Supplemental Data

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Data sets

The Full Analysis Set included all randomized patients. The [^{18}F]CTT1057 Safety Set included all patients who received [^{18}F]CTT1057. The [^{68}Ga]Ga-prostate-specific membrane antigen (PSMA)-11 Safety Set included all patients who received [^{68}Ga]Ga-PSMA-11. The Efficacy Analysis Set included all randomized patients who received [^{18}F]CTT1057, had both an evaluable [^{18}F]CTT1057 positron emission tomography/computed tomography (PET/CT) scan and at least one evaluable composite truth standard (CTS) assessment, and did not receive any prohibited systemic antineoplastic therapy before the completion of PET/CT scans and CTS procedures. Prohibited systemic antineoplastic therapy was any androgen deprivation therapy (ADT) (including luteinizing hormone-releasing hormone agonists or antagonists) as well as anti-androgens (both first- and second-generation compounds) and 5-alpha reductase inhibitors.

Hierarchical Composite Truth Standard

[^{18}F]CTT1057 PET/CT efficacy assessments were compared with a hierarchical CTS with levels 1, 2 and 3 of standard of truth (SoT) procedures, in descending order of priority. CTS level 1 was based on histopathology, if available, of prospective biopsy or salvage surgery performed within 8 weeks after the [^{18}F]CTT1057 PET/CT scan, with tissue samples assessed by local pathologists blinded to any PSMA-PET data. CTS level 2 imaging included at least a high-resolution CT scan with contrast (performed ± 8 weeks from the [^{18}F]CTT1057 PET/CT scan) and a [^{68}Ga]Ga-PSMA-11 PET/CT scan (and any other standard of care imaging diagnostic procedure, as clinically indicated for each patient which must be acquired ± 8 weeks following the [^{18}F]CTT1057 PET/CT scan), if histopathology was inconclusive, not available or negative (biopsy only) for a lesion. Three-month follow-up imaging (from baseline) was also allowed per

protocol, if clinically required for the diagnosis of particular lesions. Three central independent readers, blinded to the [^{18}F]CTT1057 PET/CT result but not to other patient data, read by consensus the CTS level 2 images. CTS level 3 was based on a 50% or greater decline in PSA 3 months after radiation therapy (RT; as long as no concomitant ADT was given) as per Prostate Cancer Working Group 3 criteria (*1*).

Imaging with [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11

Following administration of approximately 370 MBq (range: 266–407 MBq) [^{18}F]CTT1057, PET/CT was planned to be performed 90 minutes (±30 minutes) later. A CT scan was obtained from vertex to midthighs for anatomical reference and attenuation correct purposes; this was followed by a static PET emission scan over the same area, starting from midthigh.

Following administration of approximately 150 MBq (range: 111–185 MBq) of [^{68}Ga]Ga-PSMA-11, a CT was obtained from vertex to midthighs for anatomical reference and attenuation correction purposes approximately 50–100 minutes post-injection. A static PET emission scan over the same area followed this scan, starting from midthighs.

If clinically indicated, diuretic use was allowed before PET/CT image acquisition. Where appropriate (e.g. intense activity in the urinary bladder precluded appropriate assessment of the initial PET image), one delayed pelvic PET image (one bed position) was allowed 120–180 minutes post-injection.

Regions in GuidePath are defined as the prostate (comprising prostate bed/prostate gland and any local invasion of the seminal vesicles, urinary bladder, or rectum), pelvic lymph nodes (PLN), extra-PLN, skeletal, and visceral. The PLN region included perirectal, obturator, internal iliac, external iliac, and presacral lymph nodes. Common iliac lymph nodes were considered part of

the extra-PLN region.

Positive bone lesions and lymph nodes were those with PSMA uptake visually greater than physiologic bone marrow or blood pool, respectively. Positive prostate, prostate bed, and visceral lesions were those with PSMA uptake visually greater than physiologic background activity of the involved organ or anatomic site. The same rules for PSMA positivity were used for both PET scans.

PSMA true-positive patients (regions) were those who had at least one true-positive lesion, with anatomically localized correspondence between [^{18}F]CTT1057 PET imaging and the CTS. PSMA true-negative patients (regions) were those who did not show any pathological [^{18}F]CTT1057 uptake and were confirmed as not having any lesions with the CTS. PSMA false-positive patients (regions) were those who showed at least one pathological [^{18}F]CTT1057 uptake but were verified as not having any lesions with the CTS or no lesions were correctly localized in anatomical location by the CTS. PSMA false-negative patients (regions) were those who do not show any pathological [^{18}F]CTT1057 uptake but were confirmed as having at least one lesion with the CTS. Positive lesions on [^{18}F]CTT1057 PET/CT with anatomically localized correspondence with the applicable SoT from the hierarchical CTS were considered true positive for the efficacy co-primary endpoints. A region/patient was considered true positive if there was at least one true-positive lesion. The next lower level of CTS was used to verify positivity or negativity for the sensitivity analysis of the co-primary endpoints (i.e. if CTS level 1 was used as SoT for the primary estimand, CTS level 2 was used as SoT for the sensitivity analysis).

Secondary Endpoints

Secondary endpoints included patient-level and region-level sensitivity, specificity, accuracy, negative predictive value, patient-level correct detection rate and detection rate, inter-reader variability and intra-reader reproducibility, and the change in intended patient management plans attributed to [^{18}F]CTT1057 PET/CT (based on local review), as well as safety and tolerability assessments.

Inter-reader Variability and Intra-reader Reproducibility

Inter-reader variability was defined as agreement among three readers determinations and was assessed by Fleiss' Kappa statistic for all patients who received [^{18}F]CTT1057 ([^{18}F]CTT1057 Safety Set) (*2*). Intra-reader reproducibility was defined as within-reader agreement of reads at two different time points and was assessed by Cohen's Kappa statistic for the [^{18}F]CTT1057 Safety Set (*3*). Intra-reader reproducibility was calculated from 19 randomly selected [^{18}F]CTT1057 PET/CT scans which were read a second time by each of the three independent readers.

