Identifying a Subpopulation for a Tailored Therapy: Bridging Clinical Efficacy From a Laboratory-Developed Assay to a Validated In Vitro Diagnostic Test Kit

Published in: Statistics in Biopharmaceutical Research
February 2014, Vol. 6, No. 1, p.78-88

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Mid-West Biopharmaceutical Workshop
May 2015

Overview

- On July 6, 2012 , FDA approved Erbitux® (cetuximab) for use in combination with FOLFIRI for first-line treatment of patients with *K-ras* mutation-negative (wild-type), EGFR-expressing metastatic colorectal cancer (mCRC) as determined by FDA-approved tests for this use

- FDA approved concurrently the *Therascreen KRAS RGQ PCR Kit for* identifying patients with *K-ras* 'wild-type' (WT) mCRC

- The approval was based on retrospective analyses in the patient subsets according to *K-ras* mutation status in tumor samples from patients enrolled in the CRYSTAL trial and in two supportive studies

- A key component was a study bridging the laboratory assay originally used in CRYSTAL to the *Therascreen* In-Vitro Diagnostic (IVD) kit

Contents

- Background of cetuximab in mCRC
- Why a bridging study was needed
- Design of the Bridging study
- Results
- Summary

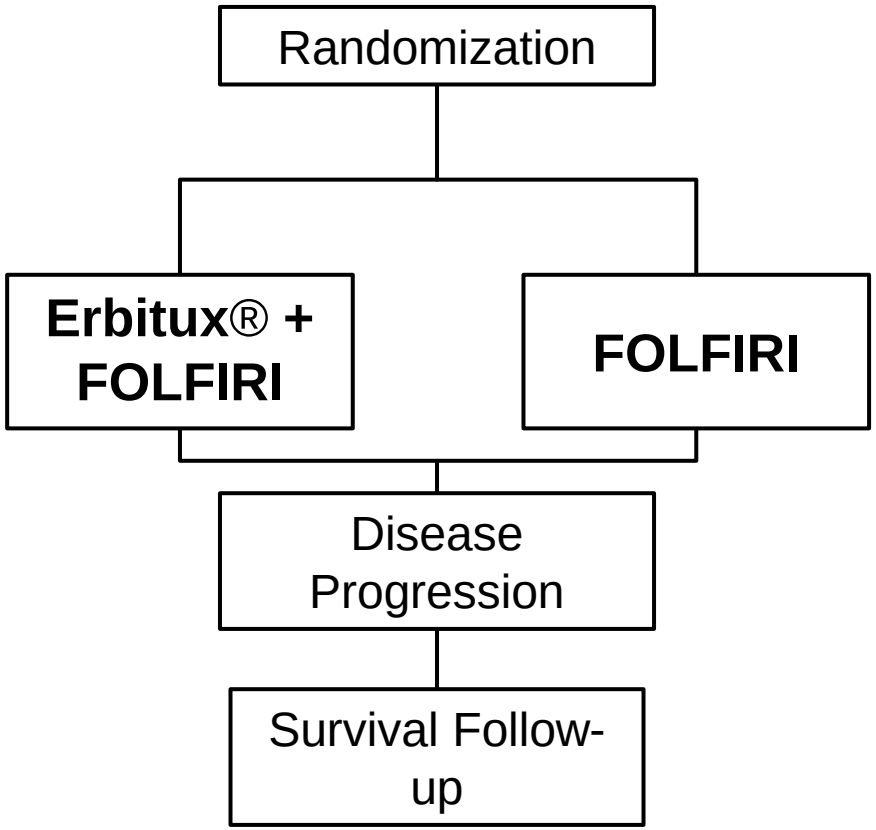
Background

Erbitux® in the treatment of Metastatic Colorectal Cancer (mCRC)

- US-Approved Indications in mCRC:
  - as a single agent after failure of prior therapies (2004 - AA, 2007 - FA)
  - in combination with irinotecan in patients refractory to irinotecan (2004 - AA)

