**Original Article**

**Folate hydrolase-1 (FOLH1) is a novel target for antibody-based brachytherapy in Merkel cell carcinoma**

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**Abstract**

**Backgrounds:** Folate Hydrolase-1 (FOLH1; PSMA) is a type II trans-membrane protein, luminally expressed by solid tumour neo-vasculature. Monoclonal antibody (mAb), J591, is a vehicle for mAb-based brachytherapy in FOLH1+ cancers. Brachytherapy is a form of radiotherapy that involves placing a radioactive material a short distance from the target tissue (e.g., on the skin or internally); brachytherapy is commonly accomplished with the use of catheters, needles, metal seeds and antibody or small peptide conjugates. Herein, FOLH1 expression in primary (p) and metastatic (m) Merkel cell carcinoma (MCC) is characterized to determine its targeting potential for J591-brachytherapy.

**Materials & Methods:** Paraffin sections from pMCC and mMCC were evaluated by immunohistochemistry for FOLH1. Monte Carlo simulation was performed using the physical properties of conjugated radioisotope lutetium-177. Kaplan–Meier survival curves were calculated based on patient outcome data and FOLH1 expression.

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The incidence rates of Merkel cell carcinoma (MCC), an aggressive cutaneous malignancy, have tripled from 0.15 cases per 100 000 individuals in 1986 to 0.7 per 100 000 in 2013, corresponding to 2488 cases/year. MCC is three times more lethal than melanoma, with a 46% disease-associated mortality rate, and 5-year disease-specific survival rates of 66% and 11%–30% for local and metastatic disease, respectively. These concerning survival rates reflect MCC’s propensity for local recurrence and regional nodal involvement, where 30-50% of locally staged patients eventually develop a distant metastasis.

MCC is often diagnosed late in its pathogenesis, thereby requiring systemic approaches early in management. Systemic therapy using standard chemotherapeutic agents such as etoposide, epirubicin, doxorubicin, cyclophosphamide and cisplatin-based chemotherapeutic regimens as radiosensitizers or as definitive treatment remains disappointing. These systemic agents are associated with high toxicity rates, transient responses, resistance and no overall survival benefits. MCC’s poor prognosis, high recurrence and mortality rates, in parallel with disappointing outcomes associated to conventional treatments, warrant evaluating alternative therapeutic modalities. The need for novel strategies to treat rare diseases like MCC is recognized by the U. S. Food and Drug Administration (FDA), assisting in drug development for diseases affecting fewer than 200 000 people by providing financial and logistical incentives.

Recent studies showing PD-L1 expression in the tumour microenvironment of MCCs, and PD-1 expression by MCC-specific tumour infiltrating and circulating T cells, supported investigating the utility of immune checkpoint inhibitors. A phase 2 trial of avelumab (a human anti-PD-L1 IgG1 monoclonal antibody [mAb]) in patients with metastatic (m) MCC that was refractory to chemotherapy, demonstrated a 31.8% durable objective response rate, according to Response Evaluation Criteria in Solid Tumors version 1.1, culminating in avelumab being the first FDA-approved immunotherapy for MCC in March 2017.

Despite these promising results with use of targeted immunotherapy, approximately half of patients do not respond to PD-1/PD-L1 axis targeting, necessitating development of alternative or additional therapeutic strategies. MCC tumours and metastatic deposits have large mitotic fractions that are susceptible to ionizing radiation damage. They are highly vascularized, leading to intrinsic sensitivity to photon and electron external beam radiation therapy (EBRT) via an increased oxygen enhancement ratio. Several studies and the NCCN guidelines promote definitive or adjuvant EBRT to optimize localized tumour control in primary (p) MCC that are surgically inoperable, resections with borderline or positive margin status, tumours greater than 1 cm in the context of a positive lymph node biopsy, presence of lymphovascular invasion, and history of immunodeficiency.

