BRING THE PROTOCOL
TO THE PATIENT

Signature

Protocol to Patient (P2P)

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Background

- This is a novel signal-finding clinical trial protocol series, termed the Novartis “Signature” program. These are tissue-agnostic; genetic alteration-specific (mutation, amplification, translocation, etc.) protocols that do not include pre-identified clinical trial sites. As these patients are identified via standard of care physician-directed profiling, we bring the ‘Protocol to the Patient’; utilizing a rapid study start-up process.

Protocols in Signature Program

Protocol	Study Medication	Genetic Alterations (Mutation, amplification, loss, rearrangement, translocation)	Enrollment Status
CBKM120ZUS40	BUPARLISIB (BKM120)	PIK3CA, PTEN, PIK3R1	Completed
CMEK162AUS11	BINIMETINIB (MEK162)	RAF, RAS, MEK, NF1	Completed
CTKI258AUS26	DOVITINIB (TKI258)	cKIT, CSF-1R, FGFR, FLT3, PDGFR, RET, TrkA, VEGFR	Completed
CLDE225XUS20	SONIDEGIB (LDE225)	PTCH1, SMO	Terminated
CLGX818AUS03	ENCORAFENIB (LGX818)	BRAFV600	Terminated
CLEE011XUS03	LEE011	CDK4, CDK6, Cyclin D1, Cyclin D3, p16	Temporary hold
CBGJ398XUS23	BGJ398	FGFR	Ongoing
CLDK378AUS23	CERITINIB (LDK378)	ALK, ROS1	Ongoing

Study Enrollment

Protocol	No. of Consented Patients	No. of Dose Patients	No. of Discontinued Patients
CBKM120ZUS40	228	146	134
CMEK162AUS11	184	110	88
CTKI258AUS26	144	80	72
CLDE225XUS20	19	10	10
CLGX818AUS03	16	12	9
CLEE011XUS03	130	70	34
CBGJ398XUS23	57	33	19
CLDK378AUS23	17	9	2
Total	**795**	**470**	**368**

Note: Based on data from 12 March 2015.

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Study Design

- Trial enrolls subjects with specific gene mutations
- Primary objective: to assess clinical benefit (CR, PR, or SD) rate based on local investigator assessment at 16 weeks.
- Multiple tumor types are enrolled in each trial
  - hierarchical modeling allows borrowing of information across tumor types
  - avoids assumption of complete homogeneity across tumor types while allowing common trends to inform across all groups
  - running separate trials in each tumor type would be inefficient.

Study Design (Cont'd)

- Statistical modeling: Let Y_i be the response indicator for the i^{th} subject, and let R_g be assumed the probability of response within a control population and $\pi_g = \Pr(Y_i = 1 \mid g_i = g)$ be the underlying probability of response for group g within the treatment group.

