Supplemental Appendix 1. Questions and Expert Responses (N=38) From USPCC Sessions on mCRPC and Aggressive Variant/Neuroendocrine Prostate Cancer

6. Aggressive Variant/Neuroendocrine Prostate Cancer

6.1 Do you use platinum-based chemotherapy for patients with mCRPC in the absence of DNA repair gene alterations?		
Answer	**#**	**%**
Yes	18	50
No	11	31
Abstain	7	19

6.2 Do you use histologic features to select patients for platinum-based chemotherapy?		
Answer	**#**	**%**
Yes	31	86
No	2	6
Abstain	3	8

6.3 Which histologic features do you use to select patients for platinum-based chemotherapy?		
Answer	**#**	**%**
Small-cell carcinoma	7	19
Small-cell carcinoma or any features of neuroendocrine prostate cancer (NEPC) on biopsy	23	64
Other histologic features	0	0
I do not use histologic features to select patients for platinum-based chemotherapy	1	3
Abstain	5	14

6.4 Do you use the clinical features listed below to select platinum-based chemotherapy for patients with CRPC (1st or 2nd line CRPC) for whom biopsy does not show small-cell carcinoma or NEPC?						
	Yes		**No**		**Abstain**	
Answer	**#**	**%**	**#**	**%**	**#**	**%**
Liver metastases	26	72.2	5	13.9	5	13.9
Low PSA ≤ 10 ng/mL plus ≥ 20 bone metastases on initial presentation or CRPC progression	15	41.7	14	38.9	7	19.4
Radiographic progression with PSA ≤ 1 ng/mL	23	63.9	10	27.8	3	8.3
Lytic bone metastases	22	61.1	11	30.6	3	8.3
Elevated serum neuroendocrine markers (eg, CEA, LDH)	15	41.7	14	38.9	7	19.4
Bulky ≥ 5 cm lymphadenopathy or high-grade tumor mass in prostate/pelvis	14	38.9	18	50	4	11.1
Short response to initial AR therapy ≤ 6 months	13	36.1	16	44.4	7	19.4

Lung metastases	8	22.2	21	58.3	7	19.4

6.5 Do you use genomic features (other than DNA repair aberrations) to select platinum-based chemotherapy for patients with CRPC when the biopsy does not show small-cell carcinoma or NEPC?		
Answer	**#**	**%**
Yes	22	61
No	9	25
Abstain	5	14

6.6 Which genomic features (other than DNA repair aberrations) do you use to select platinum-based chemotherapy for patients with CRPC when the biopsy does not show small-cell carcinoma or NEPC?		
Answer	**#**	**%**
RB1 deletion or mutation	2	6
TP53 mutation or deletion	1	3
PTEN deletion	1	3
Concurrent RB1 and TP53 loss of function	4	11
Loss of 2 of 3: RB1, TP53, PTEN	12	33
I do not use genomic features to select patients for platinum-based chemotherapy	9	25
Abstain	7	19

6.7 In which of the following situations do you consider doing a biopsy to look for small-cell carcinoma/NEPC?						
	Yes		**No**		**Abstain**	
Answer	**#**	**%**	**#**	**%**	**#**	**%**
When the development of new liver metastases in setting of low or nonrising PSA occurs?	35	97.2	0	0	1	2.8
In the case of PSMA-negative soft tissue or visceral lesions on PSMA-PET/CT?	30	83.3	3	8.3	3	8.3
When the development of parenchymal brain metastases occurs?	22	61.1	8	22.2	6	16.7
For any patient with CRPC?	6	16.7	26	72.2	4	11.1

6.8 If small-cell carcinoma/NEPC is suspected, what is the **minimum** evaluation(s) of metastatic biopsies you would complete?		
Answer	**#**	**%**
Only morphology is required (eg, small cell, large cell, mixed, adenocarcinoma, poorly differentiated)	0	0
Morphology plus immunohistochemistry (IHC) for classical NE markers (eg, SYP, chromogranin, INSM1)	10	28
Morphology plus IHC for PSA and AR	6	17
All of the above	19	53
Abstain	1	3