- The registration study, CRYSTAL, for Erbitux® as an initial treatment for mCRC was initiated in 2004

CRYSTAL Study



DESIGN*

- Phase 3, randomized, open-label, multicenter, controlled study
- Primary objective: PFS
- Key secondary objectives: OS, RR, safety, and QoL
- 1st-line mCRC (*EGFR +ve*)
- N=1217 randomized

RESULTS

- Significant PFS benefit (June 2006)
- No statistically significant survival benefit. (Dec 2007)

* Study Design did not include testing for any biomarkers apart from EGFR.

Abbreviations: OS = overall survival; PFS = progression-free survival; ORR=Overall Response Rate; QoL=Quality of Life

Emerging Data- Predictive Biomarker

- Potential signal for *K-Ras* as a predictive biomarker emerging in 2007
- Voluntary Genomics Data Submissions (VGDS) to FDA of analyses by *K-Ras* status in 5 Erbitux® mCRC studies (April 2008)
- *K-Ras* mutation status added to Erbitux® label in Europe (July 2008)
- NCCN Guidelines recommend restricting use of Erbitux® to *K-Ras* wild-type population (Oct 2008).
- FDA convened an ODAC on biomarkers, using *K-Ras* as an example (Dec 2008), and subsequently (July 2009) issued class labeling recommending anti-EGFR mAb's not be used in *K-Ras* mutant tumors (safety language)

CRYSTAL Results by *K-Ras* Status

- Following 2008 ODAC, *K-Ras* testing (increased sample ascertainment of 89%) was conducted, and an updated OS lock performed (May 2009)

	Erbitux®+ FOLFIRI (N=608)	FOLFIRI (N=609)	HR	95% CI
K-Ras Wild-Type Population† (N=676)				
PFS	9.5 mo	8.1 mo	0.70	(0.57, 0.86)
OS*	23.5 mo	19.5 mo	0.80	(0.67, 0.94)
K-Ras Mutant Population† (N=403)				
PFS	7.5 mo	8.2 mo	1.13	(0.88, 1.46)
OS*	16.0 mo	16.7 mo	1.04	(0.84, 1.29)

*Post-hoc updated OS analysis, results based on an additional 162 events. †Based on 89% ascertainment rate for *K-Ras* testing. Abbreviations: HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

OS and PFS benefit in *K-Ras* wild-type population, and no benefit in *K-Ras* mutant population.

Regulatory Path in US

- Based on the Dec 2008 ODAC and subsequent meetings with FDA, a regulatory path forward emerged;

- Submission of retrospective analyses by *K-ras* mutation status
  - in the CRYSTAL study as pivotal and
  - in two supportive studies showing predictive nature of *K-Ras*
    - CA225-025 (Ph3 study of Erbitux® v BSC in previously treated mCRC) and
    - OPUS (Ph2 study of Erbitux® in combination with FOLFOX-4 1st line mCRC)

- <u>However</u>, *K-Ras* testing in CRYSTAL had been done using a lab assay and a validated IVD kit would need to be developed for *K-Ras* testing and would be required for approval

  → a study would be needed to bridge between the lab assay and the IVD kit

First application of retrospective analysis in regulatory path for approval of a drug and companion diagnostic

Why was a Bridging study needed?

