Anti-CEA pretargeted Immuno-PET shows higher sensitivity than DOPA-PET/CT to detect relapsing metastatic medullary thyroid carcinoma: Post- hoc analysis of the iPET-MTC study.

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Running Title: Pretargeted Immuno-PET in MTC

**Keywords: Immuno-PET, MTC, carcinoembryonic antigen, bispecific antibody,
pretargeted radioimmunoimaging**

Word count: 5929

ABSTRACT

Introduction. Pretargeting parameters for use the anti-CEA (carcinoembryonic antigen) bispecific monoclonal antibody TF2 and the ^{68}Ga -labeled IMP288 peptide (^{68}Ga -IMP288) for Immuno-PET have been optimized in a first-in-human study performed in MTC (medullary thyroid carcinoma (MTC) patients (iPET-MTC study). The aim of this post-hoc analysis was to determine the sensitivity of Immuno-PET in relapsing MTC patients, in comparison with conventional imaging and ^{18}F -DOPA PET/CT (DOPA-PET/CT).

Methods. Twenty-five studies were analyzed in 22 patients. All patients received Immuno-PET 1-h and 2-h after ^{68}Ga -IMP288 injection pretargeted by TF2, in addition to neck-thoracic-abdominal-pelvic computed tomography (CT), bone and liver magnetic resonance imaging (MRI), and DOPA-PET/CT. Gold standard (GS) was histology and/or confirmation by one other imaging method and/or imaging follow-up.

Results. 190 lesions were confirmed by the GS: 89 in lymph nodes, 14 in lungs, 46 in liver, 37 in bone, and 4 in other sites (subcutaneous, heart, brain, and pancreas). 210 abnormal foci were detected by Immuno-PET. Among these, 174 (83%) were confirmed as true-positive by the GS. Immuno-PET showed a higher overall sensitivity (92%) than DOPA-PET/CT (65%). Regarding metastatic sites, Immuno-PET had a higher sensitivity than CT, DOPA-PET/CT or MRI for lymph nodes (98% vs 83% for CT and 70% for DOPA-PET/CT), liver (98% vs 87% for CT, 65% DOPA-PET/CT, and 89% for MRI) and bone (92% vs 64% for DOPA-PET/CT and 86% for MRI), whereas sensitivity was lower for lung metastases (29% vs 100% for CT and 14% for DOPA-PET/CT). Tumor SUV_{max} at 60 min ranged from 1.2 to 59.0 with intra- and inter-patient variability.

Conclusion. This post-hoc study demonstrates that anti-CEA immuno-PET is an effective procedure for detecting metastatic MTC lesions. Immuno-PET showed a higher overall sensitivity than DOPA-PET/CT for disclosing metastases, except for the lung, where CT remains the most effective examination.

INTRODUCTION

Medullary thyroid carcinoma (MTC) arises from calcitonin producing parafollicular C cells and represents 1–2% of thyroid cancers (*1*). The tumor is frequently aggressive and, on initial staging, 35% of MTC patients have tumor extending into the thyroid-surrounding tissues or regional lymph node involvement, and 13% have distant metastases, especially in the lung, liver, or bones (*2,3*). According to American Thyroid Association guidelines, when calcitonin is higher than 150 pg/ml, staging is recommended based on anatomical imaging, such as neck ultrasonography or computed tomography (CT), chest CT, liver CT or magnetic resonance imaging (MRI), and spine and pelvis bone/bone marrow MRI (*4,5*). As indolent tumors, MTC have generally low avidity for ^{18}F -fluorodesoxyglucose (^{18}F FDG); therefore, positron emission tomography with ^{18}F FDG (FDG-PET/CT) is not recommended for initial staging, but it can be useful for assessing advanced disease characterized by dedifferentiation and rapid progression. ^{18}F -L-dihydroxyphenylalanine (^{18}F -DOPA) PET/CT (DOPA-PET/CT) has a higher sensitivity and specificity than FDG-PET/CT in MTC, and can reveal occult metastases or small lesions for initial staging and at relapse. These examinations also can play a crucial role in the management of relapsing MTC patients (*6–12*).

