Correlating Surrogate Endpoints with Overall Survival at the Individual Patient Level for Precision Oncology

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What is a surrogate endpoint?

A **surrogate** endpoint replaces a **clinical** endpoint and is:

- Cheaper to collect
- Easier to measure
- Occurs earlier

Benefits of surrogate endpoints

- Shorter clinical trials lead to:
  - Lower cost
  - Less drop-out and non-compliance
- Getting effective drugs approved and to market more quickly
- Earlier detection of drug toxicity

Examples of surrogate endpoints in oncology

Clinical endpoints directly measure how people feel or function, or whether they live longer.

Examples of **surrogate** endpoints in oncology include:

- Progression-free survival
- Recurrence-free survival
- Tumor shrinkage
- Biomarkers

Criteria for assessing surrogate endpoints

Criteria used to assess surrogate endpoints:

1. The biological plausibility of the relationship
2. The demonstration of the prognostic value of the surrogate for the clinical outcome
3. Evidence from clinical trials that treatment effects on the surrogate correspond to treatment effects on the clinical outcome

The association between a potential surrogate and a clinical endpoint is insufficient!

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, https://database.ich.org/sites/default/files/E9_Guideline.pdf

Assessment of surrogate endpoints

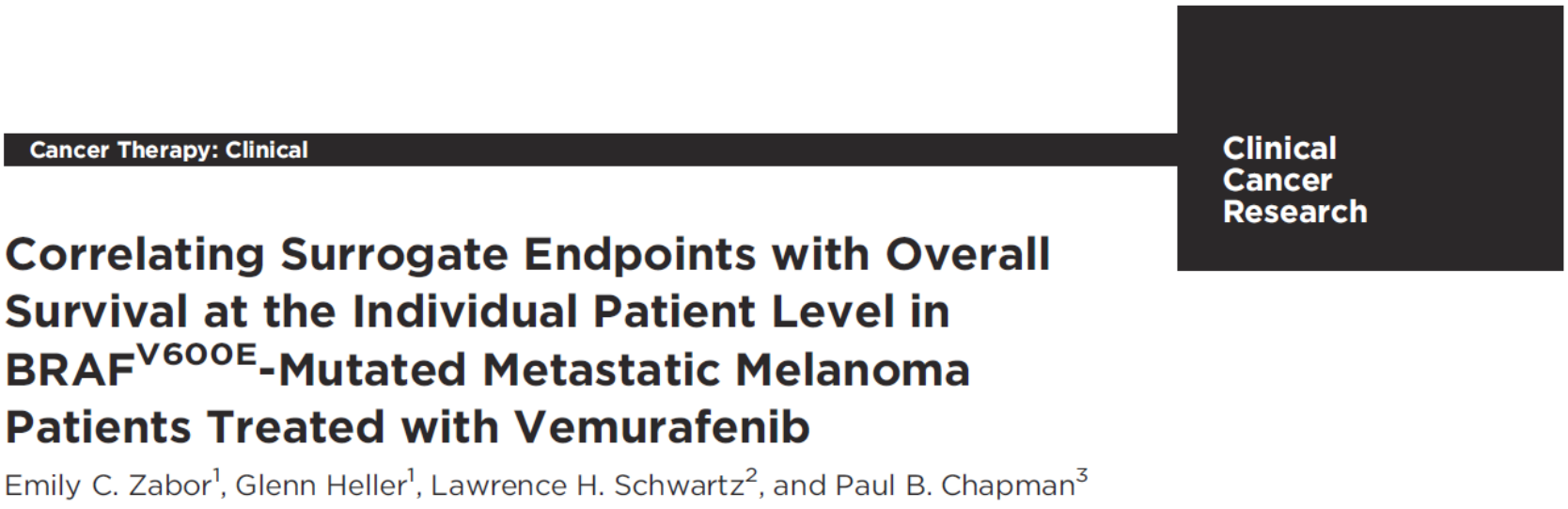
Surrogate endpoints can be assessed either on the **individual level** or the **trial level**.

Individual level association is assessed using data from a single trial.

