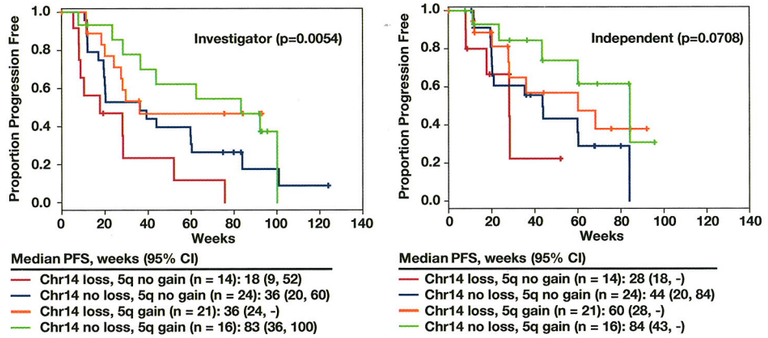
RESULTS (continued)

Figure 4. Kaplan-Meier Plots Showing Combined Chromosome 14 Loss, 5q Gain



Median PFS, weeks (95% CI)

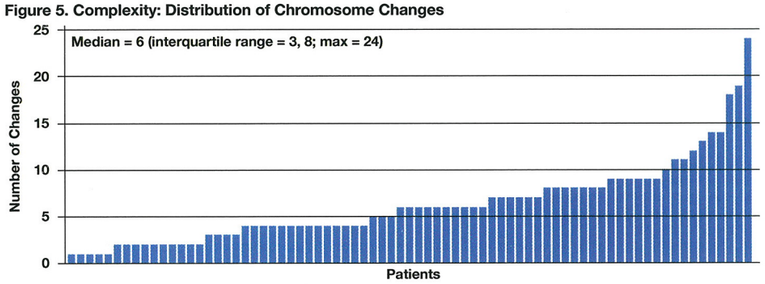
- Chr14 loss, 5q no gain (n = 14): 18 (9, 52)
- Chr14 no loss, 5q no gain (n = 24): 36 (20, 60)
- Chr14 loss, 5q gain (n = 21): 36 (24, -)
- Chr14 no loss, 5q gain (n = 16): 83 (36, 100)

Median PFS, weeks (95% CI)

- Chr14 loss, 5q no gain (n = 14): 28 (18, -)
- Chr14 no loss, 5q no gain (n = 24): 44 (20, 84)
- Chr14 loss, 5q gain (n = 21): 60 (28, -)
- Chr14 no loss, 5q gain (n = 16): 84 (43, -)

- Complexity (**Figure 5**)
  - Median = 6 chromosomal changes (interquartile range = 3, 8; max = 24)
- Possible effect on RR
  - Investigator: p=0.073, odds ratio = 0.56 (odds of response decrease with increasing complexity)
  - Independent reviewer: p=0.0317, odds ratio = 0.49 (odds of response decrease with increasing complexity)
- No effect on PFS (investigator/independent reviewer: p=0.66/0.50)

Figure 5. Complexity: Distribution of Chromosome Changes



SUMMARY

- Chromosome 14 loss: no effects
- Chromosome 5q gain
  - Patients with Chr5q gain had significantly longer time to progression
  - No association with RR
- Combined Chr14 loss, Chr5q gain exploratory result
  - Patients with Chr14 loss and no gain in Chr5q progressed most quickly
  - Patients without Chr14 loss but with gain in Chr5q had longest time to progression
- Complexity: patients with greater number of chromosome changes had lower odds of response, but no apparent change in time to progression
- Covariates: covariates in N = 75 patients were not related to PFS
  - Contrast with overall study where ECOG performance status and time from diagnosis were related to PFS
  - Covariates were not related to Chr5q gain or Chr14 loss
  - Some trends were evident but not statistically significant
  - Chr5q gain is an independent predictor of PFS in the presence of these covariates

ACKNOWLEDGMENTS

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Correlation of Chromosome 14 Loss and 5q Gain with Outcomes of Pazopanib Treatment in Patients with Metastatic Clear Cell Renal Cell Carcinoma

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ABSTRACT

Background: The identification of molecular prognostic and/or predictive determinants of outcome in patients with metastatic renal cell carcinoma (mRCC) is an important challenge. We hypothesized that specific tumor DNA copy number alterations (CNAs), loss of chromosome 14 or 14q (Chr14/14q–), and gain of chromosome 5q (Chr5q+) may predict likelihood of pazopanib treatment benefit in patients with mRCC.

