U.S. FOOD & DRUG ADMINISTRATION

Regulatory Perspective on Biomarker Development for Immuno-Oncology

SITC IO Biomarkers: Today's Imperatives for Tomorrow's Needs
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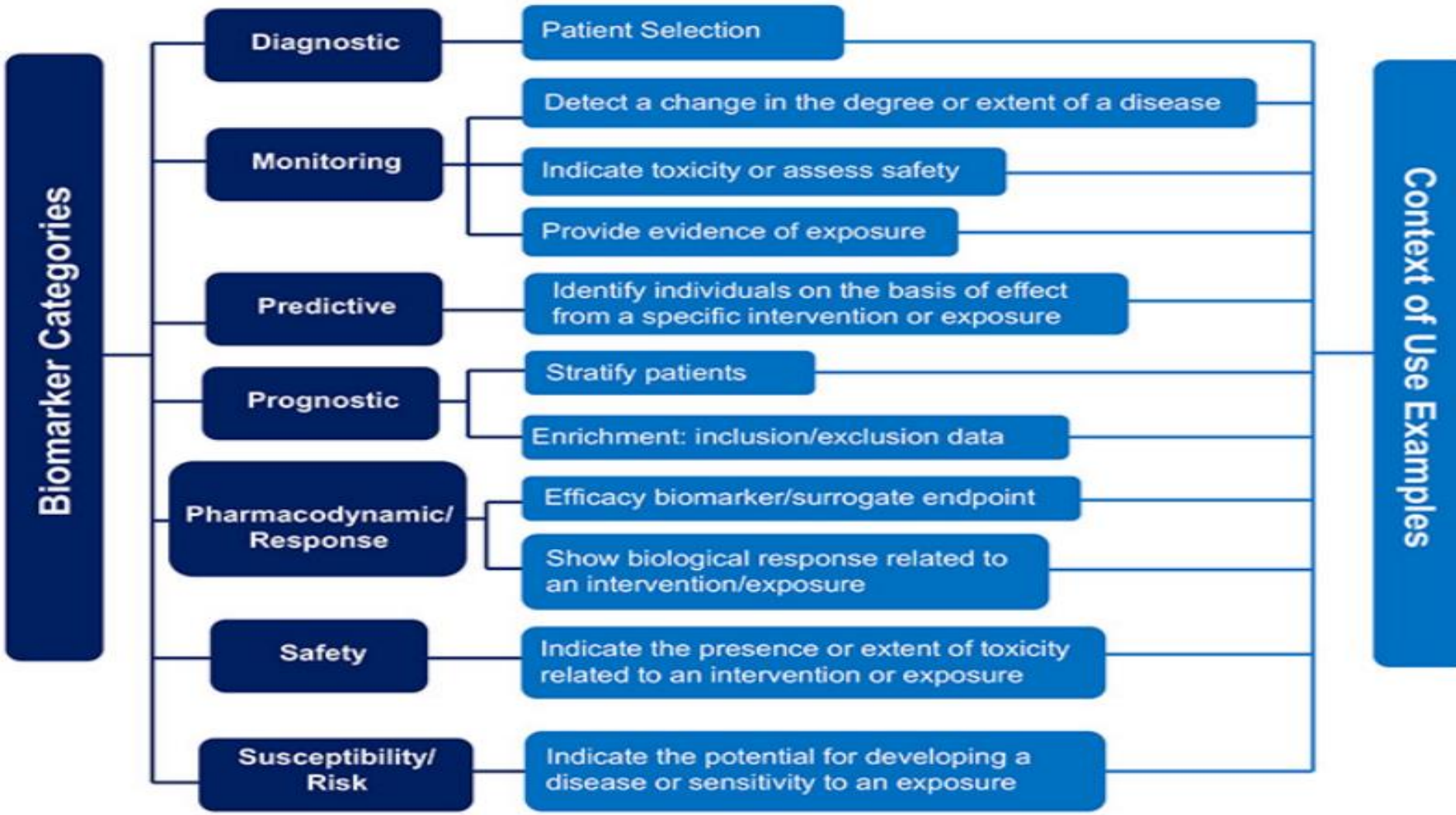
Key points

- Types of biomarkers
- Companion versus complementary dx
- Standardize/harmonize/collaborate
- Validating surrogates
- Composite/ orthogonal tests
  - Embrace complexity

Types of Biomarkers



Biomarker categories defined by the BEST (Biomarkers, EndpointS, and other Tools) Resource, available at: http://www.ncbi.nlm.nih.gov/books/NBK326791.

