

UPDATE

Open Access



Update to a randomized controlled trial of Lutetium-177-PSMA in Oligo-metastatic hormone-sensitive prostate cancer: the BULLSEYE trial

Bastiaan M. Privé¹ , Marcel J. R. Janssen¹, Inge M. van Oort², Constantijn H. J. Muselaers², Marianne A. Jonker³, Willemijn A. van Gemert¹, Michel de Groot¹, Harm Westdorp⁴, Niven Mehra⁴, J. Fred Verzijlbergen¹, Tom W. J. Scheenen¹, Patrik Zámečník¹, Jelle O. Barentsz¹, Martin Gotthardt¹, Walter Noordzij⁵, Wouter V. Vogel^{6,7}, Andries M. Bergman⁸, Henk G. van der Poel⁹, André N. Vis¹⁰, Daniela E. Oprea-Lager¹¹, Winald R. Gerritsen⁴, J. Alfred Witjes² and James Nagarajah^{1*}

Abstract

Background: The BULLSEYE trial is a multicenter, open-label, randomized controlled trial to test the hypothesis if ¹⁷⁷Lu-PSMA is an effective treatment in oligometastatic hormone-sensitive prostate cancer (oHSPC) to prolong the progression-free survival (PFS) and postpone the need for androgen deprivation therapy (ADT). The original study protocol was published in 2020. Here, we report amendments that have been made to the study protocol since the commencement of the trial.

Changes in methods and materials: Two important changes were made to the original protocol: (1) the study will now use ¹⁷⁷Lu-PSMA-617 instead of ¹⁷⁷Lu-PSMA-I&T and (2) responding patients with residual disease on ¹⁸F-PSMA PET after the first two cycles are eligible to receive additional two cycles of 7.4 GBq ¹⁷⁷Lu-PSMA in weeks 12 and 18, summing up to a maximum of 4 cycles if indicated. Therefore, patients receiving ¹⁷⁷Lu-PSMA-617 will also receive an interim ¹⁸F-PSMA PET scan in week 4 after cycle 2. The title of this study was modified to; “Lutetium-177-PSMA in Oligo-metastatic Hormone Sensitive Prostate Cancer” and is now partly supported by Advanced Accelerator Applications, a Novartis Company.

Conclusions: We present an update of the original study protocol prior to the completion of the study. Treatment arm patients that were included and received ¹⁷⁷Lu-PSMA-I&T under the previous protocol will be replaced.

Trial registration: ClinicalTrials.gov [NCT04443062](https://clinicaltrials.gov/ct2/show/study/NCT04443062). First posted: June 23, 2020.

Keywords: Hormone-sensitive prostate cancer, Lutetium-177-PSMA, Metastases-directed therapy, Oligometastases, Radioligand therapy, Urologic oncology

* Correspondence: james.nagarajah@radboudumc.nl

¹Department of Radiology and Nuclear Medicine, Radboudumc, Geert Grooteplein Zuid 10, 6525, GA, Nijmegen, The Netherlands
Full list of author information is available at the end of the article



© The Author(s). 2021 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Background

Prostate cancer is the most common non-skin cancer in males [1]. Despite surgery or external beam radiotherapy (EBRT), between 27% and 53% of patients will have a detectable prostate-specific antigen (PSA) and present with disease recurrence [2]. If there are no curative options, patients with a short PSA doubling time (e.g., <6 months) have a worse prognosis and early androgen deprivation therapy (ADT) is the treatment of choice [3–5]. While ADT delays disease progression of patients, it is associated with significant side effects and frequently impairs the quality of life [6]. Therefore, there is an increasing interest in treatments to postpone ADT while maintaining a good quality of life.

Lately, metastases-directed therapy (MDT) (e.g., EBRT) is showing promising efficacy to postpone ADT or cure selected patients with solely low-grade treatment-related side effects. Studies have reported that approximately 30–40% of patients that underwent MDT are still without ADT 5 years post-irradiation [7–10]. Particularly, patients with a limited number of metastases (≤ 5 metastases), the so-called oligometastatic prostate cancer, seem to benefit from MDT [7, 9, 11, 12]. Therefore, several pivotal trials are currently investigating MDT in an oligometastatic setting.

