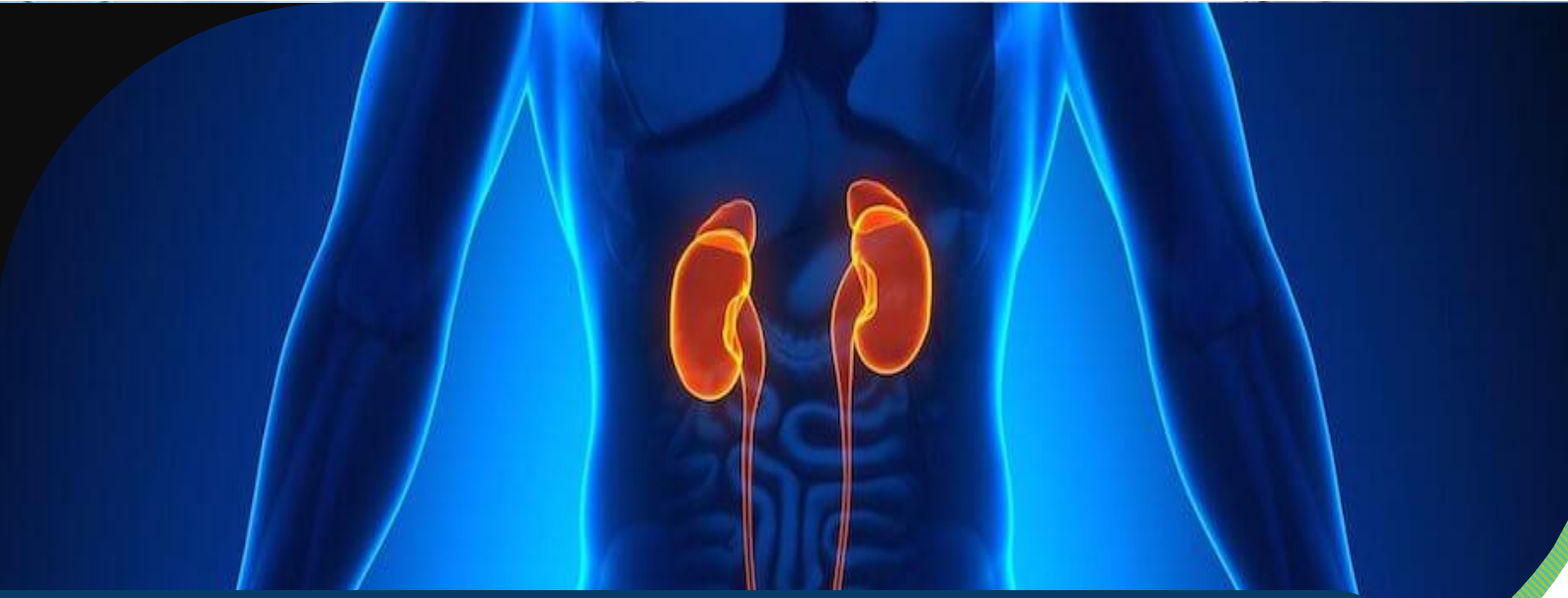

NU Rounds

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Dear Doctor,

Greetings from Micro Labs limited. We are happy to bring you "**NU Rounds**" which contains latest and interesting news in the field of Urology.

Inside This Issue:

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Looking forward to your valuable feedback

Best Regards,

Medical Team, Micro Labs Ltd

Prostate Cancer Screening with PSA more Beneficial than Previously Documented

PSA screening is correlated with a greater survival advantage for prostate cancer (PCa) than is generally known, according to an extrapolation of the results from the 16-follow-up of the European Randomized Prostate Cancer Screening Trial (ERSPC).

This latest research included simulations to predict the impact of PSA screening over a 25-year span and obtained results indicating that many less people had to be tested and diagnosed with PCa to avoid 1 PCa mortality compared with ERSPC projections, Jonathan E. Shoag, MD, of Weill Cornell Medicine, New York, and colleagues stated in the New England Journal of Medicine.

The authors concluded that as physicians monitoring, diagnosing, and managing prostate cancer patients, and as statisticians committed to studying the results of monitoring for cancer, they indicate that the combination of screening advantages and drawbacks could be more beneficial than is commonly perceived.

