NDA 212578: TOOKAD
FDA Opening Remarks

Oncologic Drug Advisory Committee Meeting

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Proposed Indication

- TOOKAD is proposed for use in the treatment of patients with localized prostate cancer meeting the following criteria:
  - Stage T1-T2a
  - Prostate-specific antigen (PSA) <10 ng/mL
  - Gleason Grade group 1 (GG1) based on transrectal ultrasound (TRUS) biopsy

    or
  - Unilateral Gleason Grade group 2 (GG2) based on multiparametric magnetic resonance imaging (MP-MRI)-targeted biopsy with < 50% of cores positive

A Different Context for ODAC

- Objective of most cancer trials:
  - Demonstrate anti-tumor EFFICACY of an anticancer agent
  - Objective- **DELAY or PREVENT cancer-related morbidity or mortality**

- Objective of focal therapy in an active surveillance (AS) population:
  - Demonstrate reduction in need to undergo morbid procedure such as radical prostatectomy (RP) or radiation therapy (XRT)
  - Objective- **DELAY or PREVENT short/long term procedure-related morbidity**

Treatment Landscape in Low Risk Prostate Cancer

- Historically- low risk prostate cancer patients often treated with RP/XRT
- More recently- AS preferred if life expectancy ≥10 years
  - Goal: reduce overtreatment of clinically insignificant disease
  - However: 20-40% of AS patients over 5 years undergo RP/XRT
- FDA Workshop (2018) discussed novel endpoint for focal therapies in localized prostate cancer: decreased pathologic upgrade
  - Might represent benefit if ALSO accompanied by:

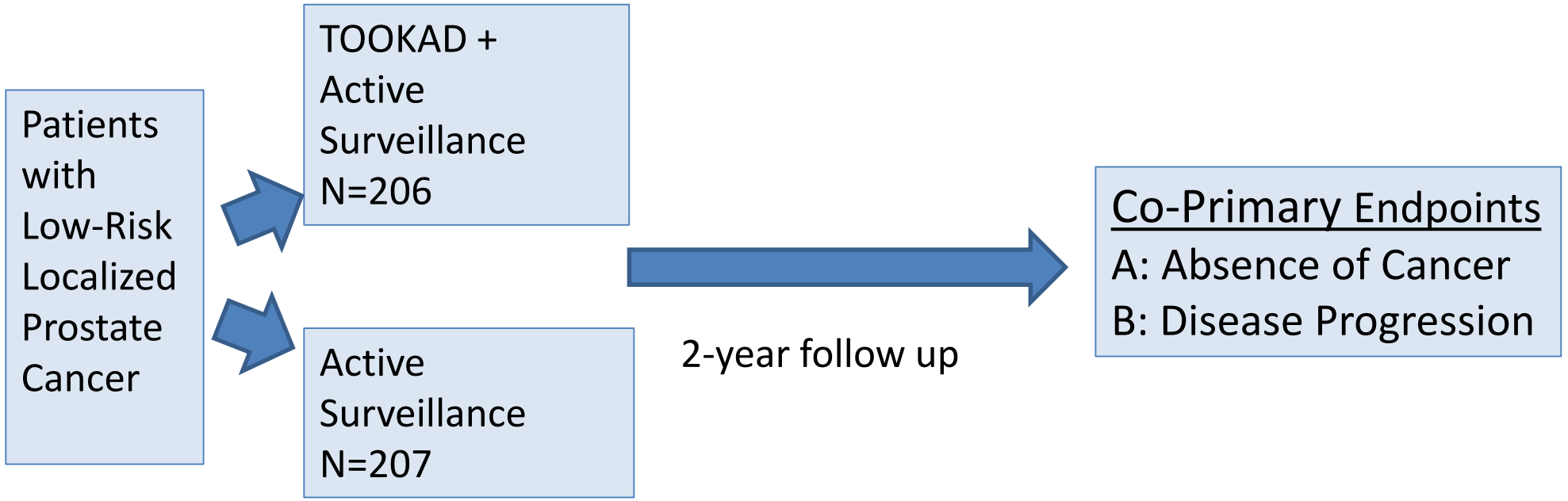
    Decrease in rate of definitive therapy

    AND

    Decrease in long term toxicity (physician and patient reported)

Tosoian JJ et. al. Nature Reviews Urology (2016)
NCCN Guidelines Prostate Cancer Version 4.2019

Study Design PCM301



- Biopsies at 12, 24 months (M12, M24)
- Study extension with 5 year follow-up
- FDA considers 2 year data basis for application
- No patient with favorable intermediate risk prostate cancer enrolled

