When Population PK modeling helps drive oncology phase I trial: First implementation of Exposure Driven dose Escalation With Overdose Control (ED-EWOC) design

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ED-EWOC as a new design for dose finding trials

• ED-EWOC can provide benefit through **exposure quantification** in the dose escalation process and in the dose recommendation:
  – When PK **variability** is large (and particularly when it can be explained by **covariates**)
  – When PK is **non linear**

• Methodology explored using simulations of similar CRM-designs[1]

• **Implemented**
  – in a multi center, open label, phase I, dose finding study in patients with late stage cancer
  – Pilot, actual dose escalation in the study was driven by EWOC

AUC explains DLT better than dose
AUC explains DLT better than dose

R² = 0.28
AUC explains DLT better than dose

AUC and DLT

DOSE and DLT

R² = 0.28

R² = 0.44
Exposure driven EWOC is an iterative adaptive process

Treat a cohort of patients at recommended Dose (RD)
- Nb. DLT
- Concentrations in blood

Informed decision by investigators on next dose

Check stopping rules
- Apply safety rules
- Assess new RD

Stop trial and declare Maximum Tolerated Dose

ED-EWOC specific

Update Dose - Exposure relationship
PopPK analysis

Update Exposure-DLT rate relationship

Compute integrated dose-DLT rate relationship
Get predictive probability of DLT

Stop trial and declare Maximum Tolerated Dose
From Cohort 3 (2.5mg) to Cohort 4 (2.75mg): dose recommendation with ED-EWOC

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**Recommended dose:** 2.75mg  
**Recommended AUC:** 8500 pg.h/mL

*Integrated Dose-AUC-DLT rate*

**Targeted toxicity**  
**Under dosing**  
**Overdosing**

AUC = Predicted AUC (pg.h/mL)

AUC = 1000 pg.h/mL  
AUC = 1500 pg.h/mL  
AUC = 2000 pg.h/mL

DLT (days)
Learnings and conclusion

Key results
- The process for dose escalation recommendation from ED-EWOC was smooth, (well specified responsibilities)
- ED-EWOC is implementable from an operational perspective, (1 additional week required for data analysis and for running design)

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<td>Advantage /</td>
<td>• Quite simple</td>
<td>• Quantitate the impact of PK variability on clinical endpoint</td>
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<td>Benefit</td>
<td>implementation</td>
<td>• Characterization of PK and PD related uncertainty</td>
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<td>• Software available</td>
<td>• Leverage prior knowledge on PK, PD</td>
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<td>(CRMPack)</td>
<td>• In line with the recent EMA Guideline recommendations[2]</td>
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<tr>
<td>Requirements</td>
<td>• Define priors on dose-DLT</td>
<td>• Define priors on dose-exposure DLT rate</td>
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<tr>
<td></td>
<td>rate</td>
<td>• population PK model developed at time of protocol set up</td>
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<tr>
<td></td>
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<td>• Team agility, PK bioanalysis and data availability</td>
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Next steps
- Quantify the gains of ED-EWOC as compared to EWOC:
  - non-linear PK, large PK variability
- Expand ED-EWOC methodology to PD biomarker to find safe pharmacology active doses
- New application to any other type of dose finding trials

Doing now what patients need next
From Cohort 3 (2.5mg) to Cohort 4 (2.75mg): dose recommendation with ED-EWOC

Recommended dose: 2.75mg as next recommended dose
EWOC dose escalation on a monotherapy study vs. ED-EWOC dose recommendation: An overview

**Cohort 0**
- Dose: 1mg
- 2 Pats, 0 DLT
- AUC: 8000 pg.hr/mL

**Cohort 1**
- Dose: 2.5mg
- 3 Pats, 2 DLT

**Cohort 2**
- Dose: 4.75mg
- 3 Pats, 2 DLT

**Cohort 3**
- Dose: 2.5mg
- 2 Pats, 0 DLT
- AUC: 9000 pg.hr/mL

**Cohort 4**
- Dose: 3.25mg
- 3 Pats, 1 DLT
- AUC: 9000 pg.hr/mL

**Cohort 5**
- Dose: 3.25mg
- 4 Pats, 1 DLT
- AUC: 8500 pg.hr/mL

**Rec. Dose**
- 3mg
- AUC: 9000 pg.hr/mL

**Stop!**
- Recommended dose: 3.25mg

**Pop PK model update**
- two compartment model
- zero order absorption
- linear clearance
- two compartment model
- 1st-order absorption
- non-linear clearance

**Fit**
Exposure driven EWOC is an iterative adaptive process

Treat a cohort of patients at recommended Dose (RD) and get data:
• Nb. DLT-evaluable pts at current dose,
• Nb. DLT
• Concentrations in blood

Informed decision by investigators on next dose

Stop trial and declare MTD

- Check stopping rules
- Apply safety rules
- Assess new RD

Update Dose - Exposure relationship
PopPK analysis

Update Exposure-DLT rate relationship based on DLT data for evaluable patients

Compute integrated dose-DLT rate relationship
Get predictive probability of DLT

Stop trial and declare MTD
Operational considerations

Data collection and analysis flow

- The amount of information available varies between patients, due to time required for PK analysis and data review.

- PK data from previous cohorts inform the pop PK model as dose escalation proceeds.
From Cohort 3 (2.5mg) to Cohort 4 (2.75mg): dose recommendation with ED-EWOC

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**Integrated Dose-DLT rate**

- **Recommended dose:** 2.75mg
- **Recommended AUC:** 8500pg.h/mL

- **Overdosing**
  - AUC=2000pg.h/mL
  - DLT rate

- **Targeted toxicity**
  - AUC=1500pg.h/mL
  - DLT rate

- **Under dosing**
  - AUC=1000pg.h/mL
  - DLT rate

**Predicted AUC (pg.h/mL)**

**Dose (mg)**
Doing now what patients need next