Trial level association is assessed using data from multiple trials, in a meta-analytic framework.

The ideal setting is **individual-level data** from **multiple trials**.

Assessing surrogate endpoints for overall survival in melanoma



Cancer Therapy: Clinical

Clinical Cancer Research

Correlating Surrogate Endpoints with Overall Survival at the Individual Patient Level in $BRAF^{V600E}$-Mutated Metastatic Melanoma Patients Treated with Vemurafenib

Emily C. Zabor[1], Glenn Heller[1], Lawrence H. Schwartz[2], and Paul B. Chapman[3]

Zabor EC, Heller G, Schwartz LH, Chapman PB. Correlating Surrogate Endpoints with Overall Survival at the Individual Patient Level in BRAFV600E-Mutated Metastatic Melanoma Patients Treated with Vemurafenib. Clin Cancer Res. 2016 Mar 15;22(6):1341-7.

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RECIST criteria as surrogate endpoint for OS

- Commonly used
- Definitions are decades old and unreliable
- Not based on correlation with OS

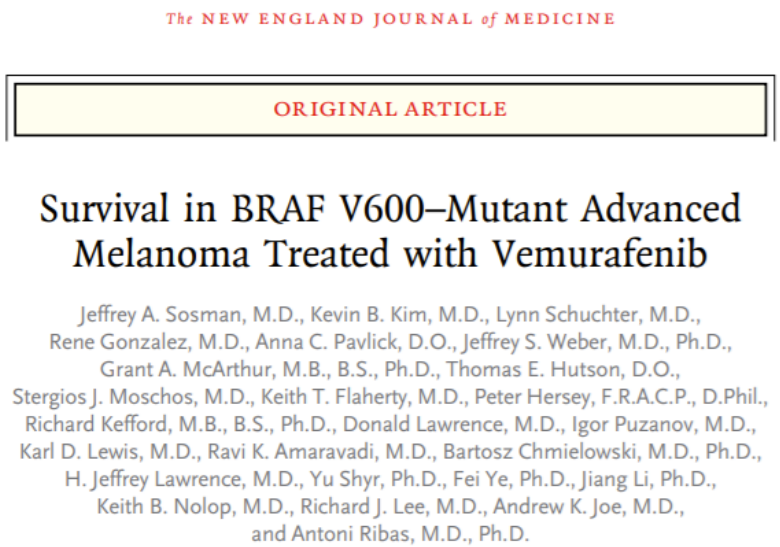
Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Clinical trials of vemurafenib in melanoma

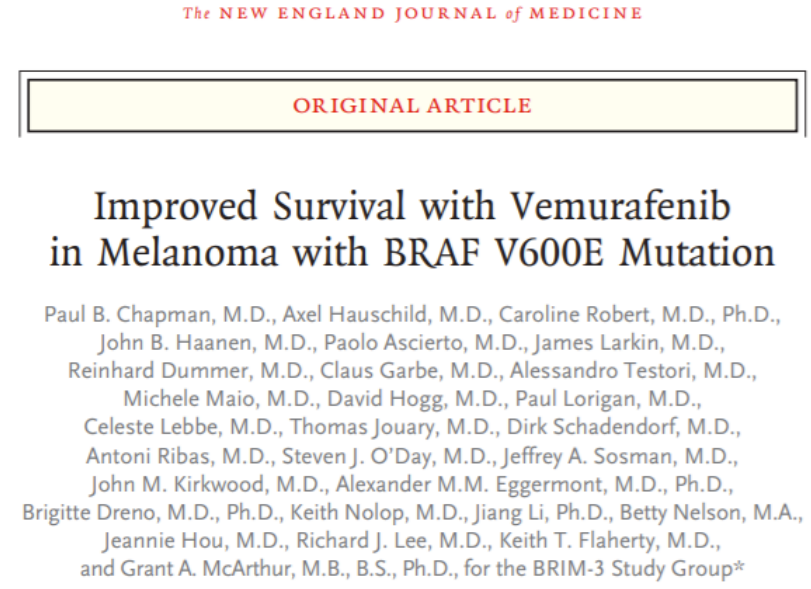


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Survival in BRAF V600–Mutant Advanced Melanoma Treated with Vemurafenib

