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BRIEF REPORT

Brief Report: High Levels of CD47 Expression in Thymic Epithelial Tumors

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ABSTRACT

Introduction: CD47 is a tumor antigen that inhibits phagocytosis leading to immune evasion. Anti-CD47 therapy is a promising new immunotherapy across numerous tumor types, but it has not been tested in thymic epithelial tumors (TETs): thymomas and thymic carcinomas. TETs are rare tumors that are difficult to treat, especially with programmed cell death protein 1/programmed death-ligand 1 checkpoint inhibitors, owing to the excessive rates of immune-related adverse events. This study investigated the levels of CD47 expression in TETs to explore the possibility of anti-CD47 therapy.

Methods: A total of 67 thymic tumors (63 thymomas and 4 thymic carcinomas) and 14 benign thymus controls and their clinical data were included. Samples were stained for CD47 expression (rabbit monoclonal antibody SP279, Abcam, Waltham, MA) and scored for both intensity and H-score (intensity multiplied by the percentage of tumor involved). Intensity was defined as follows: 0 = none, 1 = weak, 2 = moderate, and 3 = strong. H-scores ranged from 0 to 300. Samples with an intensity score below 2 or an H-score below 150 were considered $CD47^{low}$, whereas the rest were $CD47^{high}$.

Results: Compared with normal thymic tissues, TETs were more frequently CD47 positive and had significantly higher levels of CD47 expression. CD47 was positive in 79.1% of TETs compared with 57.1% of normal thymus. The level of CD47 expression was 16-fold higher in TETs (mean H-score 75.0 versus 4.6, $p = 0.003$). Multivariate analysis adjusted for age, sex, stage, resection status, and performance status revealed that CD47-high tumors were highly correlated with WHO histology type ($p = 0.028$). The most frequent $CD47^{high}$ tumors, in contrast to $CD47^{low}$ tumors, were types

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A (28.6% versus 7.5%) and AB (57.1% versus 13.2%), and the least frequent were B1 (7.1% versus 24.5%), B2 (0% versus 35.8%), B3 (7.1% versus 11.3%), and C (0% versus 7.5%).

Conclusions: In contrast to normal thymus, TETs had significantly higher levels of CD47 expression. Tumor samples with high CD47 expression were mostly WHO types A and AB. This is the first study to explore CD47 expression in thymic cancers and lends support for ongoing investigation of anti-CD47 macrophage checkpoint inhibitor therapy in these tumors.

Keywords: CD47; Thymoma; Thymic carcinoma; Immunotherapy; Thymic epithelial tumor

Introduction

Thymic epithelial tumors (TETs), classified as either thymomas or thymic carcinomas (TCs), are rare tumors of the mediastinum which affect approximately one in 100,000 patients.[1] For patients not amenable to curative surgical resection, systemic therapy is indicated with platinum-based chemotherapy regimens often used in the first-line setting. For patients who have subsequent relapsed or resistant disease, options are limited to either alternative chemotherapeutic agents or oral tyrosine kinase inhibitors with modest activity.[2] Underlying molecular aberrations are still poorly understood, and no targeted therapies are available.

In the past decade, immunotherapy targeting the CTLA-4 and the programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis has garnered tremendous success across a wide range of tumor types. Clinical activity has been noted with immune checkpoint inhibitors in TETs.[3,4] Nevertheless, the use of anti–PD-1/PD-L1 inhibitors is limited in these tumors, as high rates of severe and even fatal immune-related adverse events (irAEs) have been found in TETs, including prohibitively high and severe irAEs in thymoma. PD-1 antibodies are occasionally administered with caution in TCs, which also have higher rates of irAEs compared with other tumors.[4] TETs have been known to cause autoimmune sequelae on their own, and this predilection seems highly increased with the addition of T-cell–targeted immunotherapy. One prospective trial of pembrolizumab found rates of grade 3 or higher adverse events to range from 15% (for TCs) to as high as 70% (for thymomas), with some patients experiencing multiple autoimmune complications concurrently and several autoimmune toxicities revealed in more than 50% of patients with thymoma, limiting any further development in that patient population.[3]

