staging and treatment of high-risk localized disease, treatment of metastatic hormone-sensitive prostate cancer (mHSPC) and use of new options to treat metastatic castration-resistant prostate cancer (mCRPC).

The meeting took place in Bern on November 24, 2022. Most questions were selected from the 2022 international Advanced Prostate Cancer Consensus Conference (APCCC) [1], but some questions were reformulated to facilitate discussion, and some new questions were formulated by the corresponding authors. All questions were circulated to all experts before the meeting to allow participants to prepare. All questions were discussed and subsequently voted on. All votes were submitted electronically and anonymously. Consensus was defined as at least 80% of votes favouring a specific answer. This article summarizes the discussion and voting results and is intended to serve as guidance for the formulation of recommendations by institutional multidisciplinary tumour boards and as a basis for discussion with individual patients. However, these recommendations are not compulsory regulations and cannot replace careful and interdisciplinary shared decision making with patients while considering important individual-specific factors (figure 2).

Composition of the panel

The Swiss Group for Clinical Cancer Research (SAKK) invited a total of 22 Swiss prostate cancer experts from different specialties, including urology, radiation oncology, nuclear medicine, pathology and medical oncology, to join the panel. Experts were identified using the network of the SAKK project group for urogenital tumours. Fifteen ex-

Figure 1: The therapy landscape for prostate cancer, 2023. ADT, androgen deprivation (with LHRH agonist or antagonist or bilateral orchiectomy); ARPI, androgen receptor pathway inhibitor (i.e. abiraterone, apalutamide, enzalutamide); PLND, pelvic lymph node dissection; M0, no evidence of distant metastases; M1 evidence of distant metastases; MDT, metastasis directed therapy. Please refer to https://www.swissmedicinfo.ch for approved indications.

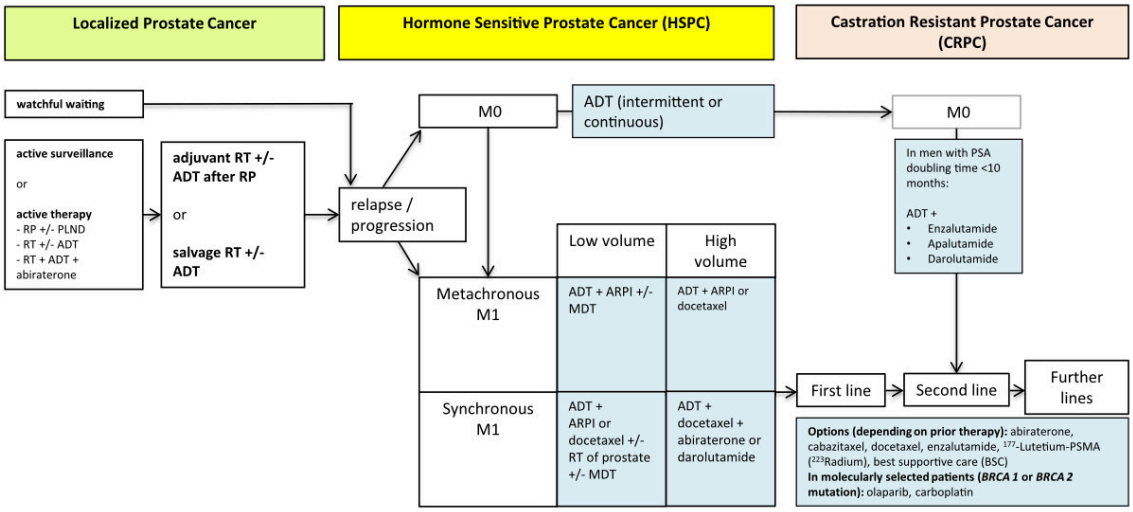
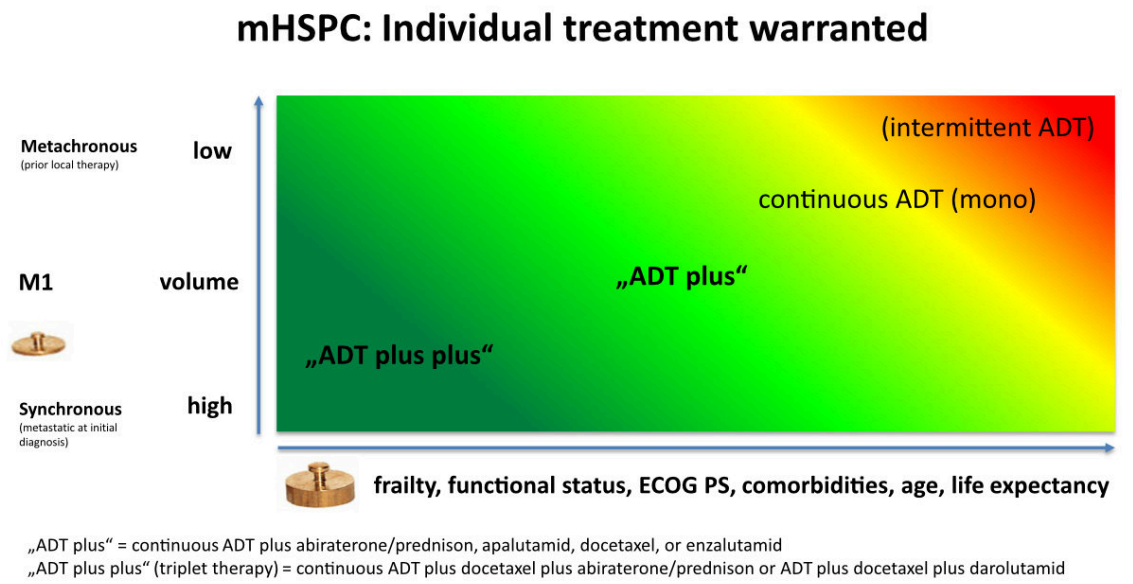


