SURROGATE ENDPOINT DEVELOPMENT

NATIONAL ACADEMIES OF SCIENCES, ENGINEERING, AND MEDICINE WORKSHOP
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Nicole Gormley, MD
Division Director
Division of Hematologic Malignancies II
Acting Associate Director for Oncology Endpoint Development
Oncology Center of Excellence
U.S. Food and Drug Administration

Potential uses of Biomarkers

- Prognostic Biomarker
- Clinical Uses
  - Screening/Early Detection
  - Monitor for relapse
  - Guide therapeutic decisions
- Regulatory Uses
  - Patient Stratification
  - Patient Selection/Enrichment
  - Risk-based treatment assignment
  - Intermediate Endpoint or Surrogate Endpoint

Biomarker as an Endpoint

- Intermediate clinical endpoint
  - Can be measured earlier than morbidity or mortality, but reasonably likely to predict clinical benefit
- Surrogate endpoint reasonably likely to predict clinical benefit
- Surrogate Endpoint
  - Clinical validation that the marker predicts clinical benefit

Development of Endpoints for Regulatory Use: Validation as a Surrogate

- Prentice Criteria
  - The surrogate must be a correlate of the true clinical endpoint
  - The treatment effect on the surrogate should capture the full effect of treatment on the clinical endpoint
- Meta-analytical methods
  - Patient-level data
  - Allow for assessment of Individual Level and Trial Level Surrogacy
    - Individual Surrogacy- Correlation between candidate surrogate and true clinical endpoint on an individual level
    - Trial Level Surrogacy- Correlation between effect of treatment on the candidate surrogate and the effect of treatment on the true clinical endpoint
  - Surrogate Threshold Effect
    - Minimum treatment effect on the surrogate necessary to predict an effect on the true clinical endpoint

Buyse Nat Rev Oncol 2010
Sargent JCO 2015

Evidentiary Criteria

- Meta-analysis Considerations
  - Inclusion of more trials increases the statistical rigor of the analysis and may allow for more interrogation of the data to address uncertainties.
  - Inclusion of trials with a range of treatment effects (positive and negative trials) increases the accuracy and precision of trial level surrogacy assessment.
  - When designing a meta-analysis, consideration of timing of biomarker assessment, missing data is important.
  - The trial populations and treatments included in the meta-analysis inform future applicability of the surrogate biomarker.

Buyse Biomet J 2016
Sargent Clinical Trials 2013

pCR Example

- Collaborative Trials in Neoadjuvant Breast Cancer
  - Conducted a pooled analysis of mature trials that had both pathologic complete response (pCR) and long-term outcome data
  - Objectives
    - Determine the association between pCR and EFS and OS
    - Determine the definition of pCR which best correlated with long-term outcomes
    - Identify breast cancer subtypes in which pCR best correlated with long-term outcome
    - Determine what magnitude of pCR improvement predicts long-term clinical benefit