PCM301 Key Results

- PCM301 met its co-primary endpoints-
  - Co-Primary Endpoint A- absence of cancer at 2 years
    - TOOKAD 49% vs. AS 13.5%
  - Co-Primary Endpoint B- time to progression of cancer
    - 2 year progression rate-TOOKAD 28% vs. AS 58%

    (HR 0.34, 95%CI [0.249,0.469])

- Time to definitive therapy was a secondary endpoint, not controlled for multiplicity
  - 2 year definitive therapy rate- TOOKAD 6% vs. AS 31%

    (HR 0.17, 95% CI [0.090, 0.313])

HR=hazard ratio CI=confidence interval

Key Issues

1. Are the endpoints and results adequate to characterize benefit?
2. Is the safety profile of TOOKAD acceptable?
3. Do uncertainties allow for reasonable assessment of benefit-risk?

Key Issues

1. Are the endpoints appropriate to characterize benefit?
2. Is the toxicity profile of TOOKAD acceptable?
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Endpoints

- Endpoint A- absence of definitive cancer-
  - Inherently difficult to interpret; without further intervention, no AS patient should have cancer absent.
  - Result does not lead to altered clinical management
- Endpoint B- decreased disease progression-
  - Improvement in this endpoint may have clinical implications if definitive therapy and resultant toxicity also decrease
  - Individual components of this composite endpoint may not be objective clinical triggers for intervention
  - Whether endpoint B translated into a meaningful benefit in PCM301 is unclear as overall toxicity rates were high

Utility of Endpoint A unclear
Ability of Endpoint B to translate into meaningful benefit unclear

Key Issues

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2. Is the safety profile of TOOKAD acceptable?
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Safety Profile

- Long Term Toxicity
  - Urinary dysfunction similar to AS arm
  - Rate of unresolved erectile dysfunction (ED) in TOOKAD arm at M24= 23%
- Limited data on long-term outcomes-
  - Potential for compromised cure rate?
  - Potential harm after RP/XRT

Higher rates of unresolved erectile dysfunction
Long term outcomes unclear

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Data Uncertainties

- Both co-primary endpoints based on biopsy data, however, biopsy in this setting may be unreliable
  - Missing M24 biopsies (~13%); false negative biopsies (14% on AS arm)
  - Other sampling errors and potential misattributions
- **No** adverse event (AE) data recorded after definitive therapy for many:
  - Active Surveillance arm: 40/64; **19% overall in AS arm**
  - TOOKAD arm: 5/12; **2% overall in TOOKAD arm**

Uncertainties exist regarding data; difficult to quantify effect of missing data on study conclusions

Planned Trial PCM306

- Favorable intermediate risk patients, randomized to TOOKAD vs. AS
- Scheduled biopsies up to 5 years → long term endpoint data
- Longer follow up of safety, Patient Reported Outcomes (PRO) data → long term toxicity data
- Pre-specified criteria for definitive therapy → less subjectivity

Question to the Committee

VOTE: Do the results of PCM301 represent a favorable benefit/risk profile for TOOKAD in patients with low-risk early stage prostate cancer?

NDA 202578: TOOKAD
FDA Presentation

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February 26, 2020

FDA Review Team

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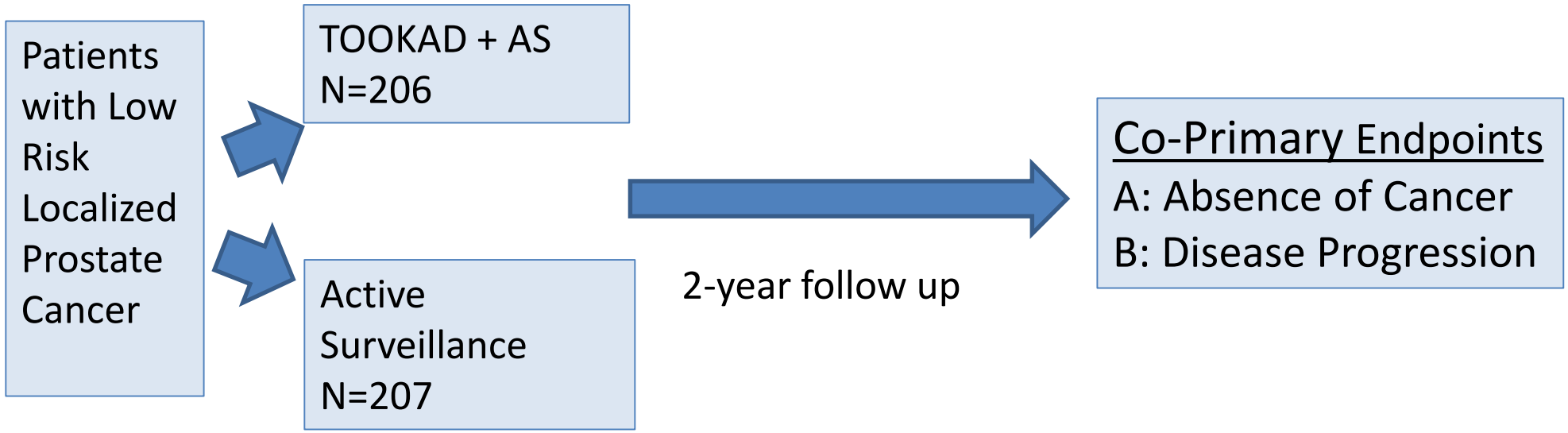
- Deputy Center Director, OCE: Paul Kluetz, MD
- Director, OCE; Acting Director, OOD: Richard Pazdur, MD