Context of Use is Central to Biomarker Validation, Approval/Clearance, Qualification

- Considerations when developing context of use
  - Identify the question you are trying to answer
  - Identify the biomarker
  - Purpose of use in drug development
  - Interpretation and decision/actions made based on the biomarker

Amur, S. FDA's Biomarker Qualification Program Educational Module Series. https://www.fda.gov/BiomarkerQualificationProgram

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Companion versus complementary diagnostic

- Companion diagnostic: test that is ***essential*** for the safe and effective use of a drug

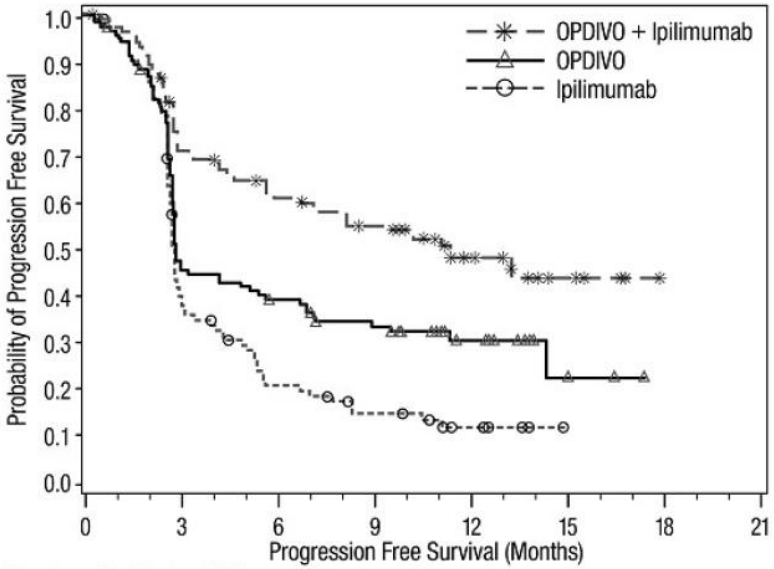
- Complementary diagnostic: a test that may ***inform*** or ***improve*** the benefit-risk of a drug for a given patient

Selected Examples of FDA approved therapies and Companion Dx

Therapy	Biomarker and disease	Device Trade Name(s)	Tech
Afatinib; gefitinib	EGFR mutations in mNSCLC	Therascreen EGFR RGQ PCR Kit	PCR
Erlotinib; osimertinib	EGFR mutations in mNSCLC	Cobas EGFR Mutation Test V2 (for both tissue and plasma)	PCR
Pembrolizumab	PD-L1 expression mNSCLC	PD-L1 IHC 22C3 pharmDx	IHC
Crizotinib	ALK rearrangement in mNSCLC	Vysis ALK Break Apart FISH Probe Kit, VENTANA ALK (D5F3) CDx Assay	FISH, IHC
Trametinib; dabrafenib	BRAF mutations in melanoma	THxID BRAF Kit	PCR
Dabrafenib; trametinib, crizotinib; gefitinib	BRAF mutations, ROS1 rearrangements, EGFR mutations in mNSCLC	Oncomine Dx Target Test (NGS)	NGS
Venetoclax	17p deletion CLL	Vysis CLL FISH	FISH
Rucaparib	BRCA ovarian cancer	Foundation Focus CDx BRCA Assay	NGS