Carcinoembryonic antigen (CEA) is a cell-surface glycoprotein over-expressed in a number of solid tumors, including MTC, and functional imaging using radiolabeled anti-CEA monoclonal antibodies (MAb) represents potentially an interesting method for detection of MTC metastases (*13*). TF2 is an engineered bispecific MAb (BsMAb) composed of an anti-hapten Fab-fragment derived from the murine 679 antibody recognizing the histamine-succinyl-glycine (HSG) motif, and two humanized anti-CEA Fab-fragments derived from the hMN-14 antibody (labetuzumab), formed into a trivalent 157 kD protein by the Dock-and-Lock® procedure (*14*). IMP288 is a

bivalent HSG hapten that can be labeled with a variety of radionuclides for therapy (^{90}Y and ^{177}Lu), scintigraphy (^{111}In), or PET (^{124}I , ^{68}Ga and ^{18}F) (15–17).

We previously reported the optimization of the pretargeting parameters (BsMAb and peptide molar doses and pretargeting delay) of pretargeted Immuno-PET using TF2 and ^{68}Ga -IMP288 in the iPET-MTC first-in-human study performed in MTC patients (18). The aim of this post-hoc analysis was to determine the sensitivity of this novel imaging method in relapsing MTC patients, in comparison to conventional imaging (CI) and DOPA-PET/CT.

MATERIALS AND METHODS

Population

The inclusion and exclusion criteria have been reported previously (18). Briefly, all eligible adult patients had a histologic diagnosis of MTC treated by complete surgery and presenting a calcitonin serum level of 150 pg/mL or more with at least 1 lesion 10 mm or greater on CI. In the 4 weeks preceding Immuno-PET, a staging workup that included a complete history, physical examination, CEA and calcitonin serum level measurements, and DOPA-PET/CT were performed for each patient. CI, including contrast-enhanced CT of the neck, chest, abdomen, and pelvis, as well as bone and liver MRI, were performed. The iPET-MTC trial, sponsored by Nantes University Hospital, was approved by the responsible ethics committee (CPP), registered at ClinicalTrial.gov (NCT01730638), and all patients signed a written informed consent.

Investigational agents and study design

Radiopharmaceuticals manufacturing and premedication protocols have been previously reported (18). For pharmacokinetics optimization purposes, the first 16 Immuno-PET studies were performed under 5 different pretargeting conditions (molar doses of BsMAb and peptide, and delay); 3 patients were included per cohort from cohort 1 to cohort 5 (18). One patient included in the third cohort did not receive the full hapten dose and was excluded and replaced in the optimization phase of the study. This patient was re-integrated in this part of the study evaluating performances of Immuno-PET. The last 9 Immuno-PET studies were performed with the cohort 2 scheme considered as optimal after the optimization phase (Table 1).

Safety was assessed by monitoring vital signs, physical examination, and adverse events. Human anti-human antibody titers were measured by Immunomedics (Morris Plains, New Jersey) at 3 and/or 6 months, using an ELISA method (abnormal when ≥ 50 ng/mL).

PET acquisition

Immuno-PET and DOPA-PET/CT were performed using a 4-ring Siemens Biograph mCT system with time of flight capability and reconstructed using a 3D ordinary Poisson-OSEM, with point-spread function correction and time of flight mode (3 iterations, 21 subsets, 2-mm full width at half maximum Gaussian post-filtering, voxel size: $4'4'2$ mm³). Whole-body acquisitions were performed under normal tidal respiration for 2.5 min per bed position. CT was obtained using a variable mAs, 120 kVp, and a pitch of 1 without contrast enhancement. Acquisitions were performed from the top of the head to mid-thigh (6 to 8 steps per patient). Immuno-PET were performed 60 and 120 minutes (min) after 150 MBq ⁶⁸Ga-IMP288 injection and DOPA-PET/CT 60 min after 3 MBq/Kg ¹⁸F-DOPA injection

Conventional Imaging acquisition

Patients were scanned with multi-detector CT. A contrast-enhanced series was acquired after intravenous injection of non-ionic iodinated contrast (350ml, 1.5 mL/kg, rate 3mL/s using a power injector), visualizing the body from the neck to the pelvis. MRI was conducted using a 1.5T whole-body MRI systems. The liver was imaged in the axial plane including T2-weighted (-w), MR diffusion-w sequences, transverse breath-hold three-dimensional T1-w fat-suppressed spoiled gradient recalled echo sequences before and after administration of gadolinium chelate. Standard protocol for spine and pelvis included T1-w turbo spin echo (TSE), T2-w short T1 inversion recovery (STIR) with fat suppression, and contrast-enhanced T1-w TSE with fat suppression MR sequences. The whole spine was explored in sagittal views with or without complementary axial views and the pelvis in coronal and axial views.

