



^{99m}Tc -tilmanocept for lymphoscintigraphy

Vital blue dyes and radiolabeled colloids are widely used globally for intraoperative lymphatic mapping and sentinel lymph node biopsy. Until very recently, however, no radiolabeled agents were specifically approved for lymphoscintigraphy and none have been tested in prospective clinical trials. ^{99m}Tc -tilmanocept was designed for use in lymphoscintigraphy and sentinel node biopsy, and has been evaluated in Phase II and Phase III clinical trials. In nonrandomized, prospective comparisons with vital blue dye, ^{99m}Tc -tilmanocept reproducibly localized in regional lymph nodes after injection at the site of primary breast carcinomas and melanomas undergoing sentinel node biopsy, detecting nearly all visibly blue nodes and identifying more tumor-containing nodes overall, without missing any blue tumor-containing nodes. A Phase III trial in head and neck squamous cell carcinomas, with all patients undergoing complete node dissection after removal of the nodes detected with ^{99m}Tc -tilmanocept, is currently underway. On 13 March 2013, the US FDA approved ^{99m}Tc -tilmanocept (Lymphoseek) for use in lymphatic mapping procedures to assist in the localization of lymph nodes draining a primary tumor in patients with breast cancer or melanoma. Available evidence does not permit a definitive comparison with the other colloids that are commonly used for lymphoscintigraphy, but does suggest that ^{99m}Tc -tilmanocept is an effective option with some potential, but as yet unproven, advantages.

KEYWORDS: breast cancer • intraoperative lymphatic mapping • lymphoscintigraphy • melanoma • sentinel lymph node biopsy

Lymphoscintigraphy & intraoperative lymphatic mapping for sentinel lymph node biopsy in breast cancer & melanoma

The concept of sentinel node biopsy is based on the anatomic observation that lymphatic flow proceeds in an orderly fashion from the site of a primary tumor (at least for tumors on the skin or in the breast and probably for visceral tumors as well), to one or a few primary draining lymph nodes, which may or may not be within a regional node basin [1]. The histologic status of these 'sentinel' lymph nodes is highly predictive of the remaining lymph nodes; in general, less than 5% of patients with melanoma or breast cancer whose sentinel lymph nodes are negative for malignancy ever manifest evidence of regional nodal metastasis [2]. Furthermore, by removing only one or a few lymph nodes, morbidity is dramatically reduced compared with a full regional lymphadenectomy and enhanced techniques of histologic assessment can be used to detect even very small metastatic deposits, far below the resolution of any available imaging technique.

But while lymphatic flow is orderly, it is not necessarily predictable in a specific individual or tumor. Time-honored concepts of lymphatic anatomy such as Sappey's lines, which divide the

trunk into four quadrants that ostensibly drain to the nearest regional node basin, have proven insufficiently accurate for clinical use, and the rich and varied lymphatic drainage of the head and neck provides a particular challenge [3,4]. Lymphatic mapping utilizing preoperative radionuclide lymphoscintigraphy with ^{99m}Tc -labeled colloidal suspensions, supplemented by intraoperative injections of vital blue dyes, have allowed surgeons to identify all regional nodal basins at risk and also find 'in-transit' nodes when they exist outside the anatomic confines of standard basins [5]. Sentinel node biopsy is a minimally invasive surgical technique that has virtually eliminated elective node dissection from the management of melanoma and breast cancer. By providing superior staging with decreased morbidity, the use of sentinel node biopsy has helped to revolutionize the staging and treatment of melanoma and breast cancer in the last two decades, and will probably have a role to play in staging other cutaneous malignancies (e.g., Merkel cell carcinoma) and potentially many noncutaneous tumors (e.g., squamous cell carcinoma of the upper aerodigestive tract) where complete lymphadenectomy is currently the standard staging approach. The authors' intent is to review the available literature on a newly US FDA-approved agent for intraoperative

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lymphatic mapping, ^{99m}Tc -tilmanocept (Lymphoseek), without speculating on data or topics that are currently not substantiated.