Outline

- Key Issues
  - Are the endpoints appropriate to characterize benefit?
  - Is the safety profile of TOOKAD acceptable?
  - Do uncertainties allow for reasonable assessment of benefit-risk?
- Summary
- Question for ODAC

Study Design PCM301



- Study extension with 5 year follow-up
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Key Issues

1. Are the endpoints appropriate to characterize benefit?
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Co-Primary Endpoint A - Absence of Cancer

- Definition: Absence of definitive cancer at 2 years
- Results:
  - TOOKAD: 49% had no cancer on biopsy at 2 years
  - AS: 14% had no cancer on biopsy at 2 years
- Missing biopsy data in both arms
  - TOOKAD 18% vs. Active Surveillance (AS) 42%*
- Potential for unblinding of central pathologist due to necrosis on TOOKAD arm

* Includes lack of biopsy data from 6% in TOOKAD arm and 27% of patients in AS who received definitive therapy

Uncertainty with Co-Primary Endpoint A

Absence of Definitive Cancer

- Utility of the endpoint unclear
  - Surveillance arm expected to have 100% rate of cancer
  - Result won't alter clinical management
- Uncertainties in assessment of the endpoint
  - AS arm: Many patients with false negatives or missing biopsy data
  - Limitations of biopsy in this setting well-documented
- Endpoint not agreed upon by FDA previously due to these concerns

Co-primary Endpoint B
Time to Disease Progression

Primary Analysis for Endpoint B

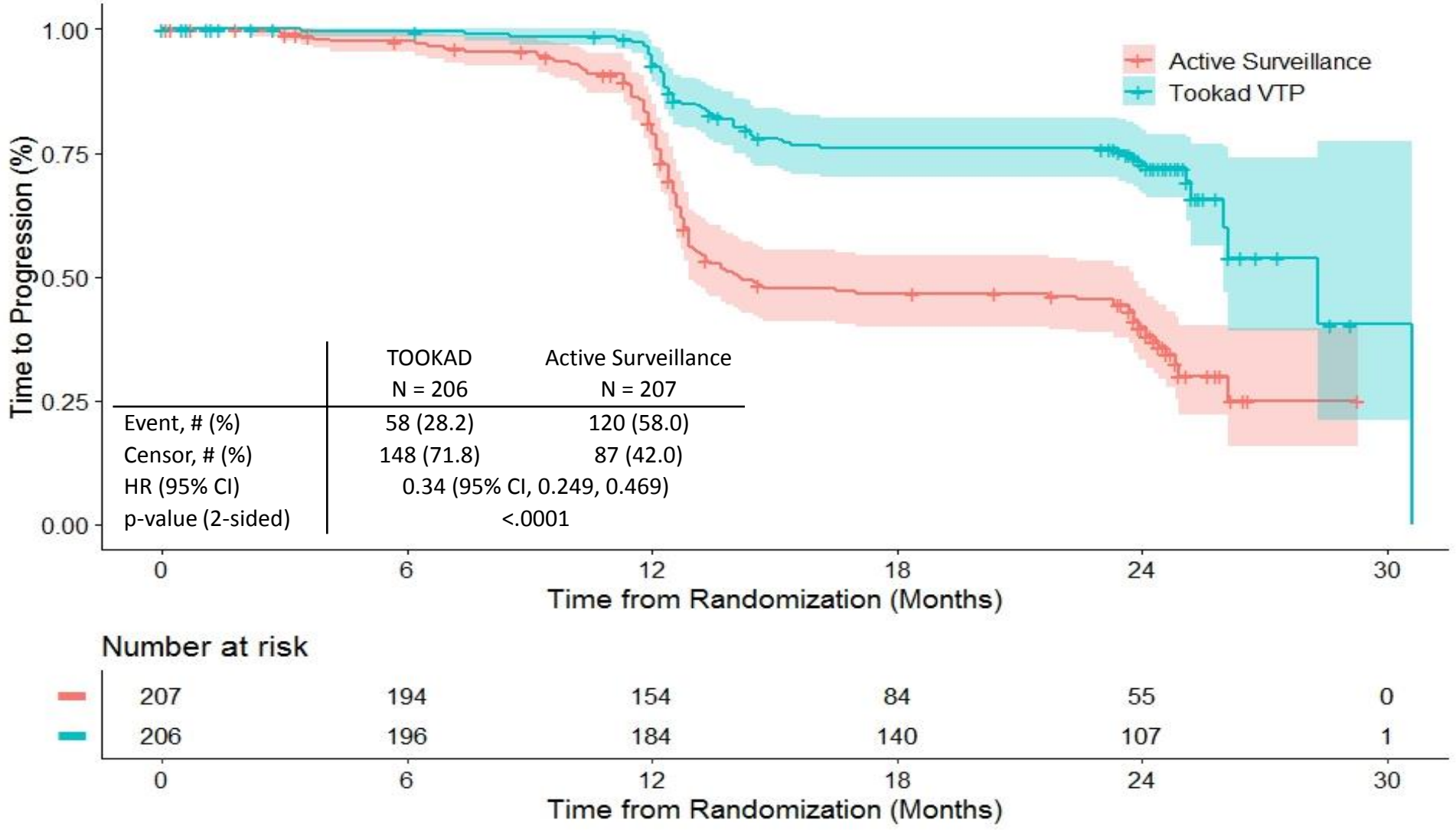
- Sponsor uses “Rate of local disease progression”
- FDA uses “Time to Disease Progression”

