TULSA-PRO®

TACT 12-Month Data | April 2019

PROFOUND MEDICAL

TACT (TULSA-PRO® Ablation Clinical Trial) pivotal study is designed to support Profound's application to the U.S. Food and Drug Administration for 510(k) clearance to market TULSA-PRO® in the United States.

Real World Context and Outcomes

	Prostatectomy [1-4]	Radiation [1-5]	HIFU [6-8]	TULSA (TACT)
Biopsy / Histology	16 – 24% Pos. Surg. Margin (Meta-Analysis, Tewari *et al* 2012) 10 – 15% Pos. Surg. Margin (RCT, Yaxley *et al* 2016) 24% Pos. Surg. Margin (ProtecT, Hamdy *et al* 2016)	50% Negative (Complete response) 25% Insignificant disease (Positive w. treatment effect) 25% Positive clinically significant Pca (Meta-Analysis Page 5, Approx. No.)	59 – 61% Negative (Complete response, FDA IDE Studies DEN150011 & K153023, Intent to treat analysis) 63% Negative, after 40% having repeat HIFU and 39% ADT (n=774, Crouzet *et al* 2013)	65% Negative (Complete response) 14% Insignificant disease (GG1, ≤2 cores, < 50% CCL) 21% Positive clinically significant Pca
Erectile Dysfunction erections insufficient for penetration	79% *(Range: 25 – 100%)*	63% *(Range: 7 – 85%)*	58% *(Range: 38 – 67%)*	20% – 25% - Grade 2 medication indicated. No Grade 3 ED
Urinary Incontinence moderate to severe	15% *(Range: 0 – 50%)*	4% *(Range: 2 – 15%)*	3% *(Range: 3 – 22%)*	2.6% - Grade 2 pads indicated. No Grade 3 Incontinence
Urethral Stricture moderate to severe	9% *(Range: 3 – 26%)*	2% *(Range: 1 – 9%)*	35% *(Range: 9 – 35%)*	2.6%
GI Toxicity, moderate to severe diarrhea, urgency, incontinence, fistula	15% *(Range: 0 – 24%)*	25% *(Range: 0 – 40%)*	7% *(Range: 1 – 21%)*	No GI Toxicity

References

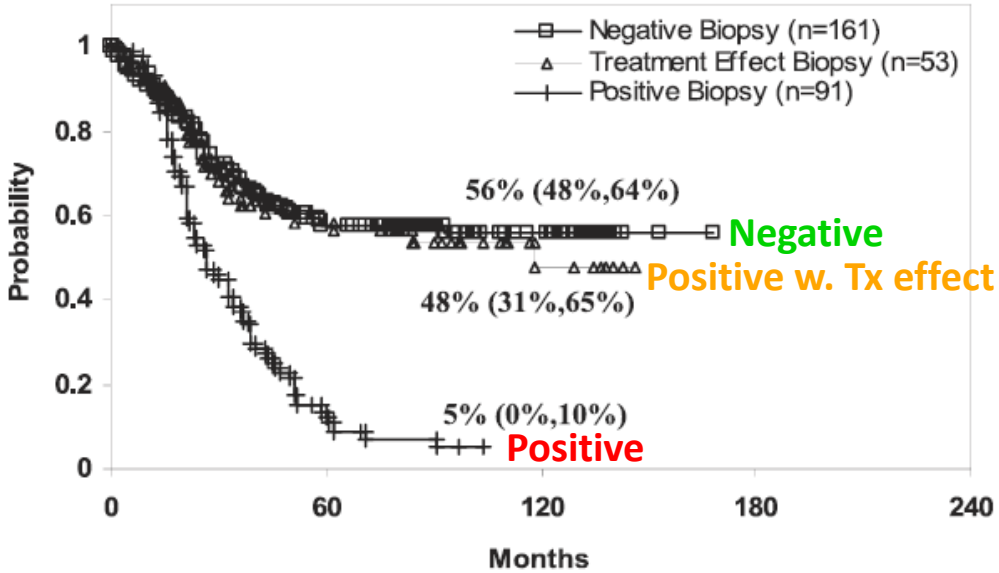
1. Thompson (Chair) *et al,* AUA prostate cancer clinical guideline update panel, J Urol 2007
2. Resnick et al, Prostate Cancer Outcomes Study (PCOS), NEJM 2013
3. Potosky *et al*, Prostate Cancer Outcomes Study (PCOS), J NCI 2004
4. Elliott *et al*, CaPSURE database, J Urol 2007
5. Budaus *et al*, Review, Eur Urol 20012
6. FDA IDE Study K153023
7. FDA IDE Study DEN150011
8. Crouzet *et al*, Whole-gland HIFU, Eur Urol 2014

Standard of Care Context – **Focus on Clinical Significance**

- Standard of care prostate cancer management relies on assessment of Clinically Significant Disease
- **Active surveillance** based on:
  - Insignificance of GG1, Gleason pattern 3 (no metastatic potential)
  - Natural disease progression similar to no cancer
- **Radiation therapy** categorizes post-treatment biopsy: **Negative**, **Positive w. treatment effect** & **Positive**
  - Crook *et al*, Int J Radiation Oncology Biol Phys, 2000
  - Zelefsky *et al*, J Urol, 2008
  - Considers Positive with treatment effect as insignificant disease (similar to Negative) due to similar natural disease progression
  - Additional therapy only if PSA failure
- **Prostatectomy** relies on a comprehensive set of factors (disease grade, margin length and volume, PSA), not only Positive Surgical Margins (PSM), to determine the need for additional therapy

Standard of care uses comprehensive assessment of clinically significant disease to manage patients before and after cancer treatment

Post-RT PSA relapse-free survival, as a function of biopsy status



Patients with negative and severe treatment effect biopsies had similar 10-year PSA relapse-free survival outcomes that were markedly different from outcomes in those with positive treatment biopsies. (Zelefsky *et al*, J Urol, 2008)

