A product-profile-driven clinical utility index (CUI) analysis to balance benefits and risks for dose selection in oncology

Bill Poland (1), Russ Wada (1), Qi Liu (2), Luna Musib (2), Daniel Maslyar (2), Eunpi Cho (2), Wei Yu (2), Han Ma (2), Jin Yan Jin (2), Nageshwar Budha (2), Rui Zhu (2)

(1) Certara, Menlo Park, CA, USA; (2) Genentech, Inc., South San Francisco, CA, USA

Objectives

(1) Characterize exposure-efficacy and exposure-safety relationships for ipatasertib (**Ipat**) in combination with abiraterone in patients with metastatic castration-resistant prostate cancer (**mCRPC**).

(2) Trade off benefits and risks vs. dose to support phase III dose selection

(3) Compare this CUI implementation to others recently used in oncology

Background

- Ipat is a potent, novel, selective, ATP-competitive, small-molecule inhibitor of the activated form of Akt that disrupts PI3K/Akt signaling, which is involved in cancer pathogenesis.
- It is rapidly absorbed (Tmax 1-2 hrs) with mean effective half-life of ~24 hours.
- Combining ipat with abiraterone (an androgen synthesis inhibitor) may show improved anti-cancer activity over abiraterone alone in metastatic prostate cancer
- The A.MARTIN Phase II Study [1] randomized 240 mCRPC patients 1:1:1 to abiraterone + Ipat 400mg QD/200mg QD/placebo.
  - Radiographic progression-free survival (**rPFS**) hazard ratio (**HR**) vs. placebo for
    - 400mg: 0.75 (90% CI: 0·54-1·05)
    - 200mg: 0.94 (90% CI: 0.69-1.28).
  - At 400mg, diarrhea, hyperglycemia, and rash (reversible and manageable) increased modestly vs. placebo.