Progression Criteria

- Gleason ≥ 4
- More than 3 cores positive
- Cancer core length > 5 mm
- PSA > 10 ng/mL in 3 consecutive measures
- Any T3 prostate cancer
- Metastasis
- Prostate cancer-related death

*SAP defines endpoint as “Failure of treatment due to progression of cancer from low to moderate or higher risk over the 24 month follow-up”

Co-Primary Endpoint B – Time to Disease Progression



	TOOKAD N = 206	Active Surveillance N = 207
Event, # (%)	58 (28.2)	120 (58.0)
Censor, # (%)	148 (71.8)	87 (42.0)
HR (95% CI)	0.34 (95% CI, 0.249, 0.469)	
p-value (2-sided)	<.0001	

Enrollment Criteria vs. Disease Progression

Enrollment Criteria
Up to Gleason 3+3
2-3 Positive Cores
Max core length 5 mm
PSA ≤10 ng/ml
Clinical stage up to T2a
No metastatic disease
N/A

Progression Criteria	TOOKAD (%)	AS (%)
Gleason ≥ 4	24	44
More than 3 Positive Cores	11	28
Cancer core length > 5 mm	12	25
PSA >10 ng/ml x 3 times	1	7
Any T3 prostate cancer	0	2
Metastasis	0	0
Prostate cancer death	0	0

- Some progression criteria that contribute to composite endpoint may not be objective clinical triggers for intervention:
  - For some criteria, small incremental change from enrollment → progression
  - Rationale for criteria selection unclear

