# Four-year Follow-up of a Phase-3 Prospective Randomized Trial of Partial Gland Ablation with Vascular-Targeted Phototherapy versus Active Surveillance for Low-risk Prostate Cancer

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**Abstract**

**Introduction**: The prospective trial PCM301 randomized 413 men with low-risk prostate cancer to partial gland ablation with vascular-targeted photodynamic therapy (VTP; n=207) or active surveillance (AS; n=206). Two-year outcomes were reported previously (Lancet Oncology 18: 181, 2017). Herein we report four-year outcomes and post-hoc analyses.

**Materials & Methods:** Four-year outcomes evaluated rates of crossover to radical therapy (RT), and metastasis-free, cancer-specific and overall survival rates. Post-hoc analyses evaluated overall biopsy results, progression in Gleason Grade Group (GG), spatial location (apex, mid-gland, base), as well as 'in-field' (VTP treated lobe, or lobe with the index cancer in the AS cohort) and 'out-of-field' results.

**Results:** Three and 4-year follow-up was available in 69% and 64% of patients, respectively. Subjects in the VTP arm had lower rates of cross-over to RT at 2 years (7% vs 33%), 3 years (14% vs 44%) and 4 years (24% vs 53%) compared to AS (HR=0.31, 95% CI=0.21-0.45; p<0.001). Four-year metastasis-free (99% vs 99%), cancer-specific (100% vs 100%) and overall survival (98% vs 99%) rates were similar between cohorts. At 2 years, rates of disease progression were lower in subjects randomized to VTP for overall progression (HR=0.35; 95%CI = 0.25-0.48) and for grade progression (HR=0.42; 95%CI = 0.29-0.59). Reductions were even more pronounced when focusing on 'in-field' biopsy results for overall disease progression (HR=0.21; 95%CI = 0.14-0.31) and grade progression (HR=0.25; 95%CI = 0.16-0.40). Overall absence of cancer on biopsy also favored the VTP cohort (50% vs 14%; RR=3.48, 95% CI=2.44-4.98; p<0.0001). On post-hoc analysis, fewer VTP subjects had an 'in-field' positive biopsy (25% vs 65%; RR=0.38, 95% CI=0.30-0.50; p<0.0001) and 'in-field' progression to GG >1 (10% vs 34%; RR=0.30, 95% CI=0.19-0.47; p<0.0001). After VTP treatment, the rate of negative biopsies was similar in the apex (72%), mid-gland (78%), and base (74%), indicating that treatment was equally effective in each area.

**Conclusions:** In this prospective randomized trial of men with low risk prostate cancer, VTP significantly reduced the subsequent finding of GG 2 or higher cancer on biopsy relative to AS. Additionally, fewer men in the VTP cohort crossed over to RT, a clinically meaningful benefit that lowers treatment-related morbidity, with stable risk reduction over 4 years.

## Introduction

Given the low probability of mortality from low-risk prostate cancer (PCa), therapeutic choices should reflect a balance between cancer control and quality-of-life. Current guidelines recommend active surveillance (AS) as the preferred treatment option.[1,2] In practice, however, treatment algorithms are more complex, influenced by the substantial rates of reclassification or progression to higher grade or larger volume cancer over time, and by patient choice. Low-risk PCa does not always remain indolent and modern surveillance strategies are imperfect at detecting its biological transition to more threatening disease. In published cohorts of men on AS, some 25-60% cross-over to radical therapy (RT; radical prostatectomy, radiation therapy) within 5-10 years, exposing them to substantial treatment-related morbidity.[3-6] Over the last decade, various technologies have been developed for focal ablation of the prostate (e.g., cryotherapy, high intensity focused ultrasound (HIFU), vascular-targeted photodynamic therapy (VTP)) with the aim of reducing cancer progression while preserving quality of life.

