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Outcomes of patients with metastatic renal cell carcinoma that do not meet eligibility criteria for clinical trials

D. Y. C. Heng[1*], T. K. Choueiri[2], B. I. Rini[3], J. Lee[4], T. Yuasa[5], S. K. Pal[6], S. Srinivas[7], G. A. Bjarnason[8], J. J. Knox[9], M. MacKenzie[10], U. N. Vaishampayan[11], M. H. Tan[12], S. Y. Rha[13], F. Donskov[14], N. Agarwal[15], C. Kollmannsberger[16], S. North[17] & L. A. Wood[18]

[1]Tom Baker Cancer Center, Calgary, AB, Canada; [2]Dana-Farber Cancer Institute, Harvard Medical School, Boston; [3]Taussig Cancer Institute, Cleveland Clinic, Cleveland, USA; [4]University of Ulsan College of Medicine, Asan, South Korea; [5]Department of Urology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; [6]Department of Medical Oncology and Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte; [7]School of Medicine, Stanford Cancer Institute, Stanford University, Stanford, USA; [8]Sunnybrook Odette Cancer Centre, Toronto, ON; [9]Princess Margaret Hospital, University of Toronto, Toronto, ON; [10]London Health Sciences Center, London, ON, Canada; [11]Karmanos Cancer Institute, Wayne State University, Detroit, USA; [12]Department of Medical Oncology, National Cancer Centre and Institute of Bioengineering and Nanotechnology, Singapore; [13]Yonsei Cancer Centre, Yonsei University College of Medicine, Seoul, South Korea; [14]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; [15]University of Utah Huntsman Cancer Institute, Salt Lake City, USA; [16]British Columbia Cancer Agency, Vancouver Cancer Center, Vancouver; [17]Cross Cancer Center, University of Alberta, Edmonton, AB; [18]Queen Elizabeth II Health Sciences Center, Halifax, NS, Canada

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Background: Targeted therapies in metastatic renal cell carcinoma (mRCC) have been approved based on registration clinical trials that have strict eligibility criteria. The clinical outcomes of patients treated with targeted agents but are ineligible for trials are unknown.

Patients and Methods: mRCC patients treated with vascular endothelial growth factor-targeted therapy were retrospectively deemed ineligible for clinical trials (according to commonly used inclusion/exclusion criteria) if they had a Karnofsky performance status (KPS) <70%, nonclear-cell histology, brain metastases, hemoglobin ≤9 g/dl, creatinine >2× the upper limit of normal, corrected calcium ≥12 mg/dl, platelet count of $<100 \times 10^3$/uL, or neutrophil count <1500/mm^3.

Results: Overall, 768 of 2210 (35%) patients in the International Metastatic RCC Database Consortium (IMDC) were deemed ineligible for clinical trials by the above criteria. Between ineligible versus eligible patients, the response rate, median progression-free survival (PFS) and median overall survival of first-line targeted therapy were 22% versus 29% ($P = 0.0005$), 5.2 versus 8.6 months, and 12.5 versus 28.4 months (both $P < 0.0001$), respectively. Second-line PFS (if applicable) was 2.8 months in the trial ineligible versus 4.3 months in the trial eligible patients ($P = 0.0039$). When adjusted by the IMDC prognostic categories, the HR for death between trial ineligible and trial eligible patients was 1.55 (95% confidence interval 1.378–1.751, $P < 0.0001$).

Conclusions: The number of patients that are ineligible for clinical trials is substantial and their outcomes are inferior. Specific trials addressing the unmet needs of protocol ineligible patients are warranted.

Key words: metastatic renal cell cancer, outcomes, clinical trials, ineligible

introduction

In the past decade, there has been a marked shift in the treatment and outcome of patients with metastatic renal cell carcinoma (mRCC). The understanding of the molecular changes associated with mRCC has led to the development of multiple new agents which largely target the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways. The initial targeted agents including sorafenib, sunitinib, bevacizumab, and temsirolimus moved quickly from the preclinical setting into phase I, II, and III clinical trials. The data from these pivotal phase III clinical trials led to the rapid approval of these agents [1–5]. Further trials have resulted in the approval of other agents in both the first- and second-line setting including pazopanib, axitinib, and everolimus [6–8]. The positive outcome from these large, well-conducted phase III clinical trials has led to major changes in the way we manage mRCC worldwide.

