correspondence

TP53 Gene Indels Impact on Cancer Outcomes

TO THE EDITOR:

Thiel et al[1] have performed an important study on the impact of *TP53* mutations on the response of endometrial cancer to bevacizumab plus chemotherapy relative to temsirolimus plus chemotherapy. Gene mutations were identified by next-generation sequencing and p53 protein levels by immunohistochemistry (IHC). Progression-free survival (PFS) and overall survival (OS) were determined in a randomized phase II study.

The p53 overexpression by IHC was associated to the most striking treatment effect favoring bevacizumab (PFS hazard ratio [HR], 0.46; 95% CI, 0.26 to 0.88; OS HR, 0.31; 95% CI, 0.16 to 0.62). Patients with *TP53* missense mutations and p53 protein overexpression had a similar impact on PFS (HR, 0.41; 95% CI, 0.22 to 0.83) and OS (HR, 0.28; 95% CI, 0.14 to 0.59), favoring bevacizumab. The concordance between *TP53* mutation profiles and p53 IHC was 88%. This increased when cases with *TP53* mutations and mismatch repair deficiency were removed.

Determination of p53 by IHC has been shown to be a strong prognostic[2] and predictive[3,4] risk indicator in several types of cancers. High levels of p53 protein by IHC were suggested to associate with missense mutations.[5] Conversely, lack of immunostaining in mutated *TP53* gene was most often seen in tumors harboring nonsense mutations or insertions/deletions (indels).[6] However, this streamlined picture[7] failed to account for several experimental observations, indicating that the relationship between DNA mutations and protein overexpression had to be revisited.[8]

We analyzed a breast cancer case series, whereby lymph node diffusion, tumor size, grading, proliferation rate, and hormone receptors expression were complemented by whole-exon *TP53* gene sequencing and IHC p53 determination.[9] This explored the correlation between *TP53* gene mutation classes and IHC p53 protein levels. Findings were correlated with clinical phenotypes (Fig 1). Notably, *TP53* indels were only detected in relapsed cancer cases. However, not all *TP53* indels were negative by IHC. At the other end of the spectrum, we found that not all *wtTP53* were negative by IHC. Furthermore, not all missense mutated *TP53* proved positive by IHC.

These findings and those of other groups[2,8] indicate that relationships between *TP53* gene alterations and levels of the p53 protein are much more complex than previously suggested. Among the reasons for such complexity are intricate sets of regulatory mechanisms, for example, ubiquitination, protein degradation, mRNA translation regulation, and positive/negative selection of mutation-bearing cells.[10] Hence, simplified suggestions of feedback regulation of p53 protein levels for restoring function appear weakly supported.[10]

Our findings that all *TP53* indels underwent metastatic relapse suggest heavy biological impact, a finding that proved broadly consistent across most studies.[2,8] Hence, we argue that *TP53* indels should be separately categorized from missense mutations. IHC-determined p53 protein levels on the remaining cases may require separate classification of p53 high/nil versus *TP53* wt/mutated, clearly taking subgroup patient number into account.

It would be important to know whether such a categorization can extend the predictive power of the study and further augment its impact on endometrial cancer care.[1]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Case No.	pT	pN	Grade	ER	PgR	Ki67	p53 IHC	Relapse	*TP53* Gene Mutation
1	1	1	3	0	0	0	**10**	**Yes**	P278L
3	1	0	2	70	100	0	**15**	**Yes**	wt
4	2	2	3	25	40	0	**60**	**Yes**	C275F
5	2	0	3	0	0	10	**75**	**Yes**	Deletion 161-165
8	1	0	2	0	0	10	**0**	**Yes**	wt
9	2	2	3	90	25	4	**70**	**Yes**	P359L
10	1	0	2	5	95	30	**0**	**Yes**	wt
13	2	0	3	0	0	0	**80**	**Yes**	Insertion L272-273
14	2	0	3	0	0	70	**90**	**Yes**	R273H
15	4	0	3	0	0	45	**70**	**Yes**	wt
16	3	0	2	5	50	0	**25**	**Yes**	A364T
17	1	0	3	0	70	8	**5**	**Yes**	wt
18	1	0	2	10	75	5	**0**	**Yes**	Deletion P72
19	2	2	3	0	0	40	**70**	**Yes**	wt
20	1	1	3	15	15	3	**0**	**Yes**	wt
22	1	0	2	5	40	0	**0**	No	P300S; S362N
23	1	0	1	5	80	3	**0**	No	wt
24	1	0	2	70	40	10	**0**	No	wt
25	1	0	2	90	35	3	**0**	No	wt
26	1	0	1	0	90	2	**0**	No	P300S
27	1	0	2	70	80	10	**0**	No	P71S; R72P; A76V
28	1	2	3	0	0	0	**0**	No	E286K
29	1	0	2	5	70	10	**0**	No	wt
30	1	0	2	0	65	8	**0**	No	P89L; P92S
31	2	1	2	5	80	10	**15**	No	R248Q
33	2	2	3	0	0	20	**75**	No	Y234N
34	2	1	2	0	70	0	**0**	No	wt
35	2	2	3	95	5	10	**0**	No	wt
36	2	0	3	0	5	10	**90**	No	E287K; L344R
37	2	1	2	60	0	0	**0**	No	R379C; K386E
38	2	1	3	80	10	25	**0**	No	wt
39	2	0	2	25	90	5	**0**	No	wt
40	2	1	2	80	95	25	**0**	No	wt
41	1c	0	3	10	45	1	**4**	No	wt
42	2	3	2	0	0	1	**0**	**Yes**	wt
43	2	0	3	0	0	2	**75**	No	R333H; G361R
44	2	1	2	30	72	2	**8**	No	wt
45	3	0	3	39	14	0	**0**	No	A364T
46	2	3	3	0	0	2	**2**	**Yes**	G245R
47	2	1	3	16	22	9	**0**	**Yes**	wt
48	1c	1	3	92	0	33	**85**	**Yes**	Stop codon E339*
49	2	1	3	55	12	1	**0**	**Yes**	wt
50	3	2	2	85	25	4	**8**	**Yes**	wt
51	1a	0		15	0	0	**0**	**Yes**	wt
52	2	0		77	3	5	**5**	**Yes**	G245D; A364T
53	1c	0		88	90	8	**3**	No	wt

FIG 1. Missense mutations and indels versus IHC p53 protein detection. Modified from Guerra et al.[9] All IHC parameters are percent stained cells. p53 IHC: light gray: < 10%, dark gray > 10% positive cells. *TP53* gene mutations are listed, and indels are in light gray. Tumor relapse is indicated. pT, pN, and grade are indicated. ER, estrogen receptor; IHC, immunohistochemistry; Ki67, proliferating cell fraction; PgR, progesterone receptor.

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