All these studies rely on imaging modalities such as positron emission tomography (PET) to detect and target these tumor metastases [13–16]. The currently favored PET tracers in prostate cancer are Gallium-68 (^{68}Ga) or Fluor-18 (^{18}F)-labeled prostate-specific membrane antigen (PSMA) ligands (PSMA-11, DCFPyL, or PSMA-1007). However, PSMA ligands, such as PSMA-617 & PSMA-I&T, can also be labeled with beta emitters like Lutetium-177 (^{177}Lu) for radioligand therapy to deliver high local radiation doses to tumors directly [17–22].

^{177}Lu -labeled PSMA is a promising new therapeutic approach with the pending registry in the 3rd or 4th line castration-resistant prostate cancer [21]. Recently, we showed that ^{177}Lu -PSMA is also highly effective in the hormone-sensitive setting with low volume disease because of high tumor uptake of PSMA targeted radioligands in small lesions, such as oligometastatic prostate cancer [17, 18, 23]. Moreover, the favorable toxicity profile of ^{177}Lu -PSMA seen in our pilot study supports this new treatment in this setting. Therefore, we initiated a prospective randomized multicenter phase II study that evaluates the efficacy of ^{177}Lu -PSMA in oHSPC to postpone disease progression and to avert the need for ADT. This study protocol was published in 2020, but was recently amended. The changes to the protocol are described in the present report [24].

Changes to the protocol

The original protocol was designed using the PSMA ligand PSMA-I&T, which can be labeled with ^{177}Lu in our

local laboratory following GMP conditions. Unfortunately, due to COVID-19-related issues (e.g., personnel shortage, remote working, and increased demand for hospital resources), the production of ^{177}Lu -PSMA-I&T for our study did not receive a priority designation in our hospitals. Therefore, the study required a third party for the stable production of ^{177}Lu -PSMA and a logistical party to supply all participating centers. The study will now use ^{177}Lu -PSMA-617 as Advanced Accelerator Applications stepped in for support. The study also received a new title “Lutetium-177-PSMA in Oligometastatic Hormone Sensitive Prostate Cancer.”

As some patients may have a residual disease with good PSMA uptake after two cycles of 7.4 GBq ^{177}Lu -PSMA, with no or only low-grade side effects, the present protocol enables an additional two cycles if this is thought beneficial for patients. Thus, patients in the therapeutic arm (or those in the control arm that met the primary endpoint and now receive ^{177}Lu -PSMA) are eligible for another two cycles of 7.4 GBq of ^{177}Lu -PSMA given 12 and 18 weeks after cycle one. To evaluate if the residual disease is present after the first two cycles, patients will also undergo an interim ^{18}F -PSMA PET scan 4 weeks (± 1 week) after cycle two.

Study progress

Since recruitment began in July 2020, only three patients were included prior to the amendments reported above. One patient was allocated to the therapeutic arm and received two cycles of ^{177}Lu -PSMA-I&T. This patient will be replaced by a new patient under the amended protocol. The two control arm patients will not be replaced and will be eligible to receive ^{177}Lu -PSMA-617 in case they meet the primary endpoint, which is disease progression within 24 weeks post cycle two.

Conclusion

After the publication of the original protocol, the study was amended due to COVID-19-related issues to acquire third-party support for the labeling of the radiopharmaceutical. Therefore, the study will now use ^{177}Lu -PSMA-617 instead of ^{177}Lu -PSMA-I&T. In addition, patients with residual disease on ^{18}F -PSMA PET after the first two cycles are eligible to receive an additional two cycles of 7.4 GBq ^{177}Lu -PSMA in week 12 and week 18 after cycle one, summing up to a maximum of 4 cycles if necessary.

Abbreviations

^{68}Ga : Gallium-68; ^{18}F : Fluor-18; ^{177}Lu : Lutetium-177; ADT: Androgen deprivation therapy; EBRT: External beam radiotherapy; MDT: Metastases directed therapy; oHSPC: Oligometastatic hormone-sensitive prostate cancer; PET: Positron emission tomography; PSA: Prostate-specific antigen; PSMA: Prostate-specific membrane antigen

Acknowledgements

We thank all the investigators of the study, the participating study sites, the patients, and their families.