Cortazar Ann Surg Oncol 2015

pCR Example

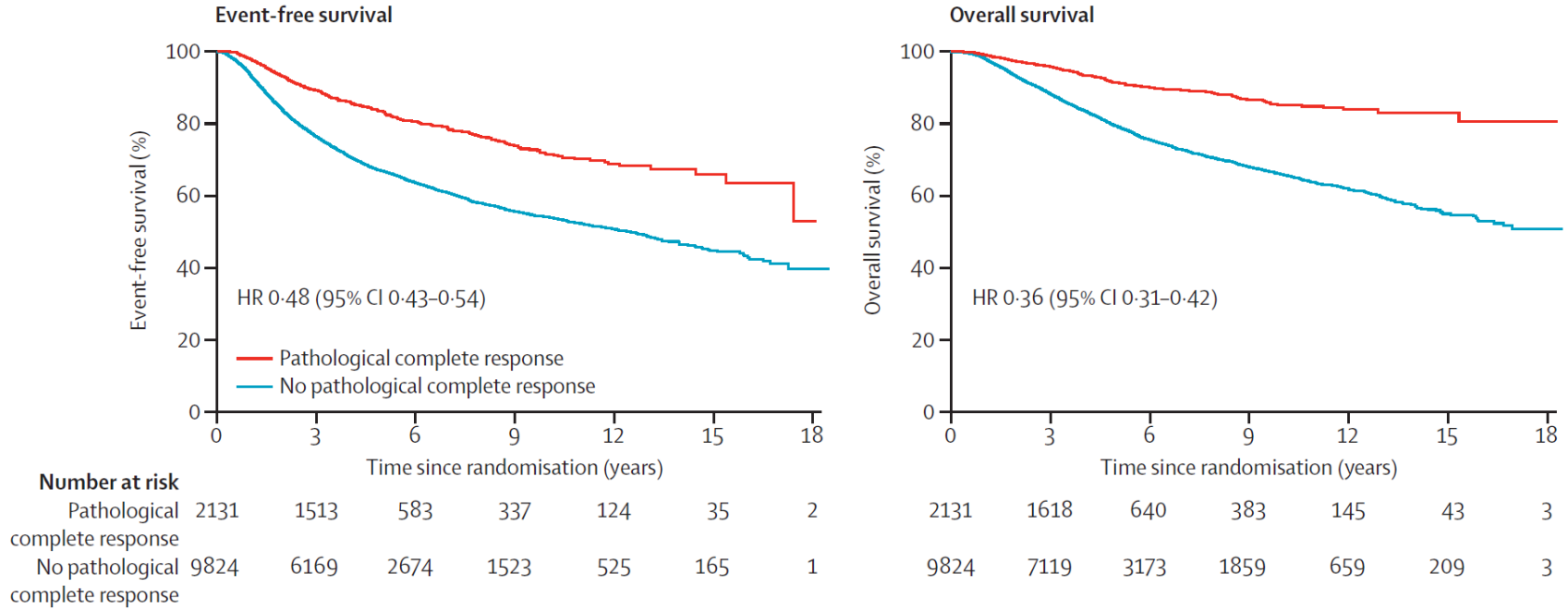
pCR Pooled Analysis Results

pCR Definition	pCR Rate %	EFS, HR (95% CI)	OS, HR (95% CI)
ypT0 ypN0	13	0.44 (0.39, 0.51)	0.36 (0.30, 0.44)
ypT0/is ypN0	18	0.48 (0.43, 0.54)	0.36 (0.31, 0.42)
ypT0/is	22	0.60 (0.55, 0.66)	0.51 (0.45, 0.58)

Cortazar Ann Surg Oncol 2015
Cortazar Lancet 2014

pCR Example

- Individual-Level Surrogacy



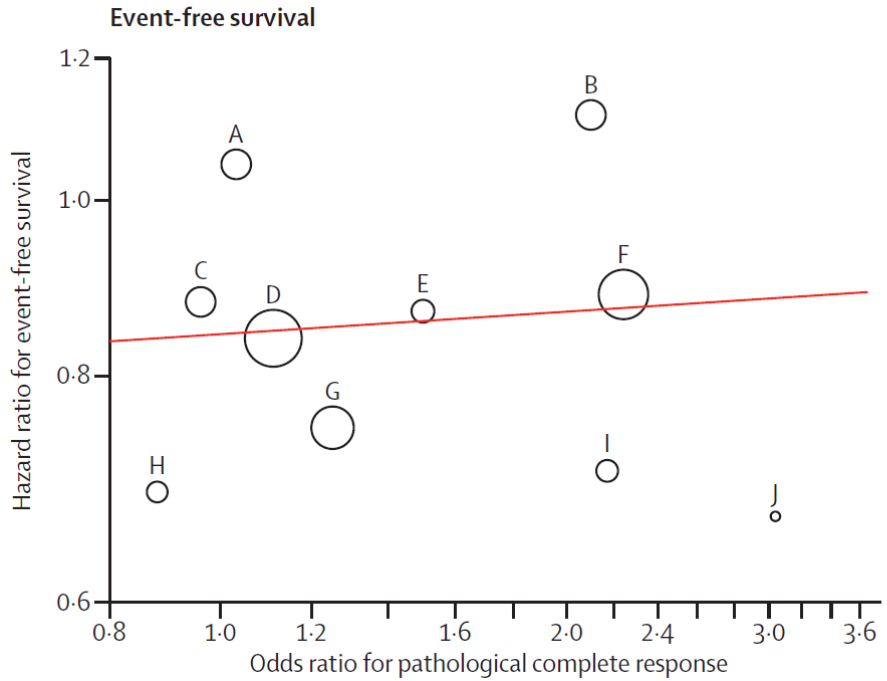
Number at risk							
Pathological complete response	2131	1513	583	337	124	35	2
No pathological complete response	9824	6169	2674	1523	525	165	1