Assessment of Patient Management Questionnaires

A patient management questionnaire was completed by the treating physician or clinical study investigator before (questionnaire 1) and within 14 days after (questionnaire 2) receiving the results of the [^{18}F]CTT1057 PET/CT imaging assessment by an independent local nuclear medicine physician or radiologist with expertise in reading oncology PET/CT scans (who was blinded to [^{68}Ga]Ga-PSMA-11 PET/CT data but to no other patient data). For patients assigned

to Sequence 1 ([^{18}F]CTT1057 PET imaging followed by [^{68}Ga]Ga-PSMA-11), questionnaire 2 was completed before the [^{68}Ga]Ga-PSMA-11 PET/CT was performed. The number and percentage of patients from the [^{18}F]CTT1057 Safety Set for each of the following categories of treatment plan in each of the two questionnaires were calculated: surgery, radiation alone, radiation alone with change in radiation treatment plan (only applicable for questionnaire 2), radiation plus ADT, ADT alone, observation/surveillance, and other (free text box). Treatment plan change was defined as a change in the reporting for any category between the two questionnaires. The number and percentage of patients from the [^{18}F]CTT1057 Safety Set with treatment plan change as defined above was calculated. Treatment plan changes between questionnaire 1 and 2 are displayed in shift tables. The number (%) of patients with and without a change in treatment plans by [^{18}F]CTT1057 PET/CT local read results (i.e. positive, negative, and inconclusive) are tabulated.

Safety Outcomes and Follow-up

Safety assessments included monitoring the incidence of adverse events, graded according to the Common Toxicity Criteria for Adverse Event version 5.0, from informed consent up to 14 days after the administration of each PET radiotracer.

Data Analysis

Region-level correct localization rate (CLR) is defined as the proportion of regions containing at least one true-positive lesion out of all regions containing at least one PET-positive finding by central assessments. Patient-level correct detection rate is defined as the proportion of true-

positive patients among all scanned patients; patient-level detection rate is defined as the proportion of true-positive and false-positive patients among all scanned patients.

Accuracy = (true positive + true negative) / (true positive + true negative + false positive + false negative. CLR = true positive / (true positive + false positive). NPV = true negative / (true negative + false negative). Positive predictive value (PPV) = true positive / (true positive + false positive). Sensitivity = true positive / (true positive + false negative). Specificity = true negative / (true negative + false positive).

The sample size calculation was based on the co-primary endpoints, region-level CLR, and patient-level PPV. For region-level CLR (with a null hypothesis of H0: region-level CLR $p0$ = 0.50 and an alternative hypothesis of H1: $p1 > 0.50$), assuming a CLR of 58% for $p1$, a sample size of 172 enrolled patients would achieve 90% power to detect a change in region-level CLR of 8% using a one-sided test at significance level of 2.5%. For patient-level PPV (with a null hypothesis of H0: patient-level PPV $p0 = 0.20$ and an alternative hypothesis of H1: $p1 > 0.20$), assuming a PPV of 33% for $p1$, a sample size of 190 enrolled patients (including the 152 [^{18}F]CTT1057 scanned patients based on 80% [^{18}F]CTT1057 positive patient rate) would achieve 90% power to detect a change in patient-level PPV of 13% using a one-sided binomial test at a targeted one-sided significance level of 2.5%. A sample size of 190 patients can ensure 92.7% statistical power for region-level CLR and 90% statistical power for patient-level PPV resulting in an overall study statistical power of at least 83.4%.

The number of true-positive and false-positive regions overall (i.e. across all five regions) and by region across all patients in the efficacy analysis set were presented, along with region-level CLR and two-sided 95% CIs estimated using the logistic regression model with random effects. The 95% CI for region-level endpoints for each region was obtained using an exact binomial

method. For patient-level PPV, the number of true-positive and false-positive patients, as well as number of positive and negative [^{18}F]CTT1057 scans were presented, along with patient-level PPV with two-sided exact binomial 95% confidence intervals (CI).

As a sensitivity analysis of the co-primary endpoints, the next lower level of CTS was used to verify positivity and negativity. For instance, if pathology (CTS level 1) was used for a lesion as the SoT for the primary estimand, the imaging component of CTS (level 2) was used as true standard for the primary estimand. Similarly, if CTS level 2 (imaging component) was used for a lesion as the true standard for the primary estimand, the changes in PSA level component of CTS (level 3) was used as true standard for the sensitivity analysis. However, for cases where changes in PSA level (CTS level 3) were used as the true standard for the primary estimand, positivity status could not be replaced by another component of CTS for sensitivity analysis; in this case the CTS level 3 value was used.

SAS version 9.4 or later was used to perform all data analyses and to generate tables, figures, and listings.

References

1. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the prostate cancer clinical trials working group 3. *J Clin Oncol.* 2016;34:1402–1418.

2. Fleiss JL. Measuring nominal scale agreement among many raters. *Psychol Bull.* 1971;76:378–382.

3. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas.* 1960;20:37–46.

SUPPLEMENTAL TABLE 1. Inclusion and Exclusion Criteria for the GuidePath Study

Inclusion criteria

• Signed informed consent was obtained prior to participation in the study.
• Biopsy-proven prostate adenocarcinoma.
• BCR following initial definitive therapy (with either RP or curative-intent RT) as defined by*
  o American Urology Association criteria for patients who underwent RP: initial serum PSA of ≥0.2 ng/mL measured at least 6 weeks after RP with a second confirmatory persistent PSA level of >0.2 ng/mL, or
  o American Society for Radiation Oncology-Phoenix criteria for patients who underwent curative-intent RT: rise of serum PSA measurement of 2 or more ng/mL above the nadir PSA observed post RT.
• Eastern Cooperative Oncology Group performance status 0–2.
• Patients must be adults ≥18 years of age.