Jeffrey A. Sosman, M.D., Kevin B. Kim, M.D., Lynn Schuchter, M.D., Rene Gonzalez, M.D., Anna C. Pavlick, D.O., Jeffrey S. Weber, M.D., Ph.D., Grant A. McArthur, M.B., B.S., Ph.D., Thomas E. Hutson, D.O., Stergios J. Moschos, M.D., Keith T. Flaherty, M.D., Peter Hersey, F.R.A.C.P., D.Phil., Richard Kefford, M.B., B.S., Ph.D., Donald Lawrence, M.D., Igor Puzanov, M.D., Karl D. Lewis, M.D., Ravi K. Amaravadi, M.D., Bartosz Chmielowski, M.D., Ph.D., H. Jeffrey Lawrence, M.D., Yu Shyr, Ph.D., Fei Ye, Ph.D., Jiang Li, Ph.D., Keith B. Nolop, M.D., Richard J. Lee, M.D., Andrew K. Joe, M.D., and Antoni Ribas, M.D., Ph.D.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffrey A. Sosman, M.D., John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*

Sosman JA, Kim KB, ..., Ribas A. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med. 2012 Feb 23;366(8):707-14.
Chapman PB, Hauschild A, ..., McArthur GA; BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011 Jun 30;364(26):2507-16.

Analysis of individual-level patient data

- Main analysis in BRIM3 data
  - Phase III trial in previously untreated *BRAF*^{V600E}-mutated metastatic melanoma
  - Randomized to vemurafenib or dacarbazine
  - Study arms pooled for analysis
  - 489 analyzed for early response; 582 analyzed for TTP
- Independent validation in BRIM2 data
  - Phase II trial in previously treated *BRAF*^{V600E}-mutated metastatic melanoma
  - 49% of patients had received more than one prior therapies
  - All patients treated with vemurafenib
  - 132 analyzed for both early response and TTP

Early tumor response as surrogate endpoint

- Defined as within 12 weeks
- Sum of up to 5 target lesions at each scan time
- Relative percent reduction at each time defined as 100 x (sum baseline - sum follow-up)/(sum baseline)
- Best response = maximum relative percent reduction
- Investigated thresholds of 10%, 20%, 30%, 40%, 50%, 60%
- Landmark analysis and non-parametric weighted C-index*, normalized to 0/1 scale

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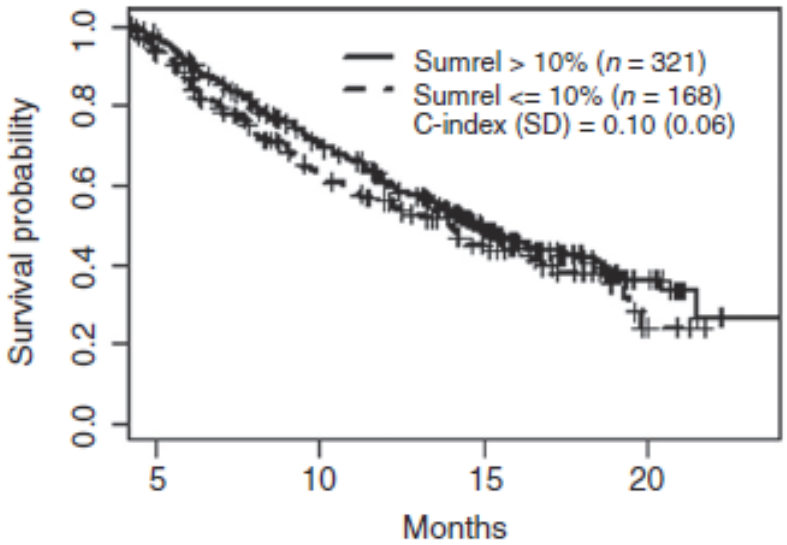
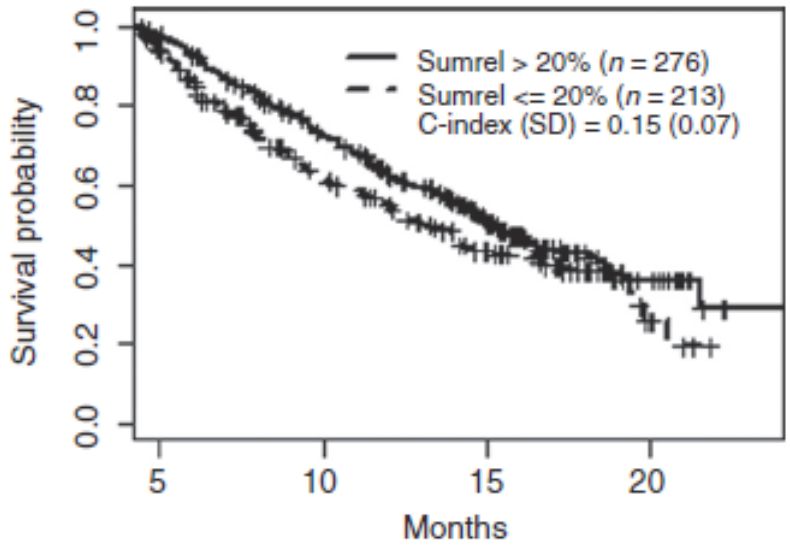
* Uno H, Cai T, Pencina MJ, D'Agostino RB, Wei LJ. On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. Stat Med. 2011 May 10;30(10):1105-17.