6.9 Do you recommend repeat genomic sequencing in a patient with small-cell/NEPC if they already had genomic sequencing of a prior CRPC biopsy?		
Answer	**#**	**%**
Yes	26	72
No	7	19
Abstain	3	8

6.10 A 69-year-old patient with mCRPC has progression after abiraterone, docetaxel, and cabazitaxel and has undergone a PSMA-PET/CT for consideration of treatment with 177Lu-PSMA-617. His PSA has risen 5 ng/mL to > 9 ng/mL and multiple new PSMA-negative liver metastases are identified, in addition to new PSMA-positive bone metastases. What would you do next?		
Answer	**#**	**%**
FDG PET	2	6
FDG PET and a biopsy of the liver lesion	11	31
Biopsy of the liver lesion	15	42
Analysis of circulating tumor DNA to look for RB1/TP53/PTEN alterations	0	0
177Lu-PSMA-617	1	3
Platinum-based chemotherapy	4	11
None of the above	0	0
Abstain	3	8

6.11 What is the preferred nomenclature for a patient with CRPC who develops new liver metastases with PSA < 1 ng/mL and has a liver biopsy that is read as poorly differentiated carcinoma with neuroendocrine features (by morphology and IHC)?		
Answer	**#**	**%**
Neuroendocrine prostate cancer	5	14
Small cell neuroendocrine prostate carcinoma (SCNPC)	7	19
Aggressive variant prostate cancer (AVPC)	18	50
AR-indifferent prostate cancer	2	6
CRPC	1	3
Not sure	1	3
Abstain	2	6

6.12 Which of the following treatments would you use for a patient with CRPC and treatment-emergent small-cell carcinoma/NEPC after progression on ADT plus abiraterone followed by docetaxel with new liver metastases? Serum PSA is < 1 ng/mL. Liver biopsy shows pure small-cell carcinoma, AR-negative, PSA-negative by IHC. A TMPRSS2-ERG gene fusion is detected by DNA sequencing.		
Answer	**#**	**%**
Carboplatin plus etoposide	7	19
Carboplatin plus etoposide, plus atezolizumab, followed by atezolizumab maintenance	8	22
Carboplatin plus cabazitaxel	9	25
Cabazitaxel	0	0
Other	1	3
Abstain	11	31

6.13 What is preferred treatment for a patient with CRPC who develops new liver lesions and has a PSA < 1 ng/mL after progression on ADT plus abiraterone followed by docetaxel? A biopsy shows poorly differentiated adenocarcinoma that is AR-positive and PSA-negative.		
Answer	**#**	**%**
Carboplatin plus etoposide	3	8
Carboplatin plus etoposide and atezolizumab, followed by atezolizumab maintenance	2	6
Carboplatin plus cabazitaxel	18	50
Cabazitaxel	2	6
PSMA PET and Lu-PSMA-617, if PSMA positive	3	8
Other		
Abstain	8	22

6.14 Do you recommend brain MRI for patients with treatment-emergent pure small-cell carcinoma/NEPC for staging in the absence of neurological symptoms?		
Answer	**#**	**%**
Yes	18	50
No	15	42
Abstain	3	8

6.15 Which of the following therapies would you use as the next line of therapy (off trial) for a fit patient with treatment emergent small-cell carcinoma/NEPC after progression on therapy with carboplatin plus etoposide?		
Answer	**#**	**%**
Lurbinectedin	6	17
Pembrolizumab	5	14
Taxane	5	14
Other	5	14
Hospice	1	3
Abstain	14	39

6.16 Which of the following treatments would you use as the next line of therapy (off trial) for a patient who has AVPC without features of small-cell carcinoma/NEPC after progression on therapy with carboplatin plus cabazitaxel and is PSMA-negative on PET?		
Answer	**#**	**%**
Lurbinectedin	5	14
Pembrolizumab	4	11
Mitoxantrone	1	3
Other	8	22
Hospice	3	8
Abstain	15	42