However, it is well known that there are strict criteria for clinical trial eligibility for safety reasons and to maintain internal validity and patient homogeneity within the clinical trial. The 'everyday' patient in routine clinical practice may not meet these

*Correspondence to: Dr Daniel Y. C. Heng MD MPH FRCPC, Tom Baker Cancer Center, University of Calgary, 1331–29th St NW, Calgary, AB, Canada T2N 4N2. Tel: +1-403-521-3166; Fax: +1-403-283-1651; E-mail: daniel.heng@albertahealthservices.ca

criteria. This begs the question as to whether patients in the 'real world' behave in a similar manner to those highly selected patients on clinical trials. The question of generalizability to the entire mRCC patient population arises.

The objective of this study was to review the clinical outcome of a contemporary cohort of patients managed with VEGF-targeted therapy and determine whether these patients would have been eligible for clinical trials with targeted therapy (trial eligible) or if they would never have been able to participate in clinical trials (trial ineligible). Secondary objectives were to compare the outcomes of trial eligible patients with those deemed potentially trial ineligible.

patients and methods

study population

The study population includes patients in the International Metastatic RCC Database Consortium (IMDC) who were treated with contemporary VEGF-targeted therapy, as their first-line targeted therapy. This Consortium includes consecutive, population-based patient samples from 2005 to 2011 at 19 international cancer centers from Canada, United States of America, South Korea, Japan, Singapore, and Denmark. Patients initially treated with mTOR inhibitors were excluded since the initial landmark trial with temsirolimus specifically looked at a poorer risk population of patients and had generally different eligibility criteria (such as the including of patients with nonclear-cell histology) than the VEGF-targeted therapy trials [5]. Patients may have been treated on clinical trial or off protocol and may have been treated at major academic centers or community oncology centers. Baseline patient characteristics and outcome data were collected using uniform data collection templates. Demographic, prognostic factor, and outcome data were collected. Nonclear-cell carcinoma was ascertained when clear-cell histology was not the predominant subtype. Regulatory approval from local institutional review boards or research ethic boards was obtained for each center.

eligible versus ineligible patients

Patients were retrospectively deemed ineligible for clinical trials according to commonly used inclusion/exclusion criteria found in the phase III registration trials. The major exclusion criteria were as follows:

- Karnofsky performance status (KPS) <70%
- Nonclear-cell histology
- Brain metastases
- Hemoglobin ≤9 g/dl
- Creatinine >2 × upper limit of normal (ULN)
- Corrected calcium ≥12 mg/dl
- Platelet count $<100 \times 10^3/\mu l$
- Neutrophil count $<1500/mm^2$

If patients had any one or more of these exclusion criteria, they were considered trial ineligible. If patients had missing data on some of these parameters, they were still deemed trial ineligible if they fulfilled one or more of these exclusion criteria. If patients had missing data on one or more parameters but were trial eligible for all other parameters, they were considered trial eligible to provide the most conservative estimate of eligibility. A sensitivity analysis categorizing these patients with missing data as trial ineligible was also carried out which revealed similar outcomes. All other patients were assumed to be potentially eligible for the clinical trials.

statistics

Descriptive statistics were generated and compared using χ^2 tests for proportions and *t*-tests for means. Response rates were defined by the proportion of patients with best response as partial responses (PR) or complete responses (CR) by RECIST 1.0 criteria out of the overall population [9]. Patients with progressive disease or stable disease were classified as nonresponders. First-line progression-free survival (PFS) was defined as time from first VEGF-targeted therapy drug initiation to progression, death, drug cessation, or censored at the last follow-up. Second-line PFS was defined as time from initiation of second targeted therapy drug to progression, death, drug cessation, or censored at the last follow-up. Overall survival (OS) was defined as time from first-line targeted therapy drug initiation to death or censored at the last follow-up. Kaplan–Meier curves were constructed and log-rank tests were carried out to compare first-line PFS, second-line PFS, and OS in trial eligible versus ineligible patients. Proportional hazards regression was carried out to OS hazard ratio (HR) estimates by patient prognostic groups according to the IMDC criteria [10, 11]. The case deletion method was used to handle missing data. All analyses were carried out on SAS 9.2 (SAS Institute, Inc., Cary, NC).

results

Overall, 2210 patients with mRCC treated with VEGF-targeted therapy were included in this analysis. As shown in Figure 1, 768 (35%) of patients were deemed trial ineligible and 1442 (65%) were deemed trial eligible. The most common first-line therapy was sunitinib, followed by sorafenib, bevacizumab, and pazopanib. Two patients received axitinib as part of a clinical trial and were appropriately deemed trial eligible.