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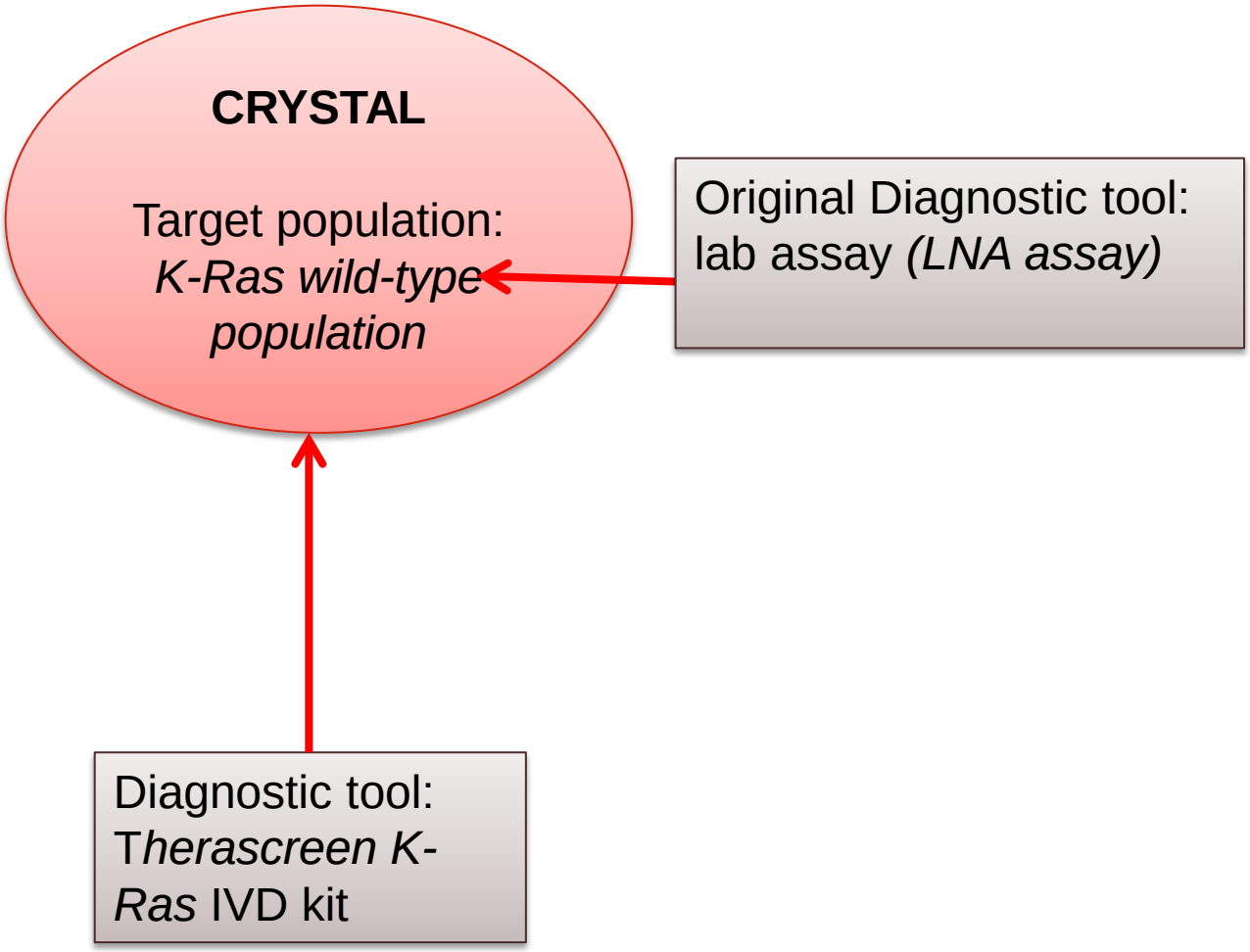