According to the 2019 ERSPC update published in European Urology, an estimated 570 men between 55 and 69 years of age would need to be screened and 18 new cases of PCa would need to be diagnosed to prevent 1 PCa death over 16 years from study randomisation. It advantage is qualitatively comparable to guidelines to promote breast cancer screening, including the requirement to test 1250 people aged 50 to 59, and 769 women aged 70 to 74 to avoid one death from breast cancer at age 10.

Nonetheless, Dr Shoag 's team noted that 16 years of research randomization follow-up does not have a "reasonable time period" to evaluate the mortality gain from screening since people frequently start screening in their 50s and the median age at PCa 's death is 80 years. Based on their analysis, they estimated that 385 men would need to be screened and that 11 additional PCa cases would need to be diagnosed to prevent 1 PCa death over a period of 25 years.

In an interview, Dr Shoag found such estimates highly pessimistic and pointed out that PSA screening has benefits beyond minimizing the likelihood of PCa mortality, such as metastatic disease avoidance and the reduced quality of life correlated with its diagnosis.

Regarding the PSA test, he observed, it has been in use for 3 decades, and based on misguided assumptions, we are turning our backs on it. Data show that the frequency of metastatic PCa on diagnosis is increasing after several years of deterioration, and this obvious pattern is part of the explanation for performing the latest study, said Weill Cornell Medicine co-investigator Jim C. Hu, MD, MPH. A plausible explanation for this trend is a decline in screening that discouraged screening following the release of US Preventive Services Task Force (UPSTF) guidelines for 2012.

Dr Hu said the knowledge disseminated by the task force regarding PSA screening is inaccurate and focused on obselete results. In specific, he has concerns with a patient chart named "Is Prostate Cancer Screening Correct for You," in which the task force advises that the choice to seek PSA screening will be an independent one for people aged 55 to 69 years. The chart tells patients of the series of events put in motion by PSA screening, starting with the screening provided by 1000 people. According to the table, 240 would have a positive test indicating an elevated degree of PSA, of which 100 would be detected on a prostate biopsy to be PCa. The chart also reports on the potential side effects of prostate biopsies (pain, bleeding, and infection) and treatment complications, namely erectile dysfunction and urinary incontinence. Dr Hu said the knowledge in the graphic is old, does not reflect recent developments in PCa diagnosis and management, and does not depict the actual level of treatment. One practice is to use prebiopsy magnetic resonance imaging scans to recognize suspected lesions in patients with an elevated PSA. Patients do not need to undergo biopsy if none is found. Dr Hu noted that about one third of men with high PSA do not have to undergo biopsy. Another trend is using active surveillance to manage the majority of men with low-risk PCa, thus addressing an overtreatment concern.

Source: Shoag JE, Nyame YA, Gulati R, et al. Reconsidering the trade-offs of prostate cancer screening. N Engl J Med. 2020;382:2465-2468.

Novel liquid fiducial markers for image guided radiotherapy in bladder cancer

INTRODUCTION

Bladder-preserving therapy is growing popularity as an effective choice for patients with muscle-invasive bladder cancer, initially intended for inoperable conditions, developments in the distribution of radiation (Intensity Modulated or Volumetric Modulated Arc RadioTherapy (IMRT or VMAT) in conjunction with radio-sensitizing medications culminated in chemoradiation as an analogous solution to radical cystectomy. James et al.'s research of patients suffering from T2-4 N0 M0 muscle invasive bladder cancer found that disease-free survival after bladder protection.

Chemo-radiation diagnosis after 2 years was 67 per cent and average mortality after 2 years was 48 per cent. Only 18 percent of muscle-invasive recurrences were observed, acceptably low toxicity and 89 percent functional bladder preservation. The GETUG 97-015 analysis reported comparable findings and with a longer 8-year follow-up. There is (yet) no clear link between cystectomy and chemoradiotherapy, as there is a shortage of randomized controlled trials. However, an approximate study focused on evidence from meta-analysis revealed comparable levels of survival and regulation of loco-regional tumors.

Accurate tumor delineation and image-guided radiotherapy are essential when using a focal bladder boost in terms of sparing normal tissue as well as providing the primary tumor with an adequate dose. As the bladder is a distensible organ with just certain defined ligament links at the bladder base, displacement of the bladder wall by more than 1.5 cm was recorded in up to 60 per cent of patients during the radiation course. High margins are thus required for sufficient coverage, which contributes to healthy tissue being subjected to radiation and more side effects induced by radiation.