Figure 2: Considerations for individual decisions regarding the treatment of metastatic hormone-sensitive prostate cancer.



perts were able to participate in person at the meeting. Participants were permitted to vote on all questions presented, regardless of possible conflicts of interest (e.g., authorship of scientific work discussed).

The co-authors Irene A. Burger, Daniel Eberli, Stefanie Fischer, Silke Gillessen, Guillaume Nicolas, Stephanie Kroeze, Niklaus Schaefer, Thomas Zilli, and Daniel Zwahlen could not attend the consensus meeting in person.

Staging of localized prostate cancer

In the first part of the consensus meeting, questions involving modern imaging (i.e., PSMA [prostate-specific membrane antigen] PET/CT and whole-body MRI) as staging modalities in localized prostate cancer were addressed. The possibility of staging at diagnosis using PSMA PET/CT was the centre of the discussion. There was consensus (86%) that staging with PSMA PET/CT is indicated in cases of very high-risk or high-risk localized disease, according to NCCN (National Comprehensive Cancer Network) definitions (table 1), and one-third of panellists also recommended this method of staging in cases of unfavourable intermediate risk.

The discussion highlighted that the problem of balancing false positive or ambiguous findings on one hand and sensitivity for locoregional lymph node metastasis (cN1) and/or distant metastases (cM1) on the other hand is difficult given that these findings prompt the determination of a curative versus palliative treatment strategy. Based on the available literature, the sensitivity and specificity of ^{18}F-PSMA-1007 PET/CT (the tracer most often used in Swiss institutions) for detection of locoregional lymph node metastases are 54% and 97%, respectively [2]. A comparative study of conventional staging, both whole-body MRI and ^{18}F-PSMA-1007 PET/CT showed a higher sensitivity and better inter-reader agreement for staging prostate cancer, despite the known limitation of unspecific bone uptake (UBU) [3, 4]. There are very limited data on the comparison of ^{18}F-PSMA-1007 and ^{68}Ga-PSMA-11, and both radiotracers are used in routine clinical practice.

The panel discussed how to proceed in patients with high-risk prostate cancer for whom radical local treatment (radical prostatectomy or radiotherapy) of the primary tumour is planned and who have up to three lesions in the bone with *low* uptake (as defined by the institution) evident on an upfront ^{18}F-PSMA PET/CT *without* a correlate on the CT component. The majority of experts (71%) felt that, in general, no further investigations are needed in this case. The rationale is to avoid undertreatment in the case of false positive findings (i.e., inadequate local treatment in the case of wrongly assuming distant metastatic disease). In fact, a recent PSMA PET/CT–guided biopsy study confirmed that the majority of such lesions are caused by false positive uptake [5]. In contrast, in the case of *intense* uptake (as defined by the institution), only 13% of experts considered this approach appropriate, whereas two-thirds recommended correlative imaging (usually targeted MRI), and 20% recommended a biopsy. There was consensus (93%) not to use whole-body MRI instead of PSMA PET/CT for initial staging.