Early tumor response thresholds 10% and 20% were not correlated with overall survival in BRIM3





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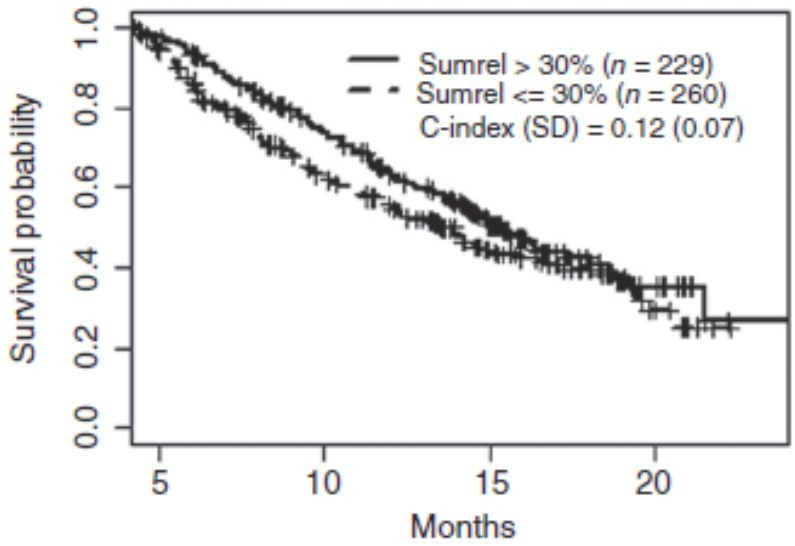
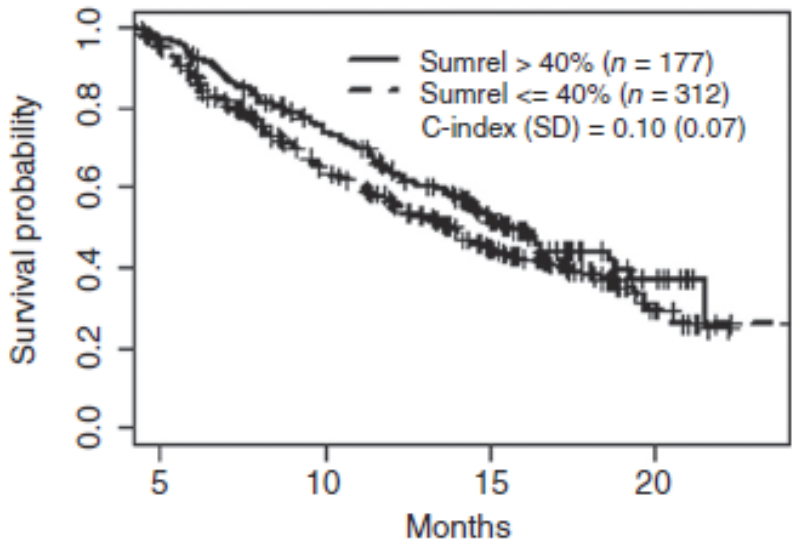
Early tumor response thresholds 30% and 40% were not correlated with overall survival in BRIM3