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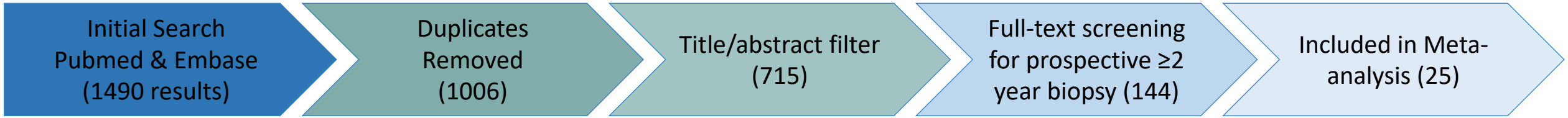
Standard of Care Context – **Radiation Therapy Meta-Analysis**



10/25 References met 2018 NCCN Guidelines:

Studies that meet 2018 NCCN guidelines for radiation therapy dose

Author	Date	Patient Risk	R-Techniq	R-Dose	R-frac	Studied N	Biopsied N	% (+) Bx	% (?) Bx	% (+/?) Bx	Bx Cores	Hx %
Levegrun	2002	Low,Int	3DCRT	75.6	1.8	554	16	12.50%	-	12.50%	6	0.00%
*Pollack	2002	Low,Int,High	3DCRT	78	2	101	81	32.10%	22.22%	54.32%	6	0.00%
Nichol	2005	Low,Int,High	3DCRT	75.6	1.8	140	71	33.80%	16.90%	50.70%	-	14.29%
Martin	2007	Low, Int	IMRT	60	3	92	25	32.00%	16.00%	48.00%	-	8.70%
Zapatero	2008	Low,Int,High	3DCRT	74	2	427	105	17.14%	-	17.14%	6	81.88%
*Zelefsky	2008	Low,Int,High	IMRT	75.6	1.8	1398	244	26.23%	25.00%	51.23%	6	39.23%
Loblaw	2013	Low	SABR; Dos	35	7	84	71	4.23%	-	4.23%	10	-
Petrongar	2013	Low,Int	IMRT	86	2	39	17	5.88%	5.88%	11.76%	6	0.00%
*Freytag	2014	Low,Int	IMRT	80	2	23	23	65.22%	-	65.22%	12	0.00%
Huang	2015	Low,Int,High	CIMRT/HII	76	2	303	86	44.19%	-	44.19%	6	30.23%

Total	4283	739	
Weighted Average			**27.06%**
Weighted Average without Hx			**32.85%**

Weighted average, all 10 studies:
27.1%; 95CI: [24.0, 30.3]

Excluding studies with adjuvant hormones:
32.9%; 95CI: [25.5, 41.1]

Data Sensitivity Analysis:

	All	Without Hx	Low, Int only	High Risk	IMRT	3DCRT	SABR exc.	Highest exc.
N	739	137	207	516	395	273	668	492
# Studies	10	4	6	4	5	4	9	9
W. Mean	27.1%	32.9%	24.2%	28.3%	32.2%	25.6%	29.4%	27.4%

TACT – TULSA-PRO Ablation Clinical Trial for FDA 510(k)

Pivotal study of whole-gland ablation in a clinically-significant patient population

Study Population

- n = 115, 13 clinical sites, 5 countries
- 45 – 80 years old
- Low (33%) & intermediate risk (67%) prostate cancer

Ablation Treatment Plan

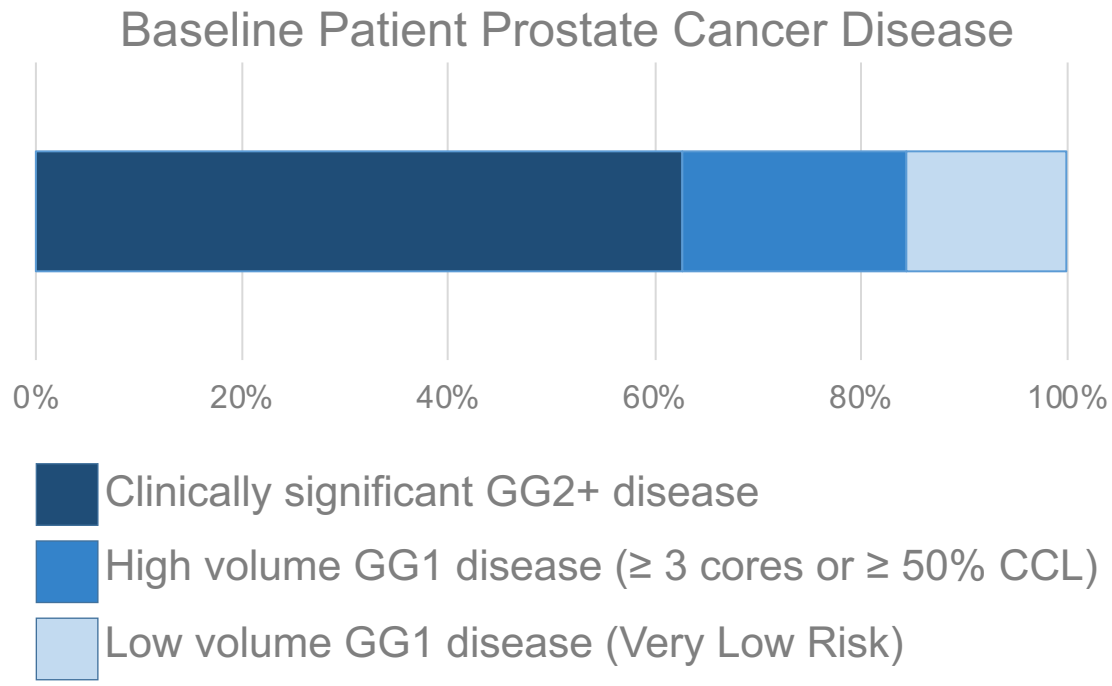
- Treatment intent was whole-gland ablation with sparing of the urethra and urinary sphincter
- Recommended by FDA to determine substantial equivalence with predicate devices and comparison with standard of care