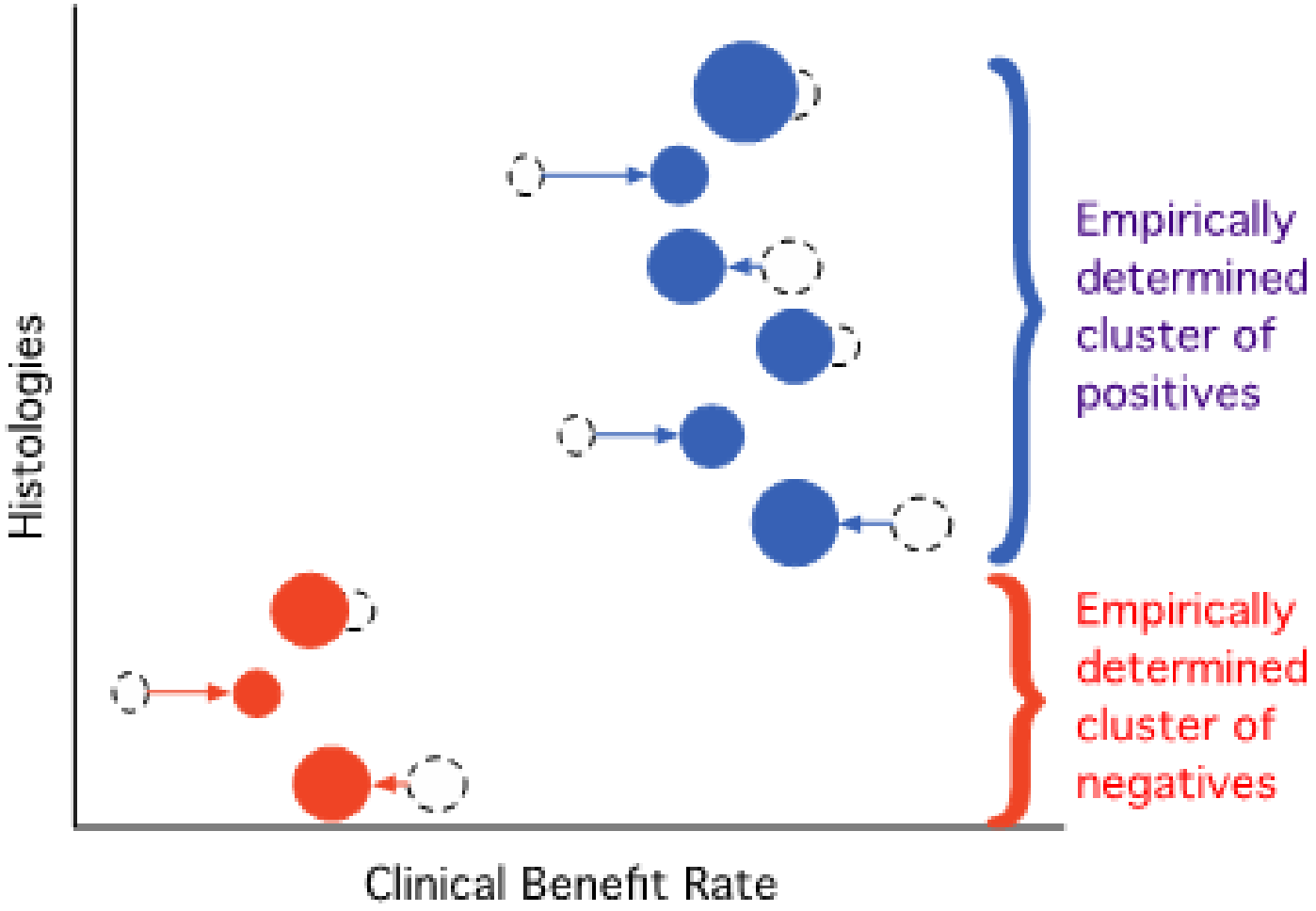
- The log-odds of the treatment effect θ_g

$$\theta_g = \log\left(\frac{\pi_g}{1-\pi_g}\right) - \log\left(\frac{R_g}{1-R_g}\right)$$

is used and the set of hypotheses $H_{0g} : \theta_g \leq 0$ and $H_{1g} : \theta_g > 0$ are used to test the treatment effect.

Study Design (Cont'd)

- A hierarchical model with two levels are used to allow borrowing of information across groups.
- At the highest level of the hierarchy a clustering mechanism is implemented to place into distinct clusters to minimize borrowing of information across groups with very different response rates.
- Borrowing of information between groups within clusters only, not across clusters.
- The clustering is implemented through a Dirichlet Process Mixture (DPM) model.



Open dashed circles show raw CBR estimates for 9 histologies. Solid circles show estimates adjusted for borrowing. Area of each circle is proportional to the "equivalent sample size" and hence to estimation precision for that histology. Raw estimates for histologies with smaller sample size and further from the cluster mean are regressed further. Histologies with raw estimates further from the cluster mean borrow less. (Results are hypothetical and effects are exaggerated to demonstrate the methodology.)

Study Design (Cont'd)

- In the second stage, hierarchical models are placed upon the groups within each cluster
- More borrowing occurs when groups are similar in response rates and less borrowing when the groups differ.
- An across group distribution of $\theta_g \sim N(\mu, \tau^2)$ is assumed.
- The across group mean μ and variance τ^2 are unknown, and have a prior distribution which is combined with the data to produce estimates of μ and τ^2.