Overview of the market

At the present time, sentinel node biopsy is widely used in the surgical management of clinically localized breast cancer, cutaneous melanoma and some other cutaneous malignancies (particularly Merkel cell carcinoma). Worldwide, there were an estimated 1.38 million cases of breast cancer diagnosed in 2008 (the last year for which global data are available), with an estimated incidence rate of 66.4 per 100,000 women in developed countries [6]. Melanoma is slightly less common worldwide (8.6–9.5 per 100,000 people in developed countries), but still a significant problem with a rising incidence rate in most of the world. The majority of patients with either breast cancer or melanoma present with clinically localized disease, and are therefore, potential candidates for lymphatic mapping and sentinel node biopsy. In many hospitals in the USA, preoperative lymphoscintigraphy for sentinel node localization is the most commonly performed nuclear medicine imaging study. Almost all sentinel node biopsy procedures for breast cancer and melanoma are performed using a radiolabeled tracer, but there is no consensus on which tracer is best (TABLE 1). Accordingly, the potential worldwide market for an agent that provides superior performance (e.g., faster clearance from the injection site, quicker uptake in the sentinel nodes, and less spread to second echelon nodes in the regional nodal basin) or offers financial advantages compared with currently available tracers would be substantial. In the future, it is possible that lymphoscintigraphy and sentinel node biopsy will be used more frequently in selected noncutaneous malignancies (particularly head and neck and gastrointestinal malignancies), which would obviously represent a substantial and dramatic increase in the potential market for radiolabeled lymphatic mapping agents.

Introduction to the compound

^{99m}Tc -tilmanocept (LymphoseekTM; Navidea Biopharmaceuticals Inc., OH, USA), is a synthetic macromolecule designed with multiple mannose moieties intended to allow specific multivalent binding to mannose receptors (CD206) expressed on reticuloendothelial cells residing in lymph nodes [7]. The CD206 receptor, mannose receptor C type 1 or MRC1, recognizes and binds macromolecules with carbohydrate side-chains terminating in a mannose glycoside [8]. Theoretically,

specific binding to receptors resident in the lymph node would allow a small molecule with rapid clearance from the primary injection site and rapid transit to the regional node to bind with high affinity and accumulate in the first node it encountered – the ‘sentinel’ node. When combined with an appropriate radiolabel for imaging, this receptor-targeted agent would have potential advantages over nonspecific colloids.

Chemistry

Vera *et al.* first described the synthesis of ^{99m}Tc -diethylenetriaminepentaacetic acid (DTPA)-mannosyl-dextran in 2001 [7]. The agent was subsequently referred to as Lymphoseek, and later given the generic name ^{99m}Tc -tilmanocept. Vera and colleagues’ initial report described high labeling yields (in excess of 98%) and stability, and very high receptor binding affinity. The equilibrium dissociation binding constant K_D in a rat liver assay was 0.12 ± 0.07 nM. The macromolecule had an average molecular weight of 28,200–35,800 g/mol [7,9], with the current formulation as tested in Phase III clinical trials being 18,000 g/mol. The molecular diameter was 7.1 nm. Dextran is very hydrophilic, which combined with the relatively low molecular weight and diameter, promotes rapid clearance of ^{99m}Tc -tilmanocept from the injection site via both lymphatic and blood capillaries [7].

Preclinical studies

Biodistribution studies in rabbits indicated that ^{99m}Tc -tilmanocept cleared the foot pad with a biological half-life of 2.21 ± 0.27 h [10], and comparison studies with filtered ^{99m}Tc -sulfur colloid revealed faster injection site clearance and lower accumulation in distal lymph nodes, but similar accumulation in the proximal nodes at 1 and 3 h after injection [7]. Biodistribution was also tested in pigs after endoscopic injection into the stomach, colon and prostate gland [11–14]. The experiments confirmed relatively rapid transit to initial draining lymph nodes, good correlation with vital blue dye staining and low uptake in distal lymph nodes.

Preclinical toxicology studies were conducted in rats and rabbits after footpad administration, and in rabbits following intramuscular or intravenous administration, using between 50- and 1000-times the scaled human dose. Other than mild hepatocyte hypertrophy in rabbits, no abnormalities in toxicology or pathology were seen. Intravenous and intramuscular administration had no effect on survival, ECGs or blood pressure [10].

Table 1. Properties of agents in use for lymphoscintigraphy.

