compared with 6 months, but statistical significance was not reached.

Where do we go from here? The older classic classification of low-risk, intermediate-risk, and high-risk localised prostate cancer is being supplemented with new molecular classifications.[7] The question of how to optimally classify patients is a key one, and the addition of genomic methods seems to be an improved approach. If one can classify risk better with newer technologies, then risk-adjusted escalation and de-escalation of systemic therapies should be considered as these new categories emerge.

Molecular imaging is now upon us.[8] CT and bone scans are far less sensitive than prostate-specific membrane antigen, fluciclovine, and choline PET assessments. Newer treatment strategies addressing the findings associated with these newer molecular imaging are both timely and appropriate.

Better forms of androgen ablative therapy and more precision targeted approaches are intriguing. Agents such as abiraterone and enzalutamide have substantial activity beyond androgen suppression alone.[9] These agents need to be tested in men at high risk of treatment failure in hopes of increasing cure rates. Lutetium-177-labelled prostate-specific membrane antigen ligands and other targeted radiopharmaceuticals are intriguing possibilities.[10] Today, they are used in advanced disease. Tomorrow, these agents will likely move into use in earlier disease stages.

Change is coming, and is coming fast. Androgen deprivation therapies and external-beam radiotherapy are the standards of care today but newer forms of molecular imaging, newer forms of androgen ablation, and newer forms of targeted therapy will be the focus in the next decade. Cure is a worthy goal, as is better quality of life. Hopefully tomorrow we will be able to achieve both.

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I have acted as a consultant for Advanced Accelerator Applications (AAA), Astellas, AstraZeneca, Bavarian-Nordic, Bayer, Bellicum, Blue Earth Diagnostics, Inc, Celgene, Constellation, Dendreon, EMD Serono, Endocyte, Johnson & Johnson, Myovant, Pfizer, Progenics, Sanofi, and Teva. I have received grants or research support from AstraZeneca, Bayer, BMS, Constellation, Dendreon, Endocyte, Innocrin, Invitae, Johnson & Johnson, Merck, Progenics, Roche, Sanofi, and SOTIO. I am a co-Chairman of the Genitourinary Committee, and a consultant on the Board of Scientific Counselors at the National Cancer Institute. I have provided expert testimony for Sanofi.

1 Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and gosarelin. *N Engl J Med* 1997; **337:** 295–300.
2 Bolla M, De Reijke TM, van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009; **360:** 2516–27.
3 D'Amico AV, Manola J, Loffredo M, et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA* 2004; **292:** 821–27.
4 Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med* 2011; **365:** 107–18.
5 Nabid A, Carrier N, Martin AG, et al. Duration of androgen deprivation therapy in high-risk prostate cancer: a randomized phase III trial. *Eur Urol* 2018; **74:** 432–41.
6 Denham JW, Joseph D, Lamb DS, et al. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): 10-year results from a randomised, phase 3, factorial trial. *Lancet Oncol* 2018; published online Dec 19. http://dx.doi.org/10.1016/S1470-2045(18)30757-5.
7 Spratt DE, Zhang J, Santiago-Jiménez M et al. Development and validation of a novel integrated clinical-genomic risk group classification for localized prostate cancer. *J Clin Oncol* 2018; **36:** 581–90.
8 Bednarova S, Lindenberg ML, Vinsensia M et al. Positron emission tomography (PET) in primary prostate cancer staging and risk assessment. *Transl Androl Urol* 2017; **6:** 413–23.
9 Sartor O, de Bono JS. Metastatic prostate cancer. *N Engl J Med* 2018; **378**: 645–57.
10 Eiber M, Fendler WP, Rowe SP, et al. Prostate-specific membrane antigen ligands for imaging and therapy. *J Nucl Med* 2017; **58** (suppl 2)**:** 67S–76S.