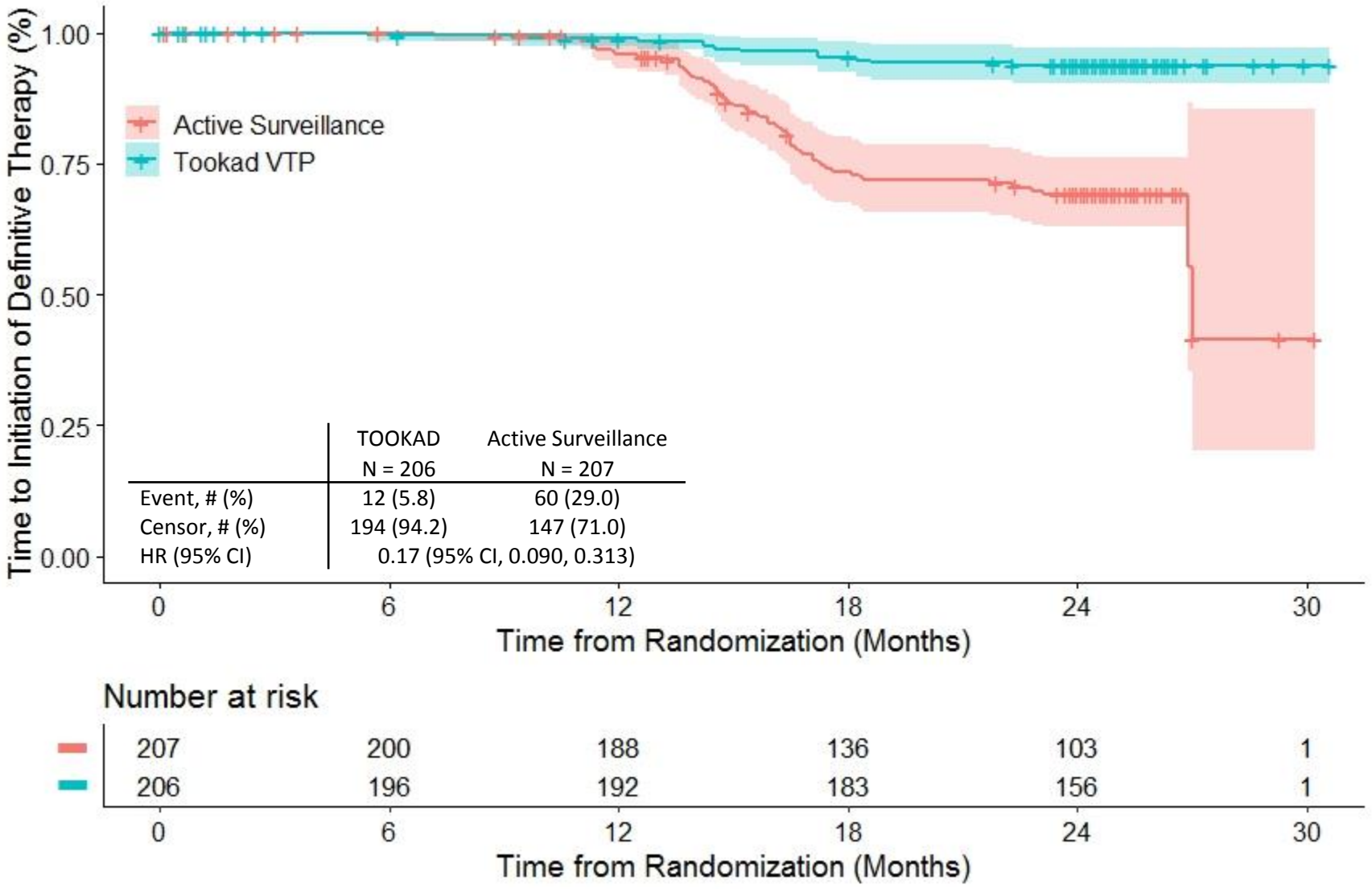
Uncertainty with Endpoint B
Time to Disease Progression

- Endpoint is affected by uncertainties related to biopsy results
  - Misattribution of grade and false negatives an issue
  - ~30% patients in AS arm had decrease in positive core number and core length with cancer despite no intervention
  - Accuracy of biopsy after TOOKAD is unknown
    - Post-procedure scarring may affect biopsy

Disease Progression and Definitive Therapy

- The value of a disease progression endpoint (endpoint B) is providing objective trigger for intervention (RP/XRT)
- However, in PCM301
  - ~50% of progressors on both arms did not undergo definitive therapy by **Month 24** and
  - Several patients underwent definitive therapy but had no disease progression
- Variability in PCM301 makes interpreting this endpoint challenging

Time to Definitive Therapy



	TOOKAD N = 206	Active Surveillance N = 207
Event, # (%)	12 (5.8)	60 (29.0)
Censor, # (%)	194 (94.2)	147 (71.0)
HR (95% CI)	0.17 (95% CI, 0.090, 0.313)	

<u>Limitations of Analysis:</u>

- Trial was open-label
- Analysis not adjusted for multiple testing
- Decision to undergo definitive therapy, with firm criteria to undergo prostatectomy not pre-specified in the protocol
- ~50% of progressors didn't undergo definitive therapy

Summary of Efficacy

- PCM301 was an open label trial
- Both prespecified co-primary endpoints were met
- Clinical relevance of endpoints unclear
- Endpoint A: Absence of Cancer:
  - Does not lead to change in management. Clinical relevance unclear
- Endpoint B: Time to Progression:
  - Limited 2-yr follow-up. Correlation with long-term outcomes is not known
  - Uncertain clinical value as defined: Only ~50% of 'progressors' underwent definitive therapy at 2 years
- Both endpoints based solely or mostly on biopsies
  - False negatives and sampling error