Agent	Particle size (nm)	Lymphoscintigraphy results	Clearance rate	Availability
Antimony trisulfide colloid	3–40	Good visualization of lymphatics and minimal visualization of second-echelon nodes	Relatively slow clearance from primary site with peak nodal uptake at 2–3 h	Australia and Asia; not available in the USA
Sulfur colloid Filtration (if done) performed immediately prior to use	Unfiltered: 300–400 Filtered: 38	Visualization of major lymphatics with minimal visualization of second-echelon nodes	Relatively slow clearance from primary site with peak nodal uptake at 2–3 h	USA
Albumin nanocolloid	3–16	Visualization of major lymphatics with minimal visualization of second-echelon nodes	Rapid clearance from primary site with peak nodal uptake in 1–2 h	Europe and Canada; limited availability in the USA
Human serum albumin	2–10	Visualization of major lymphatics with significant visualization of second-echelon nodes	Rapid clearance from primary site with optimum results in 1–2 h	Worldwide
Tilmanocept	~7	Not reported Designed to be retained in first-echelon nodes by binding to CD206 receptor	Reported in small Phase I trial to have statistically faster clearance from primary than sulfur colloid; peak nodal uptake in less than 1 h	Currently only available through clinical trials, US FDA approved 13 March 2013, expected availability 2nd quarter of 2013

Clinical studies – Phase I: biodistribution & safety

The biodistribution and safety of ^{99m}Tc-tilmanocept at various doses were tested in 18 female breast cancer patients, and compared with six additional patients who received filtered ^{99m}Tc-sulfur colloid [15]. Dose-dependent sentinel node uptake was observed and injection site clearance of ^{99m}Tc-tilmanocept was similar across doses. ^{99m}Tc-tilmanocept exhibited a significantly faster injection site clearance: the mean ^{99m}Tc-tilmanocept clearance half-time was 2.72 ± 1.57 h compared with 49.5 ± 38.5 h for filtered ^{99m}Tc-sulfur colloid (p < 0.0025) [9]. The mean sentinel node uptake, however, was not statistically significantly different for ^{99m}Tc-tilmanocept versus sulfur colloid; in fact, the values were slightly higher for filtered ^{99m}Tc-sulfur colloid [9,16]. The mean number of sentinel nodes detected was 1.3 and 1.7 for ^{99m}Tc-tilmanocept and filtered ^{99m}Tc-sulfur colloid, respectively [9].

Wallace *et al.* also conducted a Phase I trial of ^{99m}Tc-tilmanocept in patients with clinically localized melanoma [17]. In this trial, 24 patients received intradermal injections of ^{99m}Tc-tilmanocept (six patients each received 1.0, 5.0 or 10.0 nmol) or filtered ^{99m}Tc-sulfur colloid. Again, ^{99m}Tc-tilmanocept exhibited a significantly faster injection site clearance: the mean clearance half-time for all three ^{99m}Tc-tilmanocept groups was 2.17 ± 0.96 h compared with 14.7 ± 6.3 h for filtered ^{99m}Tc-sulfur colloid (p < 0.001). As in the breast cancer experience, mean sentinel node uptake was not statistically significantly different

for ^{99m}Tc-tilmanocept versus ^{99m}Tc-sulfur colloid and the mean number of sentinel nodes detected was slightly, but not statistically significantly, lower for ^{99m}Tc-tilmanocept.

Another publication described results comparing the injection site clearance and sentinel lymph node accumulation after a single intradermal injection of ^{99m}Tc-tilmanocept or unfiltered ^{99m}Tc-sulfur colloid using a 2-day protocol for breast cancer lymphoscintigraphy and lymphatic mapping [18]. A total of 11 patients with breast cancer received either an intradermal administration of 1.0 nmol of ^{99m}Tc-tilmanocept or unfiltered ^{99m}Tc-sulfur colloid and underwent surgery the next day. ^{99m}Tc-tilmanocept exhibited significantly faster injection site clearance than unfiltered ^{99m}Tc-sulfur colloid and demonstrated persistent accumulation in the sentinel node for at least 24 h. The mean sentinel lymph node uptake of ^{99m}Tc-tilmanocept was lower than unfiltered ^{99m}Tc-sulfur colloid (1.5 ± 1.7 vs 3.5 ± 3.1%), but again this difference was not statistically significant (p = 0.213). No serious adverse events related to ^{99m}Tc-tilmanocept were identified in any of the Phase I trials. Faster clearance from the injection site could potentially enhance the detection of sentinel nodes by decreasing ‘shine through’ from the primary site, but this remains an unproven theoretical consideration.

Clinical studies: Phase II & III: clinical efficacy

Clinical testing initially took place in a series of small Phase I trials, some involving a randomized

comparison with filtered ^{99m}Tc -sulfur colloid (see above). This was followed by a multi-institutional open-label Phase II trial involving patients with melanoma or breast cancer undergoing clinically indicated sentinel node biopsy [19]. More recently, two nonrandomized Phase III trials, nearly identical in design, were completed in patients with either breast cancer or melanoma, and a third nonrandomized Phase III trial is currently underway in patients with squamous cell carcinoma of the head and neck. None of the completed Phase II and III trials involved a direct or indirect comparison with any other radiolabeled lymphatic-mapping agent, but they did provide comparative data to isosulfan blue dye.