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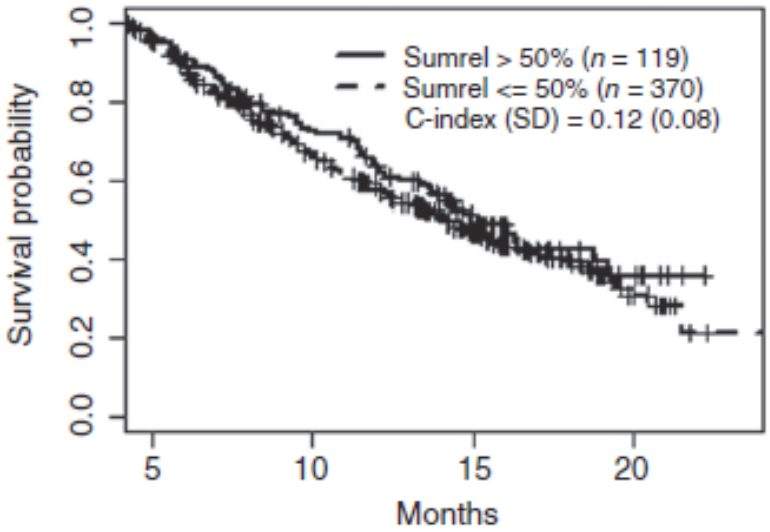
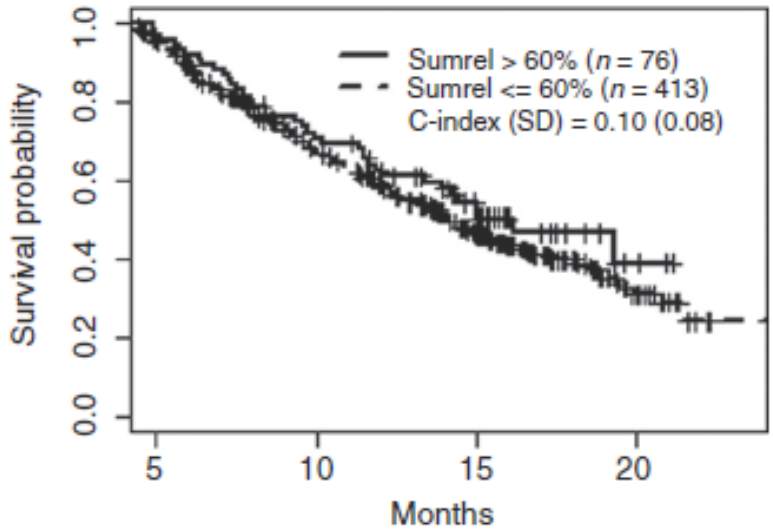
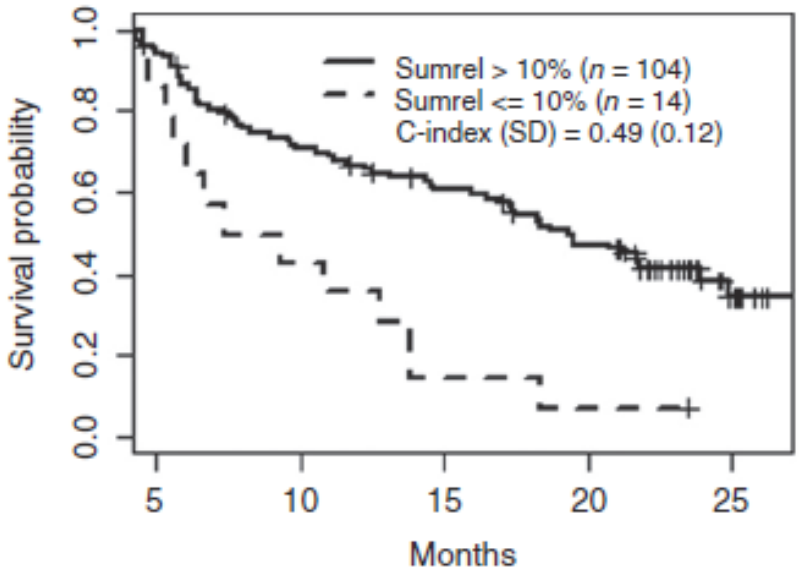
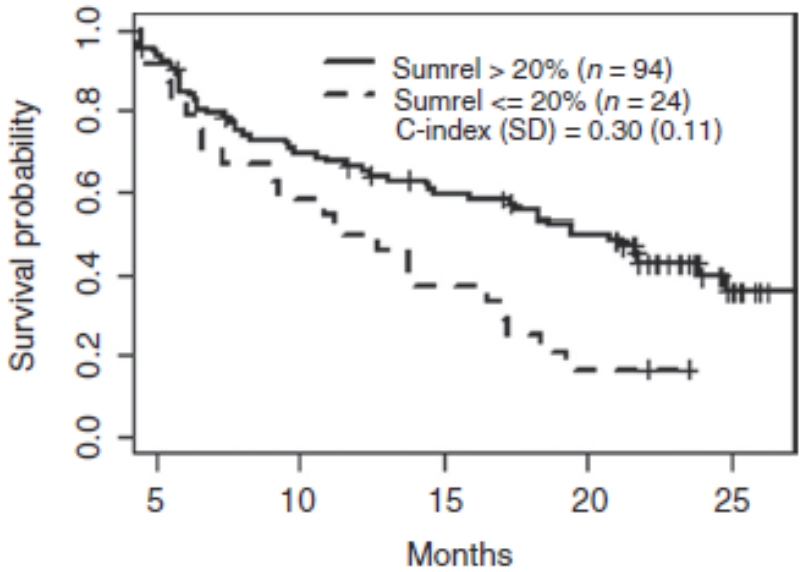
Early tumor response thresholds 50% and 60% were not correlated with overall survival in BRIM3