Image analysis

Immuno-PET abnormal uptake was defined visually as focal increase of uptake higher than the surrounding background. The attenuation-correction CT data were used in addition to PET data for the reading of Immuno-PET and DOPA-PET/CT. Tumor SUV_{max} was determined on the most intense focus in the whole-body scan confirmed as MTC. DOPA-PET/CT and Immuno-PET were interpreted separately by two nuclear medicine physicians blinded to the other diagnostic results with expertise in immunotargeting and PET (FKB and CBM).

CI was interpreted by a consensus of radiologists with expertise in endocrine tumors (EF and FT) blinded to DOPA-PET/CT and Immuno-PET but in consideration of previous CI performed. At initial CI, lesions were considered metastatic in cases of (a) pulmonary nodules for chest CT; (b) focal hepatic lesions (hyperintense at a high b value on diffusion-weighted MR images, moderately to strongly hyperintense on T2 weighted MR images (less than the signal

intensity of liquid), hypervascular or peripherally-enhanced after contrast injection on MRI or CT); (c) hyperintense on T2 and diffusion-weighted images, hypointense on T2 and T1 weighted, mixed heterogeneous intensity on MRI; (d) >1 cm short axis and/or hypervascular pattern of lymph nodes, (e) soft-tissue tumors. Appearance of lesions during the course of the disease and increase of size during follow-up were also considered.

For both ethical and practical reasons, not every suspected lesion was evaluated by histology. If necessary, complementary imaging was performed to assess the most important lesions suspected by Immuno-PET and not detected by the initial work-up. For this study, the gold standard (GS) was determined on the basis of histology and/or by confirmation of a lesion by one other imaging method and/or by imaging follow-up. Indeed, an imaging assessment with contrast-enhanced CT of the neck, chest, abdomen, and pelvis and/or bone MRI and/or liver MRI and/or DOPA-PET/CT were performed 3 months after Immuno-PET, decided by a panel of experts involving endocrinologists, radiologists, and nuclear physicians. CEA and calcitonin serum level measurements were also determined. The same panel of experts could propose a second biomarker and imaging evaluation at 6 months after Immuno-PET. EORTC or RECIST criteria were used for conventional imaging follow-up(19,20).

A lesion detected by an imaging method was considered as related to MTC (true-positive; TP) when confirmed by one other imaging method, by histopathology, or by follow-up. A lesion visualized by one imaging method which progressed during follow-up using EORTC or RECIST criteria was considered as TP. A negative finding on an imaging method was considered false-negative (FN) if positive by one other imaging method plus histopathology, or by one other imaging method plus follow-up. Sensitivity $(TP/TP + FN) \times 100$ per lesion was calculated for each imaging modality. A positive finding on an imaging method was considered as not confirmed (NC) if

confirmed neither by one other imaging method, nor follow-up or histopathology. A positive finding on an imaging method was considered as false-positive (FP) if not confirmed positive by histopathology.

Wilcoxon rank sum test were conducted to compare median tumor SUV_{max} and median tumor SUV_{max}-mediastinal blood pool ratio at 60 or 120 min and Spearman statistical tests to evaluate whether SUV_{max} were associated with CEA or calcitonin levels.

RESULTS

Patient characteristics and adverse events

The characteristics of the 22 included patients are presented in Table 2. Three patients underwent a second Immuno-PET study at least 12 months after the first procedure, coupled with a CI or DOPA PET/CT, accounting for a total of 25 Immuno-PET, CI or DOPA PET/CT studies in the 22 patients. Histopathological analysis of pathologic lesions was performed in six patients (2 non-contributive biopsies, 3 confirming MTC metastases, and 1 diagnosing another pathology).

No patient experienced an anaphylactic reaction during or after the TF2 infusion. One patient experienced a grade 3 reaction starting immediately after hapten infusion, with malaise, bronchospasm, tachycardia, and hypertension, requiring hospitalization. Therefore, the protocol was amended, and a premedication with antihistamine and corticosteroid before both TF2 and IMP288 injections was given thereafter to all patients. No further allergic reactions occurred afterwards.

Human anti-human antibody analyzed in 19 patients (at 3 and 6 months in 14 patients and only at 3 months in 5 patients) was abnormal in 3, equal to 52 ng/ml and 152 ng/ml, respectively,

at 3 months and normalized at 6 months in both, and normal at 3 months and abnormal at 6 months (244 ng/mL) in one.