Primary Endpoints (12 months)

- Safety: Frequency and severity of adverse events
- Efficacy: PSA reduction ≥ 75% (in > 50% of patients)

Secondary Endpoints (to 5 years)

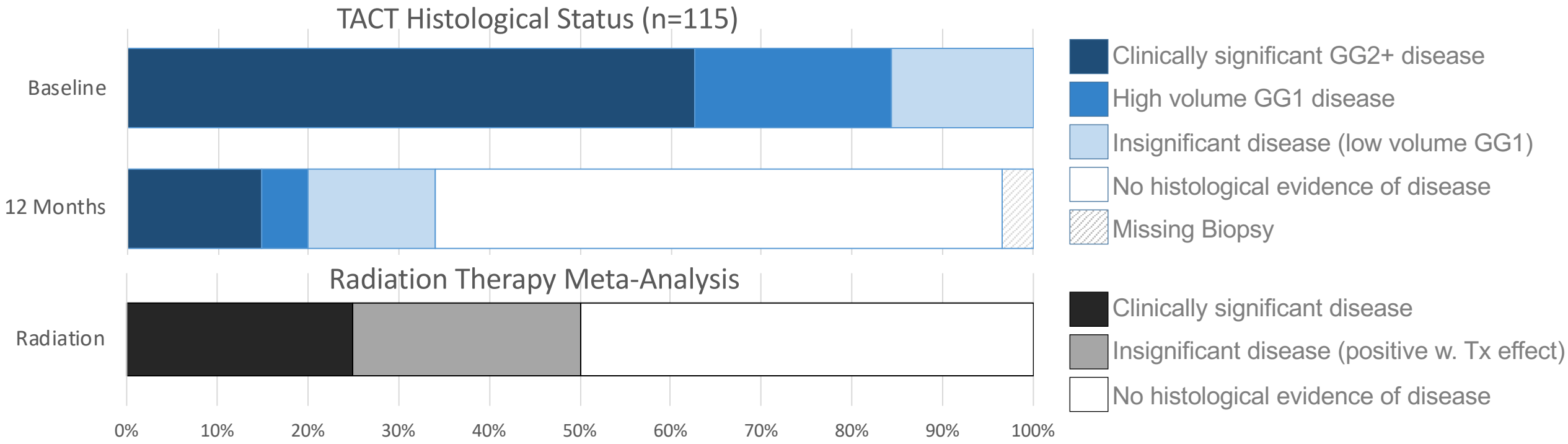
- Prostate volume reduction at 1 year
- Prostate biopsy at 1 year in all patients
- Multi-parametric MRI at 1 year (Central Radiology Lab, Cleveland Clinic)
- Functional Disability: EPIC, IIEF, IPSS



Prostate **Ablation Efficacy** – Histological Response

TACT Biopsy Outcomes (1-year, 10-core TRUS, High Sampling Density 0.4 cc / core)

- Only 4 of 115 follow-up biopsies are missing, all due to patient refusal
- Among men with pre-treatment intermediate-risk GG2 prostate cancer, 54 of 68 (79%) were free of GG2 disease
- Of men with one-year biopsy data, 72 of 111 (65%) had complete histological response and were free of any disease
- 41% (16 of 39) of positive biopsies were clinically insignificant (Very Low Risk)
- Multivariate Analysis: Among men w. pre-Tx GG2 disease and w/o calcifications at screening, **51 of 60 (85%)** were free of GG2 disease



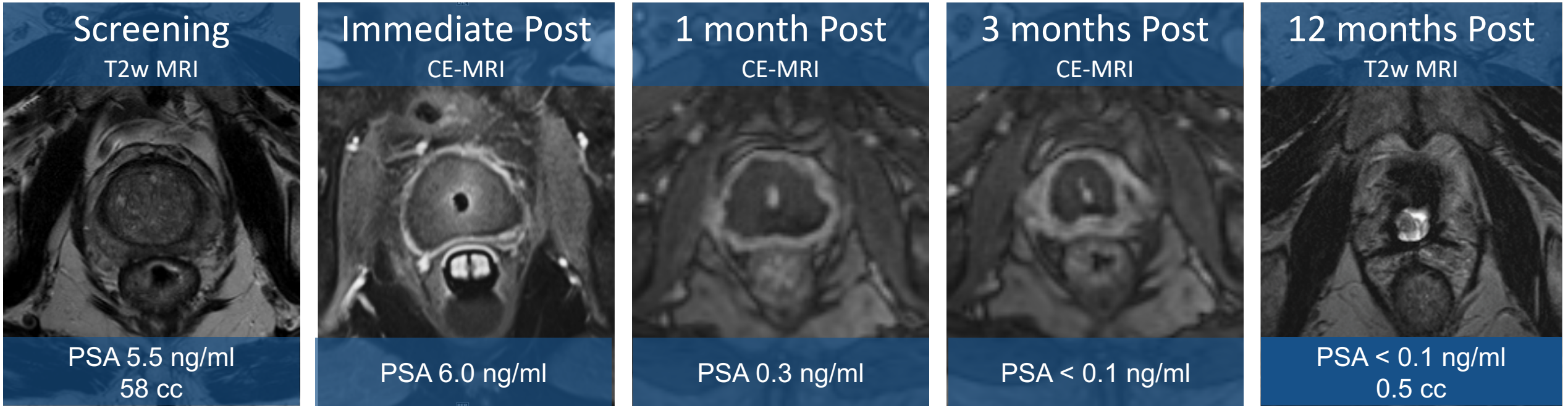
Prostate **Ablation Efficacy** – Volume Reduction on MRI

Prostate Volume significantly reduced demonstrating effective prostate ablation

- Median perfused prostate volume decreased from 41 cc to 4 cc, on MRI at 1 year (interim analysis by local radiologists)
- Prostate volume reduction to be re-assessed by Central Radiology Core Lab, as per TACT protocol
- Prostate ablation confirmed on Contrast Enhanced MRI immediately after TULSA and during follow-up