Methods: Patients' DNA samples from the Phase II pazopanib trial (VEG102616) were analyzed by using Affymetrix OncoScan. Copy number data were moving smoothed and normalized. The copy number and allele difference were profiled according to their chromosome locations to interrogate CNA and loss of heterozygosity (LOH). Objective response (OR; by RECIST) and progression-free survival (PFS) were determined by investigators (IN) and an independent review (IR) committee. OR and PFS data were analyzed using logistic regression and Kaplan-Meier tests.

Results: Tumor DNA samples from 75 patients were adequate for CNA analysis. Chr14/14q– was found in 35/75 patients (46.7%), and 5q+ was found in 37/75 (49.3%). Chr14/14q– was present in the tumors of 12/31 patients (39%) with OR by IR compared with 23/44 (52%) non-responding patients (p=0.347). Chr14/14q– did not affect PFS. Chr5q+ was present in tumors of 17/31 patients (55%) with OR and 20/44 (45%) non-responding patients (p=0.486). PFS was longer in patients with Chr5q+ tumors compared with those without Chr5q+ (log-rank p=0.026), with median PFS of 66 vs 35 weeks, respectively. The odds of achieving OR decreased as the total number of chromosomal gains/losses increased (p=0.032, odds ratio 0.49), but this had no effect on PFS (Table). In exploratory analysis, we examined the combined effect of both 14/14q– and 5q+ on PFS.

Conclusions: Patients with Chr5q+ tumors have significantly longer PFS, with no effect on OR rate. While Chr14/14q– alone had no effect on outcomes, the combination of Chr5q+ and no Chr14/14q– was associated with significantly greater PFS. Patients with more genetically complex tumors were less likely to obtain OR with pazopanib

Combined Effect of Both Chr14/14q Loss and Chr5q Gain on PFS			
Copy Number Change	**N**	**Median PFS, weeks (95% confidence limits)**	
		By IN	**By IR**
Chr14/14q– , no Chr5q+	14	18 (8, 52)	28 (18, -)
No Chr14/14q–, no Chr5q+	24	36 (20, 60)	44 (20, 84)
Chr14/14q–, Chr5q+	21	36 (24, -)	60 (28, -)
No Chr14/14q–, Chr5q+	16	83 (36, 100)	84 (43, -)
Total	75	p=0.005	p=0.071

(Modified from submitted abstract.)

Hudes GR, Pei J, Liu Y, et al. Correlation of chromosome 14 loss and 5q gain with outcomes of pazopanib treatment in patients with metastatic clear cell renal cell carcinoma. Presented at: 48th Annual Meeting of the American Society of Clinical Oncology; June 1-5, 2012; Chicago, IL. Abstract 4605

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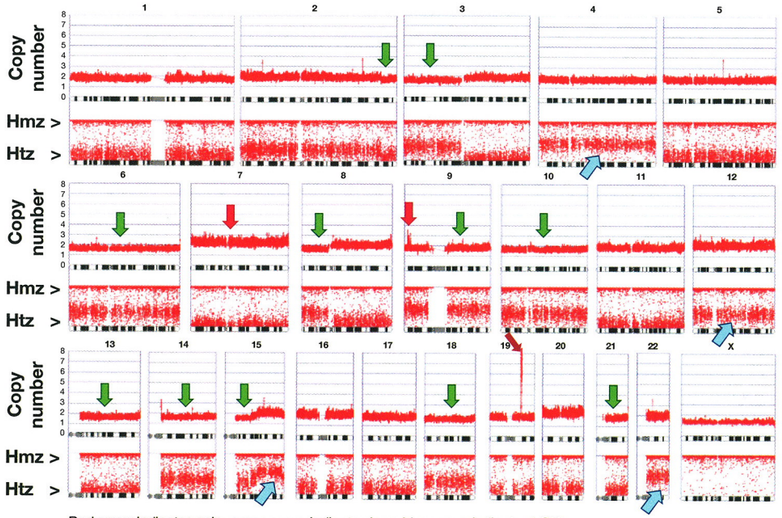
Conclusions: Patients with Chr5q+ tumors have significantly longer PFS, with no effect on OR rate. While Chr14/14q– alone had no effect on outcomes, the combination of Chr5q+ and no Chr14/14q– was associated with significantly greater PFS. Patients with more genetically complex tumors were less likely to obtain OR with pazopanib.