Breast cancer & melanoma

In a prospective, nonrandomized Phase II trial, Leong *et al.* reported on 78 patients (47 with melanoma and 31 with breast cancer) who received ^{99m}Tc -tilmanocept as part of clinically indicated sentinel lymph node biopsy procedures [19]. In 55 patients, preoperative lymphoscintigraphy was performed, and a 'hot spot' indicative of a sentinel node or nodes was identified in 94.5% of these patients. Intraoperatively, ^{99m}Tc -tilmanocept identified at least one sentinel node in 75 out of 78 patients (96.2%), and 175 out of the 182 nodes removed at surgery (95.1%) were radioactive. Out of 26 tumor-positive nodes removed, 25 were identified by ^{99m}Tc -tilmanocept; one breast cancer patient had a tumor-positive node that was not radioactive. Five serious adverse events occurred in this trial, but all were considered to be related to the surgical procedure and none were attributed to the administration of ^{99m}Tc -tilmanocept. Only three patients (3.8%) experienced adverse events that were considered possibly related to the ^{99m}Tc -tilmanocept; no patient had an adverse event considered definitely or possibly related, and there were no deaths on the study.

Two very similar nonrandomized Phase III trials, NEO3-05 and NEO3-09, were completed in patients with either breast cancer or melanoma, and have been presented in abstract form at the American Society of Clinical Oncology [20] and the Society for Nuclear Medicine [21]. These trials were designed in consultation with the US FDA with the intent of serving as registration trials for ^{99m}Tc -tilmanocept. At the time of the studies' design and conduct, the only FDA-approved agent for lymphatic mapping was isosulfan blue dye (or Patent Blue V[®], approved in Europe),

therefore, this agent was selected as the within-patient comparator and concordance with the blue dye was the primary end point. Subsequent to the completion of the Phase III trials, the FDA approved ^{99m}Tc -sulfur colloid for the localization of lymph nodes draining a primary breast cancer or melanoma, based on retrospective data demonstrating a high level of concordance with vital blue dye (see the 'Regulatory affairs' section below).

In both Phase III trials, involving a total of 332 patients with primary melanoma or breast cancer, ^{99m}Tc -tilmanocept (50 μg at 0.5–1.0 mCi ^{99m}Tc) provided superior results compared with vital blue dye. Each patient was to undergo a preoperative injection of ^{99m}Tc -tilmanocept with lymphoscintigraphy, then intraoperative injection of vital blue dye. As in most tilmanocept studies, total volume was not fixed, but instead adjusted to provide the required nanomolar concentration. Intraoperative lymphatic mapping was performed with a handheld γ -detector (Neoprobe, Devicor Medical Products Inc., OH, USA), using strict criteria (the '3-sigma rule', as described in [22]) to define radioactive nodes and visual evaluation for the presence of blue dye within nodes. All radioactive, blue or palpably abnormal nodes were excised and examined histologically. The 'intent-to-treat' group was defined as those patients with at least one blue node who had also received an injection of ^{99m}Tc -tilmanocept, as these were the patients who were evaluable for the primary end point of concordance of ^{99m}Tc -tilmanocept with blue dye. A reverse-concordance group was defined to consist of patients with at least one radioactive node who also received an injection of blue dye. The prespecified null hypothesis was that concordance was ≤ 0.90 , while the alternative hypothesis was concordance > 0.90 , using a two-sided test for significance at the $\alpha = 0.05$ level.

In both trials, ^{99m}Tc -tilmanocept was highly concordant with blue dye: over 95% of blue nodes were radioactive using the 3- σ definition, and, therefore, the null hypothesis of concordance being 90% or less was rejected statistically, meeting the prespecified end point for concordance. By contrast, reverse concordance was poor: many radioactive nodes were not visibly blue. More radioactive nodes were identified and removed than blue nodes, and a few tumor-containing nodes were radioactive but not blue. No tumor-containing nodes were blue but not radioactive, although two palpable nodes containing breast cancer in one patient were neither radioactive nor blue. Detailed results for each

trial as prospectively conducted have not been published, but recent publications have provided aggregated results for the two trials subdivided by tumor type.