Imaging results and sensitivity

All patients had abnormalities detected by Immuno-PET, CI, or DOPA-PET/CT (Table 3). A total of 190 lesions were confirmed according to the definition of GS: 89 in lymph nodes, 14 in the lungs, 46 in the liver, 37 in bone/bone marrow, and 4 in other sites (subcutaneous, heart, brain, and pancreas). Among these 190 lesions validated by GS, 174 were confirmed by another imaging method, 13 by follow-up and 3 by histology. Immuno-PET detected a total of 210 abnormal foci (1 to 22 per patient). Among these, 174 (83%) were confirmed as TP according to the GS (167 by another imaging method, 4 by follow-up and 3 by histology). 16 lesions were missed (FN lesions): 10 in lungs, 3 in bone, 2 lymph nodes, and 1 in liver (Table 3). All Immuno-PET lesions were seen at 60 as well as 120 min. Tumor SUV_{max} at 60 min ranged from 1.2 to 59.0, with intra- and inter-patient variability (Figure 1). There was no significant difference between median tumor SUV_{max} and median tumor SUV_{max} /mediastinal blood pool ratio at 60 or 120 min (19.54 [range 4.09-94.14] versus (vs) 21.31 [range 5.14-100.2] ($P=0.84$) and 8.14 [range 1.39-34.1] vs 8.5 [range 2.7-49.6] ($P=0.75$), respectively). SUV_{max} was not associated with CEA or calcitonin serum levels (Spearman $P=0.71$ and $P=0.73$, respectively).

CT, DOPA-PET/CT, liver, and bone marrow MRI detected 130, 124, 41, and 33 TP lesions, respectively, and missed 23, 66, 5, and 4 lesions (Table 3). Subcutaneous, pancreatic, and heart lesions were detected by Immuno-PET, CI, and DOPA-PET/CT, whereas a brain lesion was depicted by Immuno-PET, confirmed by brain MRI, but not detected by DOPA-PET/CT (Figure 2). No lesion was considered as FP by Immuno-PET, but 36 lesions remained NC. For DOPA-PET/CT, 7 lesions remained NC and 1 was FP: a diffuse pathological bone marrow uptake was

described on DOPA-PET/CT whereas Vaquez polycythemia was diagnosed without MTC metastases on bone marrow biopsy. Bone MRI was also FP in this patient, whereas Immuno-PET was negative. For CT, 7 lesions were NC (1 peritoneal nodule and 6 lung micro-nodules). Supplemental Table 1 summarizes the «per-patient» performances of Immuno-PET, DOPA-PET/CT, CT, liver and bone MRI.

Immuno-PET showed a higher overall sensitivity (92%) than DOPA-PET/CT (65%) (Table 3). The sensitivity of Immuno-PET was also 92% (79/86) considering only the 13 exams performed with the sub-optimal scheme. Regarding the different metastatic sites, Immuno-PET had a higher sensitivity than CT and DOPA-PET/CT for lymph nodes (98% *vs* 82% and 72%, respectively) (Figure 3) and liver (98% *vs* 87% and 65%, respectively) (Figure 4), whereas sensitivity was lower for lung metastases (29% *vs* 100% and 14%, respectively). Immuno-PET had a slightly higher sensitivity for bone evaluation than MRI and DOPA-PET/CT (92% *vs* 89% and 68%, respectively).

DISCUSSION

Currently, surgery remains the only treatment for cure of MTC patients. Once metastatic, the therapeutic options are limited. MTC cells do not concentrate radioiodine and the efficacy of chemotherapeutic agents is limited (4). In the last decade, tyrosine kinase inhibitors have been evaluated in patients with progressive metastatic disease, with benefits on progression-free survival for both vandetanib and cabozantinib (21). Locally-advanced or relapsing MTC requires a careful work-up, including of calcitonin and CEA serum level measurements, determination of their doubling time, and comprehensive imaging to determine the extent of the disease and its aggressiveness, as well as appreciating the need for therapy. Calcitonin is the most sensitive and specific tumor biomarker, and CEA represents a prognostic biomarker, since an increased CEA serum level suggests an advanced state and tumor dedifferentiation (22). Serum calcitonin and

CEA doubling times are prognostic factors of survival (21,23). Morphological imaging is often negative or doubtful in the presence of rising levels of calcitonin (3–5). Therefore, functional PET/CT imaging using different radiopharmaceuticals is recommended. ^{18}F -DOPA seems to be the most useful tracer to detect recurrent MTC based on rising biomarker levels, while ^{18}F FDG may be complementary in patients with an aggressive tumor phenotype (3,5,8,11,24).