Exclusion criteria
• Inability to complete the needed investigational and standard-of-care imaging examinations owing to any reasons (e.g. severe claustrophobia, inability to lie still for the entire imaging time). • Any additional medical condition, serious intercurrent illness, concomitant cancer, or other extenuating circumstance that, in the opinion of the Investigator, would indicate a significant risk to safety or impair study participation, including, but not limited to, current severe urinary incontinence, hydronephrosis, severe voiding dysfunction, need of indwelling/condom catheters, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, active hepatitis B or C, and coronavirus disease 2019 (COVID-19). • Prior major surgery undergone less than 12 weeks prior to screening (with the exception of any surgery related to prostatic cancer). • Known allergy, hypersensitivity, or intolerance to [^{18}F]CTT1057, [^{68}Ga]Ga-PSMA-11, or CT contrast. • Prior and current use of PSMA-targeted therapies. • Prior ADT (first or second generation), including luteinizing hormone-releasing hormone analogues (agonists or antagonists) within 9 months before screening.† • Any 5-alpha reductase inhibitors within 30 days before screening. • Use of other investigational drugs within 30 days before screening. • Castration-resistant patients. • Patients with small cell or neuroendocrine prostate cancer in more than 50% of biopsy tissue. • Prior salvage surgery or salvage radiation therapy.‡

*Inclusion criterion was updated following a protocol amendment to ensure requirements for BCR after RP or curative-intent RT were fully aligned with the definitions of BCR from the publications referred to for the American Urology Association and American Society for Radiation Oncology-Pheonix criteria and the targeted population.

†Exclusion criteria were updated following a protocol amendment to exclude patients with any prior ADT including luteinizing hormone-releasing hormone analogues (agonists or antagonists) within 9 months before screening, instead of excluding patients who had received any prior treatment with luteinizing hormone-releasing hormone analogues (agonists or antagonists).

‡Exclusion criterion was added following a protocol amendment.

ADT = androgen deprivation therapy; BCR = biochemical recurrence; CT = computed tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RP = radical prostatectomy; RT = radiation therapy.

SUPPLEMENTAL TABLE 2. Full Baseline Clinical Characteristics, [^{18}F]CTT1057 Dosing and PET Acquisition Times

Characteristic	Full Analysis Set (*N* = 190)	Efficacy Analysis Set (*N* = 161)
Age, years, median (IQR)	68.0 (63.0–73.0)	68.0 (63.0–73.0)
Race, *n* (%)*		
White	180 (94.7)	152 (94.4)
Black or African American	4 (2.1)	4 (2.5)
Asian	2 (1.1)	2 (1.2)
Unknown	4 (2.1)	3 (1.9)
Body mass index, kg/m^2, median (IQR)	27.5 (25.0–29.7)	27.4 (25.0–29.6)
Eastern Cooperative Oncology Group performance status, *n* (%)		
0	179 (94.2)	154 (95.7)
1	10 (5.3)	7 (4.3)
2	1 (0.5)	0 (0.0)
PSA level at initial diagnosis, ng/mL, median (IQR)	8.0 (5.7–12.6)	7.9 (5.7–12.3)
Primary tumor clinical stage, *n* (%)		
T2c or less	122 (64.2)	105 (65.2)
T3	7 (3.7)	4 (2.5)
T3a	32 (16.8)	28 (17.4)
T3b	9 (4.7)	7 (4.3)
T4	2 (1.1)	1 (0.6)
Tx or missing	18 (9.5)	16 (9.9)
Regional lymph node clinical stage, *n* (%)		
Nx	47 (24.7)	43 (26.7)
N0	121 (63.7)	99 (61.5)
N1	13 (6.8)	11 (6.8)
Missing	9 (4.7)	8 (5.0)
Biopsy predominant histology/cytology, *n* (%)		
Acinar adenocarcinoma	185 (97.4)	156 (96.9)
Adenocarcinoma, unspecified	2 (1.1)	2 (1.2)
Ductal adenocarcinoma	3 (1.6)	3 (1.9)
Biopsy Gleason Score, *n* (%)		
≤6	27 (14.2)	23 (14.3)
7 (3 + 4)	64 (33.7)	59 (36.6)
7 (4 + 3)	48 (25.3)	39 (24.2)
8	30 (15.8)	25 (15.5)
9 or 10	20 (10.5)	14 (8.7)
Missing	1 (0.5)	1 (0.6)

Characteristic	Full Analysis Set (*N* = 190)	Efficacy Analysis Set (*N* = 161)
Initial definitive therapy received, *n* (%)		
RP	180 (94.7)	155 (96.3)
Curative-intent RT	10 (5.3)	6 (3.7)
PSA level at screening, ng/mL†		
Overall, *n*	185	157
Median (IQR)	0.4 (0.3–0.9)	0.4 (0.3–0.8)
In patients who had prior RP, *n*	176	151
Median (IQR)	0.4 (0.3–0.8)	0.4 (0.3–0.7)
In patients who had prior curative-intent RT, *n*	9	6
Median (IQR)	3.4 (3.2–4.2)	3.3 (2.9–4.2)
PSA level at BCR diagnosis, ng/mL, median (IQR)	0.3 (0.2–0.7)	0.3 (0.2–0.6)
Nadir PSA in patients who received RT as initial definitive therapy, ng/mL		
n	10	6
Median (IQR)	0.3 (0.04 – 0.9)	0.3 (0.04–0.9)
Patients who received at least one prior antineoplastic medication, *n* (%)	10 (5.3)	7 (4.3)
Anti-androgens (bicalutamide)	2 (1.1)	2 (1.2)
Gonadotropin hormone-releasing hormone analogues (triptorelin, leuprorelin)	7 (3.7)	4 (2.5)
Hormones	1 (0.5)	1 (0.6)
Other hormone antagonists (degarelix)	3 (1.6)	2 (1.2)
Prior prostate cancer therapies, *n* (%)		
RP only	162 (85.3)	144 (89.4)
RT only	10 (5.3)	6 (3.7)
RP and RT	18 (9.5)	11 (6.8)
Margin status after RP, *n* (%)	180 (94.7)	155 (96.3)
R0	69 (36.3)	59 (36.6)
R1	86 (45.3)	73 (45.3)
Rx	25 (13.2)	23 (14.3)
Patients who received at least one prior antineoplastic RT, *n* (%)	28 (14.7)	17 (10.6)
Primary tumor pathological stage, *n* (%)		
T2c or less	73 (38.4)	64 (39.8)
T3	7 (3.7)	5 (3.1)
T3a	61 (32.1)	54 (33.5)
T3b	38 (20.0)	32 (19.9)
T4	1 (0.5)	0
NA	10 (5.3)	6 (3.7)
RP Gleason score, *n* (%)		
≤6	4 (2.1)	3 (1.9)