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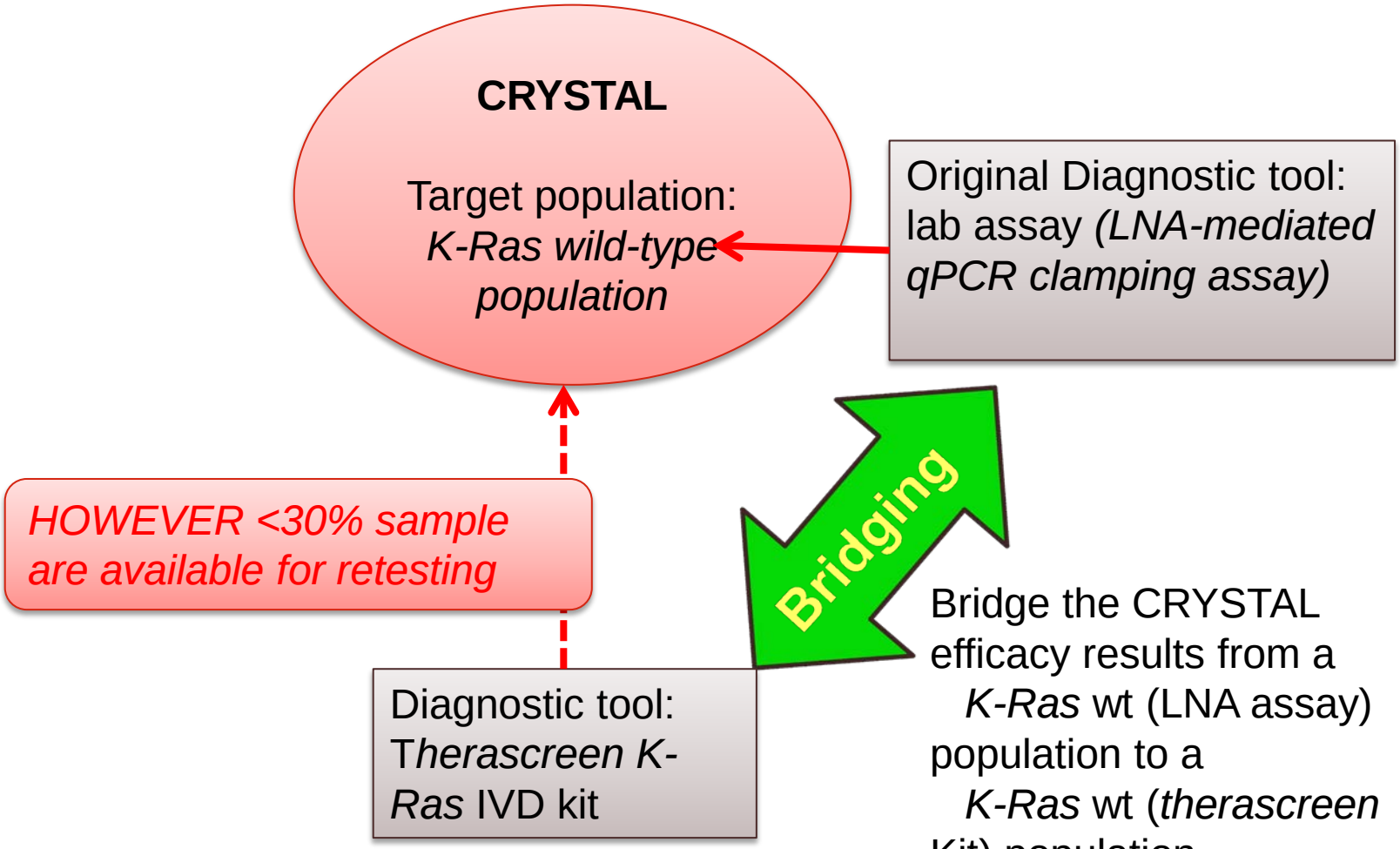

Initial Team Thoughts

		LNA Assay		
	***K-RAS* mutation status**	**Wild-Type**	**Mutant**	**Total**
***therascreen* Kit**	**Wild-Type**	a	b	a+b
	Mutant	c	d	c+d
	Total	a+c	b+d	N

Agreement = (a+d)/N

Acceptable threshold?