Table 1:
Risk stratification according to the National Comprehensive Cancer Network (NCCN).

Risk group	Clinical/pathological features			
Very low	Has all of the following:	cT1c		
		Gleason 6 (ISUP Grade Group 1)		
		PSA <10 ng/ml		
		<3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core		
		PSA density <0.15 ng/ml/g		
Low	Has all of the following but does not qualify for very low risk:	cT1–cT2a		
		Gleason 6 (ISUP Grade Group 1)		
		PSA <10 ng/ml		
Intermediate	Has all of the following:	No high-risk group features		
		No very high-risk group features		
		Has one or more intermediate risk factors:	cT2b–cT2c	
			Gleason 7 (7a = 3 + 4 or 7b = 4 + 3) (ISUP Grade Group 2 or 3)	
			PSA 10–20 ng/ml	
		Favourable intermediate	Has all of the following:	1 intermediate-risk feature
				Gleason 6 or 7a (ISUP Grade Group 1 or 2)
				<50% biopsy cores positive (e.g., <6 of 12 cores)
		Unfavourable intermediate	Has one or more of the following:	2 or 3 intermediate-risk features
				Gleason 7b (ISUP Grade Group 3)
				≥50% biopsy cores positive (e.g., ≥6 of 12 cores)
High	Has no very high-risk features and has exactly one high-risk feature:	cT3a OR		
		Gleason 8–10 (ISUP Grade Group 4 or 5) OR		
		PSA >20 ng/ml		
Very high	Has at least one of the following:	cT3b–cT4		
		Primary Gleason pattern 5		
		2 or 3 high-risk features		
		>4 cores with Gleason 8–10 (ISUP Grade Group 4 or 5)		

tion of treatment recommendations for men with *synchronous high volume* mHSPC: 60% were in favour of a triplet therapy, and 33% recommended doublet therapy (i.e., androgen deprivation therapy plus docetaxel or ARPI). In cases of *synchronous low volume* disease, there was consensus (80%) for the use of androgen deprivation therapy plus ARPI (while 20% of experts recommended androgen deprivation therapy plus docetaxel or ARPI). For men with *metachronous high volume* mHSPC, 47% of experts recommended triplet therapy, 27% androgen deprivation therapy plus ARPI and 27% androgen deprivation therapy plus docetaxel or ARPI. For men with *metachronous low volume* mHSPC, experts reached consensus (93%) for the use of androgen deprivation therapy plus ARPI. In the latter situation, 50% were in favour of treatment until progression (as in the pivotal studies), whereas 29% opted for holding both androgen deprivation therapy and ARPI in the case of a favourable response (i.e., PSA <0.2 ng/ml) after 2 years with rechallenge upon progression (21% recommended discontinuing the ARPI only with rechallenge at progression). In the case of triplet therapy, 40% and 20% of experts were in favour of using darolutamide and abiraterone, respectively, while the remaining 40% had no preference.

Low volume mHSPC (defined as up to four bone metastases) has been shown to be predictive of benefits from local radiotherapy of the prostate, with an 8% gain in absolute overall survival after 3 years [16]. However, none of the participants in this trial had received an ARPI, so it remains uncertain whether a combination of both modalities is needed. Of all Swiss panellists, 47% recommended radiation therapy of the primary tumour in addition to ARPI for the majority of patients, while 47% recommended this approach only in select patients (e.g., younger patients), and 7% did not recommend radiation of the prostate in addition to ARPI.