The first multi-center, phase 3, prospective randomized trial evaluating a focal ablative treatment for localized PCa was recently published.[7] Conducted in 47 centers in 10 European countries, CLIN1001 PCM301 is the only successfully-accrued randomized trial evaluating a novel treatment for localized PCa. VTP employs padeliporfin di-potassium (TOOKAD®), a stable, bacteriochlorophyll-derived photo-sensitizer.[8] When excited by near-infrared light (753nm), TOOKAD generates superoxide and hydroxyl radicals, which initiate a cascade of events leading to rapid vascular occlusion and subsequent coagulative necrosis of the targeted prostate tissue.[9] For prostate VTP, intravenously injected TOOKAD is excited within the prostate gland with laser light delivered via trans-perineally placed light diffusers.

PCM301 randomized 413 men with low-risk PCa to VTP or AS. The study included patients with low-risk PCa (PSA ≤ 10 ng/ml, Gleason score 6 or less (Gleason Grade Group[10] [GG] 1) and clinical stage T2a or less), having 2-3 positive cores with maximum cancer core length (MCCL) ≤5mm or 1 positive core

with MCCL between 3 and 5mm, prostate volume 25-70 cc, and at least 10 years life expectancy. Demographics, patient characteristics and exclusion criteria are detailed in the original publication.[7] PCM301 met both its co-primary as well as secondary end-points. Briefly, at 2 years, in the intent-to-treat (ITT) analysis, VTP was superior to AS for absence of cancer on end-of-study biopsy ($p < 0.001$) and lower risk of cancer progression ($p<0.001$). In the protocol, progression was defined as meeting any of the following criteria: GG >1, >3 positive cores, MCCL >5mm, persistent PSA elevation (>10 ng/ml on 3 consecutive measures), clinical stage T3 or higher, or development of metastasis. At 2 years cross-over to RT was lower in the VTP arm ($p < 0.001$). These positive trial results led to the approval of TOOKAD in 2017 by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) for the treatment of unilateral low-risk, but not very low-risk, localized PCa.

For subjects participating in PCM301, the decision to cross-over to RT was largely based upon pathologic results of per-protocol biopsies at 12 and 24 months after randomization. Since the co-primary endpoints of PCM301 were assessed at 24 months, patients who crossed over to RT after that time point were not captured in the initial report.[7] The current follow-up study presents additional data up to 4 years from randomization, as well as post-hoc analyses of 2-year biopsy outcomes and reasons for RT.

## Materials and Methods

The initial PCM 301 protocol and extended follow up (PCM301 5FU) was approved by the IRB at study initiation. To assess the intermediate results of the planned 5-year period of extended follow up, the dataset was frozen on August 30, 2017. After 24 months, study participants initially randomized to VTP or AS were managed by their physician following a 'local standard-of-care' principle. Management decisions, including the need for biopsy, were at the discretion of individual physicians and patients in each center. Using an electronic secure web application, data collection was performed per usual practice at each center for indicators of PCa progression, additional treatment, morbidity and patient-

reported quality of life. Information about each patient's vital status was specifically sought for all patients originally randomized, including those lost to follow-up.

Results at 4 years were calculated for cumulative risk of and reasons for cross over to RT, and for metastasis-free, cancer-specific and overall survival rates. Additionally, a post-hoc analysis of biopsy results during PMC301 was conducted. We assessed per patient progression in GG status to GG 2 or higher, the location and grade of positive biopsy results both 'in-field' (within the VTP treated lobe, or, for AS, within the lobe containing the largest, index cancer) and 'out-of-field' (in the untreated lobe in the VTP cohort and the contralateral lobe in the AS cohort).

Statistical analyses were done with SAS version 9.3. All randomised participants were included in the efficacy analyses according to assigned treatment (intention-to- treat, or ITT, groups). Missing data were not imputed. Time-to-progression was compared between the two treatment groups by the log-rank test and quantified using a Cox proportional hazards regression model to derive hazard ratios at 2 years. Treatment group, age, number of positive cores, prostate volume, and disease status at baseline were used as covariates. Biopsy results at 2 years were analyzed with censoring of patients at time of M12 biopsy when M24 biopsy was missing. A chi-square test and risk ratios were used to compare proportions of participants in the two treatment groups according to the biopsy outcome. Time to initiation of RT was estimated by the Kaplan-Meier method. Comparison between the two treatment groups was done using the log-rank test and quantified with a univariable Cox proportional hazards regression model to derive hazard ratio at 4 years.