Follow-up Prostate MRI predicts clinically significant disease on biopsy

- Multivariate Analysis: Absence of PIRADS ≥ 3 lesion at 1-year multi-parametric MRI has **92% Negative Predictive Value** for absence of GG2 disease on 1-year biopsy (interim analysis by local radiologists, to be re-assessed by Central Radiology Core Lab)



Prostate **Ablation Efficacy** – PSA

PSA Primary efficacy endpoint resolutely met

- Primary endpoint of PSA reduction ≥75% was achieved in 110 of 115 (96%)
- Median (IQR) PSA reduction was 95% (91-98%)
- Median PSA nadir was 0.34 (0.12-0.56) ng/ml

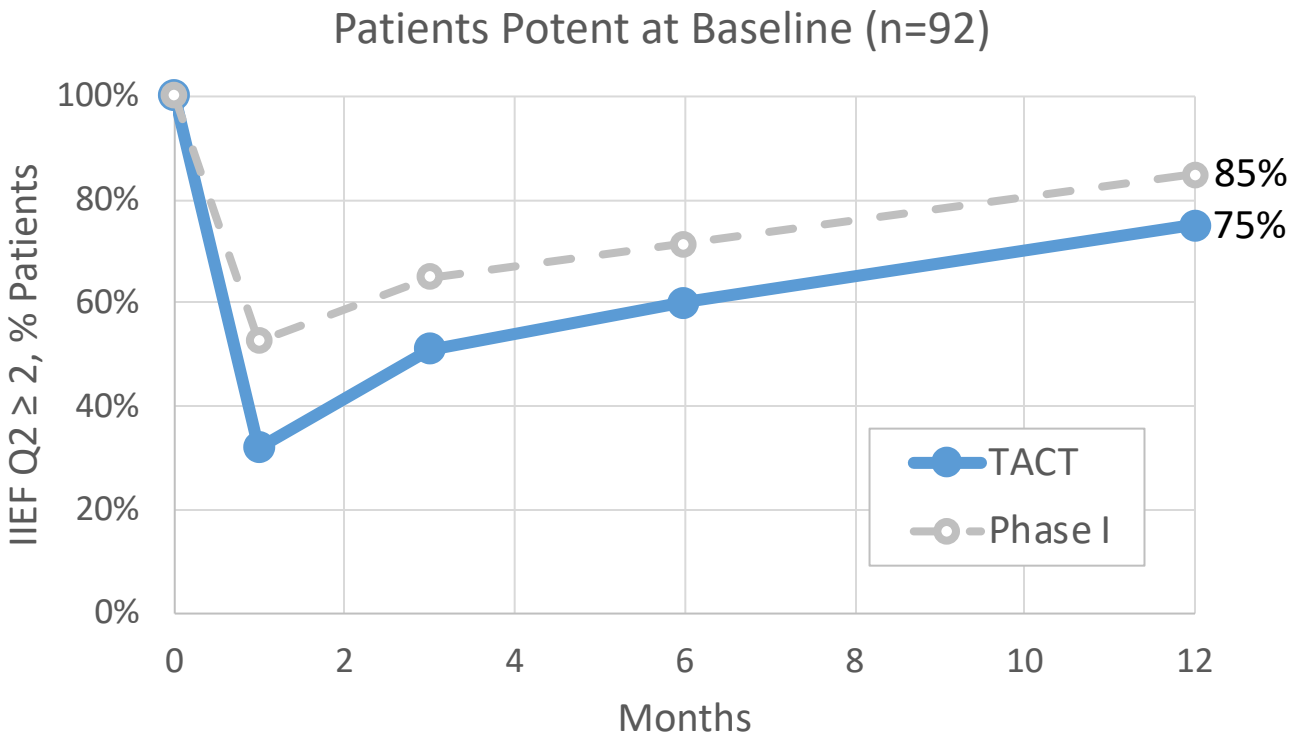
	Pre-Treatment	1 Month	3 Month	6 Month	12 Month	PSA NADIR
N	115	113	115	115	115	115
Median	**6.26**	**0.53**	**0.46**	**0.53**	**0.53**	**0.34**
IQR	4.65 – 7.95	0.30 – 1.19	0.17 – 0.95	0.20 – 1.00	0.28 – 1.25	0.12 – 0.56
Average	**6.72**	**0.90**	**0.77**	**0.77**	**0.93**	**0.51**
T-Test against baseline		<0.001	<0.001	<0.001	<0.001	<0.001