Key Issues

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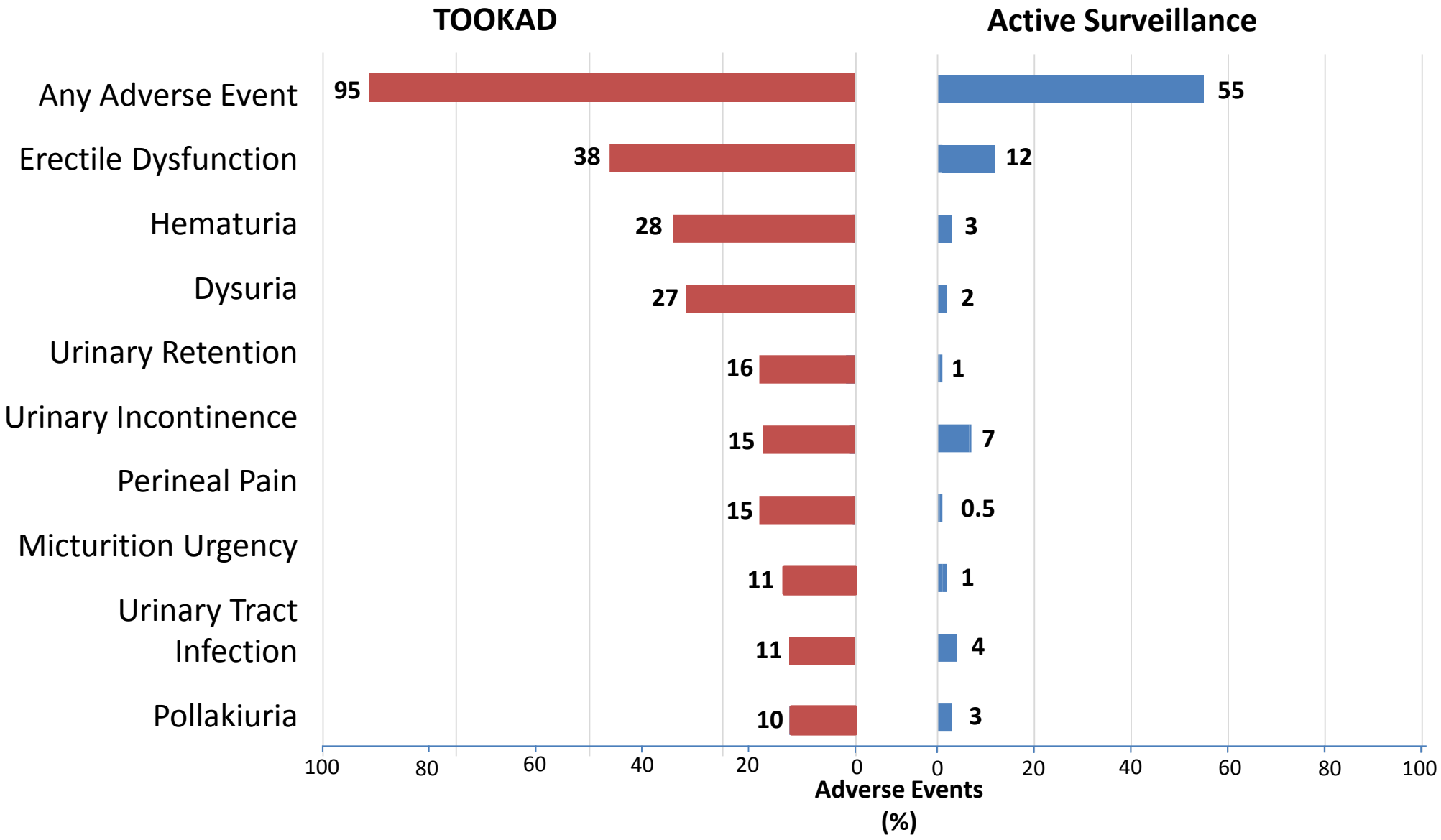
Most Common Adverse Events (AEs)



<u>Grade 1-4 Events:</u>
TOOKAD 95%
vs.
AS 55%

<u>Grade 3/4 Events:</u>
TOOKAD 22%
vs.
AS 10%

Sexual and Urinary Dysfunction AEs

- Published literature on prostatectomy, radiation:
  - Sexual dysfunction at 2 years ~14-90%
  - Urinary dysfunction at 2 years ~10-70%
- TOOKAD VTP vs. AS at 2 years:
  - Unresolved Erectile dysfunction: **23% vs. 10%**
  - Unresolved Urinary incontinence **6% vs. 5%**
- Many patients stopped reporting AEs after definitive therapy

Emanu et al. Curr Opin Support Palliat Care. 2016
Tal R, et al. J Sex Med. 2009

Missing Safety Data Makes Comparison Difficult

- **No** AE data recorded after definitive therapy for many:
  - Active Surveillance arm: 40/64
    - **19% overall in AS arm**
  - TOOKAD arm: 5/12
    - **2% overall in TOOKAD arm**
- Disproportionately affects active surveillance arm
  - True incidence of toxicity likely under-reported in AS arm
  - Accurate assessment between arms difficult