Selected examples of complementary diagnostics

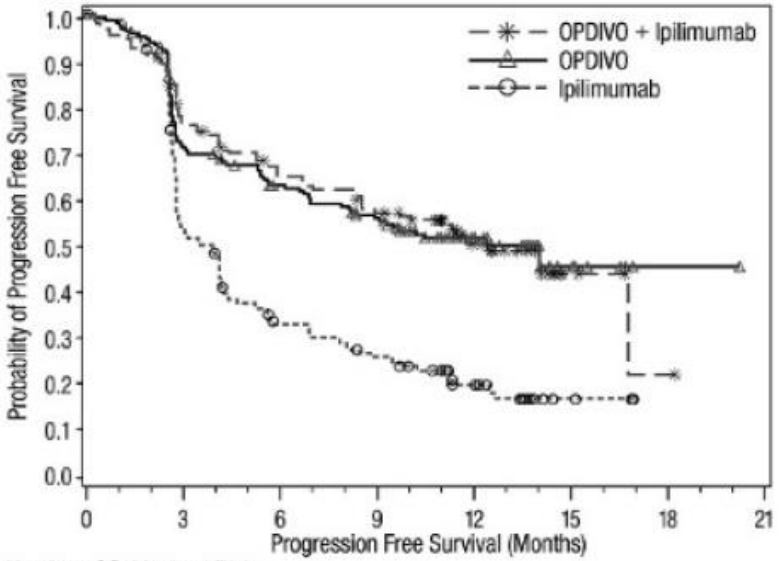
PFS by PD-L1 <1% Checkmate 067



Number of Subjects at Risk

OPDIVO + Ipilimumab	123	82	65	57	26	6	0	0
OPDIVO	117	50	42	34	13	2	0	0
Ipilimumab	113	39	19	12	5	0	0	0

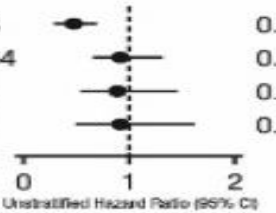
PFS by PD-L1 ≥1% Checkmate 067



Number of Subjects at Risk

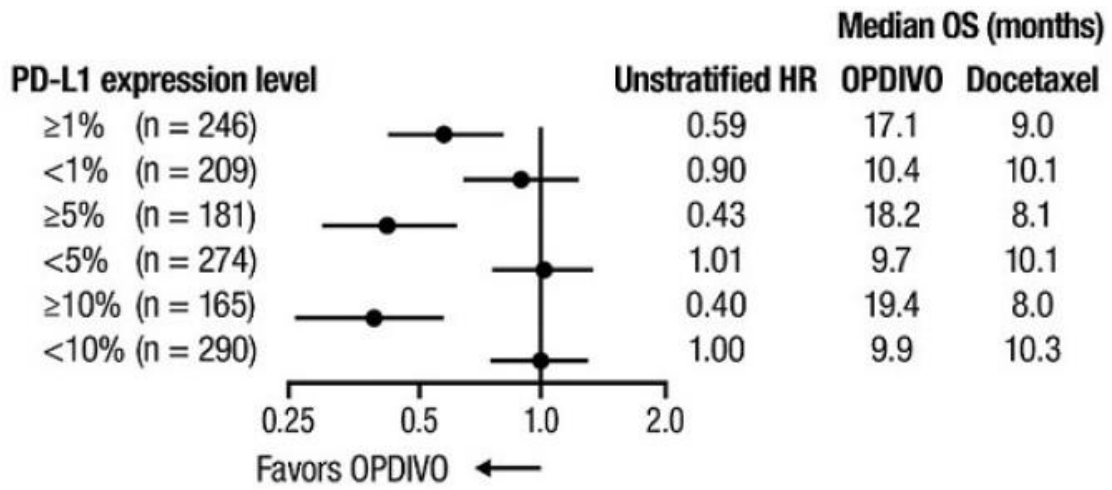
OPDIVO + Ipilimumab	155	113	91	78	32	4	1	0
OPDIVO	171	115	97	83	34	7	1	0
Ipilimumab	164	83	47	36	16	3	0	0

PD-L1 Expression Level	#Events/N OPDIVO+Ipi : OPDIVO : Ipi	OPDIVO+Ipi vs. OPDIVO Unstratified HR (95% CI)
<1%	59/123 : 76/117 : 85/113	0.56 (0.40, 0.79)
>=1%	72/155 : 79/171 : 122/164	0.95 (0.69, 1.31)
>=1%-<5%	44/87 : 46/91 : 69/89	0.93 (0.62, 1.41)
>=5%	28/68 : 33/80 : 53/75	0.96 (0.58, 1.58)