The risks of conventional T-cell–targeting checkpoint inhibition have prompted the search for alternative methods of immune activation. CD47 is a transmembrane protein expressed on tumor cells that when bound to its receptor SIRPα is an important innate immune checkpoint inhibiting macrophage phagocytosis.[5,6] Tumoral CD47 expression is a predictor of disease progression and inferior survival outcomes in multiple cancer types.[7] Anti-CD47 therapy serves as a macrophage checkpoint inhibitor and renders tumor cells susceptible to immune elimination, without causing considerable autoimmune side effects.[8] It was found to have promising activity in the relapsed/resistant setting in a number of CD47-expressing tumor types, including non-Hodgkin's lymphoma and myelodysplastic syndrome.[9,10]

Anti-CD47 therapy has not been tested in TETs, though in a phase 1/2 study of a peptide compound that blocks the CD47 immune checkpoint through expression of Tsp-1, the only response was found in a patient with thymoma.[11] Maturation of T-cells occurs in the thymus through positive and negative selection, and thymomas can produce abnormal T-cell populations.[12] CD47 expression may prevent the clearance of abnormal T-cells and the homeostasis of regulatory T-cell populations.[6] As an initial step to exploring the potential role of anti-CD47 targeting in thymic epithelial malignancies, we conducted a study to quantify the levels of CD47 expression in these tumors compared with normal thymic tissue.

Materials and Methods

A TET tissue microarray was constructed using formalin-fixed, paraffin-embedded tissue from 67 thymic tumors (63 thymomas and 4 TCs) and 14 benign thymus controls with associated clinical data included as previously described.[13,14] Patients provided informed consent, or a waiver of consent was obtained on an institutional review board–approved protocol. Samples with an average of three cores each were stained for CD47 expression in epithelial cells (rabbit monoclonal antibody SP279, Abcam, Waltham, MA) and scored for both intensity and H-score (intensity multiplied by the percentage of tumor involved). Intensity was defined as follows: 0 = none, 1 = weak, 2 = moderate, and 3 = strong. H-scores ranged from 0 to 300. Samples with an intensity score below 2 or an H-score below 150 were considered $CD47^{low}$, whereas the rest were $CD47^{high}$. The scoring pathologist (S.C.) was blinded to clinical data and sample identity.

Mann-Whitney test was used to compare the CD47 staining between TETs and controls. Fisher's exact test or chi-square test was used to evaluate the relationship

Table 1. Baseline Characteristics

Variables	All Cases (N = 67)	CD47 High[a] (n = 14)	CD47 Low (n = 53)	*p* Value (H-Score; Intensity)[b]
Age, mean (range)	56.0 (2-86)	59.1 (36-80)	55.2 (2-86)	0.44
Sex, n (%)				0.95
Male	34 (50.7)	7 (50.0)	27 (50.9)	
Female	33 (49.3)	7 (50.0)	26 (49.1)	
ECOG performance status, n (%)				**0.02**
0	33 (49.3)	10 (71.4)	23 (43.4)	
1	28 (41.8)	3 (21.4)	25 (47.2)	
2	5 (7.5)	1 (7.1)	4 (7.5)	
3	1 (1.5)	0	1 (1.9)	
WHO histology,[c] n (%)				**0.0006; 0.0006**
A	8 (11.9)	4 (28.6)	4 (7.5)	
AB	15 (22.4)	8 (57.1)	7 (13.2)	
B1	14 (20.9)	1 (7.1)	13 (24.5)	
B2	19 (28.4)	0	19 (35.8)	
B3	7 (10.4)	1 (7.1)	6 (11.3)	
C	4 (6.0)	0	4 (7.5)	
Pathologic Masaoka stage, n (%)				**0.032; 0.023**
I	30 (44.8)	11 (78.6)	19 (35.8)	
II	15 (22.4)	2 (14.3)	13 (24.5)	
IIa	12	2	10	
IIb	3	0	3	
III	12 (17.9)	1 (7.1)	11 (20.8)	
IV	10 (14.9)	0	10 (18.9)	
IVa	6	0	6	
IVb	4	0	4	
Paraneoplastic syndrome, n (%)	25 (37.3)	2 (14.3)	23 (43.4)	0.063; **0.0014**
Myasthenia gravis, n (%)	16 (23.9)	0	16 (30.2)	
Pure red cell aplasia, n (%)	2 (3.0)	0	2 (3.8)	
Hypogammaglobulinemia, n (%)	1 (1.5)	0	1 (1.9)	
Other,[d] n (%)	6 (9.0)	2 (14.3)	4 (7.5)	
None, n (%)	42 (62.7)	12 (85.7)	30 (56.6)	
Resection status, n (%)				0.058; 0.073
R0	45 (67.2)	13 (92.9)	32 (60.4)	
R1	9 (13.4)	1 (7.1)	8 (15.1)	
R2	13 (19.4)	0	13 (24.5)	