The present study reports the high imaging performance of anti-CEA TF2 BsMAb and ^{68}Ga -IMP288 in metastatic MTC patients, Immuno-PET achieving a 92% overall sensitivity, with a somewhat better sensitivity than CI and DOPA-PET/CT for lymph node, liver, and bone/bone marrow examinations. However, as in a previous study performed in breast cancer patients, Immuno-PET was less effective than CT for lung metastasis detection (25). Sensitivity of DOPA-PET/CT also was low for lung lesion detection in this population. Spontaneous breathing during PET/CT acquisition and the large positron-range of ^{68}Ga may affect PET performance for detection of small lung lesions. Indeed, the sensitivity of Immuno-PET was better than that of DOPA-PET/CT both in "overall" sensitivity but also for metastatic sites suggesting the interest of this novel functional whole-body imaging method for MTC staging and therapeutic evaluation. Except for lung lesions, only 6 lesions (3 bone, 2 in lymph nodes, and 1 liver) were considered as falsely-negative by Immuno-PET in 4 patients for whom all other MTC metastases were positive using immuno-PET. Two of these 6 lesions (1 bone and 1 node) were positive using ^{18}F -DOPA. The small size of these lesions in addition to the spontaneous breathing PET/CT acquisition may affect PET performance due to the partial volume effect. A heterogeneous expression of CEA on some metastatic lesions might also explain these Immuno-PET FN results. Despite these few FN of Immuno-PET, DOPA-PET/CT results have no impact on patient staging in this study with a higher number of FN lesions (16 for Immuno-PET versus 66 for DOPA-PET/CT), suggesting that

Immuno-PET could potentially replace DOPA-PET/CT in MTC metastatic patients if the technique were available in clinical practice.

In clinical practice, ^{18}F -DOPA, ^{18}F FDG, and somatostatin analogs labeled with ^{68}Ga are available to explore MTC patients with an increasing calcitonin serum level. ^{18}F -DOPA penetrates into tumor cells through transmembrane amino acid transporters that are significantly upregulated in neuroendocrine tumors, including MTC. In a meta-analysis including 8 studies and 146 patients, the detection rates of DOPA-PET and PET/CT, by per-patient and per-lesion analyses were 66% and 71%, respectively, with performance increasing in patients with serum calcitonin ≥ 1000 ng/L and calcitonin doubling time < 24 months (26).

^{18}F FDG is a glucose metabolism tracer, with an increased uptake in MTC undergoing dedifferentiation and becoming more aggressive (5). A meta-analysis based on 24 studies comprising 538 patients with suspected recurrent MTC reported for FDG-PET or PET/CT, using a per patient-based analysis, had a detection rate of 59 %, with performance increasing when serum calcitonin $\geq 1,000$ ng/L, CEA ≥ 5 ng/ml, calcitonin doubling time < 12 months, and CEA doubling time < 24 months (26) . Neuroendocrine tumors usually overexpress somatostatin receptors, and somatostatin analogs labeled with ^{68}Ga are useful for their assessment. A recent prospective study evaluating ^{68}Ga -DOTATATE-PET/CT in 30 MTC patients showed that ^{68}Ga -DOTATATE-PET/CT was inferior to CI except for bone scans (27) in metastatic patients. ^{68}Ga PET/CT sensitivities were 56%, 57%, and 9% for detecting neck lymph nodes, lung metastases, and liver metastases, respectively, and 100% for bone metastases.

Even if no comparative studies have been done in homogeneous populations, our results suggest that, except for lung metastasis detection, anti-CEA pretargeted Immuno-PET may have a

higher performance than other available PET/CT methods and CI to detect recurrence sites in MTC patients with rising serum biomarkers. Our previous studies showed that CEA expression seemed to be almost constant in MTC, and that high sensitivity PET imaging using CEA as a target would detect the disease independently of the prognosis (9,28–30).