There were multiple reasons why patients were deemed ineligible as shown in Table 1. The most common reason was Karnofsky performance status (KPS) <70% in 13% of patients, nonclear histology in 11%, brain metastases in 8%, and low hemoglobin (≤9) in 8%. The majority of patients (605) were excluded due to one exclusion criteria while 140 patients met two exclusion criteria and one patient had five exclusion criteria as shown in Table 2.

The baseline patient demographics are shown in Table 3 for all patients, ineligible patients, and eligible patients. There was no difference in the median age between the two groups. In terms of all other baseline demographic data, the ineligible group had poorer prognostic profiles ($P < 0.0001$) and fewer nephrectomies ($P < 0.0001$). By definition, patients in the trial ineligible group had lower KPS, more anemia, hypercalcemia, brain metastases, and nonclear-cell histology.

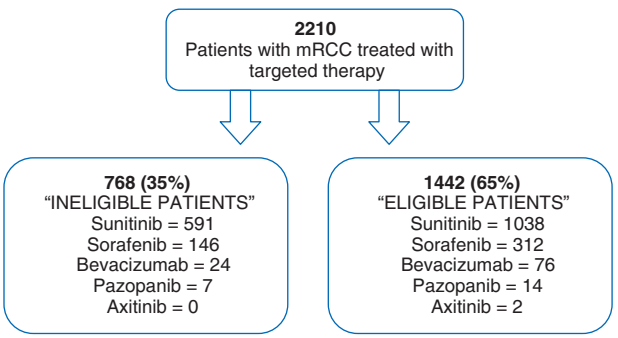

Figure 1. Trial ineligible and eligible patients.

Table 1. Number of patients excluded due to each exclusion criteria

Exclusion parameter	Number of patients excluded due to this parameter/patients with available data (%)
KPS <70%	274/2111 (13)
Nonclear-cell histology	230/2068 (11)
Brain metastases	182/2198 (8)
Hemoglobin ≤9 g/dl	156/2074 (8)
Creatinine >2× ULN	38/1607 (2)
Corrected calcium ≥12 mg/dl	38/2007 (2)
Platelet count of $<100 \times 10^3$/uL	28/2068 (1)
Neutrophil count <1500/mm^3	13/1997 (<1)
Total	959 exclusion criteria met in 768 patients

Table 2. Number of exclusion criteria met in patients

Number of exclusion criteria met	Number of patients
0	1442
1	605
2	140
3	19
4	3
5	1
Total	959 exclusion criteria met in 768 patients

patient outcomes

Response rates are based on 1790 patients who had data on RECIST 1.0 response rates (RR). Overall, 27% of patients had an objective response (CR + PR). In trial ineligible patients, the response rate was only 22% compared with trial eligible patients where it was 29% ($P = 0.0005$) as shown in Table 4. When looking at the favorable, intermediate, and poor risk patients according to the IDMC criteria, the intermediate and poor risk ineligible patients had a lower response rate than the eligible patients. In the favorable risk patients, response rates were similar (38% in ineligible and 34% in eligible, $P = 0.62$) but this may be due to smaller patient numbers or that patients with favorable risk usually have better outcomes irrespective of trial eligibility status.

The PFS of first-line VEGF targeted therapy in ineligible patients was lower than that of the eligible patients (5.0 versus 8.6 months, $P < 0.0001$) as shown in Figure 2A. The PFS with second-line targeted therapy in ineligible patients was also less than those of eligible patients (2.8 versus 4.3 months, $P = 0.0039$) as shown in Figure 2B. The OS in ineligible patients was 12.5 months compared with 28.4 months in the eligible patients ($P < 0.0001$) as shown in Figure 2C. Patients who were excluded due to KPS <70, hemoglobin ≤9 g/dl, calcium ≥12 mg/dl, brain metastases, and nonclear-cell histology had a HR for death of 3.1 [95% confidence interval (CI) 2.7–3.6], 2.4 (95% CI 2.0–2.9), 2.7 (95% CI 1.9–3.8), 1.5 (95% CI 1.2–1.7), and 1.4 (95% CI 1.1–1.6), respectively (all $P < 0.01$) on univariable analysis. The other exclusion criteria did not statistically significantly affect OS.