**Results**

The VTP cohort had a lower risk of cross-over to RT than the AS cohort at 2 years (7% vs 33%), 3 years (14% vs 44%) and 4 years (24% vs 53%) (HR=0.31, 95% CI=0.21-0.45; $p<0.001$) (Figure 1). The absolute risk reduction of RT by VTP at 2, 3 and 4 years was 26%, 30% and 29%, respectively, compared to AS. Triggers for RT were similar in the VTP and AS arms: increase in grade to GG 2 or higher (68% of

25 cross-overs in the VTP cohort vs 49% of 77 in the AS cohort), increase in cancer volume without change in grade (16% of VTP vs 32% of AS), and patient choice (16% vs 18%) (Table 1). By 3 years, there was no significant difference in the proportion of men who crossed over to RT without evidence of progression on biopsy: 4 of 25 (16%) after VTP versus 14 of 77 men (18%) in the AS arm (RR 1.14, CI 0.41-3.14). Four-year metastasis-free (99% vs 99%), cancer-specific (100% vs 100%) and overall survival (98% vs 99%) were similar between cohorts.

Rates of progression (Figure 2), and of progression in grade (Figure 3), were separately analysed post-hoc for the whole gland and the 'in-field' lobe and are reported at 2 years since biopsies were not mandated beyond that time point. Progression rates were significantly lower in the VTP than the AS cohort for overall progression (HR=0.35; 95%CI = 0.25-0.48) and progression in grade (HR=0.42; 95%CI = 0.29-0.59). Reductions were even more pronounced when focusing on biopsy results in the 'in-field' lobe, both for overall progression (HR=0.21; 95%CI = 0.14-0.31) and for progression in grade (HR=0.25; 95%CI = 0.16-0.40).

To further investigate the rate and location of positive biopsy results we conducted a post-hoc analysis with censoring of patients at time of their last available biopsy, which corrects for the higher rate of cross-over to RT with AS compared to VTP (Table 2). Rates of negative biopsy were virtually identical to those of the initial, uncensored analysis and significantly higher in the VTP arm (50% vs. 14%; RR=3.48; 95%CI=2.44-4.98; p<0.0001)[7]. Correspondingly, positive biopsy results were significantly lower in the VTP cohort compared to the AS cohort with regards to 'in-field' positive biopsy results (25% vs 65%; RR=0.38, 95% CI=0.30-0.50; p<0.0001), 'in-field' progression to GG2 or higher (10% vs 34%; RR=0.30; 95% CI=0.19-0.47; p<0.0001) and overall progression in grade (16% vs 41%; RR 0.39; 95% CI=0.28-0.56; p<0.0001) (Table 3). There were no significant differences between the two arms for rates of positive 'out-of-field' biopsy overall or for GG 2 or higher.

Spatially within the prostate gland, biopsy results were analyzed in 85 consecutive patients in the VTP arm with available data. Prior to treatment, 39 (46%), 40 (47%) and 43 (51%) patients had positive biopsy results in the apex, mid-gland and base, respectively; 21 (25%) patients had a positive biopsy at only 1 location, 46 (54%) at 2 locations, 3 (3%) at 3 locations. Location data were missing in 15 (18%) patients. There were no significant differences in the negative biopsy rates at 1 year by location in the VTP-treated lobe: 36 (92%) in the apex, 36 (90%) in the mid-gland, and 36 (84%) in the base.

Finally, adverse event data did not reveal any clinically significant issues during this extended 4-year follow-up, which remains consistent with the previous phase I and II trials.