Early tumor response threshold 10% most strongly correlated with overall survival in BRIM2





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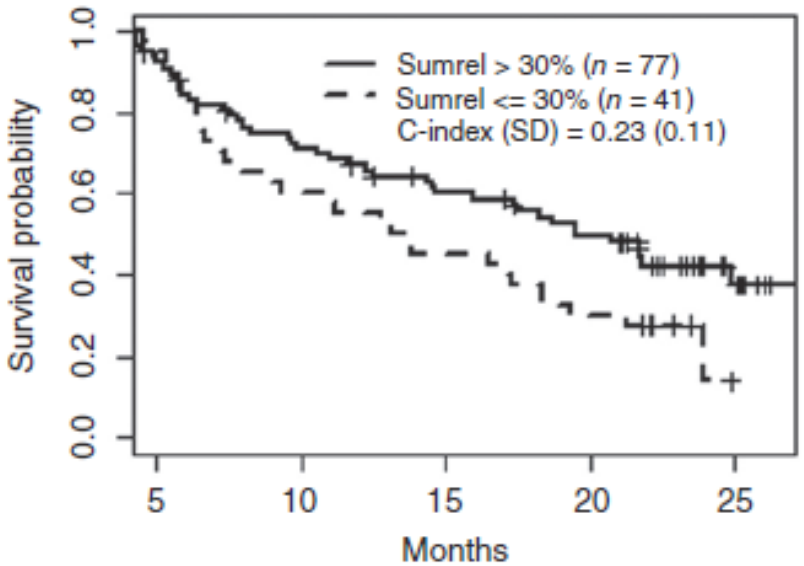
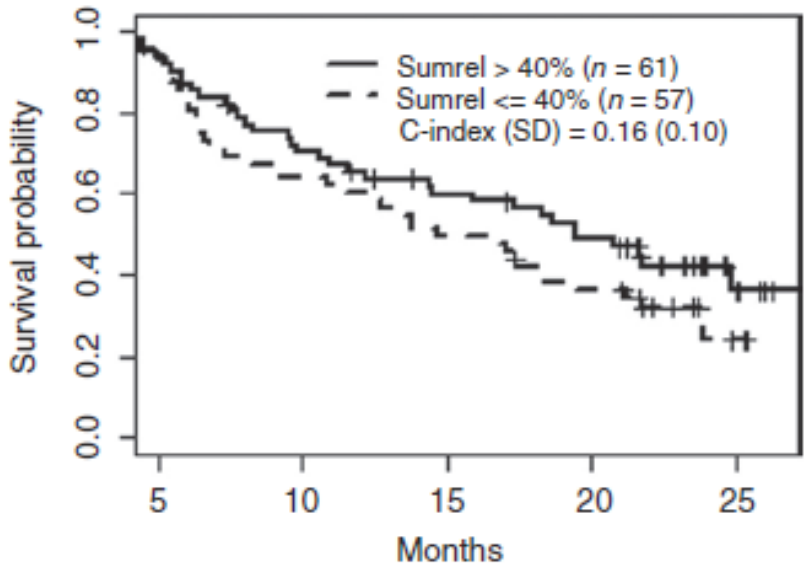
Early tumor response thresholds 30% and 40% were weakly correlated with overall survival in BRIM2