In the British BC2001 trial, the reduced high-dose volume was shown to be non-inferior with respect to toxicity and recurrence. The patients were provided with empty bladder and 3D-conform radiotherapy in this study. Image-guided adaptive radiotherapy (IGART) with a day schedule with a preparation library and a focus enhancement contributes to narrower gaps, lower dosage to safe tissue – fewer risk and therefore therefore the likelihood of tumor dosage progression that may contribute to improved tumor management. Because macroscopic tumor boundaries are difficult to determine on endoscopically implanted fiducial markers with visibility on CT scans, it is helpful to determine the most suitable plan of the day in tumor delineation, but also in daily online IGART.

The fiducial indicators presently in usage also have their own benefits and inconveniences. Gold seeds and titanium seeds are safe and feasible, but in verification imaging, up to 40 per cent of the markers are lost. Implantation of such markers often includes a stiff cystoscope, which is not convenient for the patient because it may be challenging to access all the locations in the bladder.

Water markers are considered to be secure and simple to administer, such as hydrogel and lipiodol. Nevertheless, the drawback of hydrogel is the small density that renders the symbol less noticeable on CBCT, and the physical challenge of injecting sufficient quantity.

The downside with lipiodol is the shading or blurring with colors, which renders it less effective throughout the therapy process to reliably delineate the tumor borders and the electronic visual instruction. Therefore, during the preparation and treatment stages, there is a need for a secure, simple to administer, well noticeable and positionally stable fiduciary marker to maximize IGART for care with a focal boost in bladder survival. BioXmark ® is a novel fiduciary injectable liquid and adherent marker that has shown promising results for IGRT in lung and esophageal cancer. BioXmark ® has a greater density than hydrogel, which is not supposed to distort or melt throughout the process of radiation. The purpose of this study was to assess the safety, feasibility, visibility and stability of the BioXmark ® liquid fiducial marker to be used in IGART for muscle invasive bladder cancer.

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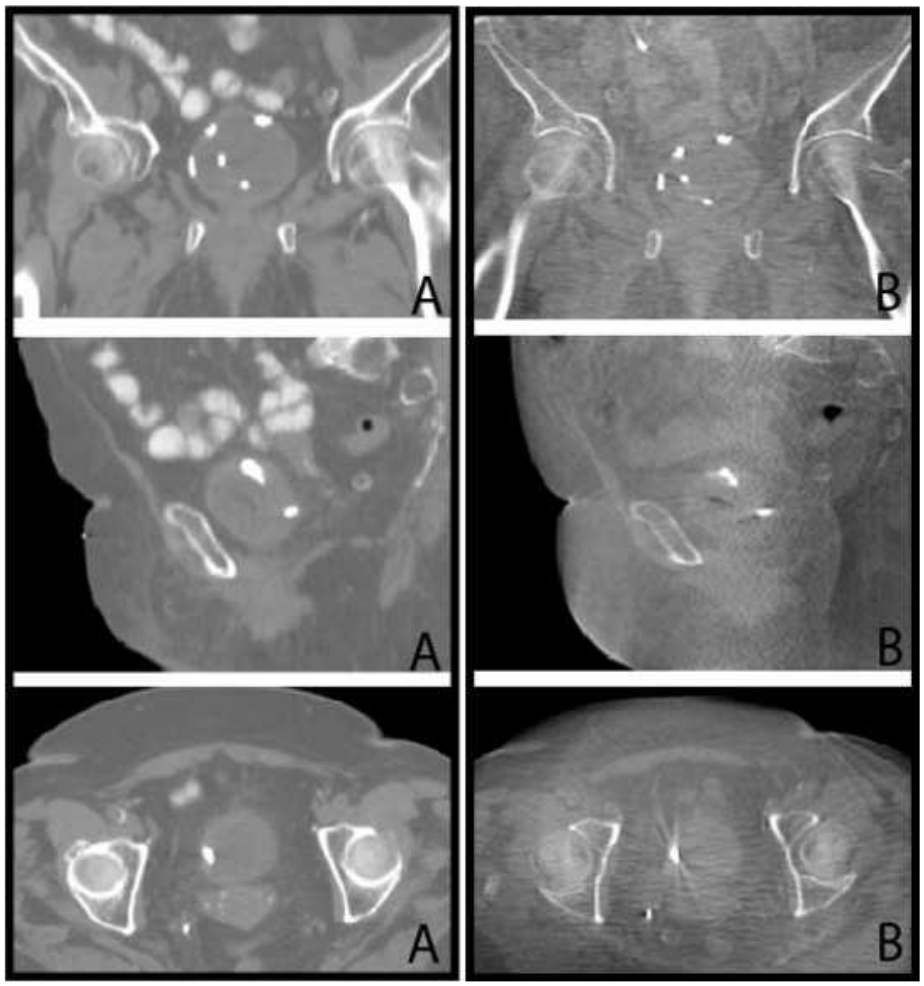
METHODS