7. mCRPC (1 of 3)

7.1 Can further manipulation of the androgen receptor axis result in clinical meaningful benefit in patients who have received next-generation galeterone analogs (NGGA)?		
Answer	**#**	**%**
Yes	17	46

No	2	5
Not sure	12	32
Abstain	6	16

7.2 Does the use of docetaxel in mHSPC, but not mCRPC in the castration-sensitive state, mean that it should not be used in the hormone-sensitive state?		
Answer	**#**	**%**
No, I do not use docetaxel for mCRPC	1	3
Yes, I would docetaxel for mCRPC	7	19
Yes, I would use docetaxel for mCRPC, but only if PFS at least 12 months post docetaxel for mHSPC	19	51
Not sure	2	5
Abstain	8	22

7.3 Would you use ARIs for patients with mCRPC if they were previously used for the patients when they had mHSPC?		
Answer	**#**	**%**
Yes	26	70
No	8	22
Abstain	3	8

7.4 Do you believe that existing checkpoint inhibitors will ever demonstrate sufficient activity in mCRPC?		
Answer	**#**	**%**
Yes	8	22
No	13	35
Not sure	15	41
Abstain	1	3

7.5 Where is the optimal place in the timeline of CRPC to test a novel agent?		
Answer	**#**	**%**
After all approved therapies have been tried	2	5
First-line mCRPC	12	32
After at least 1 androgen receptor pathway inhibitors (ARPI) and a taxane	13	35
After at least 1 ARPI, a taxane, and 177Lu-PSMA-617 (in eligible patients)	4	11
Not sure	3	8
Abstain	3	8

8. mCRPC—PARPis

8.1 Should PARPi monotherapy be only offered to men with mCRPC who harbor BRCA1/2 mutations?		
Answer	**#**	**%**
Yes	17	46
No	15	41
Not sure	2	5
Abstain	3	8

8.2 Should PARPi monotherapy be offered to men with mCRPC who have non-BRCA HRR gene mutations?		
Answer	**#**	**%**
Yes	14	38
No	14	38
Not sure	6	16
Abstain	3	8

8.3 Can ctDNA testing alone (without tissue testing) be used to identify and select men for treatment with a PARPi?		
Answer	**#**	**%**
Yes	22	59
No	4	11
Not sure	7	19
Abstain	4	11

8.4 Do you recommend rechallenge with another PARPi if the disease progresses on 1 PARPi?		
Answer	**#**	**%**
Yes	2	5
No	25	68
Not sure	6	16
Abstain	4	11

8.5 In men with mCRPC with HRR gene alterations, should PARPi monotherapy be preferably offered before or after docetaxel?		
Answer	**#**	**%**
Before	29	78
After	1	3
Not sure	5	14
Abstain	2	5

8.6 Given the potential of marrow toxicities, should there be a defined and fixed duration of treatment with PARPi in those men who continue to respond to PARPi beyond 1-2 years?		
Answer	**#**	**%**
Yes	10	27
No	13	35
Not sure	11	30
Abstain	3	8

8.7 Would you consider intermittent PARPi therapy in patients who achieve a deep response to PARPi?		
Answer	**#**	**%**
Yes	15	41
No	5	14
Not sure	15	41
Abstain	2	5

8.8a For men with BRCA altered mCRPC, would you offer PARPi + ARPi?		
Answer	**#**	**%**
Yes	31	84
No	0	0
Not sure	2	5
Abstain	4	11

8.8b If toxicities lead to discontinuation of a PARPi (without disease progression on the first PARPi), do you feel treatment with another PARPi with nonoverlapping toxicities should be offered?		
Answer	**#**	**%**
Yes	20	54
No	5	14
Not sure	10	27
Abstain	2	5

8.9 For men with mCRPC and no pathogenic alterations of HRR, would you offer PARPi + ARPi?		
Answer	**#**	**%**
Yes	10	27
No	16	43
Not sure	9	24
Abstain	2	5