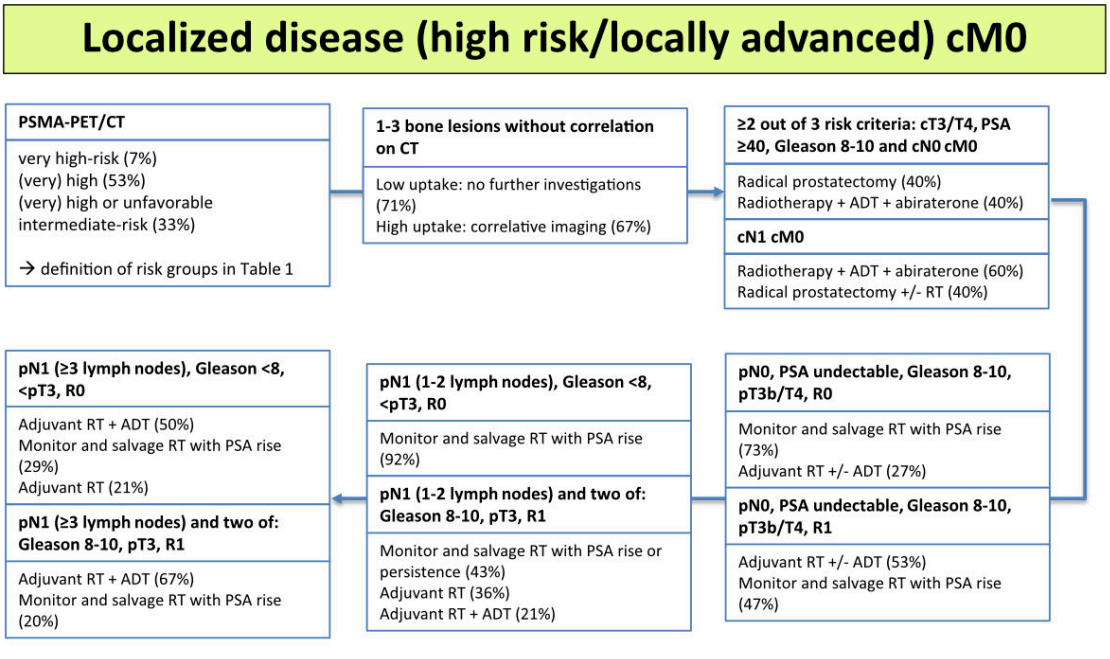
Metastasis-directed therapy (MDT)

A majority of experts (73%) agreed that treatment recommendations for MDT should not be based on conventional imaging (i.e., CT plus a bone scan) only. In cases of synchronous low volume mHSPC with one to three bone lesions on PSMA PET/CT, 57% of panellists favoured systemic therapy plus local treatment of the primary tumour plus MDT, while 36% voted for systemic therapy plus local treatment of the primary tumour only. In a similar scenario with metachronous disease, 53% of experts recommended systemic therapy plus MDT, while 27% favoured MDT without systemic treatment, and 20% favoured systemic treatment alone. Clear consensus (93%) was reached regarding the type of MDT, namely radiotherapy. For men with synchronous low volume mHSPC and one to three PSMA PET/CT–positive retroperitoneal lymph nodes, there was no preference (47% of the votes each) for systemic therapy plus local treatment of the primary tumour or systemic therapy plus local treatment of the primary tumour plus MDT. The results of relevant votes are summarized in Figure 4. Importantly, the evidence for the effectiveness of MDT in these patients is currently based on small phase 2 trials and is not supported by large trials showing improvement of relevant oncological outcomes.

Additional investigations and follow-up in mHSPC SDtients

There was consensus (87%) that molecular tests (i.e., next-generation sequencing) would not influence the decision of the first-line treatment for mHSPC even if available without restrictions. Given the lack of high-quality data on

Figure 3: Staging and treatment of (very) high-risk localized and locally advanced disease (no distant metastasis), with percentages indicating the voting results. ADT, androgen deprivation therapy; cM0, no distant metastases; cN0, no locoregional lymph node metastases; CT, computed tomography; PSA, prostate-specific antigen; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RT, radiotherapy. Please refer to https://www.swissmedicinfo.ch for approved indications.



follow-up modalities and intervals during the treatment of mHSPC, the following questions were discussed. In the absence of symptoms, 47% of experts recommended regular imaging, e.g., every 6–12 months, regardless of PSA, while 33% recommended imaging after about 6–12 months and then no more imaging until confirmed PSA progression, and 20% recommended imaging prompted only by rising PSA. As for imaging modality, 53% of panellists opted for conventional imaging (CT with or without a bone scan), whereas 27% and 13% favoured PET/CT and whole-body MRI, respectively. Again, there is very limited evidence for how to interpret, e.g., PSMA PET/CT in patients responding to systemic therapy, and, in fact, in Switzerland PSMA PET/CT is not approved or reimbursed in this situation.