Twenty patients with muscle-invasive bladder cancer were entered in this prospective, single center, phase I-II study. The novel BioXmark® liquid markers were injected around the tumor using a flexible cystoscopy. Visibility and stability of the markers were evaluated on planning-CT and cone-beam CT (CBCT). Prospectively defined threshold for success was set at a visibility of 75%.

RESULTS

In total 76 markers were implanted in 20 patients. Of those, 60 (79% 95% CI +/- 9%) were visible on CT-scan. Due to the learning curve of the technique the visibility improved in the last 75% of patients (86% visibility) compared to the first 25% of patients with 58% visibility. Concerning stability of the BioXmark® marker, all visible markers after CT-acquisition were still detectable at the last CBCT without displacement. In 15/20 (75%) of the patients 3 or more markers were visible on CT. No BioXmark® related adverse-events were reported.



Illustrative examples of BioXmark® spots in one patient on CT (A) and CBCT at end of treatment (B). Top images are in the coronal plane, middle images in the sagittal plane and the bottom images are in the axial plane

CONCLUSIONS

This novel fiducial marker's success rate was 79 per cent this is above the prospectively specified threshold limit. Over the study period a distinct learning curve of the liquid marker injection was observed. During the treatment phases, the marker showed sustained visibility and positional stability, and also appears safe and easy to inject.

REFERENCE

de Ridder M, Gerbrandy LC, de Reijke TM, Hinnen KA, Hulshof MCCM. BioXmark® liquid fiducial markers for image-guided radiotherapy in muscle invasive bladder cancer: a safety and performance trial. Br J Radiol. 2020;93(1111):20200241.

Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer

INTRODUCTION

Long-acting luteinizing hormone-releasing hormone (LHRH) agonists are widely used in the diagnosis of advanced prostate cancer as androgen depletion therapy to reach castrate testosterone levels. LHRH agonists produce an acute release in testosterone that may contribute to a severe outbreak in symptoms such as bone discomfort, obstructive urinary symptoms or, occasionally, ureteral blocking or strain of the spinal cord. The luteinizing hormone – gonadal axis is desensitized and down-regulated over a span of weeks, resulting in delayed reduction of testosterone rates. In the first few weeks after the introduction of an LHRH agonist, however, most recommendations prescribe the application of an antiandrogen agent. However, LHRH agonists do not fully inhibit the hormone-stimulating follicle (FSH), a possible mitogenic growth factor for prostate cancer cells.

The degarelix gonadotropin-releasing hormone (GnRH) antagonist is approved as a depot injection for androgen-deprivation therapy and achieves both luteinizing hormone and FSH suppression through an inhibitory effect on pituitary GnRH receptors. Degarelix results in rapid suppression of testosterone without an initial surge in testosterone but has not attained widespread clinical use. Possible reasons for such small use in clinical practice include the requirement for regular injections and a 40 per cent rate of injection-site reactions. Relugolix was formulated as an oral, highly selective, GnRH antagonist given once a day, with an efficient 25-hour half-life. Relugolix quickly prevents the pituitary secretion of luteinizing hormone and FSH, and in several phase 1 and phase 2 trials it has been shown to reduce testosterone rates. The Phase 3 HERO research aimed to determine the effectiveness and protection of oral relugolix (at a dosage of 120 mg once daily) as opposed to leuprolide in men with advanced prostate cancer.