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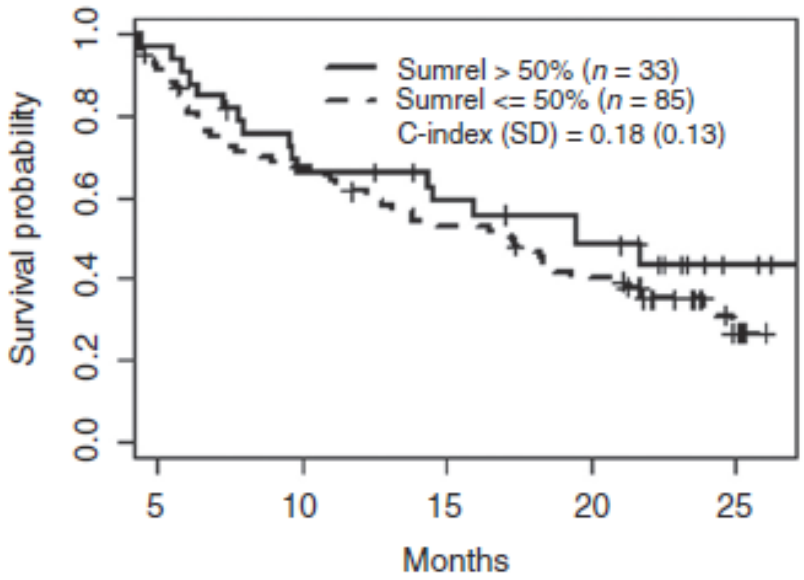
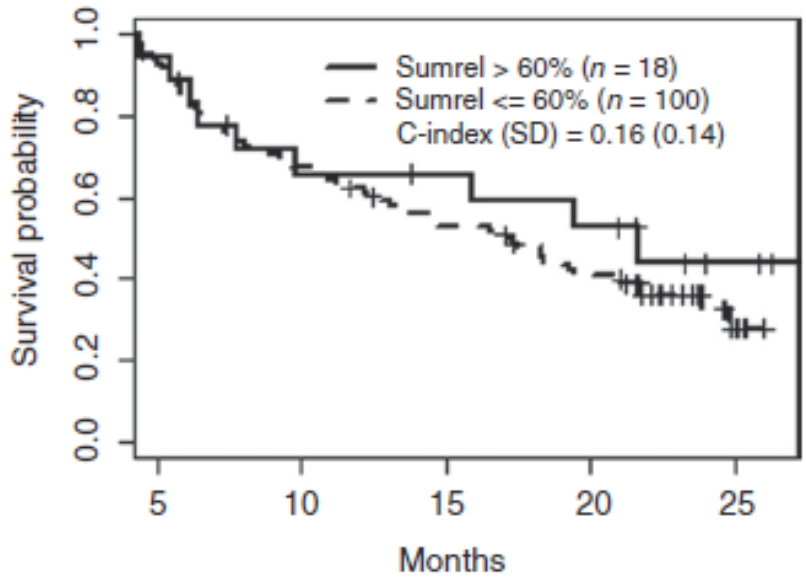
Early tumor response thresholds 50% and 60% were not correlated with overall survival in BRIM2