Characteristic	Full Analysis Set (*N* = 190)	Efficacy Analysis Set (*N* = 161)
7 (3 + 4)	62 (32.6)	60 (37.3)
7 (4 + 3)	62 (32.6)	53 (32.9)
8	29 (15.3)	22 (13.7)
9 or 10	23 (12.1)	17 (10.6)
NA‡	10 (5.3)	6 (3.7)
Time from initial diagnosis to BCR diagnosis, months, median (IQR)	33.3 (11.2–60.7)	33.3 (11.8–58.6)
Time from primary definitive therapy to BCR diagnosis, months, median (IQR)	28.0 (7.4–54.4)	26.6 (7.5–53.2)
Time from initial diagnosis to first injection, months, *n*	179	161
Median (IQR)	33.1 (11.8–57.9)	34.1 (12.7–59.1)
Time from BCR diagnosis to first injection, days, *n*	179	161
Median (IQR)	21.0 (15.0–26.0)	20.0 (15.0–26.0)
Time from injection to whole-body [^{18}F]CTT1057 PET acquisition, minutes, *n*	171	161
Median (IQR)	90.0 (84.0–91.0)	90.0 (84.0–91.0)
Time from injection to delayed pelvic [^{18}F]CTT1057 PET, minutes, *n*	24	20
Median (IQR)	143.5 (121.0-154.0)	146.0 (119.5–154.0)
Administered radioactivity, MBq, *n*	171	161
Median (IQR)	358.2 (328.2-369.4)	358.7 (333.0–369.9)

*Percentages for race categories can add up to more than 100% as patients can have multiple entries of race if applicable.

†Five patients in the Full Analysis Set and four patients in the Efficacy Analysis Set did not have evaluable PSA levels at baseline.

‡Patients who had RT as initial therapy.

BCR = biochemical recurrence; IQR = interquartile range; MBq = megabecquerel; PET = positron emission tomography; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.

SUPPLEMENTAL TABLE 3. Sensitivity Analysis of Region-level CLR of [^{18}F]CTT1057 PET/CT Using Next Lower Level of CTS (Efficacy Analysis Set)

	Central Reader 1 (*N* = 161) *n*	Central Reader 2 (*N* = 161) *n*	Central Reader 3 (*N* = 161) *n*
Overall			
True positive	42	45	47
False positive	14	22	25
Region-level CLR (95% CI)	75.0 (62.1, 84.6)	67.3 (54.2, 78.2)	65.2 (53.4, 75.4)
Prostate region			
True positive	16	14	17
False positive	7	13	14
PLN region			
True positive	18	20	19
False positive	5	5	7
Extra-PLN region			
True positive	5	5	5
False positive	0	1	1
Skeletal region			
True positive	2	4	4
False positive	1	1	3
Visceral region			
True positive	1	2	2
False positive	1	2	0

Overall = across all regions (prostate, PLN, extra-PLN, visceral, and skeletal regions). For the majority of patients who had CTS level 2 as SoT, CTS level 2 results were retained in the sensitivity analysis because no patients had CTS level 3 results available.

CLR = correct localization rate; CI = confidence interval; CTS = composite truth standard; PET/CT = positron emission tomography/computed tomography; PLN = pelvic lymph nodes; SoT = standard of truth.

SUPPLEMENTAL TABLE 4. Sensitivity Analysis of Patient-level PPV of [^{18}F]CTT1057 PET/CT Using Next Lower Level of CTS (Efficacy Analysis Set)

	Central Reader 1 (*N* = 161)	Central Reader 2 (*N* = 161)	Central Reader 3 (*N* = 161)
	n	*n*	*n*
True positive	39	40	42
False positive	12	18	23
Patient-level PPV, % (95% CI)	76.5 (62.5, 87.2)	69.0 (55.5, 80.5)	64.6 (51.8, 76.1)

For the majority of patients who had CTS Level 2 as SoT, CTS Level 2 results were retained in the sensitivity analysis because no patients had CTS Level 3 results available.

CI = confidence interval; CTS = composite truth standard; PET/CT = positron emission tomography/computed tomography; PPV = positive predictive value; SoT = standard of truth.

SUPPLEMENTAL TABLE 5. Patient-level Correct Detection Rate and Detection Rate of [^{18}F]CTT1057 PET/CT (Efficacy Analysis Set)

	Central Reader 1 (*N* = 161)	Central Reader 2 (*N* = 161)	Central Reader 3 (*N* = 161)
	n	*n*	*n*
True positive	39	40	42
False positive	12	18	23
True negative	88	83	79
False negative	22	20	17
Patient-level correct detection rate, % (95% CI)	24.2 (17.8, 31.6)	24.8 (18.4, 32.3)	26.1 (19.5, 33.6)
Patient-level detection rate, % (95% CI)	31.7 (24.6, 39.5)	36.0 (28.6, 44.0)	40.4 (32.7, 48.4)

CI = confidence interval; PET/CT = positron emission tomography/computed tomography.

SUPPLEMENTAL TABLE 6. Region-level CLR, Sensitivity, Specificity, Negative Predictive Value, and Accuracy of [^{18}F]CTT1057 PET/CT for the Detection of PSMA-positive Lesions for Each Individual Region (Efficacy Analysis Set)