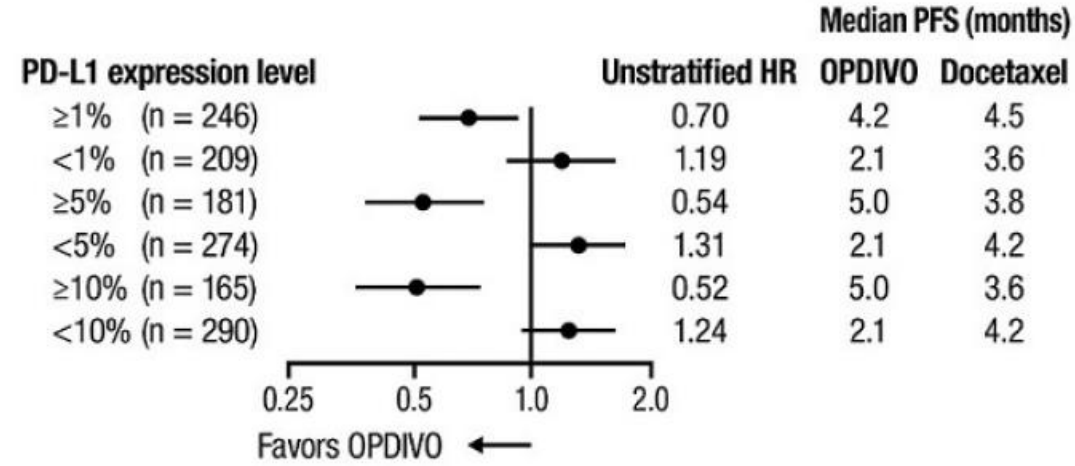


Selected examples of complementary diagnostics

Forest Plot: OS Based on PD-L1 Expression – Checkmate-057



Forest Plot: PFS Based on PD-L1 Expression – Checkmate-057



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The value of pre-competitive initiatives

- Lessons learned from PD-L1 IHC: multiple sponsors developing their own CDx in isolation may lead to confusion in the clinic
  - IASLC-AACR Blueprint effort sought to harmonize PD-L1 IHC assays
- Friends of Cancer Research: TMB harmonization
- BloodPac: data commons, developing minimal technical data elements (MTDE) for Liquid Biopsy developers
- FNIH: developing reference materials for CtDNA assays/ bake offs

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Surrogate Endpoint: “reasonably likely” versus “established”

- **Accelerated Approval**: accept surrogate endpoint reasonably likely to predict clinical benefit
  - Serious conditions/ high unmet medical need
  - Better than available therapy
  - confirmatory postmarketing studies
  - >90 AAs in Oncology since 1992, failure to confirm benefit is rare

- **Regular Approval**: established surrogates or improvement in direct measures of “feels, functions, survives”

Example #1 of validated surrogate endpoint: HIV-RNA

The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs

Jeffrey S. Murray, Michael R. Elashoff, Lauren C. Iacono-Connors, Therese A. Cvetkovich and Kimberly A. Struble

Objectives: To evaluate the utility of HIV RNA as an endpoint in antiretroviral efficacy studies.

Design: Data collected from antiretroviral efficacy trials were analyzed to explore relationships between clinical progression and the magnitude, nadir and duration of HIV RNA reductions. The proportion of patients suppressing HIV RNA below assay quantification, time to maximal virologic response, and loss of virologic response in relation to pretreatment characteristics were also analyzed.

Methods: Analyses were conducted using data from individual antiretoviral efficacy trials or groups of trials that studied similar types of drug regimens and used similar HIV RNA assays. Treatment regimens were pooled for most analyses. Clinical progression was defined as the occurrence of an AIDS-defining event (essentially Centers of Disease Control criteria) or death.

Results: Treatment-induced reductions in HIV RNA approximating total assay variability of about 0.5 $\log_{10}$ copies/ml were associated with decreases in the risk of clinical progression. Larger and more sustained reductions in HIV RNA were directly associated with lower risks for disease progression. Lower initial HIV RNA reductions were associated with more durable HIV RNA suppression.

Conclusions: For antiretoviral efficacy studies, plasma HIV RNA is a suitable study endpoint that is likely to predict a decreased risk for AIDS progression and death. Because greater and more sustained reductions in HIV RNA appear to confer greater reductions in clinical risk, maintaining maximal suppression of plasma HIV RNA, particularly below the limits of assay quantification, appears to be a rigorous benchmark for assessing the efficacy of antiretroviral regimens.