Authors' contributions

JN, AW, WG, DOL, WV, and WN as the principal investigators in different hospitals and departments and BP, MJ, MG, MJ, SM, IO, NM, and JB as the sub-investigators who conceived and designed the study. BP and JN drafted the original study protocol. The authors contributed to the manuscript and approved its submission. All authors are responsible for the daily running of the trial.

Funding

This study is funded by the Prostaatkankerstichting (Dutch prostate cancer foundation) and by Advanced Accelerator Applications, a Novartis Company. The granting will not have any role in the collection, analysis, and interpretation of data and in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol and the following amendments were approved by the Medical Review Ethics Committee Arnhem-Nijmegen, The Netherlands. All study participants will provide informed consent before study entry.

Consent for publication

Not applicable.

Competing interests

JN receives research support from ABX Pharmaceuticals and Advanced Accelerator Applications.

Author details

¹Department of Radiology and Nuclear Medicine, Radboudumc, Geert Grooteplein Zuid 10, 6525, GA, Nijmegen, The Netherlands. ²Department of Urology, Radboudumc, Nijmegen, The Netherlands. ³Department of Health Evidence, Radboudumc, Nijmegen, The Netherlands. ⁴Department of Medical Oncology, Radboudumc, Nijmegen, The Netherlands. ⁵Department of Radiology and Nuclear Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. ⁶Department of Radiology and Nuclear Medicine, NKI Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands. ⁷Department of Radiation Oncology, NKI Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands. ⁸Department of Medical Oncology, NKI Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands. ⁹Department of Urology, NKI Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands. ¹⁰Department of Urology, Amsterdam University Medical Center, Amsterdam, The Netherlands. ¹¹Department of Radiology and Nuclear Medicine, Amsterdam University Medical Center, Amsterdam, The Netherlands.