	Central Reader 1	Central Reader 2	Central Reader 3
All regions, *n*	805	805	805
True positive	42	46	47
False positive	14	21	25
True negative	712	705	699
False negative	37	33	34
Prostate region, *n*	161	161	161
True positive	16	14	17
False positive	7	13	14
True negative	129	124	122
False negative	9	10	8
Region-level CLR, % (95% CI)	69.6 (47.1, 86.8)	51.9 (32.0, 71.3)	54.8 (36.0, 72.7)
Region-level sensitivity, % (95% CI)	64.0 (42.5, 82.0)	58.3 (36.6, 77.9)	68.0 (46.5, 85.1)
Region-level specificity, % (95% CI)	94.9 (89.7, 97.9)	90.5 (84.3, 94.9)	89.7 (83.3, 94.3)
Region-level negative predictive value, % (95% CI)	93.5 (88.0, 97.0)	92.5 (86.7, 96.4)	93.8 (88.2, 97.3)
Region-level accuracy, % (95% CI)	90.1 (84.4, 94.2)	85.7 (79.3, 90.7)	86.3 (80.1, 91.2)
PLN region, *n*	161	161	161
True positive	18	20	19
False positive	5	5	7
True negative	130	129	126
False negative	8	7	9
Region-level CLR, % (95% CI)	78.3 (56.3, 92.5)	80.0 (59.3, 93.2)	73.1 (52.2, 88.4)
Region-level sensitivity, % (95% CI)	69.2 (48.2, 85.7)	74.1 (53.7, 88.9)	67.9 (47.7, 84.1)
Region-level specificity, % (95% CI)	96.3 (91.6, 98.8)	96.3 (91.5, 98.8)	94.7 (89.5, 97.9)
Region-level negative predictive value, % (95% CI)	94.2 (88.9, 97.5)	94.9 (89.7, 97.9)	93.3 (87.7, 96.9)
Region-level accuracy, % (95% CI)	91.9 (86.6, 95.6)	92.5 (87.3, 96.1)	90.1 (84.4, 94.2)
Extra-PLN region, *n*	161	161	161
True positive	5	5	5
False positive	0	1	1
True negative	151	150	150
False negative	5	5	5
Region-level CLR, % (95% CI)	100 (47.8, 100)	83.3 (35.9, 99.6)	83.3 (35.9, 99.6)
Region-level sensitivity, % (95% CI)	50.0 (18.7, 81.3)	50.0 (18.7, 81.3)	50.0 (18.7, 81.3)
Region-level specificity, % (95% CI)	100 (97.6, 100)	99.3 (96.4, 100)	99.3 (96.4, 100)

	Central Reader 1	Central Reader 2	Central Reader 3
Region-level negative predictive value, % (95% CI)	96.8 (92.7, 99.0)	96.8 (92.6, 98.9)	96.8 (92.6, 98.9)
Region-level accuracy, % (95% CI)	96.9 (92.9, 99.0)	96.3 (92.1, 98.6)	96.3 (92.1, 98.6)
Skeletal region, *n*	161	161	161
True positive	2	4	4
False positive	1	1	3
True negative	152	152	150
False negative	6	4	4
Region-level CLR, % (95% CI)	66.7 (9.4, 99.2)	80.0 (28.4, 99.5)	57.1 (18.4, 90.1)
Region-level sensitivity, % (95% CI)	25.0 (3.2, 65.1)	50.0 (15.7, 84.3)	50.0 (15.7, 84.3)
Region-level specificity, % (95% CI)	99.3 (96.4, 100)	99.3 (96.4, 100)	98.0 (94.4, 99.6)
Region-level negative predictive value, % (95% CI)	96.2 (91.9, 98.6)	97.4 (93.6, 99.3)	97.4 (93.5, 99.3)
Region-level accuracy, % (95% CI)	95.7 (91.3, 98.2)	96.9 (92.9, 99.0)	95.7 (91.3, 98.2)
Visceral region, *n*	161	161	161
True positive	1	3	2
False positive	1	1	0
True negative	150	150	151
False negative	9	7	8
Region-level CLR, % (95% CI)	50.0 (1.3, 98.7)	75.0 (19.4, 99.4)	100 (15.8, 100)
Region-level sensitivity, % (95% CI)	10.0 (0.3, 44.5)	30.0 (6.7, 65.3)	20.0 (2.5, 55.6)
Region-level specificity, % (95% CI)	99.3 (96.4, 100)	99.3 (96.4, 100)	100 (97.6, 100)
Region-level negative predictive value, % (95% CI)	94.3 (89.5, 97.4)	95.5 (91.0, 98.2)	95.0 (90.3, 97.8)
Region-level accuracy, % (95% CI)	93.8 (88.9, 97.0)	95.0 (90.4, 97.8)	95.0 (90.4, 97.8)

CI = confidence interval; CLR = correct localization rate; PET/CT = positron emission tomography/computed tomography; PLN = pelvic lymph node; PSMA = prostate-specific membrane antigen.

SUPPLEMENTAL TABLE 7. Summary of Change in Intended Treatment Plans by Local Read Assessment of [^{18}F]CTT1057 PET/CT Scans ([^{18}F]CTT1057 Safety Set)

	***N* = 171** ***n* (%)**
Patients with no change in treatment plans	107 (62.6)
Positive	36 (21.1)
Negative	71 (41.5)
Inconclusive	0
Patients with change in treatment plans	61 (35.7)
Positive	40 (23.4)
Negative	21 (12.3)
Inconclusive	0

Positive: patient with at least one lesion that is visually positive on scan in any region. Negative: patient without any lesion that is visually positive on scan in any region. All regions (i.e. prostate region, PLN region, extra-PLN region, skeletal region and visceral region) were considered.

PET/CT = positron emission tomography/computed tomography; PLN = pelvic lymph node.

SUPPLEMENTAL TABLE 8. Shift Table on Responses to Questionnaires on Change in Intended Treatment Plan After the [^{18}F]CTT1057 PET/CT Scan ([^{18}F]CTT1057 Safety Set)

Questionnaire 1 (*N* = 171)		Questionnaire 2 (*N* = 171)							
	***n* (%)**	**Surgery, *n* (%)**	**Radiation alone, *n* (%)**	**Radiation plus ADT, *n* (%)**	**ADT alone, *n* (%)**	**Observation/ surveillance, *n* (%)**	**Radiation alone with change in radiation treatment plan, *n* (%)**	**Other, *n* (%)**	**Missing, *n* (%)**
Surgery	5 (2.9)	1 (20.0)	1 (20.0)	2 (40.0)	0	1 (20.0)	0	0	0
Radiation alone	62 (36.3)	1 (1.6)	40 (64.5)	14 (22.6)	2 (3.2)	3 (4.8)	1 (1.6)	0	1 (1.6)
Radiation plus ADT	67 (39.2)	3 (4.5)	5 (7.5)	49 (73.1)	2 (3.0)	3 (4.5)	0	3 (4.5)	2 (3.0)
ADT alone	6 (3.5)	0	0	3 (50.0)	2 (33.3)	1 (16.7)	0	0	0
Observation/surveillance	24 (14.0)	0	4 (16.7)	4 (16.7)	1 (4.2)	12 (50.0)	0	3 (12.5)	0
Other	7 (4.1)	0	1 (14.3)	2 (28.6)	1 (14.3)	0	0	3 (42.9)	0
Missing	0	0	0	0	0	0	0	0	0

Percentages for questionnaire 1 are based on *N*. Percentages for questionnaire 2 value are based on Questionnaire 1 *n*.