Despite the excellent sensitivity of pretargeted Immuno-PET, our study has some limitations. A small number of patients were included (22 patients; 25 Immuno-PET). This limited number is explained on the one hand by the tumor concerned being relatively rare, and on the other hand by our intention to test this new pre-targeting system in parallel in MTC and breast cancer patients (24). Moreover, we evaluated the performance of Immuno-PET in the whole population and not only for the 12 examinations performed under the optimal pre-targeting conditions defined by the optimization study. This bias could penalize us because 13 procedures were performed under sub-optimal conditions; however, the sensitivity of Immuno-PET was the same in this sub-group and the overall population (92%). The absence of systematic early acquisition time for DOPA-PET/CT although ^{18}F -DOPA clearance can sometimes be fast in this tumour could also represent a bias explaining that global sensitivity of DOPA-PET/CT was slightly lower than usually reported in the literature (12).

Finally, and this bias is recurrent in many imaging studies, 36 lesions detected by Immuno-PET remain unconfirmed by the GS during the follow-up period. Despite a relatively “extensive” definition of the GS, confirmation cannot be obtained for all lesions. Indeed, Immuno-PET visualized more lesions than the other modalities, lesions that were often very small in size, not confirmed by conventional assessment and inaccessible to histological analysis. Indeed, only 6 biopsies were performed in our study, 2 non-contributive, 3 confirming the MTC metastases, and

1 diagnosing another pathology. This lack of confirmation does not allow us to assess accurately the positive predictive value and specificity of this new imaging technique.

Pretargeted Immuno-PET could also be a theranostic procedure for qualitative and quantitative whole-body tumor biomarker cartography to select patient candidates for an antibody-based therapy. Our team reported the promising results of radionuclide therapy using a previous generation of pretargeting reagents (anti-CEA $\times$ anti-diethylenetriaminepentaacetic acid (DTPA) BsMAb hMN-14 $\times$ m734 and ^{131}I -di-DTPA-indium hapten) (28–31). In 42 metastatic, progressing, MTC patients included in a phase II study, a 76.2% disease control rate (durable stabilization plus objective response) was observed (2). Using the new generation IMP288 peptide, the feasibility and safety of theranostics using TF2 and $^{111}\text{In}/^{177}\text{Lu}$ -IMP288 have been reported in metastatic colorectal and lung cancer patients (32,33). Moreover, anti-CEA antibody-drug conjugates are under preclinical and clinical development, where Immuno-PET using ^{68}Ga -IMP288 could select patients for these therapeutic strategies (34,35).

CONCLUSION

This post-hoc analysis demonstrated that anti-CEA Immuno-PET using the trivalent BsMAb TF2 and the ^{68}Ga -IMP288 peptide is a safe and effective procedure for detecting MTC metastatic lesions. Immuno-PET targeting CEA showed a higher overall sensitivity than DOPA-PET/CT for disclosing metastases, including dissemination to the bone marrow and brain. However, CT remains the most effective imaging method for lung examination. Moreover, in the era of precision medicine, Immuno-PET represents a potential theranostic molecular imaging technique to select patients for an antibody-based therapy.

ACKNOWLEDGEMENT

This work has been supported in part by grants from the French DHOS INCA in 2010, the French National Agency for Research, called “Investissements d’Avenir” IRON Labex n° ANR-11-LABX-0018-01, ArronaxPlus Equipex n° ANR-11-EQPX-0004, and by a grant INCa-DGOS-Inserm_12558 (SIRIC ILIAD). The proprietary TF2 and IMP288 reagents were provided by Immunomedics, Inc., and IBC Pharmaceuticals, Inc.

DISCLOSURES

D. M. Goldenberg and R. M. Sharkey own Immunomedics stock or stock options, and D.M Goldenberg has royalty-bearing patented inventions. D.M Goldenberg is the founder and retired Chairman and Chief Scientific Officer of Immunomedics, Inc., and the founder and retired Chairman of IBC Pharmaceuticals, Inc. R. M Sharkey was Senior Director of Scientific and Regulatory Affairs, and then a consultant to Immunomedics, Inc. No other potential conflicts of interest relevant to this article were reported. The proprietary TF2 and IMP288 reagents were provided by Immunomedics, Inc., and IBC Pharmaceuticals, Inc.

KEY POINTS

QUESTION: What is the sensitivity of anti-CEA Immuno-PET using the trivalent BsMAb TF2 and the ^{68}Ga -IMP288 peptide in relapsing MTC patients?

PERTINENT FINDINGS: The overall sensitivity of Immuno-PET was 92%, higher than DOPA-PET/CT (65%) for disclosing metastases, including dissemination to the bone marrow and brain. CT remains the most effective imaging method for lung examination.