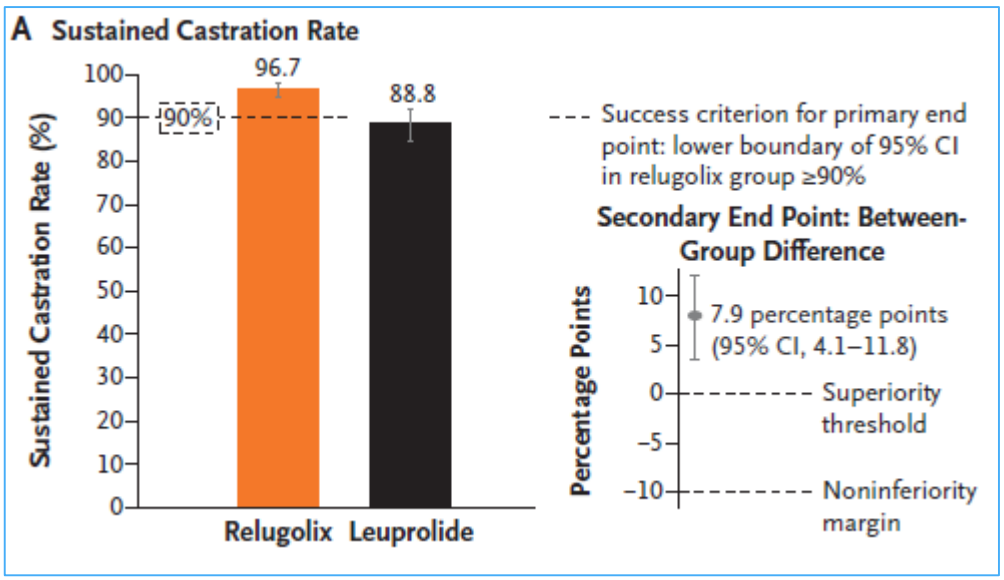
METHODS

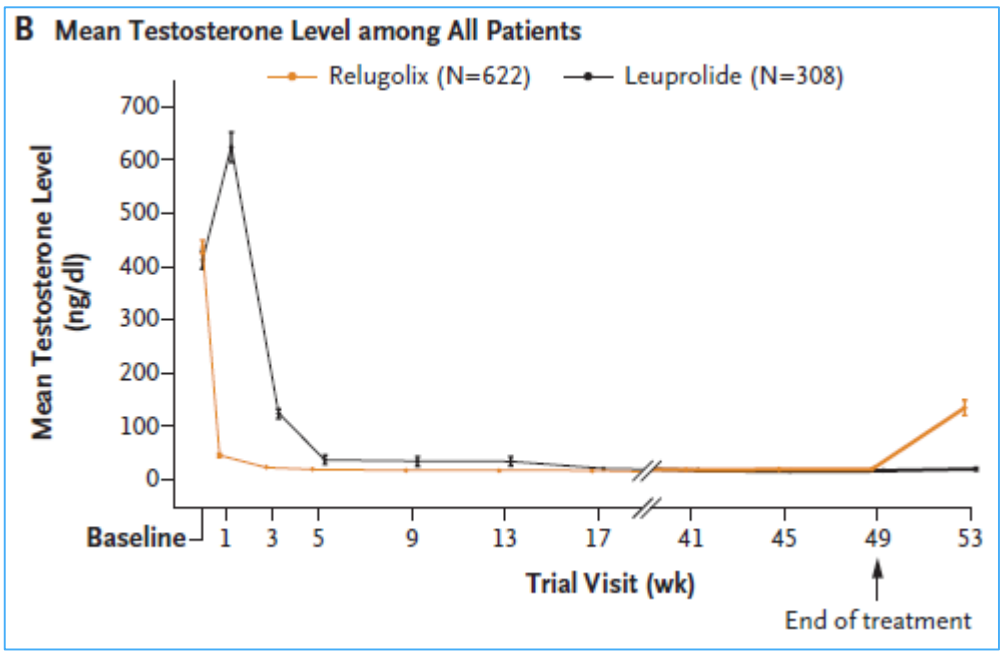
In this phase 3 trial, we randomly assigned patients with advanced prostate cancer, in a 2:1 ratio, to receive relugolix (120 mg orally once daily) or leuprolide (injections every 3 months) for 48 weeks. The primary end point was sustained testosterone suppression to castrate levels (<50 ng per deciliter) through 48 weeks. Secondary end points included noninferiority with respect to the primary end point, castrate levels of testosterone on day 4, and profound castrate levels (<20 ng per deciliter) on day 15. Testosterone recovery was evaluated in a subgroup of patients.