Table 3. Baseline patient characteristics

Parameter	Ineligible ($N = 768$)	Eligible ($N = 1442$)
Age (median, years)	60 ($N = 768$)	61 ($N = 1442$)
IMDC prognostic category		
Favorable	9% (65/688)	24% (297/1217)
Intermediate	48% (329/688)	59% (721/1217)
Poor	43% (294/688)	16% (199/1217)
KPS (median, range)	80 (range 20–100) ($n = 746$)	90 (range 70–100) ($n = 1365$)
Anemia (below LLN)	70% (518/741)	52% (698/1333)
Hypercalcemia (above ULN)	15% (111/717)	6% (82/1290)
Brain metastases present	24% (182/765)	0% (0/1433)
Nonclear-cell histology	32% (230/727)	0% (0/1341)
Prior nephrectomy	72% (552/768)	83% (1192/1440)

Table 4. First-line response rates (RR)

IMDC prognostic group	All available patients RR	Eligibility status		*P*-value comparing ineligible to eligible patients
		Ineligible RR	Eligible RR	
All patients ($N = 1790$)*	27% (481/1790)	22% (129/594)	29% (352/1196)	0.0005
Favorable ($N = 309$)	35% (107/309)	38% (21/56)	34% (86/253)	0.6176
Intermediate ($N = 885$)	28% (252/885)	24% (65/274)	31% (187/611)	0.0359
Poor ($N = 372$)	20% (73/372)	15% (32/209)	25% (41/163)	0.0177

*Patients in risk groups do not add up to 1790 because not all patients had prognostic group and response rate data available.