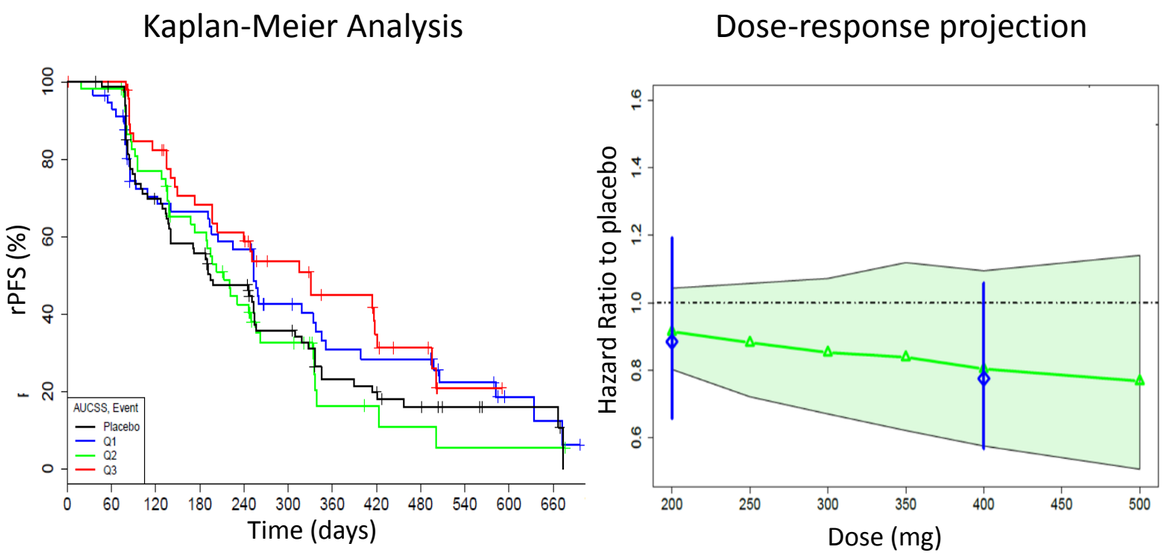
Methods

- Dose intensity modeling accounted for dose modification.
- A proportional-hazards model characterized exposure-efficacy (ER) in terms of rPFS HR, with lognormal uncertainty.
- Logistic regression models characterized exposure-diarrhea and exposure-rash in terms of probability of grade ≥3 adverse events (AEs), with lognormal uncertainty.
- CUI analysis (multi-criteria decision analysis) put these endpoints onto the same scale and combined them.
  - $CUI = \sum w_i U_i(x_i)$ where x_i = endpoint, w_i = weight, U_i = endpoint utility function
- Pre-defined minimal, target, and optimistic product profiles (**PPs**) determined utility scales for each endpoint.
- The safety endpoints were weighted 40% (30% diarrhea + 10% rash) in the CUI function.
- Sensitivity analyses varied these weights and the AE grade threshold (3 vs. 2).

Results

- Efficacy showed a modest trend toward improvement at higher exposures.
- Safety endpoints showed consistent worsening over the exposure range.
- CUI results with sensitivity analysis supported a 400 mg QD phase III dose.
  - This dose had higher expected utility and probability of reaching minimal and target PPs than other doses evaluated (Figure 3).

Figure 1. Exposure-efficacy model



Results (continued)

Figure 2. Example of exposure-AE models

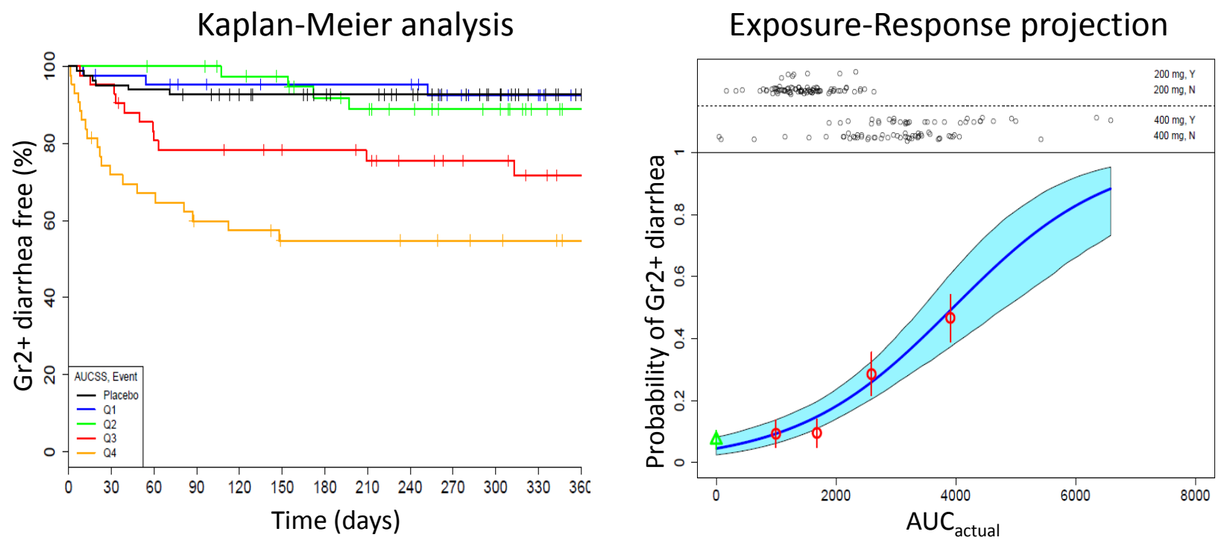
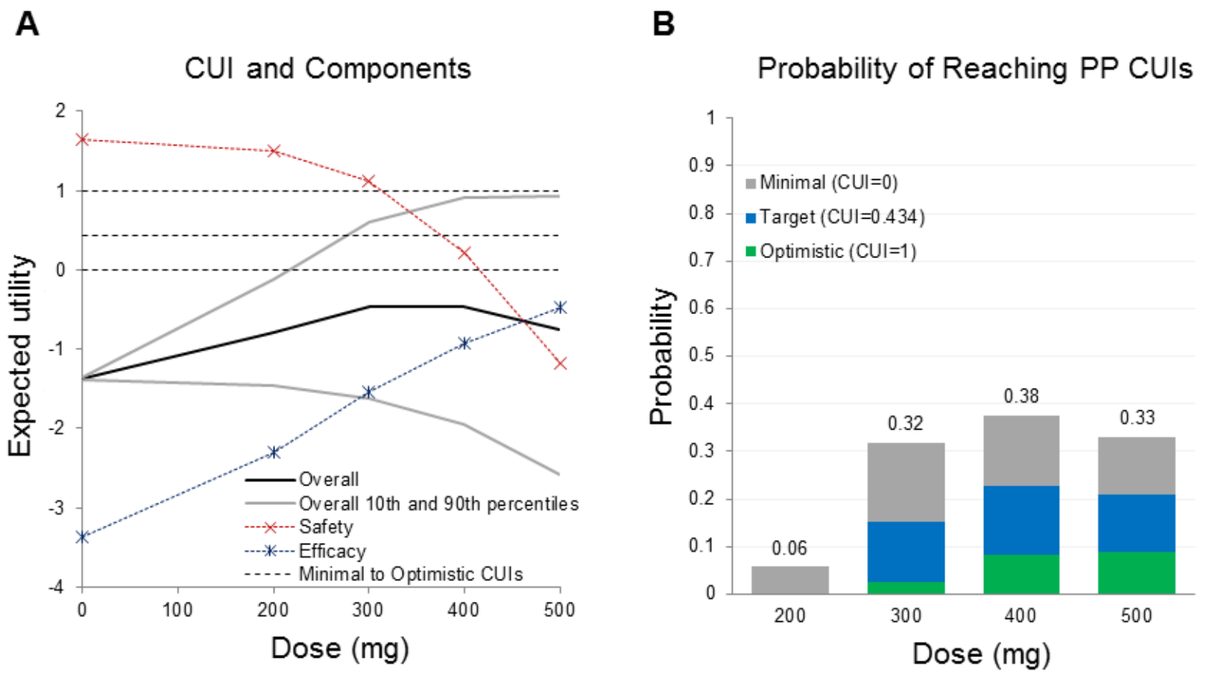