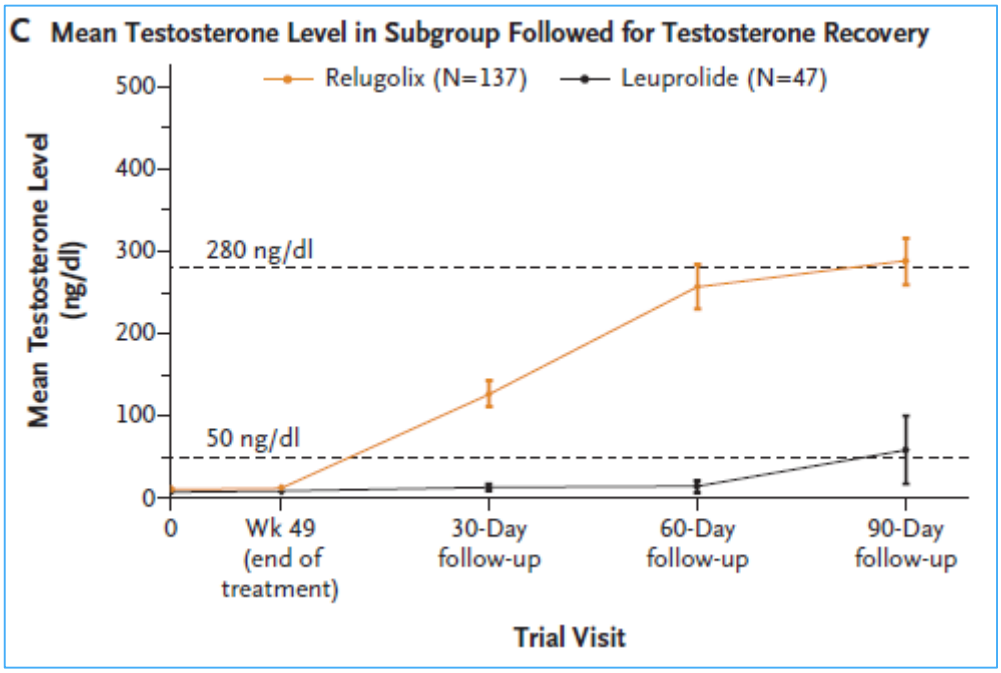
RESULTS

A total of 622 patients received relugolix and 308 received leuprolide. Of men who received relugolix, 96.7% (95% confidence interval [CI], 94.9 to 97.9) maintained castration through 48 weeks, as compared with 88.8% (95% CI, 84.6 to 91.8) of men receiving leuprolide.

The difference of 7.9 percentage points (95% CI, 4.1 to 11.8) showed noninferiority and superiority of relugolix (P<0.001 for superiority). All other key secondary end points showed superiority of relugolix over leuprolide (P<0.001). The percentage of patients with castrate levels of testosterone on day 4 was 56.0% with relugolix and 0% with leuprolide. In the subgroup of 184 patients followed for testosterone recovery, the mean testosterone levels 90 days after treatment discontinuation were 288.4 ng per deciliter in the relugolix group and 58.6 ng per deciliter in the leuprolide group. Among all the patients, the incidence of major adverse cardiovascular events was 2.9% in the relugolix group and 6.2% in the leuprolide group (hazard ratio, 0.46; 95% CI, 0.24 to 0.88).