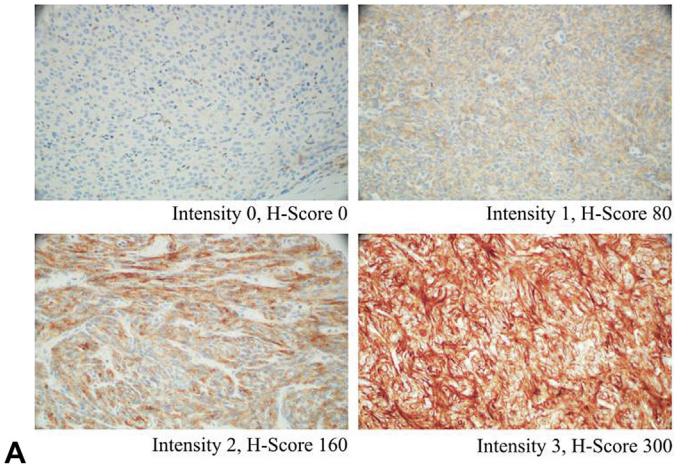
Note: Bolded values are two-sided *p* values less than 0.05 and are considered statistically significant.
[a]CD47 high based on H-score $\geq$ 150; CD47 low based on H-score $<$ 150.
[b]Chi-square or Fisher's exact test.
[c]A micronodular thymoma with lymphoid stroma was classified as type A; one classified as C as mixed B3/C.
[d]Other paraneoplastic syndromes were autoimmune enteropathy, dermatomyositis, Guillain-Barré syndrome, lymphocytic myocarditis, minimal change nephrotic syndrome, and rheumatoid arthritis.
ECOG, Eastern Cooperative Oncology Group.

between staining and categorical variables. Multivariate linear regression analysis of CD47 H-scores was adjusted for age, sex, performance status, WHO type, stage, and resection status (Prism 9, GraphPad). Univariate survival analysis was performed with Mantel-Cox test, whereas multivariate survival analysis was done with a Cox regression model. Survival analyses were performed using Prism version 9, GraphPad, and R version 4. Overall survival (OS) was measured from date of diagnosis to the date of death. Event-free survival (EFS) was measured from date of diagnosis for those patients without metastasis at diagnosis to the date of first recurrence or death from any cause. A two-sided *p* value less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

Samples from a total of 67 patients with TETs were included in this analysis (Table 1). The average age of the patients was 56 (range: 2–86) years, with 51% men and 49% women. All patients except one had Eastern Cooperative Oncology Group performance status of 0 to 2 at diagnosis. The pathologic Masaoka-Koga stage was predominantly early stages I and II at 45% and 22%,



B

CD47 Tumor Expression (N = 67)	n (%)
Intensity (mean ± SD)	0.57 ± 0.96
0	12 (17.9)
1	30 (44.8)
2	14 (20.9)
3	11 (16.4)
Percentage of Tumor Involved (mean ± SD)	35.74 ± 37.54
0-25	35 (52.2)
25-50	6 (9.0)
50-75	12 (17.9)
75-100	14 (20.9)
H-Score (mean ± SD)	74.49 ± 94.31
0-74	43 (64.2)
75-149	10 (14.9)
150-224	6 (9.0)
225-300	8 (11.9)