ADT = androgen deprivation therapy; PET/CT = positron emission tomography/computed tomography.

SUPPLEMENTAL TABLE 9. Adverse Events Experienced By Patients Who Received [^{18}F]CTT1057 ([^{18}F]CTT1057 Safety Set)

	[^{18}F]CTT1057 Safety Set *N* = 171	
	All grades *n* (%)	**Grade ≥3 *n* (%)**
Number of participants with at least one event	20 (11.7)	2 (1.2)
Asthenia	5 (2.9)	0
Lipase increased	3 (1.8)	1 (0.6)
Amylase increased	2 (1.2)	0
Coronavirus disease 2019 (COVID-19)	2 (1.2)	0
Blood creatine phosphokinase increased	1 (0.6)	0
Diarrhea	1 (0.6)	0
Dizziness	1 (0.6)	0
Dyspnea	1 (0.6)	1 (0.6)
Eosinophilia	1 (0.6)	0
Fatigue	1 (0.6)	0
Hematuria	1 (0.6)	0
Headache	1 (0.6)	0
Injection site warmth	1 (0.6)	0
Muscle spasms	1 (0.6)	0
Paresthesia	1 (0.6)	0
Paresthesia oral	1 (0.6)	0
Renal pain	1 (0.6)	0
Thirst	1 (0.6)	0

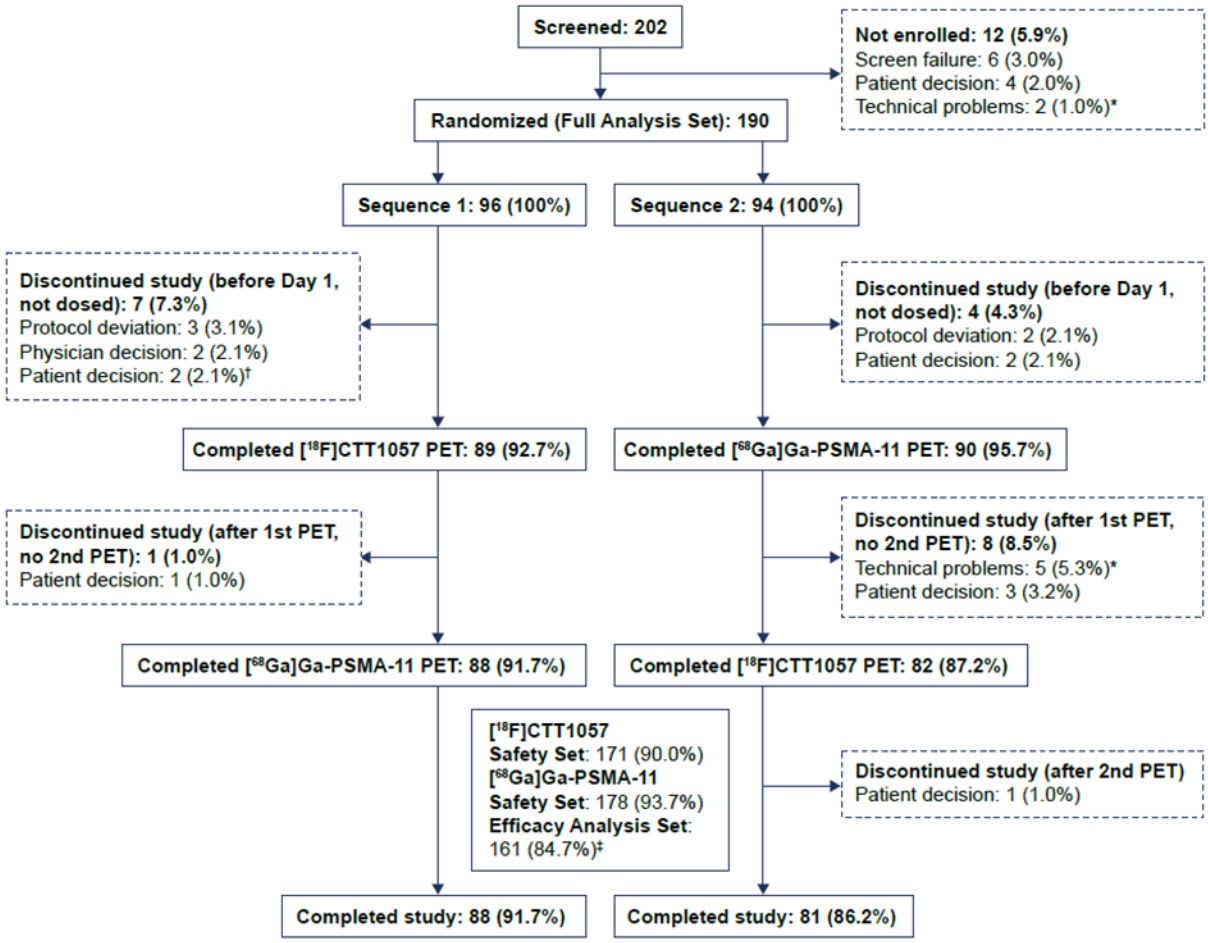
Adverse events that occurred within 14 days after [^{18}F]CTT1057 scan as long as prior to [^{68}Ga]Ga-PSMA-11 dose (if applicable), and for events related to [^{18}F]CTT1057 irrespective of time of onset, are summarized. Numbers (*n*) represent counts of patients.

PET/CT = positron emission tomography/computed tomography.