Metastatic castration-resistant prostate cancer (mCRPC)

Selection of first-line therapy and treatment sequence

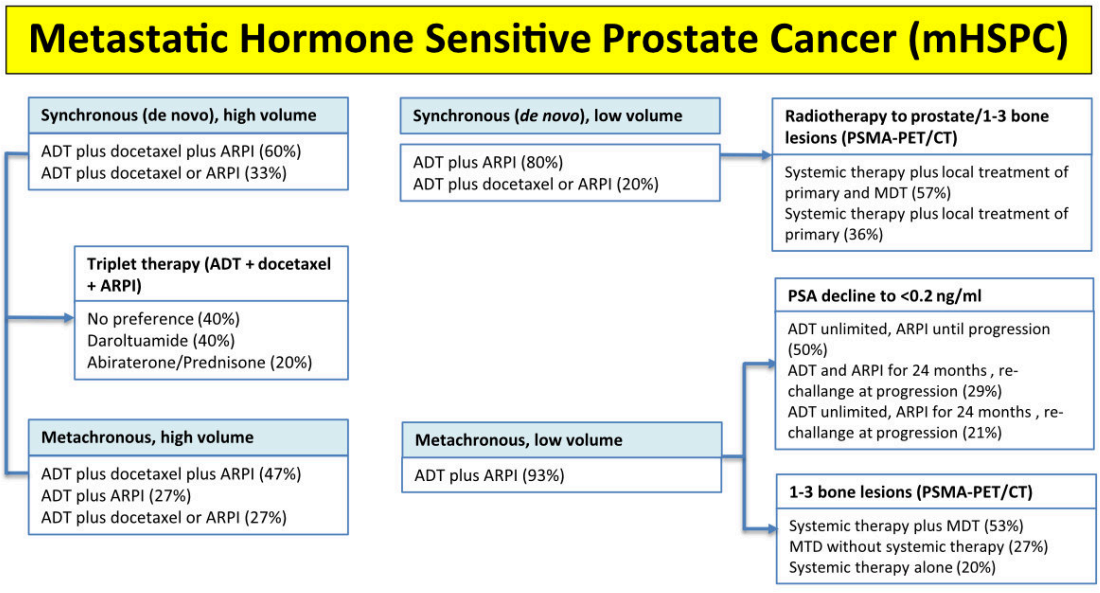
In the absence of alterations of DNA damage response and repair (DDR) genes, all experts (100%) recommended an ARPI as a first-line therapy for mCRPC in men who received androgen deprivation therapy as monotherapy for mHSPC. In cases of time to castration resistance of less than 6 months (i.e., progression within 6 months of the start of androgen deprivation therapy), the use of ARPI or chemotherapy was considered adequate (both options were recommended by 47% of experts). For men treated with an ARPI in the case of mHSPC, all panellists (100%) recommend a switch to chemotherapy, irrespective of time to castration resistance.

Most experts (64%) did not recommend a switch to another ARPI therapy in the majority of patients who have received one line of ARPI and then have progressed. By contrast, 29% deemed a switch appropriate in select patients who had a prior response to abiraterone and subsequently progressed. The basis for the latter recommendation is a study showing a PSA response rate of 19% in this situation [17], while, e.g., abiraterone after enzalutamide was associated with a very low PSA response rate of around 1% [18].

PARP inhibition

In around 10% of mCRPC cases, tumours harbour a pathogenic *BRCA1/2* alteration (around half of which is germ line) [19, 20] that is predictive of benefits from PARP inhibition. Recently, studies combining new endocrine therapies (e.g., abiraterone or enzalutamide) with PARP inhibitors (e.g., olaparib, niraparib or talazoparib) have reported longer radiographic progression-free survival with the combination, irrespective of DDR status, at the cost of increased toxicity and no improvement in overall survival for unselected populations [21–23]. In all these studies, in most cases castration resistance had occurred in patients receiving androgen deprivation therapy as monotherapy. There was consensus (93%) not to combine ARPI with a PARP inhibitor as first-line therapy for mCRPC, irrespective of DDR status. However, for men with mCRPC with a pathogenic *BRCA1/2* alteration who developed castration resistance during androgen deprivation therapy and an ARPI (with or without docetaxel), 38% of experts recommended a switch to PARP inhibitor monotherapy, whereas others favoured a switch to chemotherapy (31%) or the addition of a PARP inhibitor to continued ARPI (31%). In cases of other (i.e., not *BRCA1/2*) pathogenic DNA repair gene alterations, there was consensus (86%) to switch to chemotherapy.