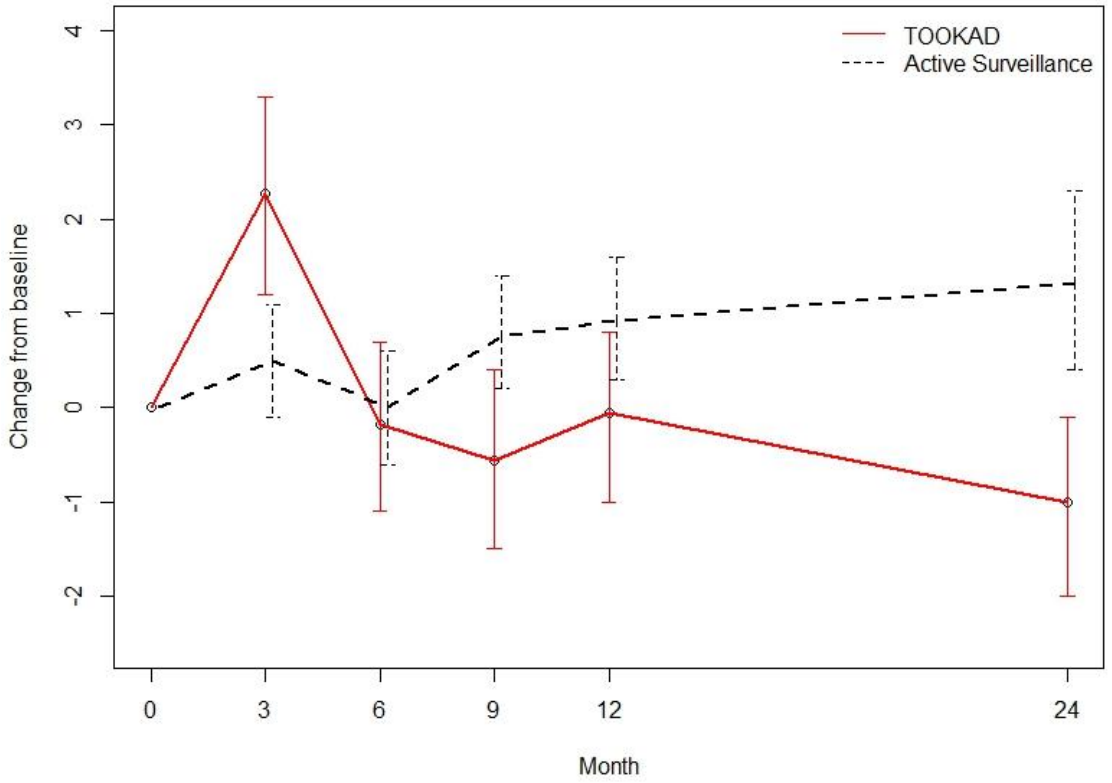
Patient Reported Outcomes (PRO) in PCM-301

- Assessed via IIEF-15 (**erectile function**), IPSS (**urinary symptoms**), EQ-5D-5L (**Quality of Life**)

- Schedule of assessment and completion rates:
  - IIEF, IPSS- baseline, 7 days post TOOKAD, months 3, 6, 9, 12, 24
  - EQ-5D- baseline, months 12 and 24
  - Higher proportion of missing data in AS arm
  - Completion rates at 24 months:
    - IIEF: **72.4%** in AS arm VS. **80.4%** in TOOKAD arm
    - IPSS: **75.9%** in AS arm VS. **84.5%** in TOOKAD arm