SUPPLEMENTAL TABLE 10. Adverse Events Experienced by Patients Who Received [^{18}F]CTT1057 Suspected to be Related to [^{18}F]CTT1057 ([^{18}F]CTT1057 Safety Set)

	[^{18}F]CTT1057 Safety Set (*N* = 171)	
	All grades *n* (%)	**Grade ≥3 *n* (%)**
Number of participants with at least one event	6 (3.5)	0
Amylase increased	1 (0.6)	0
Dizziness	1 (0.6)	0
Eosinophilia	1 (0.6)	0
Headache	1 (0.6)	0
Injection site warmth	1 (0.6)	0
Lipase increased	1 (0.6)	0
Paresthesia	1 (0.6)	0
Paresthesia oral	1 (0.6)	0
Thirst	1 (0.6)	0

Adverse events that occurred within 14 days after [^{18}F]CTT1057 scan as long as prior to [^{68}Ga]Ga-PSMA-11 dose (if applicable), and events that are related to [^{18}F]CTT1057 irrespective of time of onset, are summarized. Numbers (*n*) represent counts of patients.



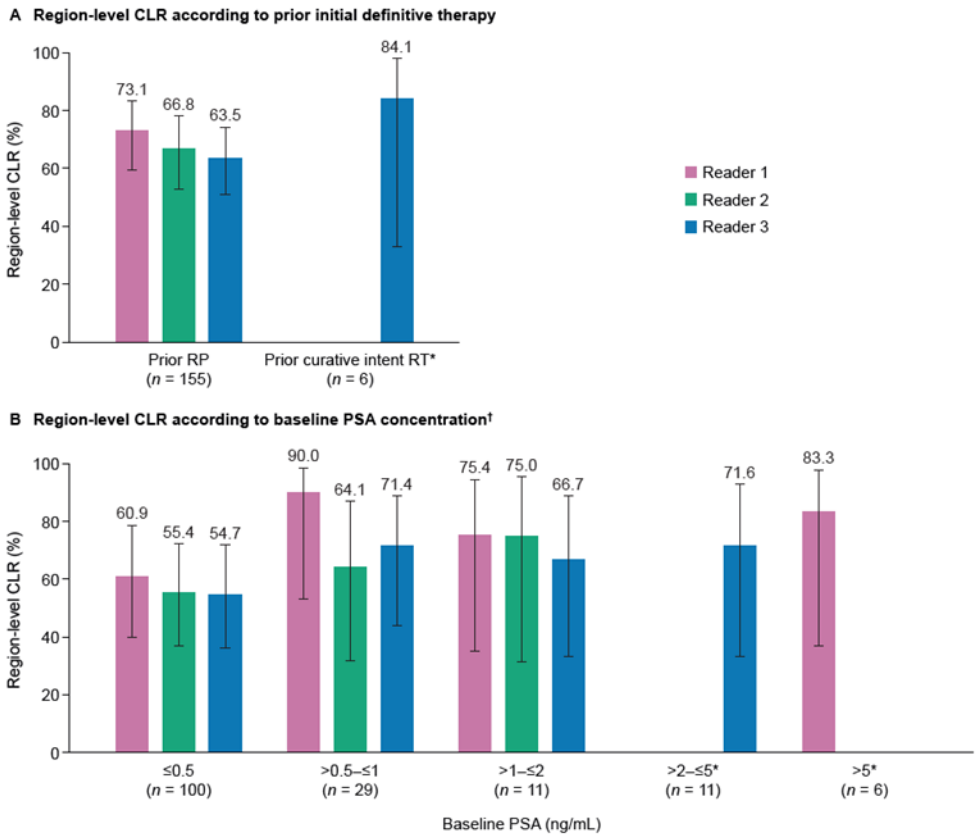
SUPPLEMENTAL FIGURE 1. Flow Diagram of Study Participants.

*[^{18}F]CTT1057 manufacturing issue or batch failure.

†One patient was not dosed on Day 1 owing to a technical problem and, discontinued the study (patient decision).

‡29 patients who were randomized were excluded from the Efficacy Analysis Set: 19 did not receive [^{18}F]CTT1057, nine due to use of prohibited concomitant medications before completion of all CTS procedures, and one due to lack of evaluable CTS assessment.

CTS = composite truth standard; PET = positron emission tomography.



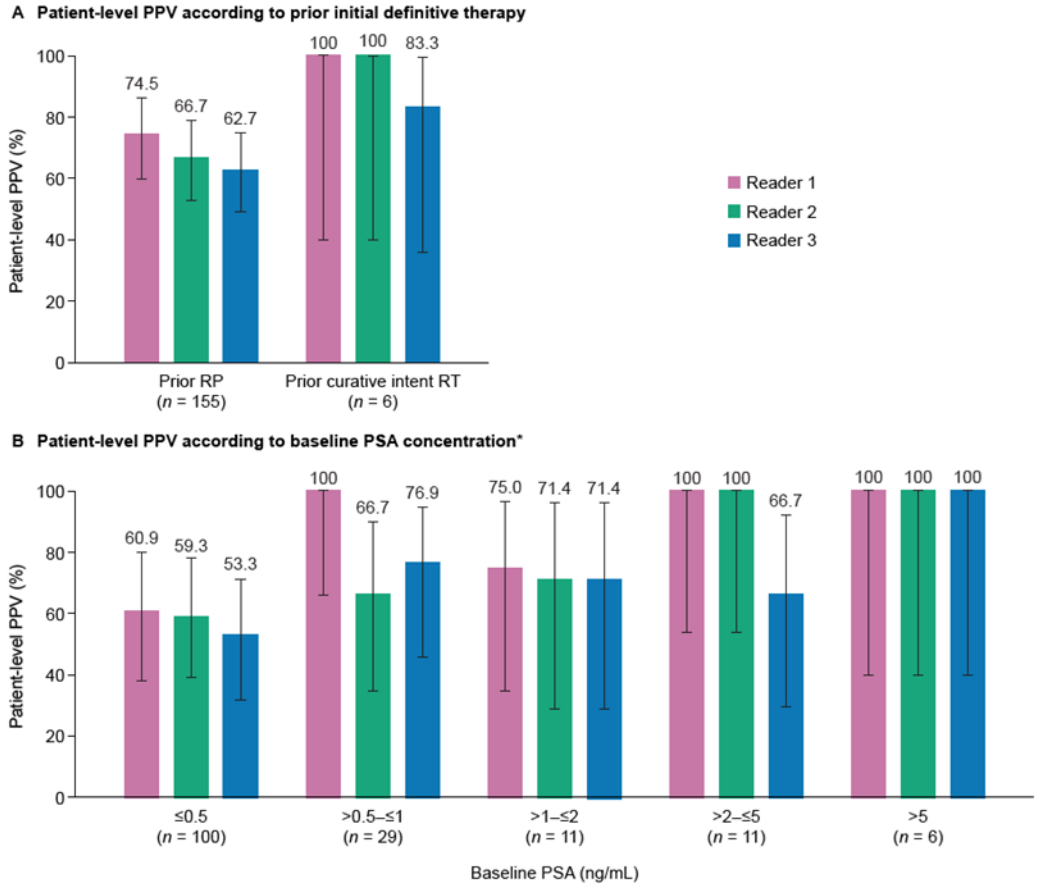
SUPPLEMENTAL FIGURE 2. Region-level CLR of [^{18}F]CTT1057 PET/CT According to Prior Initial Definitive Therapy (A) and Baseline PSA Concentration (B) (Efficacy Analysis Set).

