafenib on substance transport systems
In vitro studies have demonstrated that vemurafenib is an inhibitor of the efflux transporter (P-gp). The clinical relevance of this finding is unknown. It cannot be excluded that vemurafenib may increase the exposure of other medicines transported by P-gp.

The possible effect of vemurafenib on other transporters (e.g., BCRP) is currently unknown.

Effects of concomitant medicines on vemurafenib
In vitro studies suggest that CYP3A4 metabolism and glucuronidation are responsible for the metabolism of vemurafenib. Biliary excretion appears to be another important elimination pathway. There are no clinical data available showing the effect of strong inducers or inhibitors of CYP3A4 and/or transport protein activity on vemurafenib exposure. Vemurafenib should be used with caution in combination with potent inhibitors of CYP3A4, glucuronidation and/or transport proteins (e.g., ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, atazanavir).

Concomitant administration of potent inducers of P-gp, glucuronidation, and/or CYP3A4 (e.g., rifampicin, rifabutin, carbamazepine, phenytoin or St John’s Wort [hypericum perforatum]) may lead to supoptimal exposure to vemurafenib and should be avoided.

In vitro studies have demonstrated that vemurafenib is a substrate of the efflux transporter, P-gp. The effects of P-gp inducers and inhibitors on vemurafenib exposure are unknown. It cannot be excluded that vemurafenib pharmacokinetics could be affected by medicines that inhibit or influence P-gp (e.g., verapamil, clarithromycin, cyclosporine, ritonavir, quinidine, dronedarone, amiodarone, itraconazole, ranolazine).

It is currently unknown whether vemurafenib is a substrate also to other transport proteins.
Examples: Pemetrexed (1)

- **Indication:** NSCLC, malignant pleural mesothelioma
- **Substance class:** Folic acid analogue, antimetabolit
- **Recommended dose:** 500 mg/m² BSA iv every 3 weeks
- **Metabolism:** Minimal; 70-90% renally unchanged within 24h with active tubular secretion
- **Rationale for DDI:** Investigation of NSAIDs/ASA effects on renal clearance due to structural similarity to MTX and its established DDI
- **Design:** Substudy within dose-finding study in 24 advanced cancer patients with mild renal impairment of GFR ≥ 60ml/min
  - ASA 325 mg or Ibuprofen 400 mg every 6h for 2d until 1 hour prior to pemetrexed 500 mg/m² iv
- **ConMed:** Dexamethasone, folic acid, vitamin B12
Examples: Pemetrexed (2)

- **In/Ex Criteria:**
  GFR ≥60 mL/min,
  ANC ≥1.5x10⁹/L, platelets≥100 x10⁹/L

- **Result assessment:**
  No significant effect on PK of pemetrexed by ASA 4x325mg/d.
  Significant 20% ↑ AUC, 15% ↑ £max
  and 17% ↓ of CL by 1600 mg/d ibuprofen

- **SmPC section 4.5:**

  In patients with normal renal function (creatinine clearance ≥ 80 ml/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen > 1600 mg/day) and aspirin at higher dose (≥ 1.3 g daily) may decrease pemetrexed elimination and, consequently, increase the occurrence of pemetrexed adverse events. Therefore, caution should be made when administering higher doses of NSAIDs or aspirin, concurrently with pemetrexed to patients with normal function (creatinine clearance ≥ 80 ml/min).

  In patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min), the concomitant administration of pemetrexed with NSAIDs (e.g. ibuprofen) or aspirin at higher dose should be avoided for 2 days before, on the day of, and 2 days following pemetrexed administration (see section 4.4).

  In the absence of data regarding potential interaction with NSAIDs having longer half-lives such as piroxicam or rofecoxib, the concomitant administration with pemetrexed in patients with mild to moderate renal insufficiency should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration (see section 4.4).
Conclusions

- Increasing interest of regulatory authorities on drug-drug interactions to improve clinical safety
- SmPCs should provide as precise recommendations as possible
- If possible, study DDI in healthy volunteers, e.g. for non-cytotoxic drugs
- If DDI studies are not possible, put emphasis on high quality non-clinical and mass-balance data and use PBPK modelling
- No definite regulatory guidance on DDI studies in oncology patients
- Study decisions remain on a case-by-case basis dependent on the drug substance