IMPLICATIONS FOR PATIENT CARE: Anti-CEA Immuno-PET is an effective procedure for detecting metastatic MTC lesions and represents a potential theranostic molecular imaging technique to select patients for an antibody-based therapy.

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TABLE 1. Scheme of the cohorts.

	Number of patients	TF2 dose	delay	⁶⁸ Ga-IMP288 dose and activity	TF2/IMP288 molar dose ratio
Cohort I	3	120 nmol	24h	6 nmol 150 MBq	20
Cohort II	3 + 9*	120 nmol	30h	6 nmol 150 MBq	20
Cohort III	3 + 1**	120 nmol	42h	6 nmol 150 MBq	20
Cohort IV	3	120 nmol	30h	3 nmol 150 MBq	40
Cohort V	3	60 nmol	30h	3 nmol 150 MBq	20

*: 3 patients in the optimization phase of the study and 9 in the validation part.

**: Patient 8 did not receive the full hapten dose and was excluded and replaced for the optimization phase study, but was reintegrated for the sensitivity study.

TABLE 2. Patient characteristics.

Total number of patients	22
Median age in years (range)	62 (28-75)
Sex, <i>n</i> (%)	
Male	15
Women	7
Median time from diagnosis in years (range)	5.5 [0.5-31]
Median calcitonin concentration in pg/ml (range)	488 (154-39000)
Median CEA concentration in ng/ml (range)	18 (3-1443)
Location of disease, <i>n</i>	
Lymph node	19
Lung	8
Liver	13
Bone	13
Other	4

CEA: carcinoembryonic antigen

TABLE 3. Sensitivity of Immuno-PET, DOPA-PET/CT and conventional imaging.

	Immuno-PET	DOPA-PET/CT	CT	Liver MRI	Bone marrow MRI
Nodes	87/89 (98%)	64/89 (72%)	73/89 (82%)	NA	NA
Lung	4/14 (29%)	2/14 (14%)	14/14 (100%)	NA	NA
Liver	45/46 (98%)	30/46 (65%)	39/46 (87%)	41/46 (89%)	NA
Bone marrow	34/37 (92%)	25/37 (68%)	NA	NA	33/37 (89%)
Others	4/4 (100%)	3/4 (75%)	4/4 (100%)	NA	NA
Global sensitivity	174/190 (92%)	124/190 (65%)	130/153 (85%)	NA	NA

NA: Not Applicable.

FIGURE 1

Immuno-PET/CT with anti-CEA BsMAb and ^{68}Ga -IMP288 peptide showing cervical (A), mediastinal (B) subcutaneous (C), and bone metastasis (D). SUV max were heterogeneous, ranging from 3.0 to 20.1.

FIGURE 2

Immuno-PET/CT with anti-CEA BsMab and ^{68}Ga -IMP288 showing a temporo-parietal uptake in the brain (A), whereas DOPA-PET/CT was negative (B). Brain MRI «guided by Immuno-PET» confirmed the pathologic temporo-parietal lesion (C).

FIGURE 3 Immuno-PET/CT with anti-CEA BsMab and ^{68}Ga -IMP288 showing multiple pathological cervical and mediastinal nodes (A) confirmed by CT but not visualized by DOPA-PET/CT. The MTC metastatic involvement was confirmed by histological analysis (HES x 12,5 and x 200 magnification) (D).

FIGURE 4

Immuno-PET/CT with anti-CEA BsMab and ^{68}Ga -IMP288 showing multiple liver lesions (A), whereas DOPA-PET/CT was negative (B). MRI confirmed the lesion (C).

Supplemental Data:

TABLE 1. Performances of immuno-PET, DOPA-PET/CT and conventional imaging per exam.