AIDS 1999, **13**:797–804

- **Prior to 1997**
  - death or OI approval endpoint
- **After 1997**
  - 24-week HIV-RNA→ accelerated approval
  - 48-week HIV-RNA→ regular approval
- Combination antiretroviral therapy (cART) has transformed life expectancy

Example #2 of validated surrogate endpoint: BCR-ABL PCR in CML

Frequency of Major Molecular Responses to Imatinib or Interferon Alfa plus Cytarabine in Newly Diagnosed Chronic Myeloid Leukemia

Tim P. Hughes, M.D., Jaspal Kaeda, Ph.D., Susan Branford, Zbigniew Rudzki, Ph.D., Andreas Hochhaus, M.D., Martee L. Hensley, M.D., Insa Gathmann, M.Sc., Ann E. Bolton, B.Sc.N., Iris C. van Hoomissen, B.Sc.N., John M. Goldman, D.M., and Jerald P. Radich, M.D., for the International Randomised Study of Interferon versus STI571 (IRIS) Study Group*

ABSTRACT

BACKGROUND

In a randomized trial, 1106 patients with chronic myeloid leukemia (CML) in chronic phase were assigned to imatinib or interferon alfa plus cytarabine as initial therapy. We measured levels of BCR-ABL transcripts in the blood of all patients in this trial who had a complete cytogenetic remission.

METHODS

Levels of BCR-ABL transcripts were measured by a quantitative real-time polymerase-chain-reaction assay. Results were expressed relative to the median level of BCR-ABL transcripts in the blood of 30 patients with untreated CML in chronic phase.

RESULTS

In patients who had a complete cytogenetic remission, levels of BCR-ABL transcripts after 12 months of treatment had fallen by at least 3 log in 57 percent of those in the imatinib group and 24 percent of those in the group given interferon plus cytarabine (P=0.003). On the basis of the rates of complete cytogenetic remission of 68 percent in the imatinib group and 7 percent in the group given interferon plus cytarabine at 12 months, an estimated 39 percent of all patients treated with imatinib but only 2 percent of all those given interferon plus cytarabine had a reduction in BCR-ABL transcript levels of at least 3 log (P<0.001). For patients who had a complete cytogenetic remission and a reduction in transcript levels of at least 3 log at 12 months, the probability of remaining progression-free was 100 percent at 24 months, as compared with 95 percent for such patients with a reduction of less than 3 log and 85 percent for patients who were not in complete cytogenetic remission at 12 months (P<0.001).

CONCLUSIONS

The proportion of patients with CML who had a reduction in BCR-ABL transcript levels of at least 3 log by 12 months of therapy was far greater with imatinib treatment than with treatment with interferon plus cytarabine. Patients in the imatinib group with this degree of molecular response had a negligible risk of disease progression during the subsequent 12 months.

Hughes TP, Kaeda J, et al. NEJM 2003

Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS)

*Timothy P. Hughes,[1] *Andreas Hochhaus,[2] Susan Branford,[3] Martin C. Müller,[4] Jaspal S. Kaeda,[5] Letizia Foroni,[6] Brian J. Druker,[7] François Guilhot,[8] Richard A. Larson,[9] Stephen G. O'Brien,[10] Marc S. Rudoltz,[11] Manisha Mone,[11] Elisabeth Wehrle,[12] Vijay Modur,[13] John M. Goldman,[6] and Jerald P. Radich,[14] on behalf of the IRIS investigators

[1]Department of Haematology, SA Pathology, Royal Adelaide Hospital, Adelaide, Australia; [2]Abt Hämatologie und internistische Onkologie, Klinik für Innere Medizin II, Universitätsklinikum Jena, Jena, Germany; [3]Molecular Pathology, SA Pathology, Adelaide, Australia and School of Medicine, University of Adelaide, Adelaide, Australia; [4]III Medizinische Klinik, Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany; [5]Department of Hematology, Central Hospital of Coimbra, Coimbra, Portugal; [6]Haematology Department, Hammersmith Hospital, London, United Kingdom; [7]Knight Cancer Institute, Oregon Health & Science University, Portland, OR; [8]Centre d'Investigation Clinique CIC P 802, Inserm, Centre Hospitalier Universitaire de Poitiers, Poitiers, France; [9]University of Chicago, Chicago, IL; [10]Newcastle University Medical School, Newcastle, United Kingdom; [11]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [12]Novartis Pharma AG, Basel, Switzerland; [13]Novartis Institute of Biomedical Research, Cambridge, MA; and [14]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA

This study examines the prognostic significance of early molecular response using an expanded dataset in chronic myeloid leukemia patients enrolled in the International Randomized Study of Interferon and STI571 (IRIS). Serial molecular studies demonstrate decreases in *BCR-ABL* transcripts over time. Analyses of event-free survival (EFS) and time to progression to accelerated phase/blast crisis (AP/BC) at 7 years were based on molecular responses using the international scale (IS) at 6-, 12-, and 18-month landmarks. Patients with *BCR-ABL* transcripts > 10% at 6 months and > 1% at 12 months had inferior EFS and higher rate of progression to AP/BC compared with all other molecular response groups. Conversely, patients who achieved major molecular response [MMR: *BCR-ABL* (IS) ≤ 0.1%] by 18 months enjoyed remarkably durable responses, with no progression to AP/BC and 95% EFS at 7 years. The probability of loss of complete cytogenetic response by 7 years was only 3% for patients in MMR at 18 months versus 26% for patients with complete cytogenetic response but not MMR ($P < .001$). This study shows a strong association between the degree to which *BCR-ABL* transcript numbers are reduced by therapy and long-term clinical outcome, supporting the use of time-dependent molecular measures to determine optimal response to therapy. This study is registered at www.clinicaltrials.gov as NCT00006343. (*Blood*. 2010;116(19):3758-3765)

Hughes TP, Hochhaus, et al. Blood 2010

Example #2 of validated surrogate endpoint: BCR-ABL PCR in CML

	Dasatinib (N=259)	Imatinib (N=260)
MMR		
12 month	52%	34%
60 month	76%	64%

MMR (at any time) defined as BCR-ABL ratios <0.1% by RQ-PCR in peripheral blood samples standardized on the international scale. These are cumulative rates representing minimal follow-up for the time frame specified

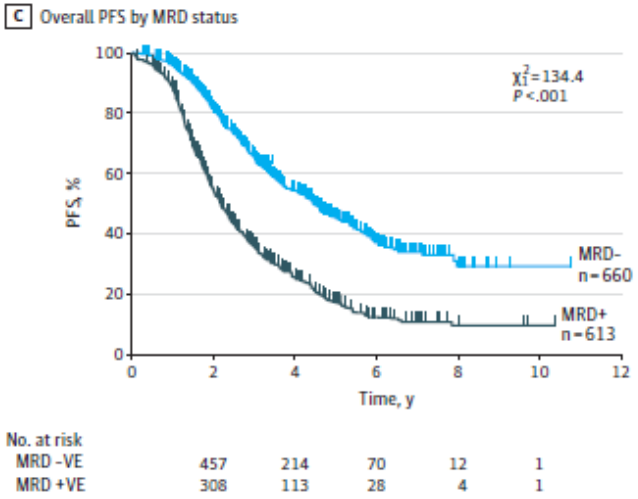
	Nilotinib (N=282)	Imatinib (N=283)
MMR		
12 month	44%	22%
24 month	62%	38%
60 month	77%	60%

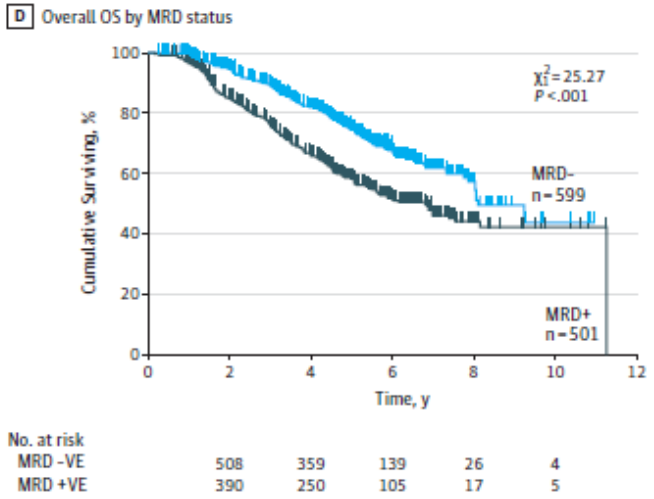
MMR defined as BCR-ABL/ABL ratios <0.1% by RQ-PCR in peripheral blood samples standardized on the international scale, which corresponds to a greater than or equal to 3 log reduction of BCR-ABL transcript from standardized baseline.