Although MCC is intrinsically radiosensitive, the field size of conventional treatment with EBRT for
widespread disease is limited by the radiation tolerance of normal tissues or organs at risk surrounding tumour deposits (e.g., optic nerve, spinal cord, lung).

Brachytherapy is an alternative form of radiotherapy that involves placing a radioactive material a short distance from the target tissue (e.g., on the skin or internally); brachytherapy is commonly accomplished with the use of catheters, needles, metal seeds and antibody or small peptide conjugates. Antibody-based brachytherapy is a clinically validated form of radiation therapy that uses a mAb to deliver radioactive isotopes directly to sites of local and metastasized cancer. The intrinsic properties of radioisotope lutetium-177 ($^{177}$Lu), make it an ideal candidate for antibody-based brachytherapy: $^{177}$Lu decays by $\beta$ particle (i.e., electrons) emission (0.497 MeV; $t_{1/2} = 6.74$ days) of relatively short-range (0.2–0.3 mm). The calculated optimal tumour size for treatment with $^{177}$Lu is thought to be 1.2–3 mm$^3$. For larger tumours, the clinical efficacy of longer range $\beta$ emitters has been

FIGURE 1  FOLH1 is expressed in the neo-vasculature of primary and meta-stastic Merkel cell carcinoma (a) Immunohistochemistry staining of metastatic MCC paraffin sections with a mouse IgG1 monoclonal anti-human FOLH1. (b) Immunofluorescent co-labelling of FOLH1 (green) with the endothelial marker CD31 (red) in a case of meta-static MCC. Arrows indicate co-labelling of FOLH1 and CD31 (yellow). FOLH1, folate hydrolase-1; MCC, Merkel cell carcinoma

FIGURE 2  Semi-quantification of FOLH1 staining intensity. The MCC cases were classified as $(\cdot\cdot\cdot\cdot)$, $(\cdot\cdot\cdot)$, $(\cdot\cdot\cdot\cdot\cdot)$ and $(\cdot\cdot\cdot\cdot\cdot\cdot)$ staining intensities; $(\cdot\cdot\cdot\cdot\cdot)$ was characterized as maximal staining as seen in prostate cancer where there is both cellular and neo-vascular staining. Both primary and metastatic MCC expressed significantly more FOLH1 as compared to healthy skin. $^{*}\ p < 0.01$. FOLH1, folate hydrolase-1; MCC, Merkel cell carcinoma
demonstrated, for example, yttrium-90 (Y). Clinical data on FOLH1-targeting with α-emitters (i.e., two protons and two neutrons) in prostate cancer (PCa) is promising and suggests that α-emitters could be considered for hypoxic tumours. Notably, the microdosimetry of antibody or peptide-based brachytherapy is currently in development.

The mAb J591 has demonstrated excellent tumour theragnostic specificity in PCa, and in the neo-vascularature of several solid tumours, via targeting of membrane-expressed (FOLH1; also known as prostate-specific membrane antigen) FOLH1. FOLH1 is a transmembrane enzyme receptor that is upregulated on the cell membrane of PCa, intracellularly in melanoma cells and the neo-vascular lumen of virtually all solid tumours (including PCa and melanoma). Importantly, there has not been a single patient reported to have toxicity to non-tumour-related vessels.

In vivo targeting of FOLH1 by conjugating auristatin (a cytotoxic agent) to J591 increased the therapeutic index of auristatin by 700-fold, and improved the median survival of PCa xenografts by 9 months. Clinically, 177Lu − J591 is well-tolerated, non-immunogenic, and can be fractionated. Studies with unconjugated J591 (i.e., mAb only) report no dose-limiting toxicities in patients with solid tumours. An ongoing trial is investigating in vivo localization of metastasized solid tumours with FOLH1 PET/CT imaging using positron emitting zirconium-89 (Zr)-J591, and the effects on tumour perfusion and cellularity with a cumulative dose of 70 mCi of 177Lu-J591 (NCT00967577).