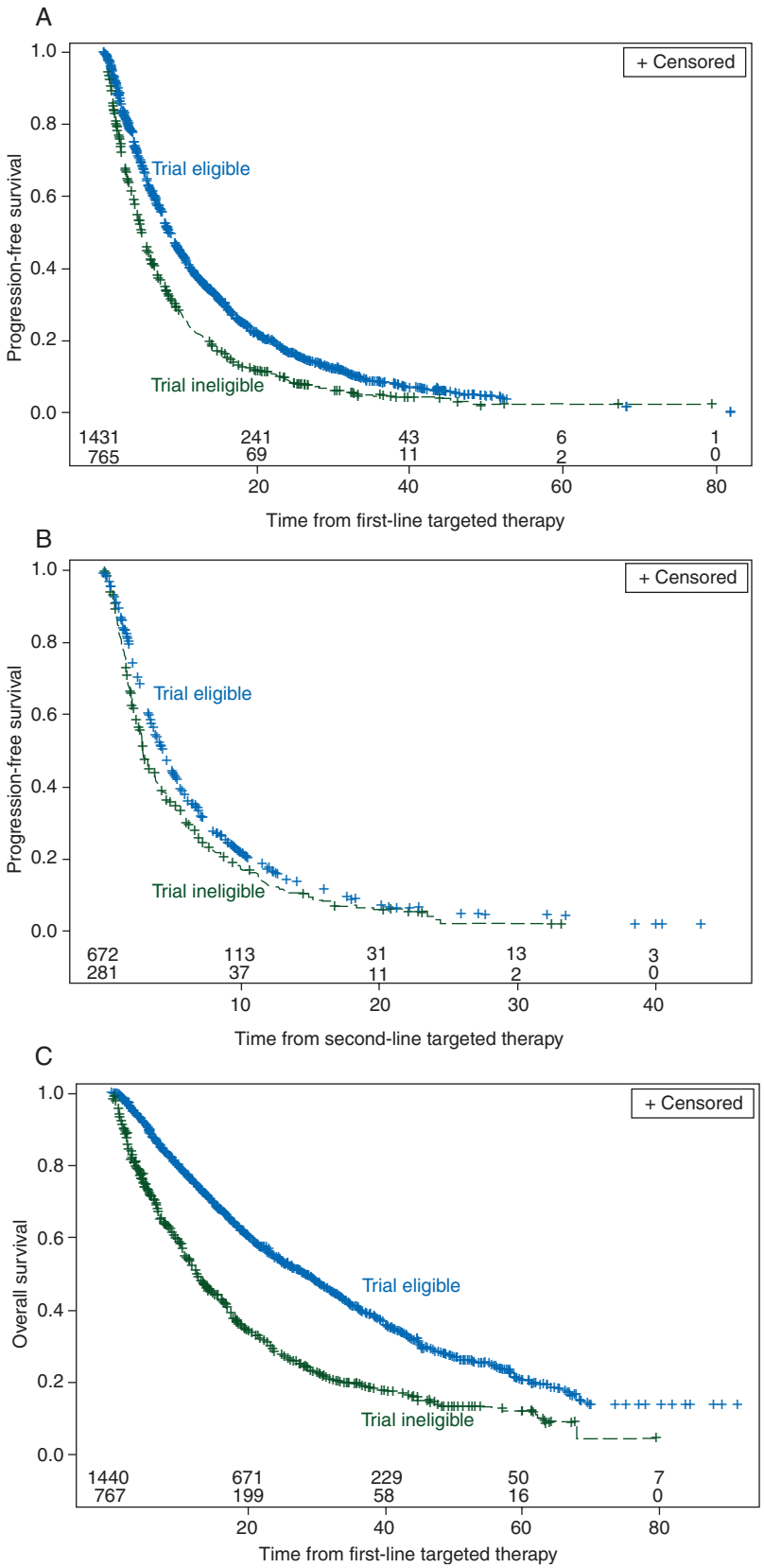

Figure 2. (A) Median PFS from first-line targeted therapy was 5.0 versus 8.6 months ($P < 0.0001$) in the trial ineligible versus trial eligible patients. (B) Median PFS from second-line targeted therapy was 2.8 versus 4.3 months ($P = 0.0039$) in the trial ineligible versus trial eligible patients. (C) Median overall survival from first-line targeted therapy was 12.5 versus 28.4 months ($P < 0.0001$) in the trial ineligible versus trial eligible patients.

When adjusted by the IMDC prognostic criteria, the HR for death between the trial ineligible versus trial eligible patients was 1.55 (95% CI 1.378–1.751, $P < 0.0001$). The HR for PFS from initiation of first-line therapy was 1.32 (95% CI 1.19–1.46). These results were very similar if adjusted by the MSKCC prognostic criteria.

discussion

Well-conducted clinical trials are essential for the development of new treatment advances that prolong OS in cancer. Despite this, <5% of all cancer patients are enrolled in clinical trials and we often use these results to generalize our treatment decisions to all patients seen in cancer centers around the world (http://www.cancer.gov/clinicaltrials/conducting/boosting-trial-participation/Page3).

To our knowledge, this is the largest study of its kind to demonstrate that, in the real world, 35% of mRCC patients would not have met the eligibility criteria for VEGF-targeted therapy clinical trials based on routine exclusion criteria. This high percentage translates into a large number of patients given therapy based on data that do not apply to them. It is not surprising that the two most common reasons for ineligibility were a lower KPS and nonclear-cell histology. Many 'real-world' patients are more ill than those on clinical trials, often on the basis of disease burden. It is common for clinicians to extrapolate data from clinical trials to sicker patients with poorer prognostic factors in order to try to improve patient survival.

Most of the VEGF-targeted therapy phase III clinical trials did not allow nonclear-cell histology, given the VEGF pathway may not be the optimal target in these patients, based on the biology of this disease around VHL inactivation. Unfortunately, the optimal therapy for nonclear-cell RCC is still unknown and, thus, it is not surprising that many of these patients received VEGF-targeted therapy.

Trial ineligible patients had a worse outcome in terms of RR, PFS, and OS with the adjusted HR for death about 1.55 for ineligible versus eligible patients. For the trial eligible patients, the PFS of 8.6 months and the OS of 28.4 months in our study are similar to the outcomes reported in the pivotal phase III trial comparing Suntinib to Interferon where the PFS for sunitinib-treated patients was 11.0 months and the OS of 26.4 months [12]. In the trial ineligible patients, the PFS of 5.0 months and the OS of 12.5 months appear much worse than the pivotal phase III trial as well as the Expanded Access trial patients where the PFS was 10.9 months and the OS was 18.4 months [13].