## Discussion

Among patients newly diagnosed today low-risk cancers are the most common group, constituting 40-50%.[11] In the context of low cancer-specific mortality, AS has become widely adopted for men with low-risk PCa in the last decade and is accepted as initial management by nearly half of patients, attracted by delaying or avoiding the morbidity and adverse effects on quality of life associated with radical surgery or irradiation therapy (RT).[2] However, half of the patients with low-risk cancer elect RT initially,[12,13] and 25-60% of those who initially choose AS cross over to RT within 5-10 years.[14,15] Hence, there remains an unmet need for more effective control of low-risk cancers with treatments that pose minimal risks to urinary, sexual or bowel function. Partial gland ablation with vascular targeted phototherapy (VTP) is one such therapeutic approach.

With the safety and efficacy of hemi-gland ablation with VTP established in phase 1-2 trials,[16-19] PCM301 was designed as a prospective, randomized controlled trial to compare outcomes against AS, the standard of care for men with low-risk cancers.[7] Of particular interest was the ability of VTP to eliminate biopsy-detectable cancer within the prostate and to prevent “progression” in cancer grade and extent, which typically leads patients to cross-over to RT. In this phase 3 trial, progression was defined as an increase in Gleason group to GG 2 or higher or an increase in cancer extent on biopsy

beyond the inclusion criteria. In this study, no attempt was made to distinguish progression from "reclassification".[20]

In the initial report of the results of PCM301, VTP substantially reduced progression overall and by each preselected biopsy criterion compared to AS at 24 months.[7] In that time frame, crossovers to RT in either arm were driven largely by the new finding of GG 2 or higher on biopsy and were substantially lower in the VTP cohort than in the AS group. Morbidity was low and sexual, urinary and bowel functions were preserved, despite subsequent contralateral VTP treatment in 32%, ipsilateral retreatment in 11% and both contralateral treatment and retreatment in 2% of the VTP cohort.

In the present analysis of longer term outcomes, the reduced risk of cross over to RT at 2 years in the VTP cohort was maintained through 4 years (Fig. 1). Crossover in both arms was largely the consequence of progression to higher grade cancer on follow up biopsy (Table 1). Compared to AS, VTP significantly reduced overall biopsy progression to GG 2 or higher, with even stronger reduction in the 'in-field' lobe (Figures 2 and 3). End-of-study biopsies at 24 months identified GG 2 or higher cancer in only 16% of the VTP cohort compared to 41% of the AS group (Table 3). In-field progression to GG 2 or higher was identified in only 10% after VTP compared to 34% with AS, while progression rates were similar for VTP and AS 'out-of-field' (6% vs 7%), supporting the ablative efficacy of VTP treatment without increasing progression in untreated, 'out-of-field' areas. Finally, conversion to negative biopsy results after VTP was equally likely throughout the prostate (apex, mid-gland and base).

There are important implications of this study. In men on AS for low-risk prostate cancer, progression to or the finding of GG 2 or higher on biopsy commonly triggers definitive RT (prostatectomy, radiation therapy), since further progression in grade is associated with higher rates of metastases and death from cancer.[3] Crossing over to RT risks adverse effects on sexual, urinary and bowel function.[2] Thus, in men on AS, progression to GG 2 or higher is strongly associated with RT,

making presence of GG 2 or higher a useful predictive biomarker for cancer progression and subsequent treatment-related morbidity. [3, 6, 10, 14]

Post hoc analysis of the biopsy data in PCM301 assessed the efficacy of VTP in different areas of the prostate gland and confirmed that all areas within the prostate (apex, mid-gland and base) were ablated with similar efficacy. In contrast, concerns have been raised about other ablative therapies, including cryotherapy and HIFU, where spatial under-treatment, especially of the apex, may expose patients to local recurrence.[21,22]