Herein we aim to validate the expression of FOLH1 in pMCC and mMCC. Paraffin sections of pMCC and mMCC were provided by academic medical centers in Switzerland, Czech Republic, Germany and the United States. A total of 81 MCC tumours were evaluated for FOLH1 expression by standard immunohistochemistry. One pMCC and one mMCC tumour was obtained from the same patient. Primary antibodies used were 3E6 (DAKO) mouse IgG1 monoclonal anti-human FOLH1, mouse IgG1 isotype antibody (Abcam) and anti-CD31 (IgG1, Abcam). Mouse IgG1 isotype antibody (Abcam) at corresponding concentrations was used as a negative control. Anti-CD31 (IgG1) was used as a positive control to stain vasculature. Biotinylated goat-anti-mouse (Southern Biotech) was used as a secondary antibody. Sections were imaged with Aperio ScanScope (Leica Biosystems). The MCC cases were classified as (−), (+), (++), (+++) and (++++) staining.

**Figure 3** A demonstration of the track structure of 30 electrons emitted from 177Lu. The natural decay of 177Lu occurs spherically from its point source; for clarity, only electrons emitted in a single direction and visible in a single plane that is perpendicular to neo-vessel blood flow were depicted. A mean energy of 0.147 MeV was chosen to best depict the electron tracks. The figure demonstrates 30 electrons with the same energy of 0.147 MeV emitted from the same point on a neo-vessel within a MCC tumour, in the same 2D direction. Sites of overlapping ionization points and tumour cell nuclei (DAPI; Blue) are sites of potential DNA damage and subsequent cell death. Note, that the apparent discontinuity of the tracks are due to the fact that electrons in and out of the 2-D plane depicted in this figure, i.e., the tracks scatter above and below the plane. MCC, Merkel cell carcinoma.
intensities; (++++) was characterized as maximal staining as seen in PCa. Three dermatopathologists in New York, United States reviewed all slides for FOLH1 immunostaining and intensity. The slides were reviewed independently and together; in the setting of inter‐observer measurement difference, the measurement with majority agreement was used.

Overall, 67% (54/81) of cases showed FOLH1⁺ neo‐vessels. 77% (24/31) of pMCC cases and 60% (30/50) of mMCC cases demonstrated FOLH1‐positivity. FOLH1⁺ was restricted to MCC neo‐vessels (as confirmed by co‐labelling with anti‐CD31) (Figure 1a, b). No FOLH1 tumour cell staining was identified. The majority of FOLH1⁺ vessels were identified in the periphery of infiltrating tumour cells. One FOLH1⁺ paraffin section contained both p‐ and mMCC tumours (from the same patient), suggesting that biopsy of pMCC can predict some degree of FOLH1⁺

**Figure 4** Kaplan–Meier curves for MCC‐specific survival and recurrence free survival. No significant differences were detected based on (a and b) FOLH1 status (p = 0.4718; p = 0.6470), (c and d) staining intensity score (p = 0.6966; p = 0.9841), or by (e and f) grouping staining intensity scores (− and + vs. ++, +++−, ++++) (p = 0.8022; p = 0.8496) for MCC specific survival or recurrence free survival, respectively. FOLH1, folate hydrolase‐1; MCC, Merkel cell carcinoma.
**TABLE 1** Patient demographics