METHODS

- Archival FFPE tumor samples were collected from patients enrolled in a Phase II renal cell carcinoma (RCC) study of pazopanib (Hutson, *JCO 2010*)
- Of the 225 patients enrolled in the study, 80 patients had FFPE samples available for analysis
- DNA samples were analyzed using Affymetrix OncoScan arrays and DNA was picogreen quantified
- DNA extracted from 75/80 unique patient samples was adequate for copy number analysis by Affymetrix molecular inversion probe (MIP) assay (www.affymetrix.com)
- Copy number data were moving smoothed and normalized. The copy number and allele difference were profiled according to their chromosome locations to interrogate copy number alteration (CNA) and loss of heterozygosity (LOH), as shown in **Figure 1**

Figure 1. Example of Copy Number and Allele Difference Analysis



Red arrow indicates gain; green arrow indicates loss; blue arrow indicates LOH.
Abbreviations: Hmz, homozygosity; Htz, heterozygosity.

METHODS (continued)

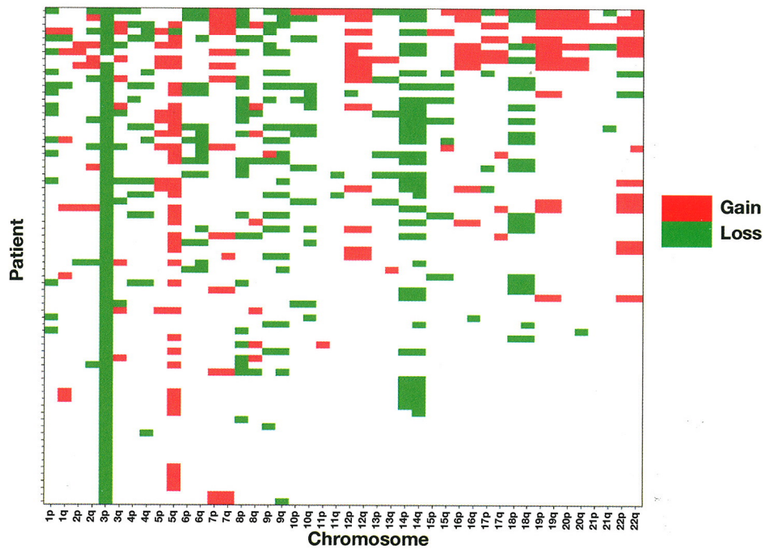
- Complexity
  - The number of chromosomal changes detected for each patient
  - Example: 1p–, 3p–, 8p–, amp(11q), 11q–, 20q– = 6 changes
- Statistical Analyses
  - Effect of chromosome loss/gain and complexity on response rate (RR) evaluated using logistic regression analysis (univariate and multivariate models)
  - Effect of chromosome loss/gain and complexity on progression-free survival (PFS) evaluated using Kaplan-Meier (log-rank) analysis and Cox regression (univariate and multivariate models)
  - Effect of covariates on PFS evaluated using Cox regression analysis
- Covariates
  - Visceral disease
  - Stage of disease
  - Eastern Cooperative Oncology Group (ECOG) performance status
  - Time from diagnosis
  - Memorial Sloan-Kettering Cancer Center (MSKCC) risk group