Nevertheless, there remain concerns about PGA for low risk prostate cancer with any technology. One issue is whether current biopsy – and imaging – techniques can sufficiently localize the index cancer, even when the therapeutic target is one entire lobe. In the present study VTP was not completely effective in eliminating cancer within the targeted lobe. Cancer was present on biopsy in 25% of patients after VTP, a rate similar to that after cryoablation (35%) and HIFU (33%).[23,24] However, only 10% of VTP treated patients had GG 2 or higher cancers within the treated lobe compared to 34% of those on AS. (Table 3)

There are other limitations to this study. Subjects' cancers were not characterized at diagnosis as thoroughly as might be done in a clinical trial of PGA today. Neither saturation biopsies nor confirmatory biopsies nor multi-parametric MRI were employed to further characterize the cancer found on the initial diagnostic biopsy. These factors may help explain the observed 53% rate of cross-over to RT in our AS arm at 4 years. Although higher than some contemporary series, this rate of RT is not inconsistent with rates observed in other large AS studies, which report RT rates within 5-10 years ranging from 25-60%.[3-6,25] Other explanations include the exclusion of very low-risk cancers in PCM301, the high compliance rate with the protocol-mandated annual biopsies, and the stringent biopsy criteria used to trigger recommendation for RT (e.g., number of positive cores and MCCL are not used in most AS studies). Nevertheless, the techniques used herein for the initial diagnostic and subsequent

monitoring biopsies (12 cores) accord with the "standard of care" in North America today. And with randomization of patients at baseline, each of these factors affected both arms similarly, magnifying the importance of the differences observed with VTP treatment.

Another limitation is the lack of protocol-mandated biopsies after 24 months, which precludes documentation of the reasons for subsequent cross-overs. Patient-reported functional outcomes (erectile dysfunction, urinary and bowel symptoms) were not uniformly collected beyond 24 months from initial randomization. Progression to clinical stage T3 cancer was more common in the AS cohort, but events were too few to assess the longterm clinical effectiveness of VTP. These data should become available in the post-marketing studies underway in Europe. Nevertheless, the present study provides the longest reported Level 1 evidence of safety and efficacy of PGA for prostate cancer published thus far.

Based on data from multiple phase 1-3 clinical trials, including PCM301, partial gland ablation, using a strategy targeting one full lobe (hemi-gland ablation) with VTP, followed by ipsilateral retreatment for persistent cancer, and contralateral ablation if significant cancer is found on subsequent biopsy, is safe.[7,16-19] Further, this strategy leads to few adverse effects on quality of life and substantially reduces the likelihood of progression to higher Gleason grade and/or larger volume cancer on subsequent biopsy, markedly reducing cross over to RT with its attendant morbidity. As such, PGA with VTP provides a clinically meaningful benefit to selected men with low risk (but not very low risk) prostate cancer.

As a result of these studies, the European Medicines Association (EMA) in 2017 announced the summary of the Opinion of the Committee for Medicinal Products for Human Use (CHMP), approving TOOKAD VTP as monotherapy for patients with previously untreated, unilateral, low-risk prostate cancer, excluding those with very low risk tumors (EMA Summary of Opinion 2017). Application for approval by the US Food and Drug Administration (FDA) has been submitted. In addition to continued

follow up of the PCM301 cohorts, an EMA-mandated 5-year post-marketing prospective observational study of the first 600 patients treated within the European market has been initiated (CLIN1501 PCM401).

## Conclusion

PCM301 is the first and only prospective randomized trial comparing partial gland ablation and active surveillance for low-risk prostate cancer. With 4 years follow up, partial gland ablation with VTP decreased the risk of overall progression and time-to-progression in grade from Gleason GG 1 to GG 2 or higher. By decreasing the risk of cancer progression, VTP substantially reduced the rate of cross-over to radical therapy, a clinically-meaningful outcome that lowers treatment-related morbidity compared to active surveillance, while improving cancer control.