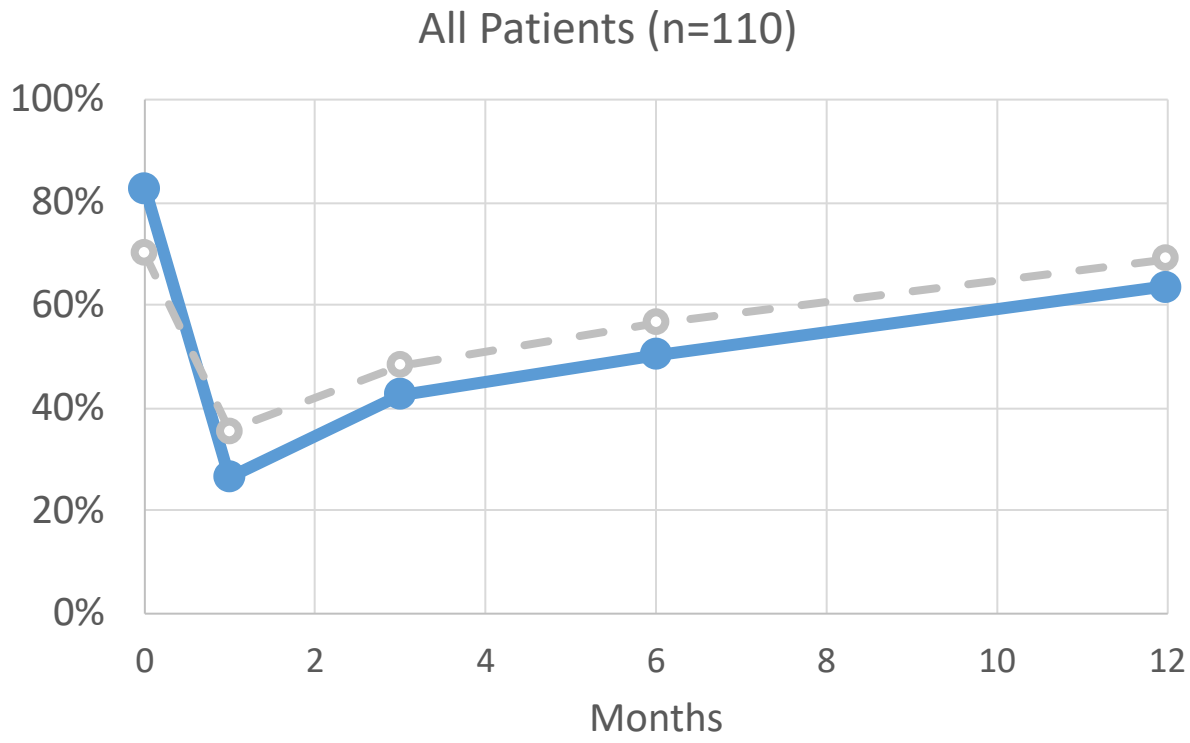
Missing values are interpolated using the LVCF method for the first timepoint after treatment.

TACT **Erectile Function** – Surgeon & Patient Reported

Erectile Function, at one year:

- 23% surgeon-assessed moderate erectile dysfunction (CTCAE Grade 2, intervention such as medication indicated)
- 0% any occurrence of severe erectile dysfunction (CTCAE Grade 3, intervention such as medication not helpful)
- 75% (69/92) of previously potent patients maintained erections sufficient for penetration (Patient reported, IIEF Q2 ≥ 2)
- Trend and recovery similar to Phase I