12 month MMR used as accelerated approval endpoint for imatinib-naïve 2nd Gen ABL KIs

Meta-analysis techniques

- **Patient level**

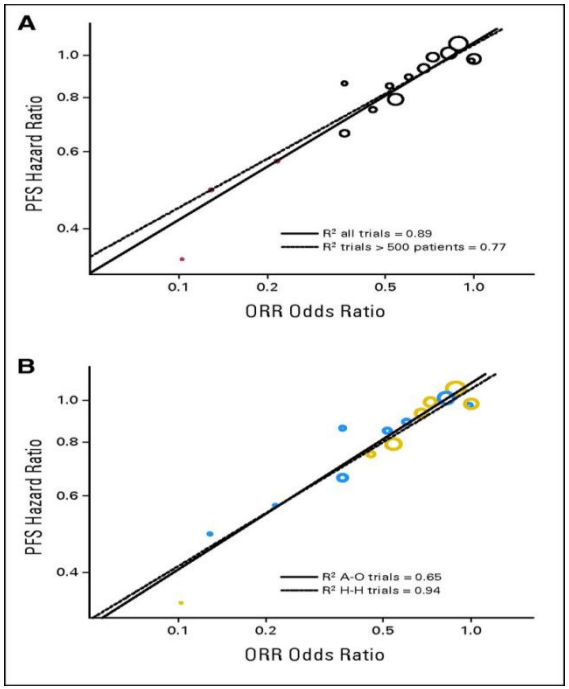


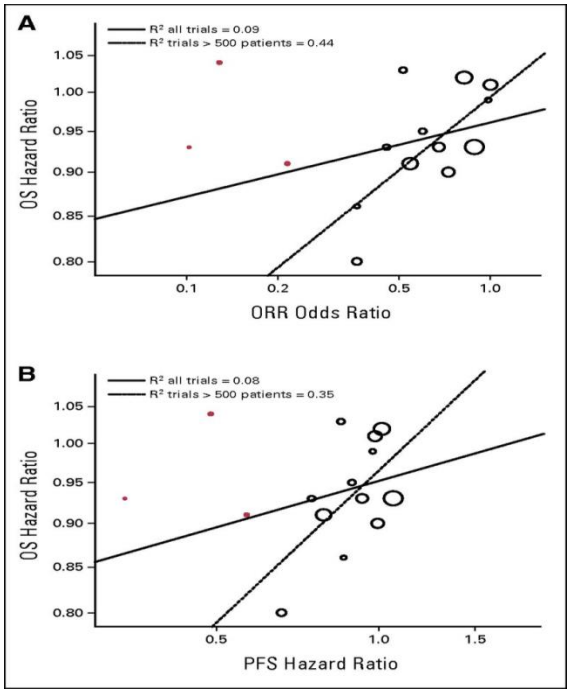


Munshi NC, Avet-Loiseau H et al. JAMA Oncology 2017

Meta-analysis techniques

- **Trial level**





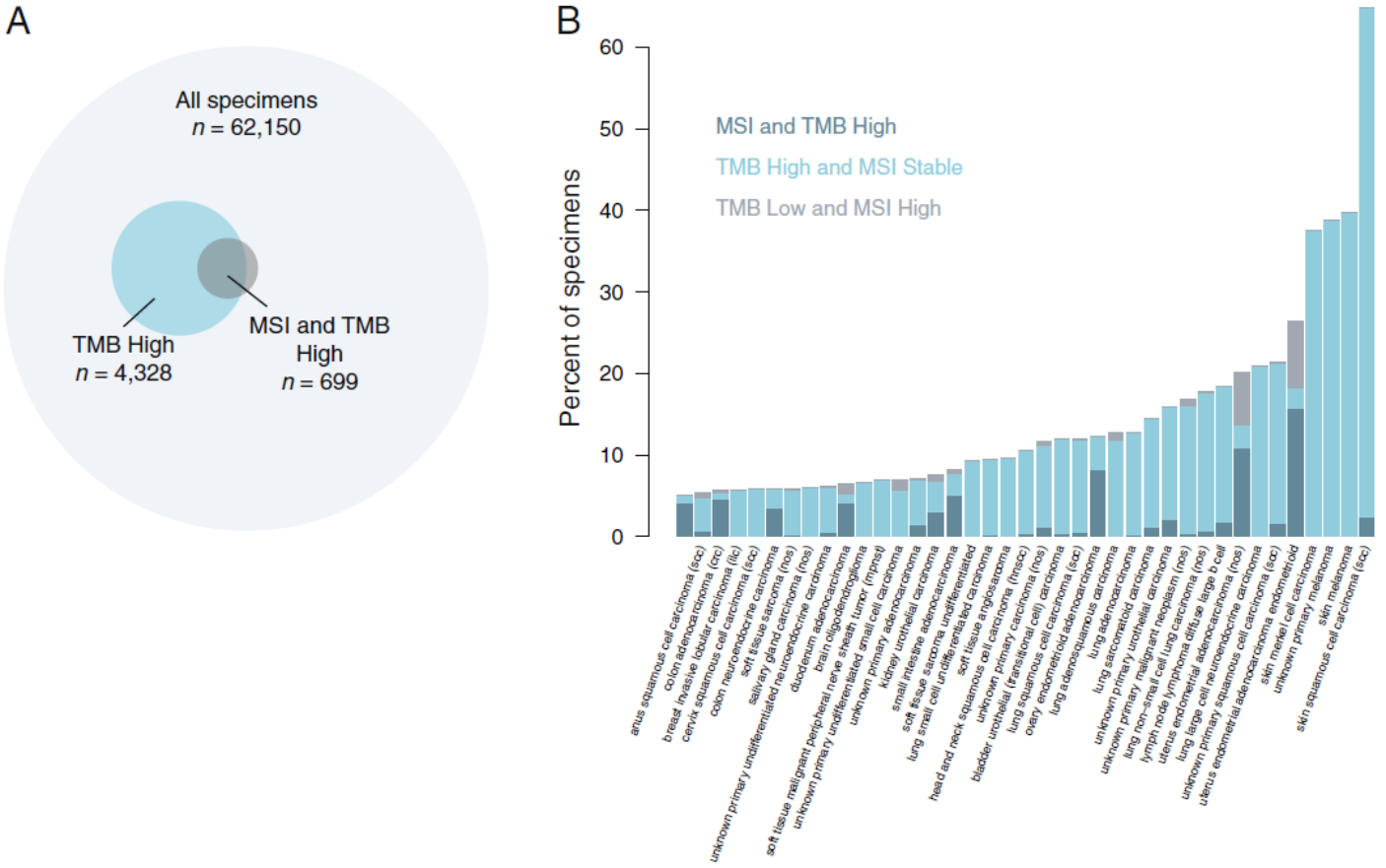
Blumenthal GM, Karuri S, Zhang H, et al. J Clin Oncol. 2015 Mar 20;33(9):1008-14.

Key points

- Types of biomarkers
- Companion versus complementary dx
- Standardize/harmonize/collaborate
- Validating Surrogates
- Composite/ orthogonal tests
  - Embrace complexity

Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden

Zachary R. Chalmers[1†], Caitlin F. Connelly[1†], David Fabrizio[1], Laurie Gay[1], Siraj M. Ali[1], Riley Ennis[1], Alexa Schrock[1], Brittany Campbell[4], Adam Shlien[4], Juliann Chmielecki[1], Franklin Huang[2], Yuting He[1], James Sun[1], Uri Tabori[4], Mark Kennedy[1], Daniel S. Lieber[1], Steven Roels[1], Jared White[1], Geoffrey A. Otto[1], Jeffrey S. Ross[1], Levi Garraway[2,3], Vincent A. Miller[1], Phillip J. Stephens[1] and Garrett M. Frampton[1*]



Chalmers et al Genome Medicine 2017

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Thank you!

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