Validation of Xenograft Dose Predictions for Clinical Efficacy in NSCLC

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Introduction The xenograft mouse model is widely used to study the response to cancer therapy. Pharmacokinetic-pharmacodynamic (PKPD) modelling of xenograft data can be performed to predict the exposure level to target in the clinical setting. However, how well these dose predictions translate to clinical efficacy is not well studied although previous attempts have been done. One example is the work done by Rochetti et al[1] where they demonstrated a good correlation between preclinical potency parameters and exposure obtained at therapeutic doses in the clinic for a range of cytotoxic agents.

Objectives The objective with this work was to further evaluate the correlation between preclinical and clinical efficacy estimates, including targeted agents representing both small molecules and biologics. Preclinical efficacy estimates derived from xenograft experiments across a range of cell lines, as well as clinical efficacy estimates from failed or successful late phase drug development programs in NSCLC, were collected from both in-house data as well as published data.

Methods One central task in this work was to collect data on preclinical and clinical efficacy estimates. The literature was surveyed for oncology compounds with Phase 3 results published in the last 10 years (2006-2016). In addition, a selected number of standard of care compounds were included in the analysis. Substances of interest were targeted kinase inhibitors, monoclonal antibodies and cytotoxics.

The preclinical anti-tumor potency parameter k_2, derived using the model developed by Simeoni et al [2], was of primary interest as an efficacy estimates. Threshold concentration, C_t, meaning concentration leading to tumor decline was derived as underlying growth rate λ_0/k_2. Ideally, preclinical k_2 values should be directly compared to translated clinical k_2 estimates. However, due to limitations in the clinical information, clinical EC_{50}-values were used. For approved compounds with no identified exposure-response (ER) it was assumed that EC_{50} was less than lowest exposure quartile in the effective dose. For failed compounds with no identified ER it was assumed that the EC_{50} was higher than highest exposure quartile for the tested dose.

The analysis of correlation of preclinical-clinical efficacy estimates focused on non-small cell lung cancer (NSCLC) and was performed in NONMEM (version 7.3.0). The regression was performed on log-log scale and the M3 method was used to account for the cases where the EC_{50} was assumed to be less than lowest exposure quartile or higher than the highest exposure quartile observed.

Results In total, 36 approved, 17 failed and 15 standard of care compounds in various indications were identified (see Table 1 for an overview of the indications and type of mechanism).

Table 1. Summary of Identified Compounds

	Indication	Mechanism
Positive n=36	NSCLC (10), Breast (5), Renal (6), Melanoma (5) Colorectal (5), GI (2), Prostatic (2), Ovarian (1)	Multi-targeted TKI (9), Targeted TKI (15), BRAF (2), PARP (2), other[b] (7)
Failed n=17	NSCLC (5), Breast (3), Hepatic (2), Renal (3), Prostate (2), Melanoma (2), GI (1)	Multi-targeted TKI (5), Targeted TKI (3), BRAF (2), other[b] (8)
Standard of care[a] n=15		taxanes, platins, topoisomerase inhibitors, nucleoside analogues, vinca alkaloids, anthracycline

[a] Standard of care includes etoposide, gemcitabine, irinotecan, paclitaxel, vinblastine, vincristine, carboplatin, topotecan, epirubicin, capacitabine, oxaliplatin ,5-fluorouracil ,cisplatin ,docetaxel ,doxorubicin. [b] Others include taxanes, anti-CTLA-4, anthracycline, CAIX, platins and more.

In total, 9 NSCLC compounds had sufficient information to be included in the correlation analysis. The correlation between preclinical k2 estimates and clinical EC50 estimates was found to be relatively high (r = 0.90) (see Figure 1). Similar relationship was seen also when excluding the failed compounds (see Figure 2). Using the threshold concentration (C_T), as preclinical efficacy estimate showed less correlation (r=0.81, see Figure 3).

Table 2. Summary of ER information

Type of ER analysis	Total	Approved	Failed	Standard of care
Total number of compounds	**68**	**36**	**17**	**15**
Descriptive	**1**	**0**	**0**	**1**
Threshold or cut-off[a] concentration identified	**14**	**9**	**0**	**5**
kd/EC50[b]/ED50[c]/ other[d]	**7**	**6**	**1**	**0**
Hazard ratio[e]	**4**	**3**	**0**	**1**
Odds ratio[f]	**3**	**2**	**1**	**0**
No ER identified	**12**	**10**	**1**	**1**
No ER identified (lack of informative data)	**6**	**6**	**0**	**0**
No information found/Not done ER[g]	**21**	**3**	**14**	**4**

[a] Either an actual threshold or just a cut-off based on e.g. median exposure
[b] Logistic regression modeling of ORR
[c] Change in tumor size (ED50 actually higher than highest dose evaluated)
[d] Tumor growth model but no Kd reported (only abstract for poster)
[e] Hazard ratio with exposure metrics as a continuous variable
[f] Odds ratio with exposure metrics as a continuous variable in 2 cases and as quartiles in 1 case
[g] Mainly failed compounds or standard of care compounds
Note, for some compounds more than one type of analysis has been done.