| Characteristic                        | FOLH1 negative (n = 6) | FOLH1 positive (n = 29) | Total cohort (n = 35) |
|--------------------------------------|------------------------|-------------------------|-----------------------|
| **Sex**                              |                        |                         |                       |
| Male (n = 21)                        | 3                      | 18                      | 0.664                 |
| Female (n = 14)                      | 3                      | 11                      | -                     |
| **Age at diagnosis**                 |                        |                         |                       |
| ≥65 (n = 26)                         | 3                      | 23                      | 0.162                 |
| <65 (n = 9)                          | 3                      | 6                       | -                     |
| **Immunosuppressed**                 |                        |                         |                       |
| Yes (n = 5)                          | 0                      | 5                       | 0.539                 |
| No (n = 18)                          | 4                      | 14                      | -                     |
| **Received RT to primary site**      |                        |                         |                       |
| Yes (n = 17)                         | 4                      | 13                      | 1                     |
| No (n = 3)                           | 0                      | 3                       | -                     |
| **Stage number**                     |                        |                         |                       |
| IA (n = 1)                           | 1                      | 0                       | 0.317                 |
| IB (n = 2)                           | 0                      | 3                       | -                     |
| IIA (n = 3)                          | 0                      | 2                       | -                     |
| IIB (n = 2)                          | 0                      | 2                       | -                     |
| IIIA (n = 7)                         | 2                      | 5                       | -                     |
| IIIB (n = 5)                         | 0                      | 5                       | -                     |
| IV (n = 3)                           | 1                      | 2                       | -                     |
| **Sentinel lymph node biopsy performed?** |                        |                         |                       |
| Yes (n = 13)                         | 3                      | 8                       | 0.616                 |
| No (n = 9)                           | 1                      | 8                       | -                     |
| **Site**                             |                        |                         |                       |
| Head & neck (n = 14)                 | 4                      | 10                      | 0.605                 |
| Trunk (n = 2)                        | 0                      | 2                       | -                     |
| Upper limb (n = 7)                   | 0                      | 7                       | -                     |
| Lower limb (n = 9)                   | 2                      | 7                       | -                     |
| Unknown primary (n = 1)              | 0                      | 1                       | -                     |
| **Received chemotherapy**            |                        |                         |                       |
| Yes (n = 6)                          | 2                      | 4                       | 0.549                 |
| No (n = 14)                          | 2                      | 12                      | -                     |
| **Local/Regional recurrence**        |                        |                         |                       |
| Yes (n = 8)                          | 1                      | 7                       | 1                     |
| No (n = 14)                          | 3                      | 11                      | -                     |
| **Draining LN recurrence**           |                        |                         |                       |
| Yes (n = 11)                         | 1                      | 10                      | 1                     |
| No (n = 9)                           | 2                      | 7                       | -                     |
| **Distant metastatic recurrence**    |                        |                         |                       |
| Yes (n = 13)                         | 2                      | 11                      | 0.587                 |
homogeneity in a meta-stasis. Semi-quantification of FOLH1 staining intensity showed that both pMCC and mMCC expressed significantly more FOLH1 as compared to healthy skin (Figure 2).

Monte Carlo simulation with MCNPX (V2.5.0) was used to calculate the tracks of 30 emitted electrons and ionization tracks in water media (as a surrogate for measuring absorbed dose in tissue or tumour) to show the penetration characteristics of $^{177}$Lu electrons (0.147 MeV mean energy) from a single point. The total range of the electrons at such energy level is in the order of 200 μm. The electron ionization tracks originating from a single point in water were then superimposed onto a neo-vessel in the histopathological image of a FOLH1+ MCC tumour to demonstrate the algorithmic predicted dose deposition points generated by FOLH1 targeting of a single point along a neo-vessel, and in a single direction perpendicular to blood flow (Figure 3). As supported by our Monte Carlo simulation, $^{177}$Lu-J591 provides a highly localized dose distribution, which permits specific, systemic targeting of disseminated disease with ionizing irradiation while limiting irradiation beyond the tumour boundaries (Figure 3).

Statistical analyses on patient survival were performed using Stata software version 14.0 (StataCorp). Survival analyses were calculated from time of diagnosis to the outcome event. For MCC-specific survival, an event was defined as death by MCC. Recurrence-free survival's event was either a MCC recurrence or death by MCC. Patients that were lost to follow-up were censored in all analyses. Kaplan–Meier survival curves were created to visualize patient survival outcome based on FOLH1 tumour expression (Figure 4). The log-rank test was performed to determine if there were differences between FOLH1 status groups and a $p$ value less than 0.05 was considered statistically significant.