Bridging Framework

Motivated by Pennello (2010)

We have:

CRYSTAL *K-Ras* wt (**LNA**) population
OS Hazard Ratio
= 0.80 (0.67 – 0.94)

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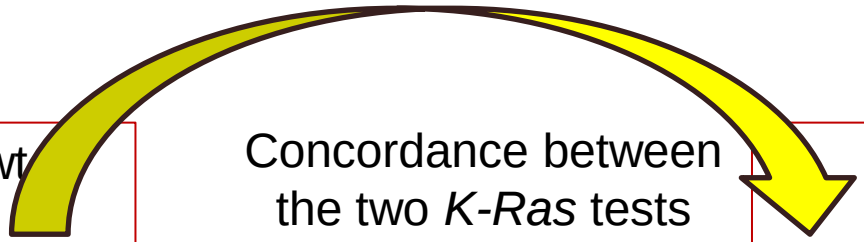


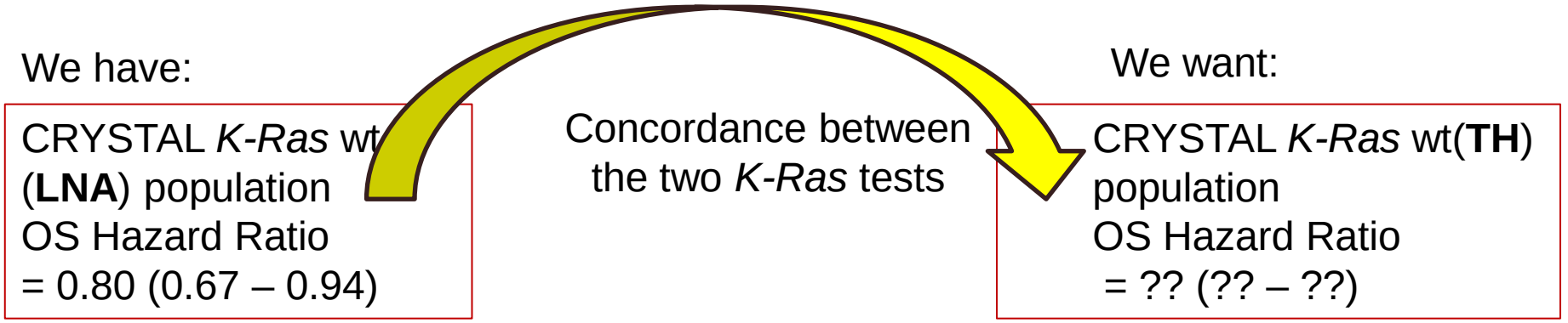
Concordance between the two *K-Ras* tests

We want:

CRYSTAL *K-Ras* wt(**TH**) population
OS Hazard Ratio
= ?? (?? – ??)

Bridging Framework

Motivated by Pennello (2010)



Advantages

- Leads to an objective threshold for concordance
  - minimum concordance for which the estimated OS HR in the *K-Ras* wt (TH) population is statistically significant.
- An estimate (and CI) for OS HR in the K-*Ras* wt (TH) population is informative

Concordance Measure and Threshold

		LNA-Assay		
	***K-RAS* mutation status**	**Wild-Type**	**Mutant**	**Total**
***therascreen* Kit**	**Wild-Type**	a	b	a+b
	Mutant	c	d	c+d
	Total	a+c	b+d	N

Under certain assumptions, it can be shown that

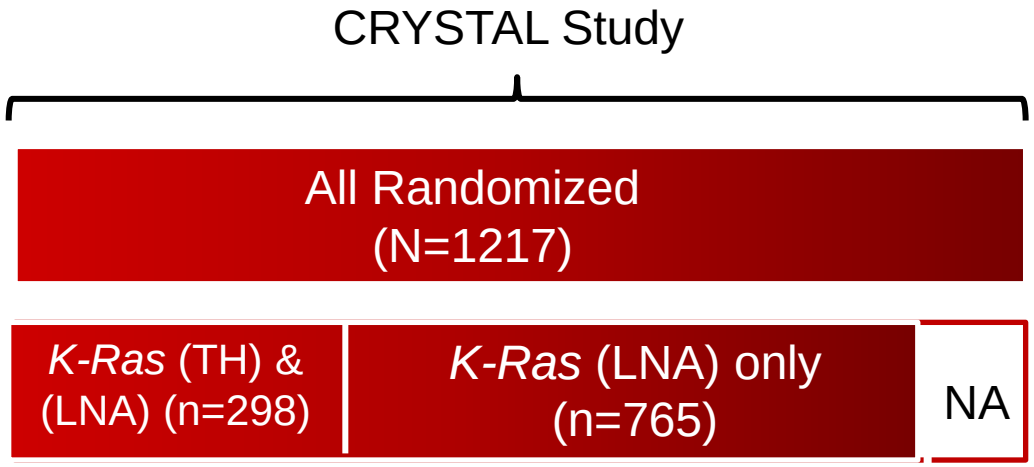
- The OS HR in the K-Ras WT(TH) population depends on