Study Design(Cont'd)

- The variance component τ controls the degree of borrowing among groups. Small values of τ result in a greater degree of borrowing while large values of τ correspond to less borrowing.
- The parameter τ is estimated using the data, so the observed between group variation is a key component of the model behavior.
- The operating characteristics of the design (power, type I error, average sample size, etc.) are assessed via simulation

Study Design(Cont'd)

- The prior distribution of μ is assumed to be a normal and the prior of τ^2 is assumed to be $IG(\alpha, \beta)$ where $IG(\alpha, \beta)$ is the inverse gamma distribution defined by:

$$f(x|\alpha,\beta) = \frac{\beta^{\alpha} e^{-\beta/x}}{x^{\alpha+1}\Gamma(\alpha)}$$

Study Design(Cont'd)
Simulation

- Model parameters are estimated by Markov Chain Monte Carlo. Requires simulating over the distribution of
  - the clustering membership variables
  - the cluster specific across group mean and variance
  - the group mean and variance
- Conditional on the clustering, groups in different clusters are independent.
  - some groups with similar effects are almost always placed in the same cluster and borrow heavily. Groups with differing effects tend to be placed in different clusters, and borrow minimally.

Study Design (Cont'd)

- The posterior distribution for each group parameter θ_g is produced by averaging over the entire range of the uncertainty in the parameters, which is then used to make the decisions in the model.

Study Design (Cont'd)
Interim Analysis

- First interim analyses performed after the first 30 patients enrolled (across all tumor groups) have been in a study for at least 16 weeks
- Interim Analyses are conducted every 13 weeks thereafter. Groups may be stopped for success or futility if the results are sufficiently clear.
- A minimum of 10 and 15 patients is required in the group to declare early futility and success, respectively.

Study Design (Cont'd)

- Unspecified groups may be created during the trial as accrual allows
- A minimum of 3 patients in any group is required to include the group in the analysis.
- No more than 30 patients are to be enrolled in any tumor type.

Study Design (Cont'd)

- **Early futility**
  - If there is less than 10% probability that the response rate π_g in a group exceeds the historical rate R_g, then the group will stop enrollment early for futility. Formally, enrollment will stop early for futility if:

$$\Pr(\pi_g > R_g) < 0.10.$$

  - A group is only eligible for early stopping once a minimum of 10 patients has been evaluated (i.e., would have reached at least 16 weeks from the first dose of the study drug) for response in that group.

Study Design (Cont'd)

- **Early success**
  - If there is at least 95% probability that the response rate π_g in a group exceeds the historical rate R_g, then the group will stop enrollment early for success. Formally, enrollment will stop early for success if:

$$\Pr(\pi_g > R_g) > 0.95.$$

  - A minimum of 15 subjects will need to be evaluated (i.e., would have reached at least 16 weeks from the first dose of the study drug) prior to declaring a group to be efficacious.

Interim Analysis Results: BKM120 example

Data cut-off: August 1, 2014

Group	CB No	CB NE	CB Yes	Observed Rate	Assumed Control Rate	Pr (beat Control rate)
CRC	12	6	0	0.00	0.64	<0.001
HNSCC	3	5	3	0.50	0.63	0.153
Ovarian	6	3	3	0.33	0.30	0.331
Sarcoma	9	4	1	0.10	0.40	0.011
Cervical	4	1	1	0.20	0.50	0.049
Anal	4	2	2	0.33	0.50	0.114
Esophageal	3	0	0	0.00	0.46	0.030
Gastroesophageal	4	1	0	0.00	0.46	0.016
Gall Bladder Ducts	2	1	1	0.33	0.25	0.294

Interim Analysis Results for BKM120 (cont'd)

- Conclusions:

  Two groups have sufficient subjects to stop for futility (requires 10 evaluable subjects)

  - CRC has Pr(beat control) < 0.001 should stop for futility
  - Sarcoma has Pr(beat control) = 0.011 should stop for futility

Summary

- The Signature program has shown that it's feasible and cost-effective to rapidly open a clinical trial at the local site a patient presents.
- It's possible to assess a drug for efficacy/safety in multiple tumor types and gene alterations in a single study with relatively small number of patients using Bayesian adaptive design.
- The Signature program experience may be incorporated into early and late stage development trials.