Patient demographics, survival outcome, and FOLH1 neo-vessel expression data was available and evaluated in a cohort of 35/81 MCC patients (Table 1). Patients with FOLH1+ (in each group of staining intensity) and FOLH1− MCC were demographically homogeneous with regards to sex, age at diagnosis, immunosuppression status, prior therapies, stage at diagnosis and local or distant recurrences. No significant differences in our limited data set were detected based on FOLH1 status ($p = 0.4718$; $p = 0.6470$), staining intensity score ($p = 0.6966$; $p = 0.9841$), or by grouping staining intensity scores (− and + vs. ++, ++++, ++++) ($p = 0.8022$; $p = 0.8496$) for MCC-specific survival or recurrence free survival, respectively. Given the rarity of MCC, our results are not powered to show that there is no significant difference (Table 1).

Other studies have shown FOLH1 expression is not prognostic in renal cell carcinoma, but has prognostic implications in multiple other solid tumours. Nevertheless, MCC expression of FOLH1 is significantly more common than the observed expression of human epidermal growth factor receptor-2 (HER-2) in breast cancer (16%; 95% CI, 12%, 21%), and than the reported ~49% PD-L1 and ~55% PD-1 expression on MCC tumour cells and infiltrating lymphocytes, respectively. Comparison of FOLH1 target expression to HER-2, PD-L1 and PD-1 expression, suggests that FOLH1 may be a viable therapeutic target for MCC patients, particularly for treatment with antibody- or peptide-based brachytherapy.

As stated above, need for novel strategies to treat rare diseases like MCC is recognized by the US FDA. Targeted molecular and mAb-based therapies for MCC are promising strategies that depend on our evolving understanding of tumour biology and disease pathogenesis. To this end, we report the first evidence of prevalent FOLH1 expression within MCC-associated neo-vessels, in 60-77% of patients in a large MCC cohort. We also demonstrate the first illustrative step towards dose calculation and radiation treatment planning for antibody-based brachytherapy (patent pending) via Monte Carlo simulation and immunohistochemistry. Given this data, and the need for alternatives to immune therapies, it is appropriate to explore the safety and efficacy of FOLH1-targeted brachytherapy for MCC.

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**TABLE 1 (Continued)**

| Characteristic | FOLH1 negative (n = 6) | FOLH1 positive (n = 29) | Total cohort (n = 35) |
|---------------|------------------------|-------------------------|----------------------|
| No (n = 7)    | 2                      | 5                       | -                    |
| MCC cells     |                        |                         |                      |
| 50%–75% (n = 7) | 2                      | 5                       | 0.587                |
| 76%–100% (n = 13) | 2                     | 11                      | -                    |

Abbreviations: FOLH1, folate hydrolase-1; LN, lymph node; MCC, Merkel cell carcinoma; RT, radiotherapy.
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CONFLICTS OF INTEREST
Dr. Neil Bander is an inventor on patents that are assigned to Cornell Research Foundation (CRF) for the PSMA/FOLH1 antibody technology utilized in this article. Dr. Neil Bander is a paid consultant to and owns stock in BZL Biologics, the company to which the patents were licensed by CRF for further research and development. Dr. Paul Nghiem serves as a paid consultant for EMD Serono. Bristol Myers Squibb has provided research support to Dr. Nghiem’s institution.