  $p = [a/(a+b)]$ ← *primary concordance measure*

- The threshold for p was derived, giving H_0: p=0.80.

- As only WT(TH) will receive Erbitux®, choice of primary measure is consistent with clinical interest in the % WT(TH) patients who are MT(LNA).

Bootstrapping with Imputation



1. Create bootstrap dataset: sample pts with replacement from *K-Ras* evaluable population;
   - complete cases: patients with *K-Ras* mutation status by both tests
   - incomplete cases: patients with *K-Ras* mutation status (LNA) only

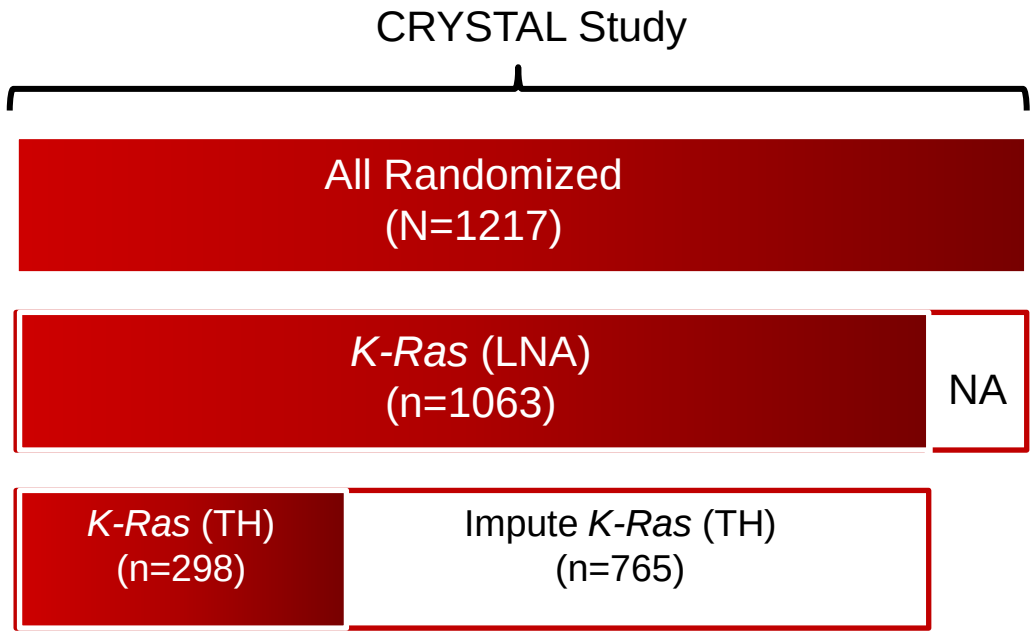
2. Fill-in each missing *K-Ras* test result for TH test by random selection among patients with observed TH test result and same LNA test result.

3. Compute the log hazard ratio based on filled-in bootstrap dataset.

4. Repeat the 3 steps of bootstrap, impute, and analyze 1000 times. Summarize the mean, SD, and 95% CI of the log hazard ratios.

Multiple Imputation (MI)

- To impute unknown *K-Ras* (TH) based on *K-Ras* (LNA) assuming Missing at Random (MAR), and then estimate OS hazard ratio in *K-Ras* (TH) patients.