Worse outcomes for patients not fulfilling trial eligibility criteria have also recently been reported in a smaller study of stage IV colorectal cancer patients [14]. Patients in the Netherlands receiving standard chemotherapy on a clinical trial were compared with those receiving the exact same treatment off a clinical trial. In this study of the 396 patients treated off trial, 85 (21.5%) did not meet the eligibility criteria. Worse PS, elevated alkaline phosphatase, and less resected primary tumors were the reasons for trial ineligibility. These patients had a worse OS compared with eligible nontrial patients (9.3 versus 15.7 months, $P < 0.01$). The authors conclude that trial results do have external validity, provided that standard eligibility criteria are observed and argue against the use of cancer treatments in patients that would not have been eligible. Other studies have shown that outcomes of patients treated off clinical trials are worse than those treated on clinical trials although there may be various reasons the patient was not enrolled on to a clinical trial other than ineligibility, such as patient preference [15].

Strengths of this study include its large patient population and the use of consecutive population-based series to prevent selection bias. Additionally, it reflects real-world treatment practice patterns as opposed to those tightly regulated by clinical trial protocols. Limitations of this study include the retrospective nature of the data collection. Not all the inclusion/exclusion criteria that would be in a formal phase III study were collected (concomitant medications, RECIST nonmeasurable disease, etc.). Thus, the number in this study may actually be an underestimate of the number of trial ineligible patients. The RECIST RR were determined by the investigators and not a central blinded reviewer but this was similar in both the eligible and ineligible patients and adds to the generalizability of the study as it reflects everyday clinical practice. There were missing data in determining each patient's eligibility status; thus, a sensitivity analysis was carried out categorizing those patients with too much missing data without any obvious exclusionary criteria as trial ineligible. This raised the trial ineligible group to 43% (959 of 2210) but all of the RR, PFS, and OS outcomes and, most importantly, the HR for death were very similar to the results presented.

Clinical trials to test new drugs and improve outcomes are imperative in oncology. It is important for clinicians to remember that data from clinical trials cannot universally be extrapolated to the real-world patients and that these discrepancies in clinical outcomes should be taken into account when discussing treatment options and outcomes with individual patients. That being said, the outcomes of the trial ineligible mRCC patients reported here are still an improvement compared with outcomes in the era of nontargeted therapy. Patients deemed trial ineligible may potentially benefit from targeted therapy, but outcome expectations may need to be tempered.

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disclosure

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A cohort study investigating aspirin use and survival in men with prostate cancer

E. M. Flahavan[1], K. Bennett[1], L. Sharp[2] & T. I. Barron[1]*

[1]*Department of Pharmacology and Therapeutics, Trinity College, University of Dublin, Dublin, Ireland;* [2]*National Cancer Registry Ireland, Cork, Ireland*

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Background: Aspirin use has been associated with reduced mortality from cancer including prostate cancer in some studies. A number of anti-cancer mechanisms of aspirin have been proposed, including the inhibition of the cyclooxygenase enzymes, through which aspirin mediates both anti-platelet and anti-inflammatory activities. This cohort study examines associations between pre-diagnostic aspirin use (overall and by dose and dosing intensity) and mortality in men with localised prostate cancer.

Patients and methods: Men with stage I–III prostate cancer were identified from Irish National Cancer Registry records, which have been linked to national prescribing data from the Irish General Medical Services scheme. Aspirin use in the year preceding prostate cancer diagnosis was identified from this linked prescription-claims data. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for associations between aspirin use and all-cause and prostate cancer-specific mortality. Associations between prescribed dose and dosing intensity were examined. The presence of effect modification by the type of treatment received and tumour characteristics was also assessed.

Results: Two thousand nine hundred and thirty-six men with a diagnosis of stage I–III prostate cancer (2001–2006) were identified (aspirin users, $n = 1131$). The median duration of patient follow-up was 5.5 years. In adjusted analyses, aspirin use was associated with a small, but non-significant, reduced risk of prostate cancer-specific mortality (HR = 0.88, 95% CI

*Correspondence to: Dr T. I. Barron, Department of Pharmacology and Therapeutics, Trinity Centre for Health Sciences, St James's Hospital, Dublin 8, Ireland. Tel: +1-443-831-3312; Fax: +353-1-453-9033; E-mail: barront@tcd.ie