AUTHOR CONTRIBUTIONS
M. K. Ramirez-Fort: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – review & editing. B. Meier-SchiESSer: Conceptualization; Data curation; Investigation; Methodology; Validation; Visualization; Writing – review & editing. K. Lachance: Data curation; Software; Validation; Visualization; Writing – original draft. S. S. Mahase: Writing – original draft; Writing – review & editing. C. D. Church: Data curation; Formal analysis; Resources; Software; Validation; Writing – review & editing. M. J. Niaz: Data curation; Investigation; Writing – review & editing. H. Liu: Conceptualization; Data curation; Formal analysis; Project administration; Supervision; Visualization; Writing – review & editing. V. Navarro: Data curation; Investigation; Methodology; Validation; Visualization; Writing – review & editing. A. Nikolopoulos: Conceptualization; Formal analysis; Writing – review & editing. D. V. Kazakov: Data curation; Resources; Writing – review & editing. E. Contassot: Data curation; Project administration; Resources; Supervision; Validation; Writing – review & editing. J. Sach: Data curation; Resources; Writing – review & editing. L. Hadravsky: Investigation; Resources; Validation; Writing – review & editing. Y. Sheng: Data curation; Formal analysis; Investigation; Software; Writing – original draft; Writing – review & editing. S. T. Tagawa: Conceptualization; Formal analysis; Validation; Writing – review & editing. X. Wu: Conceptualization; Formal analysis; Investigation; Resources; Software; Supervision; Validation; Writing – review & editing. C. S. Lange: Formal analysis; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing. L. E. French: Conceptualization; Data curation; Formal analysis; Funding acquisition; Project administration; Resources; Supervision; Validation; Writing – review & editing. P. T. Nghiem: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing. N. H. Bander: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing – review & editing.

DATA AVAILABILITY STATEMENT
Data sets related to this article can be found at https://data.mendeley.com/datasets/p74ydi8b49/1, hosted at Mendeley.

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REFERENCES
1. Hodgson NC. Merkel cell carcinoma: changing incidence trends. J Surg Oncol. 2005;89(1):1–4.
2. Lemos B, Nghiem P. Merkel cell carcinoma: more deaths but still no pathway to blame. J Invest Dermatol. 2007;127(9):2100–2102.
3. Paulson KG, Park SY, VandeVen NA, et al. Merkel cell carcinoma: current US incidence and projected increases based on changing demographics. J Am Acad Dermatol. 2018;78(3):457–463.e2.
4. Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. J Clin Oncol. 2005;23(10):2300–2309.
5. Tothill R, Estall V, Rischin D. Merkel cell carcinoma: emerging biology, current approaches, and future directions. Am Soc Clin Oncol Educ Book. 2015;35:e519–e526.
6. Tai PT, Yu E, Tonita J, Gilchrist J. Merkel cell carcinoma of the skin. J Cutan Med Surg. 2000;4(4):186–195.
7. Garneski KM, Nghiem P. Merkel cell carcinoma adjuvant therapy: current data support radiation but not chemotherapy. J Am Acad Dermatol. 2007;57(1):166–169.
8. Poulsen M, Rischin D, Walpole E, et al. High-risk Merkel cell carcinoma of the skin treated with synchronous carboplatin/etoposide and radiation: a Trans-Tasman Radiation Oncology Group Study–TROG 96:07. J Clin Oncol. 2003;21(23):4371–4276.
9. Poulsen MG, Rischin D, Porter I, et al. Does chemotherapy improve survival in high-risk stage I and II Merkel cell
metastatic castration-resistant prostate cancer. *Urol Oncol.* 2020;38(11):848.

27. Nguyen DP, Xiong PL, Liu H, et al. Induction of PSMA and internalization of an anti-PSMA mAb in the vascular compartment. *Mol Cancer Res.* 2016;14(11):1045–1053.

28. Tagawa ST, Akhtar NH, Nikolopoulos A, et al. Bone marrow recovery and subsequent chemotherapy following radiolabeled anti-prostate-specific membrane antigen monoclonal antibody J591 in men with metastatic castration-resistant prostate cancer. *Front Oncol.* 2013;3:214.