Simple imputation model: *K-Ras* mutation status (LNA) only.

Imputation model (VO): *K-Ras* mutation status (LNA) + pre-specified list of variables that might affect *K-Ras* results + OS-time + OS-censoring-indicator + treatment

Full imputation model (VHI): same as VO model above but replacing OS time with Nelson-Aalen estimator of the cumulative hazard H(T) and adding interactions with treatment

Multiple Imputation - Little and Rubin (2002), Shafer & Graham (2002), White & Royston (2009)

Representativeness of the Bridging Population

Representativeness of the Bridging Population

- Recall that <30% samples were available for retesting using the *therascreen* Kit – a potentially non-random sample
- Validity of bridging rests on the samples available for retesting with the *therascreen* kit being representative of the whole study population.

– Specifically :

  - Identifying a list of variables that could affect the test result
  - Assessing any systematic differences between bridging sample and the non-bridging sample, especially in any variables associated with lower/higher levels of concordance between the 2 tests,
  - Evaluating impact of any observed differences on the bridging study results by inclusion in the multiple imputation model

List of the Variables

- Patient characteristics:
  - Gender, Race, Age , etc…
- Disease characteristics:
  - Months from first histological diagnosis to randomization , Primary diagnosis (rectum only vs. colon), etc…
- Immediate characteristics of tumor sample:
  - Tumor type, Tumor content in sample, etc…
- Handling and processing factors:
  - Age of sample at testing, Sampling method, Enrollment site, Region, etc…

Results of the Bridging Study

Concordance Between the QIAGEN *therascreen* Kit and LNA-Mediated qPCR Clamping Assay

		LNA Assay		
	***K-Ras* mutation status**	**Wild-Type**	**Mutant**	**Total**
***therascreen* Kit**	**Wild-Type**	**141**	**7**	**148**
	Mutant	30	120	150
	Total	171	127	298

Primary concordance measure p = 141/148 = 0.953 (95% CI: 0.91-0.98)

Note: Overall Disagreement (30+7=12.4%) mostly arising from the TH kit identifying samples as MT, which the LNA assay did not.

Estimated vs. Observed OS Results in CRYSTAL *K-Ras* Wild-Type Population

	OS Hazard Ratio	95% CI
By LNA-mediated qPCR clamping assay		
CRYSTAL (observed)	0.796	0.670, 0.946
By QIAGEN *therascreen* Kit		
Analytic method	0.806	0.678, 0.958
Bootstrapping with imputation	0.800	0.668, 0.958
Multiple imputation (simple model)	0.807	0.659, 0.987
Multiple imputation (VO model)	0.805	0.658, 0.984
Multiple imputation (VHI model)	0.786	0.638, 0.968

Sensitivity analyses

“Tipping point analysis”* - systematically decrease the concordance between to examine how many addition samples would need to be discordant to lose statistical significance for the estimated OS hazard ratio in the *K-Ras* wt (TH) patients.

		LNA-Mediated qPCR Clamping Assay	
	K-RAS mutation status	Wild-Type	Mutant
QIAGEN therascreen Kit	Wild-Type	141	7
	Mutant	30	120

For each value of *k*, add the following step to the bootstrap analysis:

- Randomly select "*k*" number of patients and change the *K-Ras* status of these patients

- *k*=18 is the highest value of *k* for which the upper 95%CI for the estimated OS HR in the *K-Ras* wt (TH) population was <1, supporting robustness of results.

*Yan et al. (2009)

Summary

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- Rigorous statistical design and analysis of a bridging study enabled the efficacy from a pivotal study in a population identified by a lab assay to be bridged to a population identified by the proposed companion diagnostic
- In particular,
  - Statistical models to enable the estimation of the efficacy in the intended indicated population (i.e. based on the IVD kit)
  - Leading to an objective definition of the minimally required concordance needing to be demonstrated in the bridging study

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