A combined analysis of the melanoma patients enrolled onto these two Phase III trials has been reported [22]. A total of 154 melanoma patients from 15 centers were injected with both agents and evaluated intraoperatively. A total of 232 out of 235 blue nodes were detected by ^{99m}Tc-tilmanocept intraoperatively for 98.7% concordance with blue dye ($p < 0.001$ that the true concordance rate exceeds 90%). ^{99m}Tc-tilmanocept detected 364 nodes as 'hot' for 63.7% reverse concordance (232 out of 364 hot nodes were also blue). ^{99m}Tc-tilmanocept detected at least one node in more patients ($n = 150$) than blue dye ($n = 138$; $p = 0.002$). In 135 out of 138 patients with at least one blue node, all blue nodes were radioactive. Melanoma was identified in the sentinel nodes of 22.1% of patients; all 45 melanoma-positive sentinel nodes were detected by ^{99m}Tc-tilmanocept, whereas blue dye detected only 36 (80%) out of 45 nodes ($p = 0.004$). No melanoma-positive sentinel nodes were detected exclusively by blue dye. Four out of 34 node-positive patients were identified by ^{99m}Tc-tilmanocept only, therefore, four (2.6%) out of 154 patients were correctly staged by ^{99m}Tc-tilmanocept only. No serious adverse events were attributed to ^{99m}Tc-tilmanocept [22].

Another recent publication looked at the efficacy of ^{99m}Tc-tilmanocept in sentinel lymph node identification in breast cancer patients [23]. Concordance data from the two Phase III clinical trials of ^{99m}Tc-tilmanocept plus vital blue dye was compared with a meta-analysis of a review of the literature pertaining to 'standard of care' ^{99m}Tc-labeled nanocolloid human serum albumin (Nanocoll®, GE Healthcare Ltd, Buckinghamshire, UK). Five studies involving 6134 breast cancer patients were reviewed to calculate the aggregate sentinel node identification rate of 95.9% for ^{99m}Tc-labeled nanocolloid human serum albumin (estimated 95% CI: 94.3–97.5%). Three studies involving 1380 patients were included to calculate the number of sentinel nodes per procedure identified with ^{99m}Tc-labeled nanocolloid human serum albumin of 1.67 nodes (95% CI: 1.51–51.82). The lower bound of the CI was used for comparison with ^{99m}Tc-tilmanocept. The Phase III ^{99m}Tc-tilmanocept data included 148 breast cancer patients, and pooled analysis revealed a 98.65% sentinel node identification rate (95% CI: 95.0–99.8%) with pooled

2.16 lymph nodes per procedure (95% CI: 1.96–92.36). Using a comparison of the lower bound values of the 95% CIs, the authors concluded that ^{99m}Tc-tilmanocept was statistically superior to ^{99m}Tc-labeled nanocolloid human serum albumin for both the rate of sentinel node identification and the number of nodes identified per procedure ($p < 0.001$ and $p = 0.008$, respectively) [23]. The authors note several limitations inherent in this type of pooled analysis and retrospective review, not least of which is the variability in defining a sentinel lymph node as radioactive during standard of care surgical procedures compared with the prescribed use of standardized definitions in a prospective trial.

Head & neck squamous cell carcinoma

The two Phase III trials involving breast cancer and melanoma patients met their prespecified regulatory end points of concordance, but the trials were not designed to estimate how often neither blue dye nor ^{99m}Tc-tilmanocept identified tumor-containing nodes (i.e., how often the sentinel node procedure was falsely negative). Since complete lymphadenectomy is no longer performed for clinically node-negative breast cancer or melanoma patients unless a sentinel node is found to contain malignancy, directly estimating the 'false negative' rate of ^{99m}Tc-tilmanocept is not feasible in these patients. A nonrandomized Phase III trial was designed to address this issue in patients with squamous cell carcinomas of the head and neck, either of cutaneous or upper aerodigestive tract origin, who were undergoing clinically indicated complete cervical lymphadenectomy for clinically node-negative cancers. This trial is open and accruing patients (trial identifier NCT00911326), but as yet no results are available [101].

Other solid tumors

At the time of writing this article, no prospective clinical trials of ^{99m}Tc-tilmanocept have been conducted or are known to be planned in patients with any other tumor types.