Urinary Symptoms

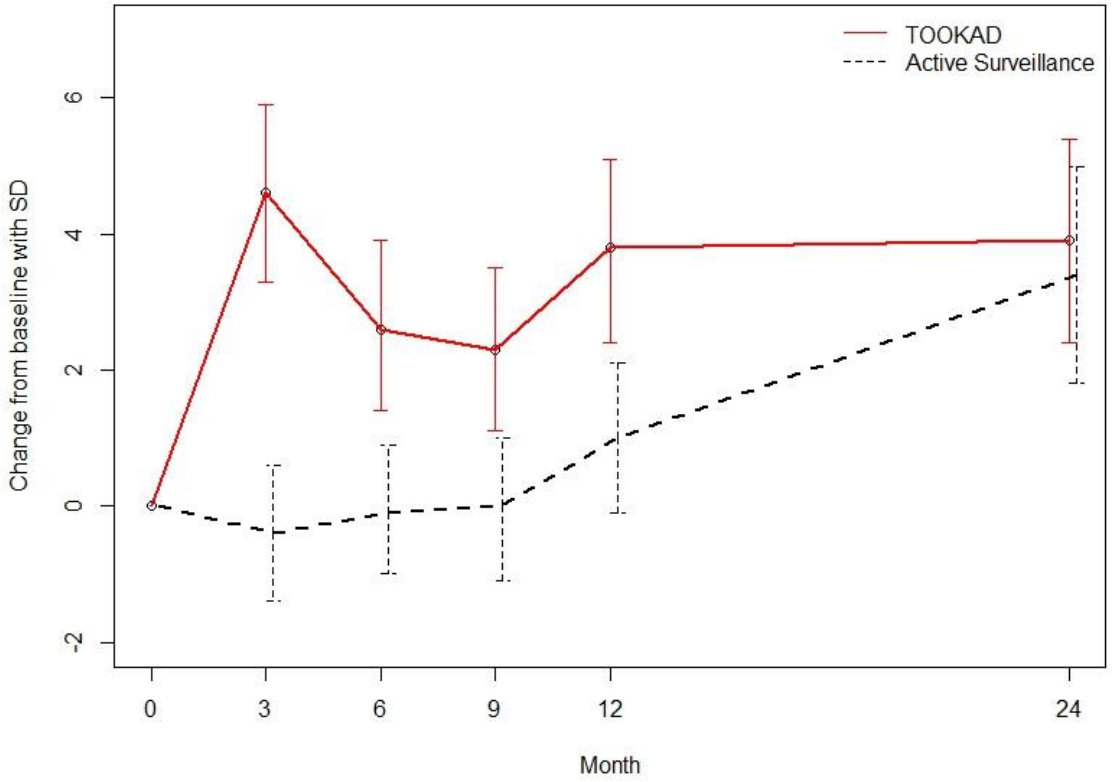
IPSS Summary Score
Mean Change from Baseline



TOOKAD	179	164	169	164	162	151
Active Surveillance	182	172	170	169	155	138

Erectile Dysfunction

IIEF - Erectile Function Domain
Mean Change from Baseline



TOOKAD	184	163	166	164	162	150
Active Surveillance	182	167	171	165	154	140

Higher = Worsening symptoms

Limitations of PROs from PCM301

- Some relevant reported AEs not assessed
  - Pelvic pain, dysuria, bowel symptoms, hematuria
- Limited Assessments of Acute and Long Term Toxicity
  - Few PRO assessments from baseline to month 6
  - Limited long term follow up
- Missing data
  - Lower Completion rate on AS arm vs. TOOKAD @ Month 24
  - Considerable amount of missing data after definitive therapy
- PRO data from PCM301 is descriptive only

Summary of Safety

- Reducing long-term toxicity important to characterize TOOKAD benefit
  - **SOME** patients on AS receive definitive treatment and have toxicity but **ALL** patients on TOOKAD have risk of toxicity upfront
- Higher incidence of toxicity on the TOOKAD arm compared to AS
  - Higher rates of all grade, grade 3-4, and erectile dysfunction events
- Disproportionate missing safety and PRO data in AS arm
  - Makes accurate comparison difficult
- Limited follow up → Long term outcomes unclear
  - Potential for compromised cure from treatment delay of definitive therapy
  - Limited data on outcomes of RP/XRT following TOOKAD

Key Issues

1. Are the endpoints appropriate to characterize benefit?
2. Is the safety profile of TOOKAD acceptable?
3. Do uncertainties allow for reasonable assessment of benefit-risk?

Data Uncertainties in PCM301

- Efficacy uncertainty
  - Absence of cancer and disease progression endpoints affected by unreliability of biopsy data (e.g., sampling errors, false negatives)
- Safety uncertainty
  - No AE and/or PRO data recorded after definitive therapy for many
  - True incidence of long term toxicity unknown
- Difficult to quantify effect of missing data on study conclusions

Proposed Trial PCM306

- TOOKAD vs. Active Surveillance in favorable intermediate risk cancer
- Endpoints-
  - objective progression of cancer
  - conversion to radical local or systemic therapy
- Measures in place to better collect data:
  - Longer follow up
  - PSA relapse post RP/XRT will be collected
  - Scheduled biopsies up to 5 years → long term endpoint data
  - Longer follow up of safety and PRO data → long term toxicity data
  - Pre-specified criteria for definitive therapy → less subjectivity

Summary of FDA Position

- PCM301 met its efficacy endpoints
- Clinical relevance of efficacy endpoints unclear
  - Disease progression as defined doesn't clearly translate into undergoing definitive therapy
- Acute toxicity worse with TOOKAD; Erectile function at M24 appears worse with TOOKAD
- Missing data, false negatives and sampling issues make accurate assessment of results difficult
- Open label trial could introduce potential bias
- Long-term efficacy and safety outcomes unknown

Question to the Committee

VOTE: Do the results of PCM301 represent a favorable benefit/risk profile for TOOKAD in patients with low-risk early stage prostate cancer?