Supplementary material 1: Selected Statistical Designs and Analysis Methods for Basket Trials

Various statistical methods have been proposed on borrowing information across disease populations to increase statistical power and efficiency. Assume all disease populations are homogeneous, Thall et al (2003) proposed a Bayesian hierarchical model (BHM) enabling information borrowing across different disease populations through a hyper prior that the effects are exchangeable and correlated (1). A trial example that implemented this design is ROAR, a phase 2 open-label trial evaluating the combination therapy of dabrafenib and trametinib in patients with BRAF V600E-mutated rare cancers. In reality, the assumption that all diseases within a basket trial are exchangeable with each other rarely holds and the BHM model may lead to excessively conservative or anti-conservative results. To overcome this limitation, various researchers proposed modified Bayesian modeling methods initially designed for subgroup analysis, including but not limited to, the Bayesian exchangeability-non-exchangeability (EXNEX) model (2), multi-source exchangeability modeling (MEM) (3) and semiparametric Bayesian model (4, 5) can potentially be used for basket trials with careful evaluation of trial-specific needs. Simon et al. (6), Cunanan et al. (7) and Liu et al. (8) proposed basket trial designs with interim assessment on subgroup heterogeneity to inform the design and analysis strategy for the next stage – perform either pooled or separate subgroup analyses. These designs tackle the problem by starting with examining the homogeneity then move on with different analyses and decision rules by either pooling all (if homogeneous) or separate each (if heterogeneous). Chen et al. (9) proposed the 'pruning and pooling' method that first prunes away the non-effective disease indications, and pool the rest of the indications together for evaluating the effectiveness of the experimental treatment to increase the study power and efficiency. Similarly, Zhou et al. (10) extended the pruning and pooling method into an optimal two-stage basket design in phase 2 trials with an interim analysis. When considering a desired basket trial design and analysis that fit the specific need, there is no one single method that is universally better than others. One needs to consider the practicality, number of cohorts evaluated, potential treatment effect in each cohort, prior information on the treatment effect, whether interim evaluation would be performed and if so, how many, as well as the resource constraints especially for

exploratory trials. Simulations are preferred prior to selecting the most appropriate design and analysis method that fits the individual need.

References:

1. Thall PF, Wathen JK, Bekele BN, Champlin RE, Baker LH, Benjamin RS. Hierarchical Bayesian approaches to phase II trials in diseases with multiple subtypes. Stat Med. 2003;22(5):763-80.
2. Neuenschwander B, Wandel S, Roychoudhury S, Bailey S. Robust exchangeability designs for early phase clinical trials with multiple strata. Pharm Stat. 2016;15:123-34.
3. Hobbs BP, Landin R. Bayesian basket trial design with exchangeability monitoring. Stat Med. 2018;37(25):3557-72.
4. Bunn V, Liu R, Lin J, Lin J. Flexible Bayesian subgroup analysis in early and confirmatory trials. Contemporary clinical trials. 2020;98.
5. Li M, Liu R, Lin J, Lin V. Bayesian semi-parametric design (BSD) for adaptive dose-finding with multiple strata. J Biopharm Stat. 2020.
6. Simon R, Geyer S, Subramanian J, Roychowdhury S. The Bayesian basket design for genomic variant-driven phase II trials. Semin Oncol. 2016;43(1):13-8.
7. Cunanan KM, Iasonos A, Shen R, Begg CB, Gonen M. An efficient basket trial design. Stat Med. 2017;36(10):1568-79.
8. Liu R, Liu Z, Ghadessi M, Vonk R. Increasing the efficiency of oncology basket trials using a Bayesian Approach. Contemp Clin Trials. 2017;63:67-72.
9. Chen C, Li X, Yuan S, Antonijevic Z, Kalamegham R, Beckman RA. Statistical design and considerations of a phase 3 basket trial for simultaneous investigation of multiple tumor types in one study 2016 Jul 2;8(3):248-57. Statistics in Biopharmaceutical Research. 2016;8(3):248-57.
10. Zhou H, Liu F, Wu C, Rubin E, Giranda V, Chen C. Optimal two-stage designs for exploratory basket trials Contemporary clinical trials 2019;85.