Error bars represent 95% CIs.

*Point estimate and 95% CI could only be estimated for one reader in this subgroup because of a lack of convergence in the model (number of false-positive regions was equal to zero).

†Four patients in the efficacy analysis set did not have evaluable PSA levels at baseline; therefore, 157 patients were included in the analysis.

CI = confidence interval; CLR = correct localization rate; PET/CT = positron emission tomography/computed tomography; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.

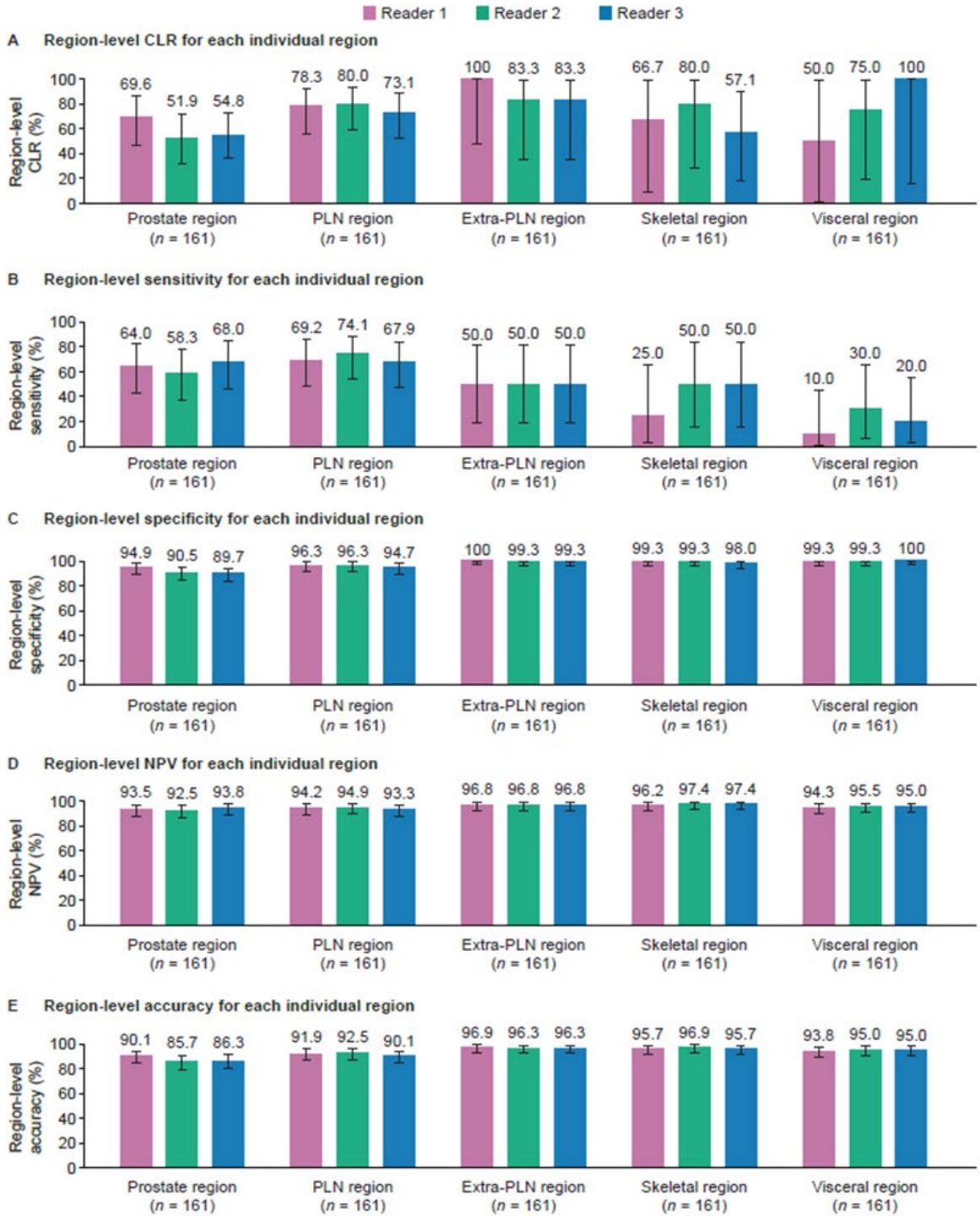


SUPPLEMENTAL FIGURE 3. Patient-level PPV of [^{18}F]CTT1057 PET/CT According to Prior Initial Definitive therapy (A) and Baseline PSA Concentration (B) (Efficacy Analysis Set).

Error bars represent 95% CIs.

*Four patients in the efficacy analysis set did not have evaluable PSA levels at baseline; therefore, 157 patients were included in the analysis.

CI = confidence interval; PET/CT = positron emission tomography/computed tomography; PPV = positive predictive value; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.



SUPPLEMENTAL FIGURE 4. Region-level CLR (A), Sensitivity (B), Specificity (C), Negative Predictive Value (D) and Accuracy (E) of [^{18}F]CTT1057 PET/CT for the Detection of PSMA-positive Lesions for Each Individual Region (Efficacy Analysis Set).

Error bars represent 95% CIs.

CI = confidence interval; CLR = correct localization rate; PET/CT = positron emission tomography/computed tomography; PLN = pelvic lymph node; PSMA = prostate-specific membrane antigen.