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Early tumor response summary

- No correlation between early tumor response and OS in BRIM3 overall, or in vemurafenib subset (not shown)
- Much stronger correlation in BRIM2
- Possibly due to a ”healthy patient effect” in BRIM2 as all patients had previously progressed on one or more therapies
- Correlation between early response and OS not robust or generalizable

Time-to-progression as surrogate endpoint

- Progressive disease defined as any, 25%, 50%, or 100% increase in sum of target tumor diameters at any time
- Calculated from baseline, and from response nadir
- Considered including and excluding new lesions as progression
- Correlation measured by Kendall's tau derived from the Clayton copula*, scaled between 0 and 1

* Oakes, D. On consistency of Kendall's tau under censoring. Biometrika. 2008 Dec;95(4):997-1001.

TTP as 50% increase had strongest correlation with OS from baseline in BRIM3

	From baseline			
	Without new lesions		With new lesions	
	Number of events	Correlation with OS (SE)	Number of events	Correlation with OS (SE)
Relative increase				
Any	287	0.330 (0.045)	451	0.411 (0.032)
25%	180	0.543 (0.046)	404	0.541 (0.032)
50%	104	0.675 (0.065)	376	0.588 (0.030)
100%	57	0.072 (0.142)	361	0.526 (0.033)

TTP as 50% increase had strongest correlation with OS from nadir in BRIM3

	From nadir			
	Without new lesions		With new lesions	
	Number of events	Correlation with OS (SE)	Number of events	Correlation with OS (SE)
Relative increase				
Any	NA	NA	NA	NA
25%	306	0.547 (0.038)	468	0.524 (0.029)
50%	207	0.638 (0.044)	423	0.568 (0.029)
100%	132	0.522 (0.075)	396	0.576 (0.029)

TTP at all thresholds had strong correlation with OS from baseline in BRIM2

	From baseline			
	Without new lesions		With new lesions	
	Number of events	Correlation with OS	Number of events	Correlation with OS
Relative increase				
Any	28	0.634 (0.091)	89	0.668 (0.053)
25%	14	NA	84	0.693 (0.046)
50%	8	NA	84	0.723 (0.037)
100%	3	NA	83	0.717 (0.038)

TTP at all thresholds had strong correlation with OS from nadir in BRIM2

	From nadir			
	Without new lesions		With new lesions	
	Number of events	Correlation with OS	Number of events	Correlation with OS
Relative increase				
Any	NA	NA	NA	NA
25%	69	0.613 (0.063)	111	0.635 (0.047)
50%	36	0.720 (0.069)	95	0.708 (0.039)
100%	16	NA	89	0.710 (0.041)

Time-to-progression summary

- Strongest correlation when progression defined as 50% or greater increase in sum of target lesions, or appearance of new lesions
- Progression on dacarbazine more frequently due to target lesion growth; progression on vemurafenib more frequently due to new lesions (not shown)
- Correlation between TTP and OS robust; validated by BRIM2

Conclusions

- Early tumor response not correlated with OS
- TTP defined as growth in sum of target lesions 50% or more, or appearance of new lesions, best correlated with OS
- PFS, which includes death without progression, may be even more appropriate
- Unclear if these correlations will hold in the context of immunotherapies
- Formal assessment of TTP defined as growth in sum of diameters of target lesions of at least 50% is needed to establish this as a valid surrogate endpoint for use in clinical trials

Acknowledgements

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- Larry Schwartz - Columbia University Department of Radiology
- Paul Chapman - Memorial Sloan Kettering Cancer Center Department of Medicine

Thank you! Questions?

Contact me: zabore2@ccf.org

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