RESULTS

- Clinical results and demographics for the 75 patients in this analysis subset were similar to overall study results (N = 225)
- Chromosome 14 loss (Chr14–) in 35/75 patients (46.7%) (**Figure 2**)
- Effect of chromosome 14 loss on RR
  - Investigator
    - Responders (Chr14–/total): 9/28 patients* (32%) vs
    - Non-responders (Chr14–/total): 26/47 patients (55%); p=0.06
  - Independent reviewer
    - Responders (Chr14–/total): 12/31 patients (39%) vs
    - Non-responders (Chr14–/total): 23/44 patients (52%); p=0.3474
- Effect of chromosome 14 loss on PFS
  - Investigator: log-rank p=0.4848
  - Independent reviewer: log-rank p=0.7294
  - Covariates: some trends were evident but were not significant in multivariate models

*Of 28 responders, 9 had chromosome 14 loss.

Figure 2. Heat Map of Gain/Loss Findings

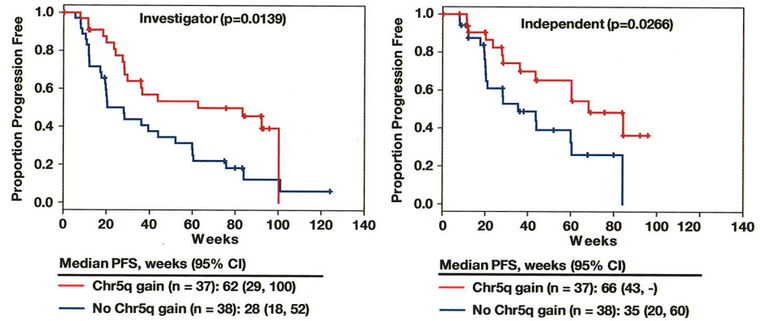


RESULTS (continued)

- Chromosome 5q gain (Chr5q+) in 37/75 patients (49.3%) (**Figure 2**)
- Effect of chromosome 5q gain on RR
  - Investigator:
    - Responders (Chr5q+/total): 15/28 patients* (54%) vs
    - Non-responders (Chr5q+/total): 22/47 patients (47%); p=0.6371
  - Independent reviewer:
    - Responders (Chr5q+/total): 17/31 patients (55%) vs
    - Non-responders (Chr5q+/total): 20/44 patients (45%); p=0.4861
- Effect of chromosome 5q gain on PFS (**Figure 3**)
  - Investigator: log-rank p=0.0139; patients with 5q gain had a 34-week increase in median PFS (62 vs 28 weeks)
  - Independent reviewer: log-rank p=0.0266; patients with 5q gain had a 31-week increase in median PFS (66 vs 35 weeks)
  - Covariates: some trends were evident but were not significant in multivariate models

*Of 28 responders, 15 had chromosome 5q gain.

Figure 3. Kaplan-Meier Plots Showing Effect of Chromosome 5q Gain



- Combined effect of chromosome 14 loss and chromosome 5q gain (**Table 1, Figure 4**)
  - Investigator: log-rank p=0.0054; patients with 5q gain and no loss of 14 had longer PFS (median 83 weeks) compared to patients with 14 loss and no gain of 5q (median 18 weeks)
  - Independent reviewer: log-rank p=0.0708; patients with 5q gain and no loss of 14 had longer PFS (median 84 weeks) compared to patients with 14 loss and no gain of 5q (median 28 weeks)
- No other chromosome gains or losses, in univariate or multivariate modelling, were associated with RR or PFS

Table 1. Combined Effect of Both Chr14/14q Loss and Chr5q Gain on PFS

Copy Number Change	N	Median PFS, weeks (95% confidence limits) By IN	By IR
Chr14/14q– , no Chr5q+	14	18 (8, 52)	28 (18, -)
No Chr14/14q–, no Chr5q+	24	36 (20, 60)	44 (20, 84)
Chr14/14q–, Chr5q+	21	36 (24, -)	60 (28, -)
No Chr14/14q–, Chr5q+	16	83 (36, 100)	84 (43, -)
Total	75	p=0.005	p=0.071

Abbreviations: Chr, chromosome; IN, investigator; IR, independent review committee; –, loss; +, gain.