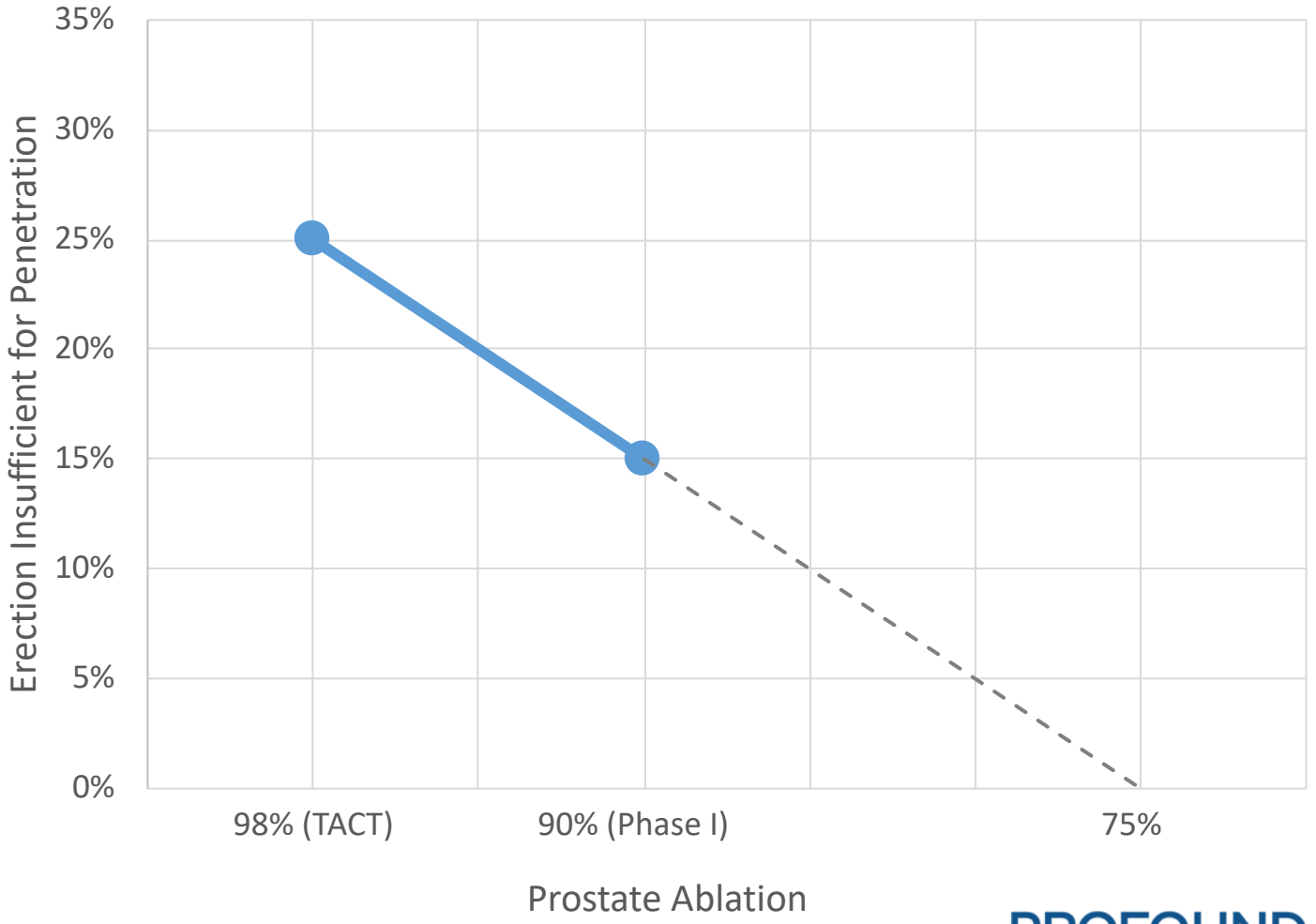




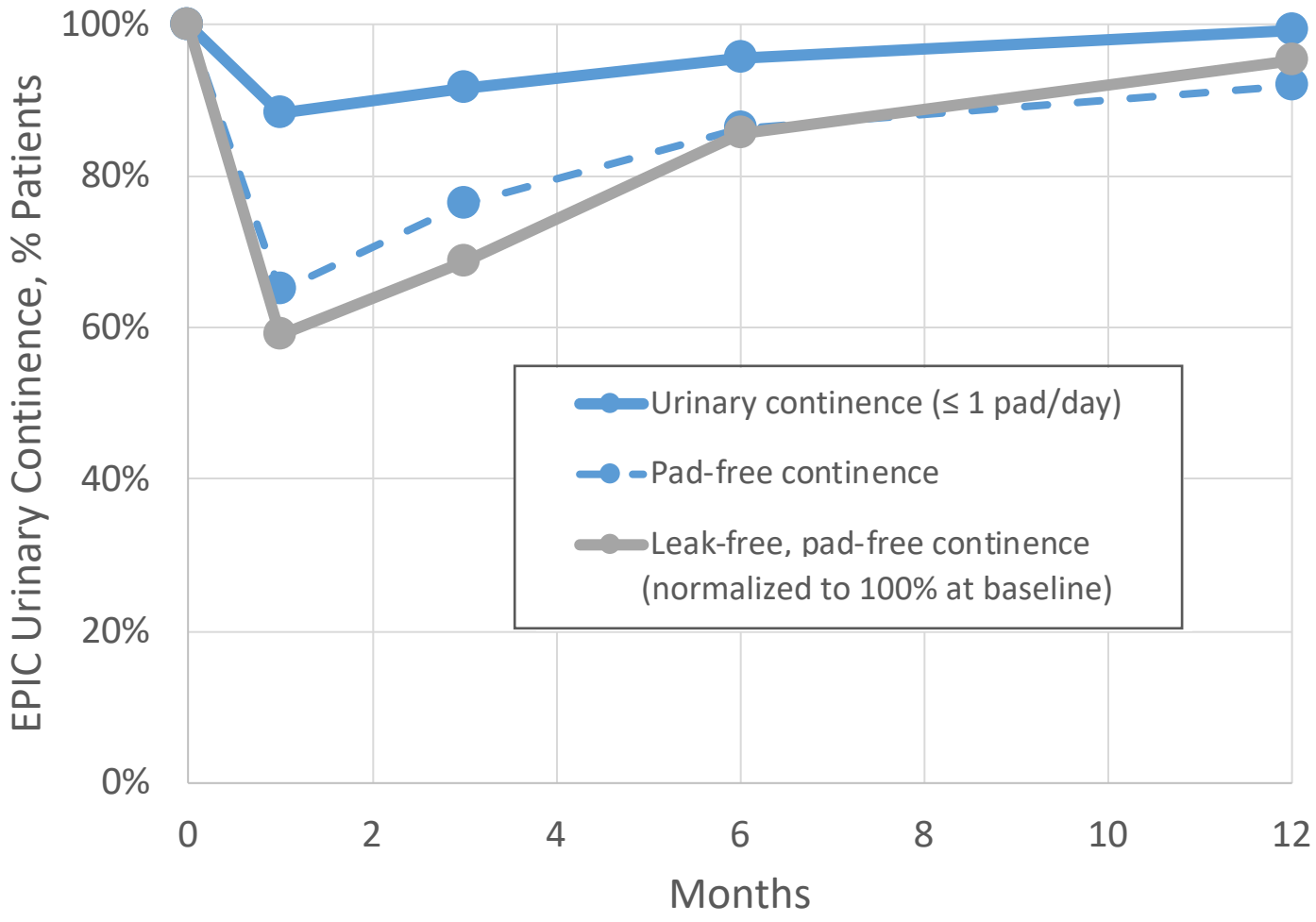
Erectile Function – Control of Treatment Margin

Effect of treatment margin on erectile function

- MRI guided treatment planning and closed-loop temperature control provide customizable prostate ablation
- Phase I and TACT studies show effect of treatment margin on erectile function
- Additional investigation may provide quantitative guidance for control of treatment margin



TACT **Urinary Incontinence** – Surgeon & Patient Reported



Urinary Incontinence, at 1 year (n=112):

- 2.6% surgeon-assessed moderate urinary incontinence (CTCAE Grade 2, pads indicated)

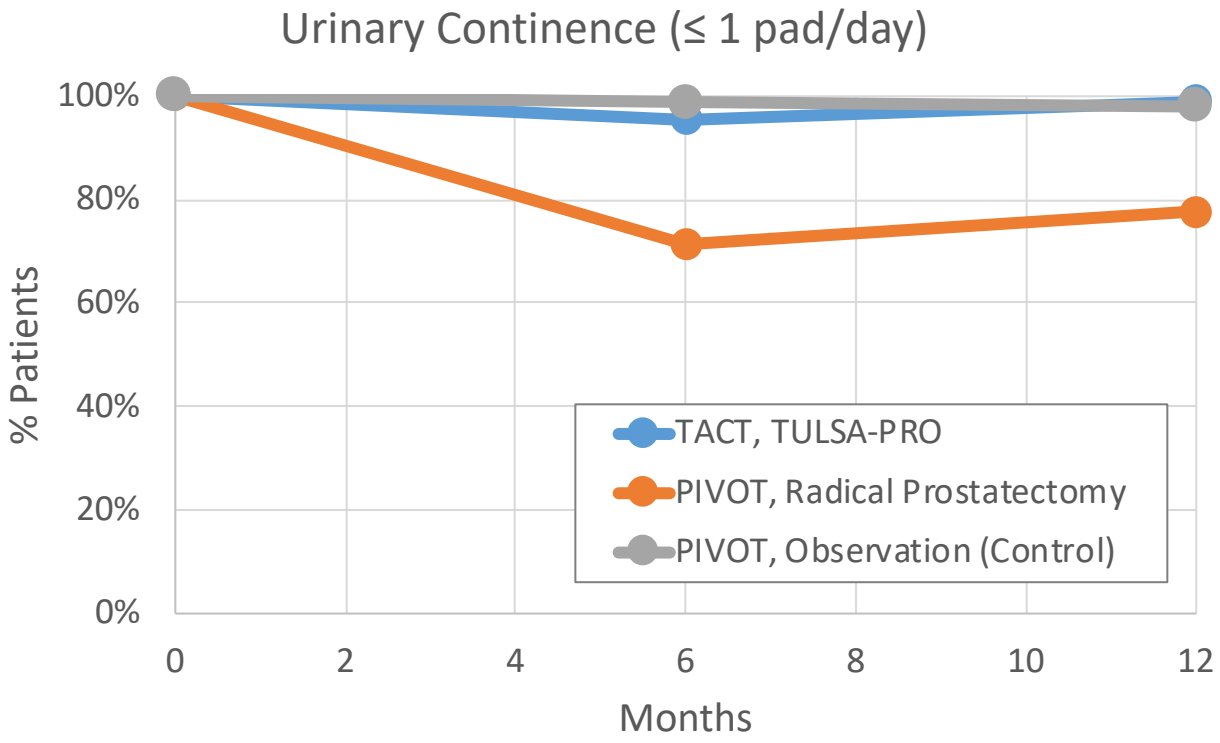
EPIC Patient Reported:

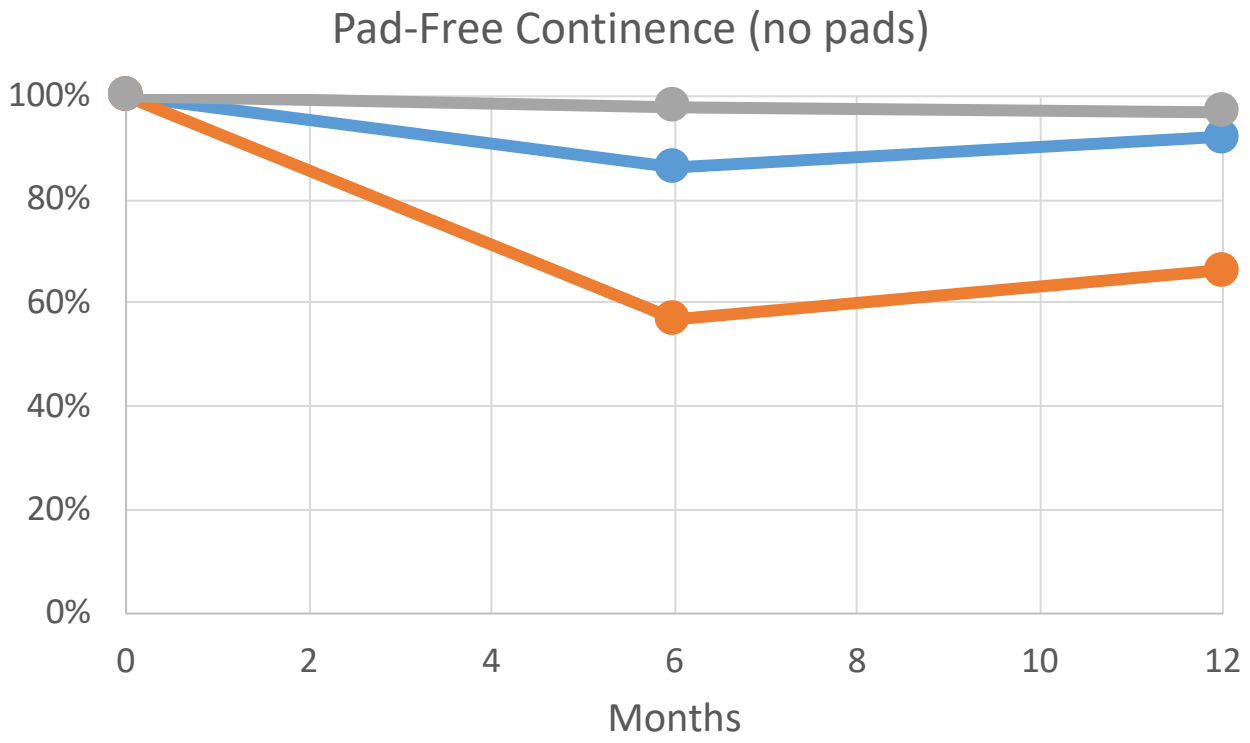
- <1% (1/112) are incontinent (EPIC, > 1 pad / day)
- 3.8% increase in patients with daily leakage (EPIC, leak ≥ 1 time / day)
- 7% (8/112) wear 1 pad / day (preventative)

Urinary Incontinence – Context to PIVOT

Urinary Incontinence (Pad use), at one year:

- TULSA Urinary Continence (≤ 1 pad/day) similar to Observation (control) arm of PIVOT study
- TULSA Pad-Free Continence (no pads) only 5%-points lower than Observation (control) arm of PIVOT study
- TULSA continence outcomes markedly superior to Radical Prostatectomy arm of PIVOT study
- PIVOT: Wilt *et al*, The New England Journal of Medicine, 2017





TACT – *All* Attributable Serious & Severe Adverse Events

- There were no rectal injuries or Grade ≥ 4 events
- All attributable serious and severe adverse events:

Adverse Event (% patients)	Serious Adverse Events (SAE)		Severe (Grade 3) Adverse Events	
	Phase I	TACT	Phase I	TACT
Overall No. Patients	6.6%	7.0%	3.3%	7.8%
GU Infection	3.3%	4.3%	3.3%	3.5%
Urinary Retention	3.3%	0.9%		1.7%
Urinoma		0.9%		0.9%
Ileus (related to SP catheter)		0.9%		
DVT		0.9%		
Urethral Stricture		0.9%		1.7%
Urethral Calculus and Pain				0.9%

(Note that some patients had more than one serious or severe adverse events)