Ramucirumab and the controversial role of α-fetoprotein in hepatocellular carcinoma

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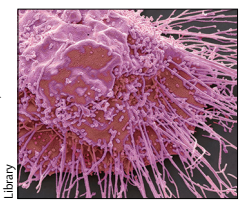
In *The Lancet Oncology*, Andrew X Zhu and colleagues report the results of REACH-2, a placebo-controlled phase 3 trial of ramucirumab in patients with hepatocellular carcinoma and baseline α-fetoprotein concentrations of 400 ng/mL or greater, who had previously received sorafenib.[1] Median overall survival was significantly improved in the ramucirumab group compared with the placebo group (8·5 months [95% CI 7·0–10·6] *vs* 7·3 months [5·4–9·1]; hazard ratio 0·710 [95% CI 0·531–0·949]; p=0·0199) at a median follow-up of 7·6 months (IQR 4·0–12·5). This work comes at a crucial time in view of the advent



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of several tyrosine-kinase inhibitors with positive outcomes in hepatocellular carcinoma, and should be congratulated.

α-fetoprotein is intricately associated with hepatocellular carcinoma, and has had many roles in diagnosis and prognostication. Measurement of α-fetoprotein concentrations used to be part of diagnostic screening for hepatocellular carcinoma among patients with certain risk factors, but was judged not to be useful, and is no longer recommended by the American Association for the Study of Liver Diseases and other organisations.[2] In advanced hepatocellular carcinoma, the prognostic value of α-fetoprotein has been shown only in a few retrospective analyses.[3] α-fetoprotein therefore remains a non-validated tumour marker. However, many cancer experts still assess α-fetoprotein concentrations in patients with hepatocellular carcinoma, and patients request such assessments, with the hope that the protein might have a surrogate role in response to therapy.

In both the first study[4] of ramucirumab versus placebo (REACH) and the follow-up study reported in this issue by Zhu and colleagues,[1] α-fetoprotein might have emerged as a novel prognostic indicator of outcomes with the drug. Zhu and colleagues did a post-hoc pooled analysis of the population from REACH with α-fetoprotein concentrations of at least 400 ng/mL and the REACH-2 population, in which ramicirumab was associated with improved median overall compared with placebo. One interpretation of these findings is that patients with high α-fetoprotein concentrations (ie, ≥400 ng/mL) could have a different disease biology from those with so-called standard hepatocellular carcinoma. Such an interpretation would be based on prognostic signatures, such as Ep-CAM expression.[5] However, high α-fetoprotein concentrations are probably coincidental and happen to manifest in patients with advanced disease, as delineated by Lee and colleagues' experienced group.[6] Lee and colleagues identified that patients with high α-fetoprotein concentrations can have more advanced Edmundson grade III disease than those with low α-fetoprotein concentrations; they interpreted this finding as unexpected, which probably accounts for the insufficient predictive power in their work when α-fetoprotein concentration was used as a sole prognostic indicator.

By default, α-fetoprotein concentrations have been measured as part of baseline assessments in several clinical trials, and sometimes followed up in parallel with radiological imaging. With no validated reference to define high or low α-fetoprotein concentrations, 20 ng/mL, 200 ng/mL, 400 ng/mL, and even 1000 ng/mL, among others, have all been used as cutoffs. In the first trial of the tyrosine-kinase inhibitor sorafenib in hepatocellular carcinoma, prognostication based on α-fetoprotein concentrations was not reported, but a later retrospective study showed worse overall survival outcomes in patients with α-fetoprotein concentrations of 200 ng/mL or higher.[7] Prospective assessments of a similar nature of the tyrosine-kinase inhibitors lenvatinib,[8] regorafenib,[9] and cabozantinib[10] all showed a trend of worse survival outcomes in patients with high α-fetoprotein concentrations (although these outcomes were not formally analysed as primary outcomes).

Thus, α-fetoprotein is not a true biomarker, but rather its effect on prognosis seems dependent on when it is measured. As the disease progresses, α-fetoprotein concentrations are more likely to increase, and thus as part of a clinical trial, patients with high α-fetoprotein concentrations who are at later stages of disease could have the same improved median overall survival of the drug tested.[8–10] All tested tyrosine-kinase inhibitors are geared towards the same targets (with some variation), and ramucirumab is not an exception to this general rule. The findings of REACH-2 are positive, but they are not, as Zhu and colleagues claim, the first positive findings from a phase 3 study done in a biomarker-selected patient population with hepatocellular carcinoma.