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## Tables

**Table 1: Reasons for cross-over to radical therapy (RT).**

| | VTP-TOOKAD n (%) | AS n (%) |
|---|---|---|
| Total no. subjects crossed over to RT within 3 years | 25 | 77 |
| Gleason grade increase to GG>1 | 17 (68%) | 38 (49%) |
| Increased volume of GG1 cancer on biopsy without GG increase | 4 (16%) | 25 (32%) |
| Patient choice | 4 (16%) | 14 (18%) |

**Table 2: Post-hoc analysis of biopsy results by ITT cohorts in the first 24 months of the initial protocol.**

| | VTP (N=206) n (%) | AS (N=207) n (%) | VTP vs. AS Risk ratio; 95% CI (p-value) |
|---|---|---|---|
| **Negative biopsy** | **104 (50%)** | **30 (14%)** | **RR=3.48; 95%CI=2.44-4.98 (p<0.0001)** |
| **'In-field' positive biopsy** | **51 (25%)** | **134 (65%)** | **RR=0.38; 95%CI=0.30-0.50 (p<0.0001)** |
| • GG 1 | • 30 (15%) | • 64 (31%) | |
| • GG 2 | • 18 (8.7%) | • 57 (28%) | |
| • GG 3 | • 1 (0.5%) | • 8 (3.9%) | |
| • GG 4 | • 2 (1.0%) | • 5 (2.4%) | |
| **'Out-of-field' positive biopsy** | **39 (19%)** | **25 (12%)** | **RR=1.57; 95%CI=0.99-2.49 (p=0.054)** |
| • GG 1 | • 27 (13%) | • 11 (5.3%) | |
| • GG 2 | • 10 (4.9%) | • 11 (5.3%) | |
| • GG 3 | • 1 (0.5%) | • 2 (1.0%) | |
| • GG 4 | • 1 (0.5%) | • 1 (0.5%) | |
| **No biopsy** | **12 (5.8%)** | **18 (9%)** | |

ITT = Intent to Treat analysis; GG = Gleason Grade Group; 'In-field' = within the VTP treated lobe, or, for AS, within the lobe containing the largest, index cancer; 'Out-of-field' = in the untreated lobe in the VTP cohort and the contralateral lobe in the AS cohort.

**Table 3: Post-hoc analysis of lobe location for biopsy results with GG>1 by ITT cohorts in the first 24 months of the initial protocol.**

| | VTP (N=206) n (%) | AS (N=207) n (%) | VTP vs. AS Risk ratio; 95% CI (p-value) |
|---|---|---|---|
| **Overall GG>1** | **33 (16%)** | **84 (41%)** | **RR=0.39; 95%CI=0.28-0.56 (p<0.0001)** |
| **'In-field' GG>1** | **21 (10%)** | **70 (34%)** | **RR=0.30; 95%CI=0.19-0.47 (p<0.0001)** |
| **'Out-of-field' GG>1** | **12 (5.8%)** | **14 (6.8%)** | **RR=0.86; 95%CI=0.41-0.1.82 (p=0.70)** |

ITT = Intent to Treat analysis; GG = Gleason Grade Group; 'In-field' = within the VTP treated lobe, or, for AS, within the lobe containing the largest, index cancer; 'Out-of-field' = in the untreated lobe in the VTP cohort and the contralateral lobe in the AS cohort.