29. Tagawa ST, Milowsky MI, Morris M, et al. Phase II study of Lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for metastatic castration-resistant prostate cancer. *Cancer Res.* 2013;73(18):5182–5192.

30. 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): 1902–1909.

31. Milowsky MI, Nanus DM, Kostakoglu L, Vallabhajosula S, Goldsmith SJ, Bander NH. Phase I trial of yttrium-90-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for androgen-independent prostate cancer. *J Clin Oncol.* 2002;20(13):2522–2531.

32. Kratochwil C, Bruchertseifer F, Rathke H, et al. Targeted alpha-therapy of metastatic castration-resistant prostate cancer with (225)Ac-PSMA-617: swimmer-plot analysis suggests efficacy regarding duration of tumor control. *J Nucl Med.* 2018;59(5):795–802.

33. Niaz MO, Sun M, Ramirez-Fort MK, Niaz MJ. Prostate-specific membrane antigen based antibody-drug conjugates for metastatic castration-resistance prostate cancer. *Cureus.* 2020;12(2):e7147.

34. Ramirez-Fort MK, Meier B, Liu H, et al. Possible cancer stem cells: Folate hydrolase-1 is expressed in a subset of Oct4-positive melanoma cells. *Poster presented at: American Association for Cancer Research.* 1-5 April 2017. Washington, DC.

35. Ma D, Hopf CE, Malewicz AD, et al. Potent antitumor activity of an auristatin-conjugated, fully human monoclonal antibody to prostate-specific membrane antigen. *Clin Cancer Res.* 2006;12(8):2591–2596.

36. Morris MJ, Pandit-Taskar N, Divgi CR, et al. Phase I evaluation of J591 as a vascular targeting agent in progressive solid tumors. *Clin Cancer Res.* 2007;13(9):2707–2713.

37. National nuclear data center ENSDCF decay data in the MIRD (medical internal radiation dose). Format for 177Lu. 2012.

38. Kim SH, Park WS, Park EY, et al. The prognostic value of BAP1, PBRM1, p56, PTEN, TGase2, PD-L1, CA9, PSMA, and Ki-67 tissue markers in localized renal cell carcinoma: a retrospective study of tissue microarrays using immunohistochemistry. *PLoS One.* 2017;12(6):e0179610.

39. Haffner MC, Laimer J, Chaux A, et al. High expression of prostate-specific membrane antigen in the tumor-associated neo-vasculature is associated with worse prognosis in squamous cell carcinoma of the oral cavity. *Mod Pathol.* 2012;25(8): 1079–1085.

40. Mhaweich-Facegula P, Smiraglia DJ, Bshara W, et al. Prostate-specific membrane antigen expression is a potential prognostic marker in endometrial adenocarcinoma. *Cancer Epidemiol Biomarkers Prev.* 2008;17(3):571–577.

41. Zeng C, Ke ZF, Yang Z, et al. Prostate-specific membrane antigen: a new potential prognostic marker of osteosarcoma. *Med Oncol.* 2012;29(3):2234–2239.

42. Perner S, Hofer MD, Kim R, et al. Prostate-specific membrane antigen expression as a predictor of prostate cancer progression. *Hum Pathol.* 2007;38(5):696–701.

43. Cronin KA, Harlan LC, Dodd KW, Abrams JS, Ballard-Barbash R. Population-based estimate of the prevalence of HER-2 positive
breast cancer tumors for early stage patients in the US. *Cancer Invest.* 2010;28(9):963–968.

44. Donepudi S, DeConti RC, Samlowski WE. Recent advances in the understanding of the genetics, etiology, and treatment of Merkel cell carcinoma. *Semin Oncol.* 2012;39(2):163–172.

45. Ramirez-Fort MK, Meier B, Lachance KS, et al. Folate hydrolase-1 (FOLH1) is a novel target for antibody-based brachytherapy in Merkel cell carcinoma. Poster presented at: European Society for Dermatological Research; September, 2017; Salzburg, Austria.

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