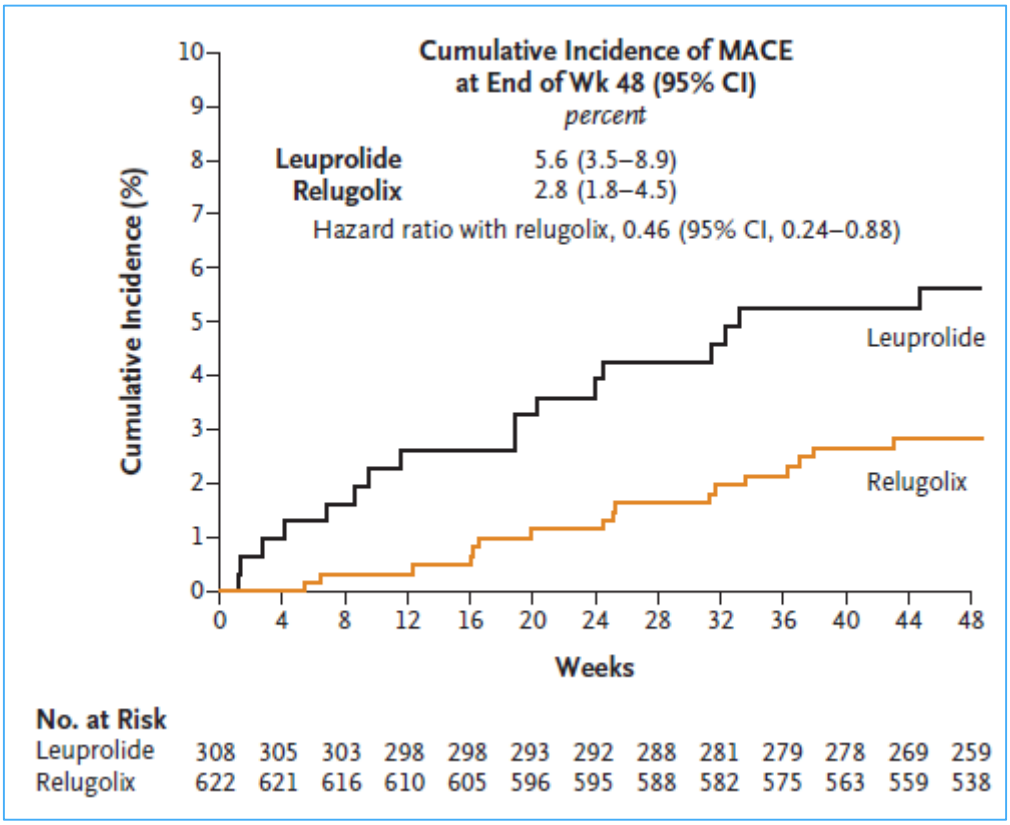


Efficacy Assessments.

- **Panel A depicts the sustained castration rate (defined as the cumulative probability of testosterone suppression to <50 ng per deciliter through 48 weeks) in the relugolix and leuprolide groups.**
- **The criterion for success with respect to the primary end point was a lower boundary of the 95% confidence interval in the relugolix group of 90% or higher; the lower boundary was 94.9%, so this criterion was met.**
- **The criterion for the secondary end point of noninferiority to leuprolide was also met, with the lower boundary of the 95% confidence interval for the difference between the relugolix group and the leuprolide group above the noninferiority margin of −10 percentage points.**
- **If noninferiority was shown, testing for superiority was permitted; superiority was shown because the lower boundary of the 95% confidence interval for the between- group difference was above zero.**
- **Panel B depicts mean testosterone levels over time, including testosterone recovery 30 days after discontinuation of trial treatment at the end of week 48.**
- **Panel C depicts the mean testosterone levels in the cohort of 184 patients followed for testosterone recovery 90 days after discontinuation of trial treatment at the end of week 48. The I bars indicate 95% confidence intervals.**

Secondary End Point	Relugolix (N=622)	Leuprolide (N=308)	P Value
Noninferiority analysis for sustained castration rates — %*	96.7	88.8	<0.001†
Cumulative probability of testosterone suppression to <50 ng/dl on day 4 — %	56.0	0	<0.001
Cumulative probability of testosterone suppression to <50 ng/dl on day 15 — %	98.7	12.0	<0.001
PSA response at day 15 followed by confirmation at day 29 — %‡	79.4	19.8	<0.001
Cumulative probability of profound testosterone suppression to <20 ng/dl on day 15 — %	78.4	1.0	<0.001
Mean FSH level at end of wk 24 — IU/liter	1.72	5.95	<0.001

Key Secondary Efficacy End Points.



Cumulative Incidence of Major Adverse Cardiovascular Events (MACE).

CONCLUSION

In this study affecting men with advanced prostate cancer, relugolix produced fast, prolonged reduction of testosterone production that was greater than that of leuprolide, with a 54 per cent reduced incidence of significant adverse cardiovascular events.

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Shore ND, Saad F, Cookson MS, et al. Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer. N Engl J Med. 2020;382(23):2187-2196.