## Figures

**Fig. 1. Kaplan-Meier analysis of cross-over to radical therapy over time in each arm.**

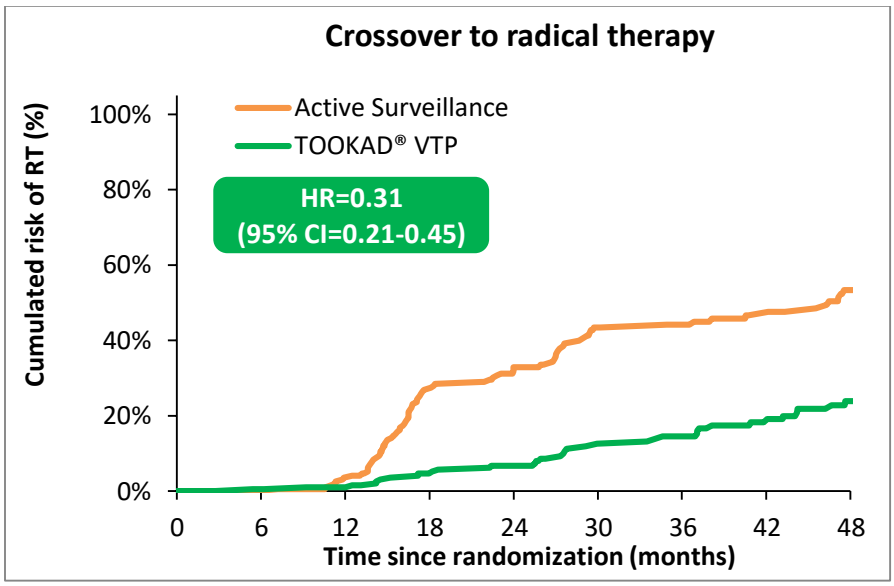


**Fig. 2. Progression rates by ITT cohorts comparing VTP to AS. (A.) Whole gland progression, defined by meeting any protocol definition of progression, and (B.) In-field progression, defined by biopsy results within the VTP treated lobe, or, for AS, within the lobe containing the largest, index cancer.**

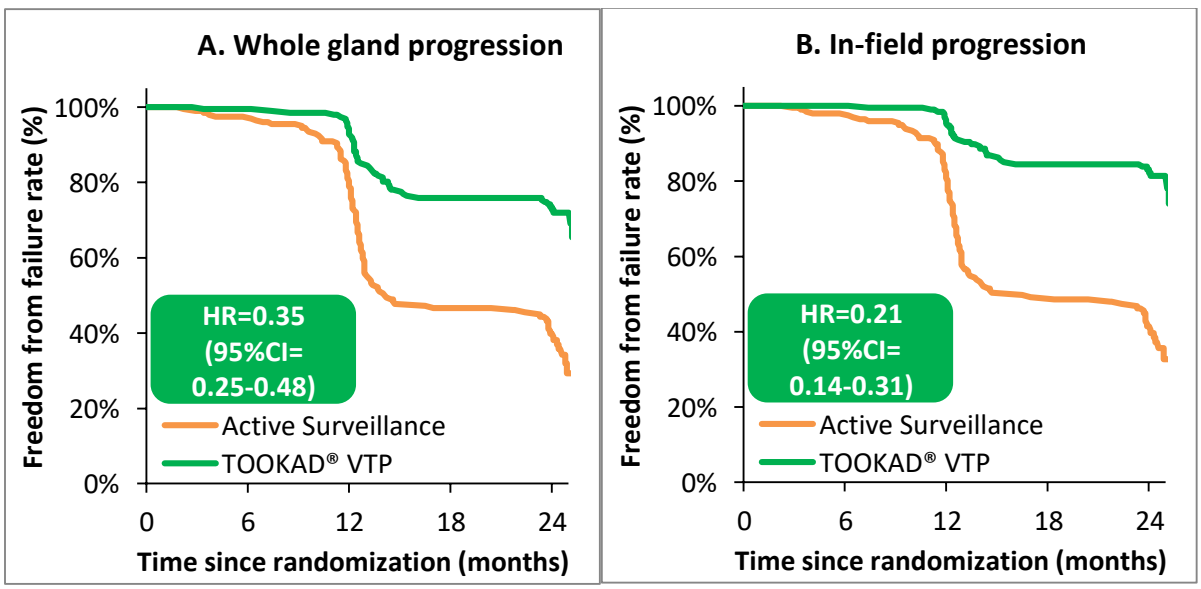

**Fig. 3: Progression in grade to GG>1 comparing VTP to AS. (A.) Whole gland progression, defined by meeting any protocol definition of progression, and (B.) In-field progression, defined by biopsy results within the VTP treated lobe, or, for AS, within the lobe containing the largest, index cancer.**