Figure 3. CUI distribution (A) and probabilities of reaching PPs (B) vs. dose



- Comparison with literature:
  - Freise 2017 [2] used CUI (with 90% CI) to optimize a dose in multiple myeloma. Logistic regression captured E-R for efficacy and a single AE, with 2:1 weighting. Sensitivity analysis showed what weightings would change the optimal dose.
  - Raju 2018 [3] reviewed 23 FDA decisions on multiply myeloma drugs, using a CUI-like metric in terms of equivalent months of overall survival, with deductions for the risks of fatal AEs, serious AEs (weighted 10% of fatal), and common AEs (weighted 0.5%).
  - Raju 2016 [4] took a similar approach in reviewing 20 FDA decisions for NSCLC drugs.

Conclusions

- This analysis supported selection of Ipat 400mg QD for the phase III CRPC study.
- This E-R-based PP-driven CUI framework may be useful to support dose selection when multiple efficacy and side effect endpoints must be balanced.
- Pre-defined PPs can help a development team reach agreement on the key components of CUI analysis: most relevant attributes, weights, and clinically meaningful cutoff/tradeoff values.
- Other recent benefit-risk assessments in oncology used simpler approaches:
  - only two attributes (efficacy vs. safety in multiple myeloma) or less generalizable scaling (all scales converted to survival time units).

References

1. de Bono, JSD et al. JCO. 34, Abstract 5017 (2016).
2. Freise KJ et al. CPT. 102, 970-976 (2017).
3. Raju GK et al. CPT. 103, 67-76 (2018).
4. Raju GK et al. CPT. 100, 672-684 (2016).

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