Received: 24 August 2021 Accepted: 19 October 2021

Published online: 04 November 2021

References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424. <https://doi.org/10.3322/caac.21492>.
- Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II—2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. *Eur Urol*. 2021;79(2):263–82. <https://doi.org/10.1016/j.eururo.2020.09.046>.
- Freedland SJ, Eastham J, Shore N. Androgen deprivation therapy and estrogen deficiency induced adverse effects in the treatment of prostate cancer. *Prostate Cancer Prostatic Dis*. 2009;12(4):333–8. <https://doi.org/10.1038/pcan.2009.35>.
- Zhou P, Chen MH, McLeod D, Carroll PR, Moul JW, D'Amico AV. Predictors of prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *J Clin Oncol*. 2005;23(28):6992–8. <https://doi.org/10.1200/JCO.2005.01.2906>.
- Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. *Eur Urol*. 2017;71(4):630–42. <https://doi.org/10.1016/j.eururo.2016.08.002>.
- Ahmadi H, Daneshmand S. Androgen deprivation therapy: evidence-based management of side effects. *BJU Int*. 2013;111(4):543–8. <https://doi.org/10.1111/j.1464-410X.2012.11774.x>.
- Deek MP, Taparra K, Dao D, Chan L, Phillips R, Gao RW, et al. Patterns of recurrence and modes of progression after metastasis-directed therapy in oligometastatic castration-sensitive prostate cancer. *Int J Radiat Oncol Biol Phys*. 2021;109(2):387–95.
- Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, Bruycker AD, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence (STOMP): five-year results of a randomized phase II trial. *J Clin Oncol*. 2020;38(6_suppl):10.
- Phillips R, Shi WY, Deek M, Radwan N, Lim SJ, Antonarakis ES, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. *JAMA Oncol*. 2020;6(5):650–9. <https://doi.org/10.1001/jamaoncol.2020.0147>.
- Schmidt-Hegemann NS, Kroeze SGC, Henkenberens C, Vogel MME, Kirste S, Becker J, et al. Influence of localization of PSMA-positive oligo-metastases on efficacy of metastasis-directed external-beam radiotherapy—a multicenter retrospective study. *Eur J Nucl Med Mol Imaging*. 2020;47(8):1852–63. <https://doi.org/10.1007/s00259-020-04708-y>.
- Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol*. 2018;36(5):446–53. <https://doi.org/10.1200/JCO.2017.75.4853>.
- Tosoian JJ, Gorin MA, Ross AE, Pienta KJ, Tran PT, Schaeffer EM. Oligometastatic prostate cancer: definitions, clinical outcomes, and treatment considerations. *Nat Rev Urol*. 2017;14(1):15–25. <https://doi.org/10.1038/nrurol.2016.175>.
- Lecouvet FE, Oprea-Lager DE, Liu Y, Ost P, Bidaut L, Collette L, et al. Use of modern imaging methods to facilitate trials of metastasis-directed therapy for oligometastatic disease in prostate cancer: a consensus recommendation from the EORTC Imaging Group. *Lancet Oncol*. 2018;19(10):e534–45. [https://doi.org/10.1016/S1470-2045\(18\)30571-0](https://doi.org/10.1016/S1470-2045(18)30571-0).
- Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multi-centre study. *Lancet*.
- Schilham MG, Zamecnik P, Privé BM, Israël B, Rijkema M, Scheenen T, et al. Head-to-head comparison of ⁶⁸Ga-prostate-specific membrane antigen PET/CT and ferumoxtran-10 enhanced MRI for the diagnosis of lymph node metastases in prostate cancer patients. *J Nucl Med*. 2021;jnumed.120.258541.
- Privé BM, Israël B, Schilham MGM, Muselaers CHJ, Zámečnik P, Mulders PFA, et al. Evaluating F-18-PSMA-1007-PET in primary prostate cancer and comparing it to multi-parametric MRI and histopathology. *Prostate Cancer Prostatic Dis*. 2020;24(2):423–30. <https://doi.org/10.1038/s41391-020-00292-2>.
- Privé B, Peters S, Muselaers C, Zamecnik P, Janssen M, Scheenen T, et al. Lutetium-177-PSMA-617 in low-volume hormone sensitive metastatic prostate cancer: a prospective study. 2020;59.
- Peters SMB, Privé BM, de Bakker M, de Lange F, Jentzen W, Eek A, et al. Intra-therapeutic dosimetry of [177Lu]Lu-PSMA-617 in low-volume hormone-sensitive metastatic prostate cancer patients and correlation with treatment outcome. *Eur J Nucl Med Mol Imaging*. 2021. <https://doi.org/10.1007/s00259-021-05471-4>.
- Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC, et al. [¹⁷⁷Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet*. 2021;397(10276):797–804. [https://doi.org/10.1016/S0140-6736\(21\)00237-3](https://doi.org/10.1016/S0140-6736(21)00237-3).
- Violet J, Jackson P, Ferdinandus J, Sandhu S, Akhurst T, Iravani A, et al. Dosimetry of (177Lu)PSMA-617 in metastatic castration-resistant prostate cancer: correlations between pretherapeutic imaging and whole-body

- tumor dosimetry with treatment outcomes. *J Nucl Med.* 2019;60(4):517–23. <https://doi.org/10.2967/jnumed.118.219352>.
21. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med.* 2021;385(12):1091–103. <https://doi.org/10.1056/NEJMoa2107322>.
 22. Privé BM, Slootbeek PHJ, Laarhuis BI, Naga SP, van der Doelen MJ, van Kalmthout LWM, et al. Impact of DNA damage repair defects on response to PSMA radioligand therapy in metastatic castration-resistant prostate cancer. *Prostate Cancer Prostatic Dis.* 2021. <https://doi.org/10.1038/s41391-021-00424-2>.
 23. O'Donoghue JA, Bardies M, Wheldon TE. Relationships between tumor size and curability for uniformly targeted therapy with beta-emitting radionuclides. *J Nucl Med.* 1995;36(10):1902–9.
 24. Privé BM, Janssen MJR, van Oort IM, Muselaers CHJ, Jonker MA, de Groot M, et al. Lutetium-177-PSMA-I&T as metastases directed therapy in oligometastatic hormone sensitive prostate cancer, a randomized controlled trial. *BMC Cancer.* 2020;20(1):884. <https://doi.org/10.1186/s12885-020-07386-z>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