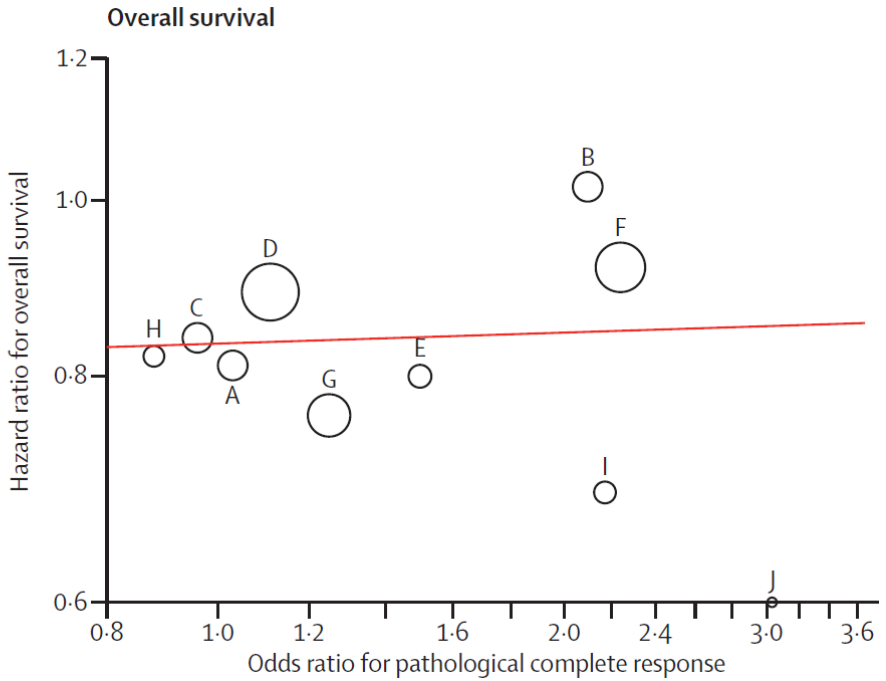
	2131	1618	640	383	145	43	3
	9824	7119	3173	1859	659	209	3

Cortazar Lancet 2014

pCR Example

- Trial-Level Surrogacy





R^2 0.03 (95%CI:0.00,0.25)

R^2 0.24 (95%CI:0.00,0.70)