Figure 1. Relationship Between Clinical EC_{50} and Pre-clinical k_2 in NSCLC

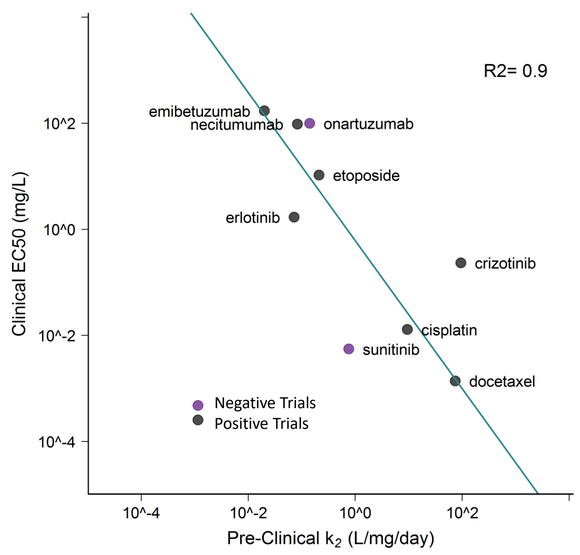

Figure 1. Correlation Between Clinical EC_{50} versus Xenograft Derived Efficacy Parameter k_2

Figure 2. Relationship Between Clinical EC_{50} and Pre-clinical k_2 in NSCLC, Positive Study Results

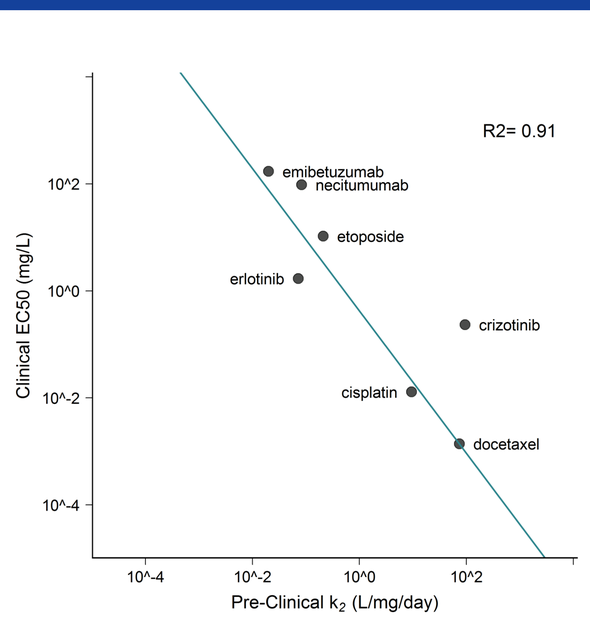

Figure 2. Correlation Between Clinical EC_{50} from Positive Trials versus Xenograft Derived Efficacy Parameter k_2

Discussion This work sought to validate the hypothesis generated by Rocchetti et al, but utilize model derived information about clinical efficacy rather than just exposure at registered dose, and include data from a broader scope of mechanisms of action.

k_2 was selected as the preclinical efficacy measure over EC_{50} as all experiments could not support an E_{max} model, and linear parameterization is commonly used in discovery screening phase. The analysis of correlation between preclinical k_2 and clinical EC_{50} derived from lung cancer was generally good, while C_t was shown to have low predictive value . This is perhaps not unexpected given the high variability in λ_0 described by Parra-Guillen et al.

λ_0 in cell lines all derived from lung cancer can vary more than tenfold, meaning also with the same target binding and target dependence C_t will also vary tenfold. Tumor growth rate in clinical lung cancer on the other hand is much less variable. If C_t values would be have all derived from the same cell line, it is likely the correlation would have looked much stronger, but as this is not viable due to cell lines commonly being selected for target dependence.

Figure 3. Relationship Between Clinical EC_{50} and Pre-clinical C_T in NSCLC, Positive Study Results

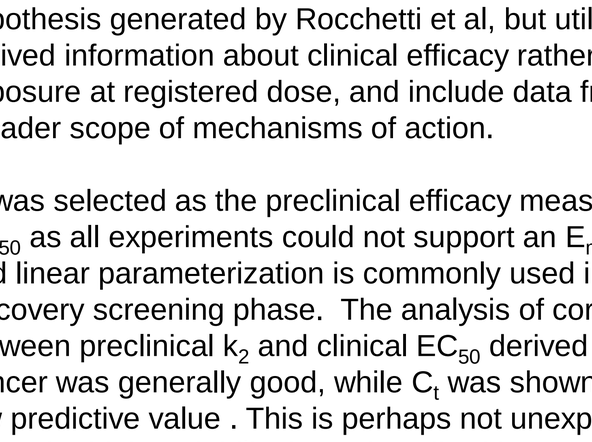

Figure 3. Correlation Between Clinical EC_{50} from Positive Trials versus Xenograft Derived Efficacious Concentration

Conclusions

A relatively strong correlation was found between the preclinical and clinical efficacy parameters, supporting the use of xenograft models to predict clinical therapeutic doses. However, this analysis was limited to data from only 9 compounds and based on one k_2 estimate from one single cell-line for each compound. Further work is ongoing to include data from additional cell-lines for each compound.

References

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