Figure 4: Treatment of metastatic hormone-sensitive prostate cancer (mHSPC), with percentages indicating the voting results. High volume: visceral disease and/or at least 4 bone metastasis of which at least one outside the pelvis and vertebral column. Low volume: high volume criteria not met. ADT, androgendeprivation therapy; ARPI, androgen receptor pathway inhibitor (abiraterone, enzalutamide, apalutamide, darolutamide); CT, computed tomography; MTD, metastasis directed therapy; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RT, radiotherapy. Please refer to https://www.swissmedicinfo.ch for approved indications.



Radionuclide therapy

The use of ^{177}Lu-PSMA has led to an overall survival benefit in patients with mCRPC and pretreatment with ARPI and docetaxel if PSMA avidity has been demonstrated on a staging PSMA PET/CT [24]. In men with symptomatic mCRPC who met criteria for treatment with both ^{223}Ra and ^{177}Lu-PSMA, there was consensus (80%) in favour of using ^{177}Lu-PSMA, while 13% of experts had no preference. Furthermore, there was consensus (93%) to recommend ^{177}Lu-PSMA after prior treatment with docetaxel and an ARPI.

Imaging and follow-up for mCRPC patients

The majority of the panel (73%) recommended imaging every 3–6 months for men being treated for mCRPC, regardless of PSA and in the absence of new symptoms. In terms of imaging modality, 47% of panellists favoured CT scans (with or without a bone scan), while 29%, 14% and 7% opted for a CT scan plus a bone scan, whole-body MRI and PET/CT, respectively.

The results of relevant votes are summarized in figure 5.

Health-economic aspects

Concerns about the availability and costs of modern therapies were prevalent among the participants in the consensus meeting. When asked whether financial cost to the health care system should be considered when making treatment decisions or recommendations, 89% of experts responded “yes, absolutely” and 11% “no, not at all”. It remains to be determined how this can be achieved in daily practice while ensuring optimal treatment for all our patients. First steps might be using generic drugs, if available; de-escalation strategies; and strict adherence to the principle that diagnostic procedures must have a therapeutic consequence.

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Potential conflicts of interest
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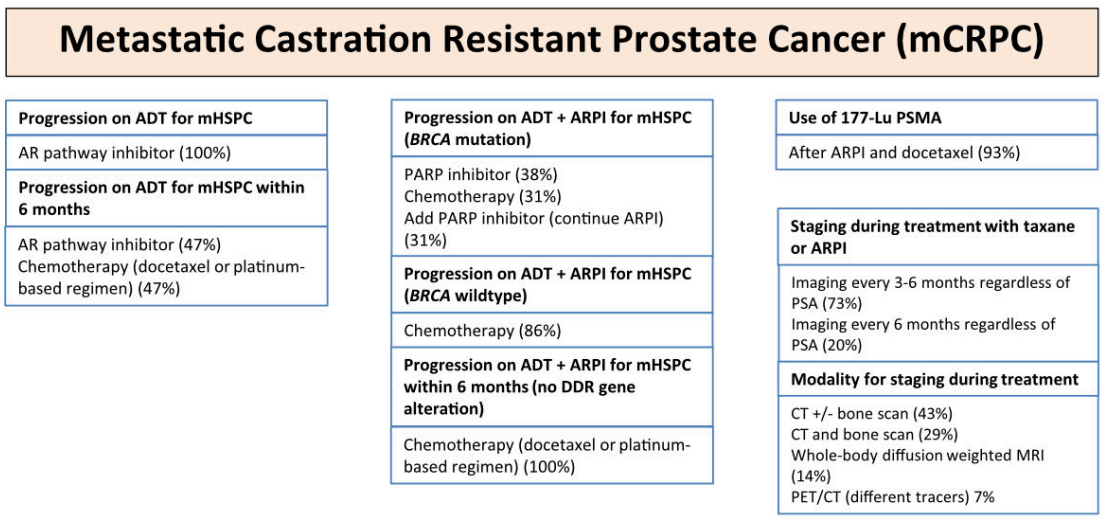
Figure 5: Treatment and staging of metastatic castration-resistant prostate cancer (mCRPC), with percentages indicating the voting results. ADT, androgendeprivation therapy; AR, androgen receptor; ARPI, androgen receptor pathway inhibitor; BRCA, breast cancer gene; DDR, DNA Damage Response and Repair; Lu, Lutetium; mHSPC, metastatic hormone sensitive prostate cancer; CT, computed tomography; MRI, magnet resonance imaging; PARP, Poly ADP-Ribose Polymerase; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen. Please refer to https://www.swissmedicinfo.ch for approved indications.



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P, personal compensation; I, compensation to institution

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