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1 Zhu AX, Kang Y-K, Yen C-J, et al. Ramucirumab after first-line treatment with sorafenib in patients with advanced hepatocellular carcinoma and increased a-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019; published online Jan 18. http://dx.doi.org/10.1016/S1470-2045(18)30937-9.

2 Forner A, Vilana R, Ayuso C, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology* 2008; **47:** 97–104.

3 Tangkijvanich P, Anukulkarnkusol N, Suwangool P, et al. Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. *J Clin Gastroenterol* 2000; **31:** 302–08.

4 Zhu AX, Park JO, Ryoo B-Y, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2015; **16:** 859–70.

5 Zucman-Rossi J, Villanueva A, Nault JC, Llovet JM. Genetic landscape and biomarkers of hepatocellular carcinoma. *Gastroenterology* 2015; **149:** 1226–39.

6 Lee JS, Chu IS, Heo J, et al. Classification and prediction of survival in hepatocellular carcinoma by gene expression profiling. *Hepatology* 2004; **40:** 667–76.

7 Bruix J, Cheng AL, Meinhardt G, Nakajima K, De Sanctis Y, Llovet J. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: analysis of two phase III studies. *J Hepatol* 2017; **67:** 999–1008.

8 Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; **391:** 1163–73.

9 Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **389:** 56–66.

10 Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med* 2018; **379:** 54–63.

CheckMate 214 patient-reported outcomes: listening to our patients

In *The Lancet Oncology*, David Cella and colleagues[1] assessed the patient-reported outcomes (PROs) of 847 patients at intermediate or poor risk with advanced or metastatic renal cell carcinoma randomly assigned (1:1) to sunitinib or nivolumab plus ipilimumab in the phase 3 randomised CheckMate 214 trial.[1,2]

The primary endpoints of the trial have been reported previously,[2] and PROs were an exploratory endpoint. The investigators assessed PROs using the Functional Assessment of Cancer Therapy-General (FACT-G), FACT-Kidney Symptom Index-19 (FKSI-19), and EuroQoL five dimension three level (EQ-5D-3L) instruments, each of which collects data on different domains. FKSI-19 collects data about functional wellbeing, treatment side-effects, and emotional, physical, and overall disease-related symptoms; FACT-G collects data about functional, physical, social and family, and emotional wellbeing; and EQ-5D-3L collects data about mobility, self-care, usual activity, pain and discomfort, and depression and anxiety, and subjective perception of wellbeing through an analogue visual rating scale (VAS).

Comparison of PRO scores at baseline with those later in the treatment regimen showed improved PROs for participants in the nivolumab and ipilimumab group compared with the sunitinib group, except for emotional symptoms (collected in FKSI-19) and emotional and social and family wellbeing (collected by FACT-G) for which no statistical difference emerged. In brief, risk of deterioration in PRO scores was lower for patients who were given nivolumab plus ipilimumab than for those given sunitinib (FKSI-19 deterioration hazard ratio [HR] 0·54, 95% CI 0·46–0·63; FACT-G deterioration HR 0·63, 0·52–0·75; and EQ-5D UK utility score HR 0·67, 0·57–0·80). Moreover, improvement in FKSI-19 and FACT-G scores were associated with decreased risk of death and disease progression.

These results could have been influenced by a number of factors, first, the difference in the toxicity profile of nivolumab plus ipilimumab immunotherapy compared with the tyrosine kinase inhibitor sunitinib.[3] Nivolumab and ipilimumab are both immune checkpoint inhibitor antibodies and endocrine and auto-immune adverse events often lead to laboratory anomalies as the first presentation of toxicity; thus, even if patients have severe toxicity, clinicians can stop treatment before the development of physical symptoms and so physical symptoms might not have been reported as they were prevented before they occurred. Additionally, such an early interuption of treatment could affect the effectivness of the treatment. However, the benefit of treatment on quality of life noticeably emerged in the PROs during the first 25 weeks of treatment—ie, not just during nivolumab administration. This observation suggests that even if the addition of ipilimumab to nivolumab led to increased immune-related adverse events,

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