Cortazar Lancet 2014

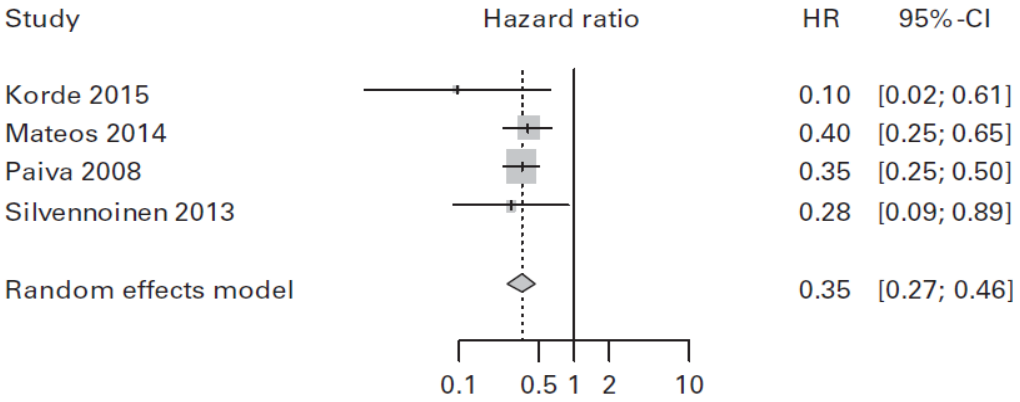
pCR Example

- CTNeoBC Summary
  - No pCR association with long-term outcomes (EFS and OS) at a trial level, only on an individual level
  - A standard definition that includes assessment of the nodes (ypT0ypN0 or ypT0/isypN0) should be used in future trials
  - Magnitude of pCR improvement that predicts long-term clinical benefit could not be established
    - Possibly due to heterogeneity of population, low pCR rates, lack of targeted therapies