Safety & tolerability

Overall, the reported data – particularly from Phase II and III evaluations of ^{99m}Tc-tilmanocept alone or in combination with vital blue dye – suggest this agent is safe and very well tolerated. No agent-specific serious adverse events have been identified, and most of the reported adverse events in the Phase II and III trials appear to have been associated with the sentinel node biopsy procedure rather than

^{99m}Tc-tilmanocept. Whether tilmanocept is more tolerable than currently used colloids has not been systematically evaluated, although it has been suggested that it could be associated with less injection site discomfort than filtered ^{99m}Tc-sulfur colloid [19]. Demonstrating improved tolerability, however, would require prospective comparisons (ideally randomized) involving additional numbers of patients.

Regulatory affairs

Until very recently, none of the colloids commonly used for intraoperative sentinel node identification around the world were specifically approved for that purpose. Isosulfan blue dye is approved by the FDA for lymphatic identification and hence has featured prominently in the design of Phase III trials intended to support registration of ^{99m}Tc-tilmanocept specifically for this purpose. In July 2011, the FDA granted approval to Pharmeducence Inc. (MA, USA) to add the location of lymph nodes in breast cancer patients to the label indications for its ^{99m}Tc-sulfur colloid product [102]. This approval was based not on prospective trial data, but rather on a systematic literature review involving 15 'prospectively designed studies' reporting results from 9213 breast cancer sentinel node procedures. Overall, ^{99m}Tc-sulfur colloid was present in at least one lymph node in 94.1% of procedures, while blue dye was present in at least one lymph node in only 85.1%. Furthermore, ^{99m}Tc-sulfur colloid in conjunction with blue dye was also superior to blue dye alone in this analysis [102]. Subsequently, in August 2012, the FDA added localization of lymph nodes in melanoma to the label indications for the Pharmeducence Inc. ^{99m}Tc-sulfur colloid for injection, based on similar literature review data [103]. On 13 March 2013, the FDA approved ^{99m}Tc-tilmanocept (Lymphoseek injection) as a radioactive diagnostic agent indicated for lymphatic mapping with a handheld γ counter to assist in the localization of lymph nodes

draining a primary tumor site in patients with breast cancer or melanoma [104].

The FDA's decision to approve ^{99m}Tc-sulfur colloid has potential implications for the future of ^{99m}Tc-tilmanocept. By accepting a nonrandomized comparison with vital blue dye as the basis for approval, the case for approval of ^{99m}Tc-tilmanocept based on rigorous prospective clinical trial data was markedly strengthened. On the other hand, the fact that ^{99m}Tc-sulfur colloid is now approved for breast cancer and melanoma lymphatic mapping may increase the pressure from practitioners or payors (and even some regulatory agencies worldwide) to directly demonstrate the advantages of ^{99m}Tc-tilmanocept over ^{99m}Tc-sulfur colloid in prospective, randomized trials. Of course, this would be influenced by the cost, convenience and potential for reimbursement when ^{99m}Tc-tilmanocept is brought to market.

Conclusion & future perspective

^{99m}Tc-tilmanocept is an interesting agent designed specifically for the pre- and intra-operative identification of sentinel lymph nodes. Sentinel node biopsy is widely used globally in the management of breast cancer and melanoma, and may have a role in a variety of other solid tumors. In most of the world, no radiopharmaceutical is approved specifically for use in this procedure, and no new imaging agents have been introduced into clinical practice for more than a decade. Therefore, the availability of a new agent with advantages over current alternatives is of great potential interest. The clinical trial data available to date support the conclusion that ^{99m}Tc-tilmanocept is an effective and safe agent for identifying sentinel lymph nodes in melanoma and breast cancer; however, it remains unclear how much of an improvement, if any, it will represent over traditional agents.

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Executive summary

- Sentinel node biopsy is widely used in breast cancer and melanoma, as well as in other cutaneous malignancies, and could potentially have a role in many noncutaneous tumors.
- A synthetic macromolecule, ^{99m}Tc-tilmanocept, is designed specifically for the localization of sentinel lymph nodes through binding to CD206 receptors expressed on reticuloendothelial cells residing in lymph nodes.
- In two open-label, nonrandomized Phase III trials where vital blue dye was used as a comparator, ^{99m}Tc-tilmanocept identified sentinel nodes as well as or better than blue dye, meeting the prespecified end points for efficacy, and identified more tumor-containing lymph nodes than blue dye.
- On 13 March 2013, the US FDA approved ^{99m}Tc-tilmanocept (Lymphoseek) for use in lymphatic mapping with a handheld γ counter to assist in the localization of lymph nodes draining a primary tumor site in patients with breast cancer or melanoma.
- Other available colloids have not been directly compared with ^{99m}Tc-tilmanocept for sentinel node identification in large-scale studies.

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