	I-PET			DOPA-PET/CT			CT			Liver MRI			Bone MRI		
Nº	Se	NC-FP*	FN	Se	NC-FP*	FN	Se	NC-FP*	FN	Se	NC-FP*	FN	Se	NC-FP*	FN
1	100 (2/2)	0-0	0	50 (1/2)	1-0	1	100 (1/1)	1-0	0	100 (1/1)	0-0	0	0 (0/0)	0-0	0
2	100 (13/13)	9-0	0	54 (7/13)	2-0	6	70 (7/10)	0-0	1	100 (1/1)	0-0	0	100 (3/3)	0-0	0
3	100 (6/6)	0-0	2	50 (3/6)	0-0	3	80 (4/5)	0-0	1	100 (1/1)	0-0	0	100 (1/1)	0-0	0
4	75 (6/8)	0-0	2	88 (7/8)	1-0	1	50 (3/6)	0-0	3	0 (0/0)	0-0	0	100 (2/2)	0-0	0
5	100 (8/8)	0-0	0	75 (6/8)	0-0	2	0 (0/2)	0-0	2	0 (0/0)	0-0	0	67 (4/6)	0-0	2
6	100 (2/2)	1-0	0	100 (2/2)	1-0	0	0 (0/1)	0-0	1	0 (0/0)	0-0	0	100 (1/1)	0-0	0
7	100 (2/2)	7-0	0	100 (2/2)	0-0	0	0 (0/2)	0-0	2	100 (2/2)	0-0	0	0 (0/0)	0-0	0
8	100 (14/14)	4-0	0	86 (12/14)	0-0	2	92 (12/13)	1-0	1	100 (2/2)	0-0	0	0 (0/0)	0-0	0
9	100 (7/7)	0-0	0	43 (3/7)	0-0	4	100 (7/7)	1-0	0	0 (0/0)	0-0	0	0 (0/0)	0-0	0
10	67 (4/6)	1-0	2	17 (1/6)	0-0	5	83 (5/6)	0-0	1	100 (1/1)	0-0	0	0 (0/0)	0-0	0
11	83 (5/6)	0-0	1	83 (5/6)	1-0	1	100 (6/6)	2-0	0	0 (0/0)	0-0	0	0 (0/0)	0-0	0
12	85 (11/13)	7-0	2	85 (11/13)	0-0	2	100 (13/13)	0-0	0	60 (6/10)	0-0	4	100 (1/1)	0-0	0
13	100 (2/2)	0-0	0	50 (1/2)	0-0	1	0 (0/2)	0-0	2	0 (0/0)	0-0	0	0 (0/0)	0-0	0
14	100 (8/8)	0-0	0	75 (6/8)	0-0	2	86 (6/7)	0-0	1	100 (1/1)	0-0	0	0 (0/1)	0-0	1
15	71 (5/7)	0-0	2	71 (5/7)	0-0	2	100 (6/6)	0-0	0	100 (1/1)	0-0	0	100 (1/1)	0-0	0
16	0 (0/0)	1-0	0	0 (0/0)	0-1	0	0 (0/0)	0-0	0	0 (0/0)	0-0	0	0 (0/0)	0-1	0
17	100 (5/5)	5-0	0	60 (3/5)	0	2	100 (5/5)	0-0	0	0 (0/0)	0-0	0	0 (0/0)	0-0	0
18	100 (8/8)	4-0	0	50 (4/8)	0	4	100 (5/5)	0-0	0	0 (0/0)	0-0	0	100 (3/3)	0-0	0
19	82 (14/17)	1-0	3	71 (12/17)	0	5	56 (5/9)	0-0	4	75 (3/4)	0-0	1	100 (9/9)	0-0	0
20	100 (3/3)	3-0	0	100 (3/3)	0	0	100 (3/3)	0-0	0	100 (3/3)	0-0	0	0 (0/0)	0-0	0
21	100 (14/14)	1-0	0	21 (3/14)	0	11	100 (10/10)	0-0	0	100 (10/10)	0-0	0	100 (4/4)	0-0	0
22	100 (2/2)	0-0	0	50 (1/2)	0	1	0 (0/2)	0-0	2	0 (0/0)	0-0	0	0 (0/0)	0-0	0
23	83 (5/6)	0-0	1	83 (5/6)	1-0	1	100 (6/6)	2-0	0	0 (0/0)	0-0	0	0 (0/0)	0	0
24	90 (18/20)	0-0	2	55 (11/20)	0-0	9	100 (16/16)	0-0	0	0 (0/0)	0-0	0	100 (4/4)	0-0	0
25	100 (10/10)	0-0	0	100 (10/10)	0-0	0	100 (10/10)	0-0	0	100 (10/10)	0-0	0	0 (0/0)	0-0	0
Total	92 (174/190)	36- 0	16	65 (124/190)	7-1	66	85 (130/153)	7-0	23	89 (41/46)	0-0	5	89 (33/37)	0-1	4

*histologically confirmed.

I-PET: Immuno-PET; Se:sensitivity; NC-FP: Not confirmed or false-positive; FN: False-negative.