8.10 Which PARPi ARPi combinations would you consider offering today if it were FDA approved? Select all that apply		
Answer	**#**	**%**
Olaparib + abiraterone	27	73
Talazoparib + Enzalutamide	21	57
Niraparib + Abiraterone	10	27
Not sure	2	5
Abstain	3	8

8.11 For men with BRCA altered mCRPC, would you offer PARPi + ARPi to men who have progressed on a prior ARPi?		
Answer	**#**	**%**
Yes	18	49
No	13	35
Not sure	4	11
Abstain	2	5

8.12 Setting aside regulatory decisions about approval of PARPi ARPi combinations, will you recommend a combinations that improves rPFS but falls short of statistical significance for improving OS?		
Answer	**#**	**%**
Yes	23	62
No	6	16
Not sure	5	14
Abstain	3	8

8.13 Should carboplatin be presented to patients with HRRm disease as a less-expensive alternative to PARPi?		
Answer	**#**	**%**
Yes	13	35
No	6	16
Not sure	2	5
Only for those who cannot afford a PARPi or who are ineligible for a PARPi	12	32
Abstain	4	11

8.14 If initial NGS testing of the primary tumor reveals no deleterious alterations in HRR genes, do you recommend repeating NGS when the disease progresses to mCRPC?		
Answer	**#**	**%**
Yes	30	81
No	4	11
Not sure	1	3
Abstain	2	5

8.15 Assuming a patient was eligible for PARP inhibitor and radium 223, how would you sequence the two?		
Answer	**#**	**%**
PARP before radium 223	21	57
PARP after radium 223	2	5
PARP in combination with radium 223	3	8
It depends (open ended response)	9	24
Abstain	2	5

9. mCRPC—Theranostics

9.1 What are the minimum requirements for PSMA PET in patient selection for 177Lu-PSMA-radioligand therapy (RLT) in the VISION population?		
Answer	**#**	**%**
No PSMA PET imaging is necessary for patient selection in postchemo population with limited options	0	0
Any PSMA uptake > background in any lesion	3	8
PSMA SUV mean > 10	2	6
PSMA > liver in some active lesions (but a minority can be PSMA low/negative)	7	19
VISION study protocol (≥ 1 PSMA-positive metastatic lesion [PMSA > liver parenchyma in ≥ 1 metastatic lesion of any size in any organ system] and no PSMA-negative lesions)	16	44
TheraP study protocol (≥ 1 site with SUV max ≥ 20, no FDG+/PSMA-	2	6
PSMA SUV mean > 10		
Not sure	4	11
Abstain	2	6

9.2 Does it matter which PSMA PET agent is utilized?		
Answer	**#**	**%**
Yes	0	0
No	34	94
Abstain	2	6

9.3 Should both PSMA and FDG PET be used in patient selection for 177Lu-PSMA-RLT?		
Answer	**#**	**%**
Yes	5	14
No	21	58
Not sure	9	25
Abstain	1	3

9.4 Should most patients being treated in the VISION setting receive combination therapy with ARPI?		
Answer	**#**	**%**
Yes	11	31
No	11	31
Not sure	13	36
Abstain	1	3

9.5 Should patients who have PSMA positive mCRPC who are naïve to chemotherapy receive 177Lu-PSMA-RLT?		
Answer	**#**	**%**
Yes	1	3
Yes, if they are unfit for chemo	7	19
Yes, if they have balanced discussion and refuse chemo	2	6
Not until full data for randomized trials are released	17	47
Not until guidelines are stated are in favor	1	3
Not until FDA approval	5	14
Never	0	0
Only on trial	1	3
Not sure	0	0
Abstain	2	6

9.6 What is the minimum pretreatment hemoglobin level used in patient selection for 177Lu-PSMA-RLT?		
Answer	**#**	**%**
10 g/dL	3	8
9 g/dL	7	19
8 g/dL	13	36
7 g/dL	1	3
Doesn’t matter if due to marrow infiltration	5	14
Not sure	6	17
Abstain	1	3