TACT – FDA 510(k) **Regulatory Assessment**

	EDAP Ablatherm 510(k) (K153023)	Profound Medical TACT
Population	135 patients, all low-risk, 64.1 ± 6.7 years	115 patients, low and intermediate risk, 63.9 ± 6.8 years
Prostate Volume Reduction	Average 60% Reduction, from 22.7 cc to 9.0 cc	Average 90% reduction, from 41 cc to 4 cc *(interim analysis)*
PSA Reduction	Average reduction at nadir 88% Average PSA nadir 0.53 ng/ml Average PSA at 12m 0.91 ng/ml	Average reduction at nadir 92% Average PSA nadir 0.51 ng/ml Average PSA at 12m 0.93 ng/ml
Biopsy	Intent to Treat: 80 / 135 = 59% Negative Biopsy Per Protocol: 80 / 118 = 68% Negative Biopsy Missing biopsy: 17 (12.6%)	Intent to Treat: 72/115 = 63% Negative Biopsy Per Protocol: 72/111 = 65% Negative Biopsy Missing biopsy: 4 (3.5%)
Severe (G3) Adverse Events	34% any occurrence	7.8% any occurrence
Erectile Dysfunction	67% any occurrence 52% any occurrence, moderate and severe 44% ongoing at 2 years 38% ongoing at 2 years, moderate and severe	43% any occurrence 29% any occurrence, moderate (no severe) 36% ongoing at 12 months 23% ongoing at 12 months, moderate (no severe)
Urinary Incontinence	36% any occurrence 14% any occurrence, moderate and severe 11% ongoing at 2 years 3.0% ongoing at 2 years, moderate and severe	23% any occurrence 6.1% any occurrence, moderate (no severe) 10% ongoing at 12 months 2.6% ongoing at 12 months, moderate (no severe)
Urethral Stricture	35% moderate and severe (urethral stricture and bladder outlet contracture)	2.6% moderate and severe (urethral stricture and bladder neck obstruction)
Urinary Retention	27% any occurrence, moderate and severe	8.7% any occurrence, moderate and severe

Standard of Care Context – **Failures & Retreatment**

"For every 100 patients on whom I perform a prostatectomy: 20 will recur anyway, 60 didn't need it, and 20 will benefit" – *Prominent Chief of Urology*

In properly selected patient groups:

- **Active surveillance** accepts 20% progression to radical therapy at 2 years, and 50% progression to radical therapy within 10 years (ProtecT, Hamdy *et al*, NEJM 2016)
- **Radiation therapy** accepts 30 – 40% recurrence rate requiring additional therapy
- **Prostatectomy** accepts 20% rate of further treatment due to rising or persistent PSA (intermediate-risk, PIVOT, Wilt *et al*, NEJM 2017)

Ablative therapy consensus:

- **20% retreatment rate** of clinically significant disease is acceptable (Donaldson *et al,* Eur Urol 2014)

TULSA-PRO **Addressing Unmet Need**

TULSA provides patients

- Favorable safety profile with low impact on men's natural functional abilities
- Significant PSA reduction with low rates of residual clinically significant GG2 disease
- Ideal first-line therapy for intermediate-risk and selected high-volume low-risk patients

TACT demonstrated local disease control

- Treatment day: Ablation visualized on MRI thermometry and CE-MRI
- First year: PSA, MRI and Biopsy
- Beyond: Monitor patient with PSA and MRI

Long-term outcomes

- TACT study protocol continues to monitor patients to 5 years
- TULSA does not preclude additional intervention with any modality, if needed in the future

TULSA-PRO Inside-Out Prostate Ablation

Customizable
Leading to flexibility to treat various prostate conditions to meet each patient's exact need

Predictable
Leading to confidence and high throughput

Incision-free
Leading to fast patient recovery

	Prostatectomy	Radiation	TULSA
Treatment type	Whole gland	Typically whole gland, limited customization possible	Customized to exact need of the patient
Outcome	Predictable	Not known for up to 2 years	Immediately confirmed and predictable even for partial gland therapy
Procedures/day	2 typically, 3 if longer day	Multiple sessions - 20 to 40 over 4 - 8 weeks	Consistently 4 in a routine day. Higher possible
Patient recovery	Weeks	Deterioration over time	2 days

TULSA-PRO Value Proposition – Customizable

Treat different types of prostate diseases – Single device multiple uses

- Whole gland, Partial gland - focal or disease targeted, RT-salvage, Palliative, BPH (Clinical trials ongoing NCT03350529, NCT03814252)

Treat each patient uniquely – 'My life should not have to change'

- Patients and Physicians can discuss customized approach to accommodate patient priorities and disease treatment necessities
- Physician has the control to manage possible side effects
- TULSA procedure can be repeated if desirable

Treat various shapes and sizes of prostate

- TULSA-PRO has been used to treat prostates up to 250cc
- Real-time MRI and closed-loop control manages variability in prostate shape and tissue properties

TULSA-PRO Value Proposition – Predictable

Actively protect urethra and rectum during treatment to preserve natural functions

- Side effect profile – *superior to other treatments – Phase I and TACT data*

Physician defines the treatment plan, the robot follows the instructions

- The physician in charge - defines the region and volume to be treated, predictably avoids treating healthy tissue. Ablation process is automated and precise
- Following treatment, TULSA and MRI provide negative predictive value
- Predictable prostate volume reduction by 90%
- If necessary, preserves follow up treatment options with TULSA, radiation or surgery

TULSA-PRO Value Proposition – Incision-Free

Real-time MRI Guidance and closed loop temperature control

- Treat 4 patients in a routine day consistently
- Patient tolerability – minimal pain, fast recovery, no post treatment scars or marks
- MR Suite significantly less expensive to operate than an operating room
- Reduced post operative complication costs

Transurethral Ultrasound Ablation

- No concern about long term effects as compared to ionizing radiation treatment
- No hot or cold spot inside the patient. No charring, no boiling of tissue that could cause longer term negative response. No skipped lesions