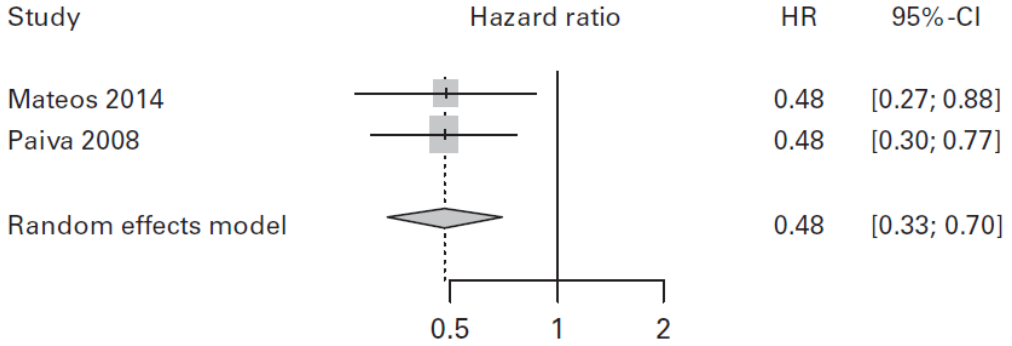
Cortazar Lancet 2014

MRD in MM Meta-analyses

Progression-Free Survival

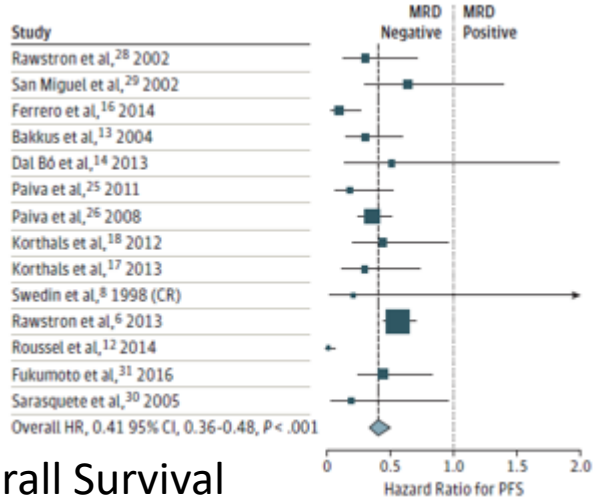


Overall Survival

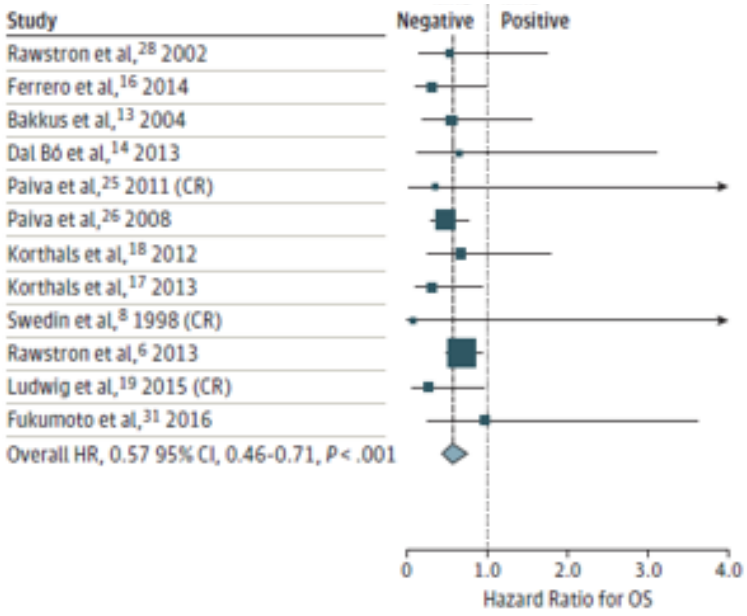


Landgren BMT 2016

Progression-Free Survival



Overall Survival



Munshi Jama Oncol 2016

MRD in MM Meta-analyses

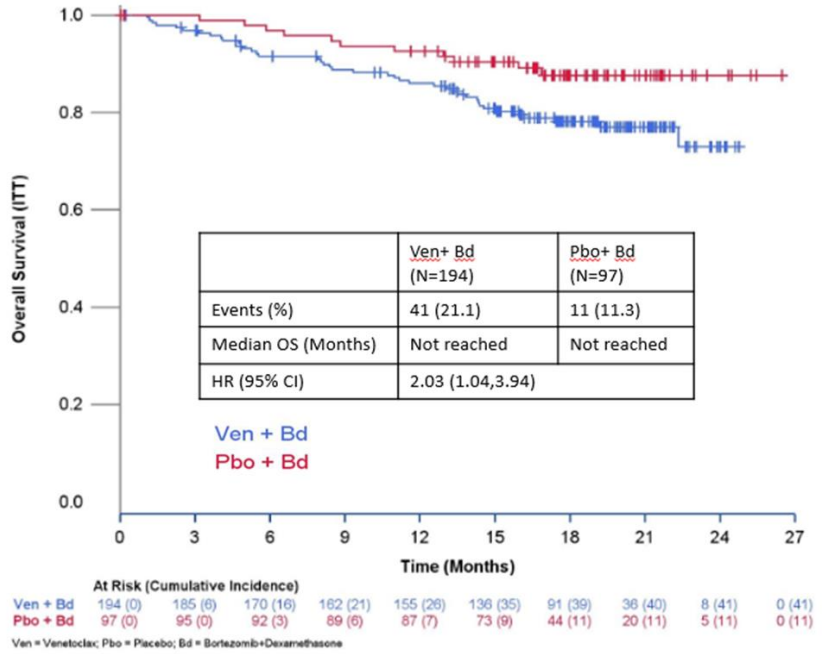
- Remaining Questions
  - Does MRD in MM have trial level surrogacy using individual patient level data?
  - What is the threshold that best correlates with clinical benefit?
  - What is the appropriate timing of assessment?
  - Does Sustained MRD better correlate with long-term outcomes?
  - Should MRD be assessed in those only in CR, VGPR, PR?

Gormley Jama Oncol 2016

BELLINI Trial: A Cautionary Tale

- Phase 3, double-blind, randomized, placebo-controlled trial of bortezomib and dexamethasone with or without venetoclax in patients with relapsed/refractory, multiple myeloma who had received 1-3 prior lines of therapy

	Venetoclax Arm	Placebo Arm
ORR	82.0% (75.8, 87.1)	68.0% (57.8, 77.1)
MRD negativity rate (10^{-5})	13.4% (8.9, 19.0)	1.0% (0.0, 5.6)
Median PFS (mos) (95% CI)	22.4 (15.3, NR)	11.5 (9.6, 15.0)
Hazard Ratio (95% CI)	0.63 (0.44, 0.90)	



https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-risks-associated-investigational-use-venclexta-multiple-myeloma

Conclusions

- Meta-analyses can be used to validate endpoints for regular approval
- pCR and MRD are not validated surrogate endpoints
- Existing uncertainty and remaining questions regarding these endpoints for regulatory purposes
- MRD, pCR and other biomarker assessments in clinical trials should be discussed with the Agency
- FDA is committed to working with the community on the development of biomarkers.

Thanks…

- Laleh Amiri- Kordestani
- Marc Theoret
- Julia Beaver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