9.7 What is the minimum pretreatment platelet count used in patient selection for 177Lu-PSMA-RLT?		
Answer	**#**	**%**
100 x 10^9/L	9	25
75 x 10^9/L	12	33
50 x 10^9/L	5	14
25 x 10^9/L	0	0
Doesn't matter if due to marrow infiltration	3	8
Not sure	6	17
Abstain	1	3

9.8 What is the minimum pretreatment neutrophil count used in patient selection for 177Lu-PSMA-RLT?		
Answer	**#**	**%**
1.5 x 10^9/L	12	33
1 x 10^9/L	10	28
Doesn't matter if due to marrow infiltration	4	11
Not sure	8	22
Abstain	2	6

9.9 What is the maximum pretreatment serum creatinine used in patient selection for 177Lu-PSMA-RLT?		
Answer	**#**	**%**
Upper limit of normal (ULN)	0	0
1.5 x ULN	18	50
2.5 x ULN	3	8
3 x ULN	0	0
Doesn't matter as long as other parameters are OK	2	6
Not sure	11	31
Abstain	2	6

9.10 Should anyone receive less than 7.4 GBq (200 mCi) of 177Lu-PSMA-617 in cycle 1 (ie, should there be initial "dose" reductions)?		
Answer	**#**	**%**
Yes	4	11
No	16	44
Not sure	14	39
Abstain	2	6

9.11 Should we calculate normal organ dose limits with prior lifetime radiation exposure prior to dosing with therapeutic radionuclide therapy?		
Answer	**#**	**%**
Yes, I would not treat even if organ function was adequate	1	3
Yes, I would adjust radioactivity dose even if organ function was adequate	9	25
No, I would ignore prior exposure as long as organ function was adequate	13	36
Not sure	9	25
Abstain	4	11

9.12 Should most patients undergo regular postinfusion SPECT after each treatment with standard of care 177Lu-PSMA-RLT?		
Answer	**#**	**%**
Yes, with most or all doses	8	22
Yes, at least once per course	6	17
No, only for research	14	39
Not sure	7	19
Abstain	1	3

9.13 Should patients have serial PSMA PET during treatment with standard of care 177Lu-PSMA-RLT?		
Answer	**#**	**%**
Yes, PSMA PET is standard imaging to assess response/progression	5	14
Yes, most patients should have at least 1 follow-up PSMA PET	14	39
No, only for research	14	39
Not sure	2	6
Abstain	1	3

9.14 Should patients with excellent response (>95% PSA reduction, no symptoms of disease, favorable imaging) stop therapy early (less than planned treatment course outside of a study) with planned restart of treatment upon progression?		
Answer	**#**	**%**
Yes, with up to 1 consolidation cycle	6	17
Yes, only if excellent response is accompanied by PSMA low/negative imaging	13	36
No, in the absence of toxicity, patients should complete their treatment course	12	33
Not sure	3	8
Abstain	2	6

9.15 In your opinion, after clinical trials have been completed, what will be the optimal disease state for 177Lu-PSMA-RLT?		
Answer	**#**	**%**
Postchemo mCRPC	3	8
Prechemo mCRPC	20	56
Overtly (conventional imaging) metastatic noncastrate PC	6	17
Biochemically recurrent PSMA PET plus PC	1	3
High-risk nonmetastatic PC in combination with local therapy	2	6
Not sure	3	8
Abstain	1	3

9.16 Do you believe that targeted alpha particles will be better than beta particles?		
Answer	**#**	**%**
Yes	5	14
Yes for efficacy, but I worry about toxicity	17	47

Yes for safety, but I worry about efficacy in the setting of bulky disease	4	11
No, overall therapeutic index of betas will prove more acceptable	0	0
No	0	0
Not sure	9	25
Abstain	1	3

9.17 Should we use PROs instead of CTCAE to assess nonlaboratory toxicity?		
Answer	**#**	**%**
Yes	6	17
Yes, for subjective items such as dry mouth	13	36
No, not until there is a validated instrument	9	25
No	1	3
Not sure	5	14
Abstain	2	6
Yes	6	17