Figure 1. CD47 expression in thymic epithelial tumors. (*A*) Representative immunohistochemical staining of CD47 (brown signal) in a tissue microarray with intensity and H-scores presented. Magnification, ×400. (*B*) CD47 expression levels in 67 tumor samples.

respectively. The most frequent histology types were AB, B1, and B2. Most patients had a R0 resection (67%). Just more than a third of patients (37.3%) had a paraneoplastic syndrome (PNS), with myasthenia gravis being the most common (64%).

CD47 Expression in TETs

Samples were graded by both CD47 intensity and H-score (intensity multiplied by proportion of tissue staining), as reported previously (Fig. 1).[1] Compared with normal thymic tissues, TETs were more frequently CD47 positive and had significantly higher levels of CD47 expression. CD47 was positive in 79% of TETs (≥1% by H-score), compared with 57% of normal thymus. Importantly, CD47 expression was significantly higher in TETs than in normal thymic tissues (Fig. 2*A* and *B*). The mean intensity score was 1.36 for TETs compared with 0.57 for control ($p = 0.004$), and the mean H-score was 75.0 compared with 4.59 ($p = 0.003$). The level of expression, based on H-score, was on average 16-fold higher in TETs. The mean H-score for thymomas (75.33, n = 63) was not significantly different than that for TCs (61.25, n = 4; $p = 0.77$).

Higher CD47 Expression Was Associated With Less Aggressive WHO Histologies

Tumors that exhibited high CD47 expression (20.9% with H-score ≥ 150, n = 14) were significantly associated with a lower Masaoka stage ($p = 0.032$). Most CD47-high tumors (78.6%, n = 11 of 14) were stage 1, compared with only 35.8% of CD47-low tumors (n = 19 of 53). There was a trend toward more complete resection (R0 resection) with CD47-high tumors ($p = 0.058$).

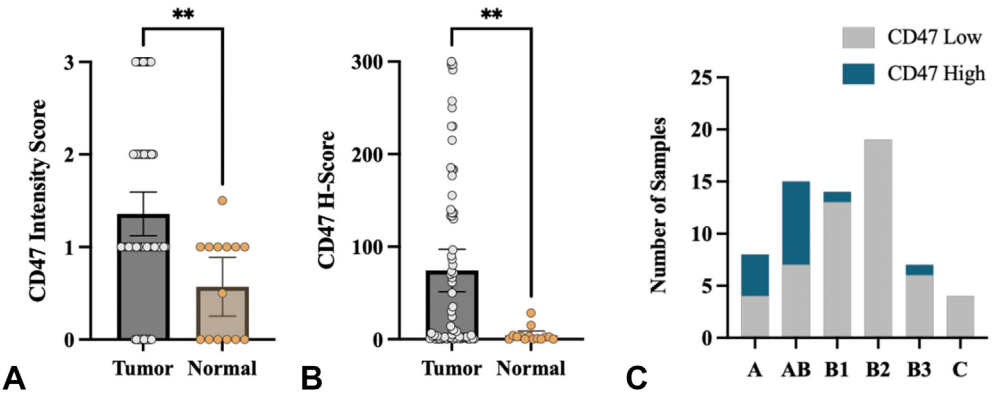


Figure 2. CD47 expression levels. (*A*) CD47 staining intensity scores. *p* value was 0.004. (*B*) CD47 staining H-scores (intensity multiplied by percentage of tumor cells involved). *p* value was 0.003. ** denotes a *p* value of less than 0.01. Error bars denote 95% confidence intervals. (*C*) Proportions of CD47-high and CD47-low patient tumors within each WHO histology type.

CD47-high tumors were more often characterized by less aggressive WHO histology types when compared with CD47-low tumors ($p = 0.0006$; Fig. 2*C* and Table 1).[15] CD47-high tumors were of types A and AB 85.7% of the time (n = 12 of 14), compared with 20.7% of CD47-low tumors (n = 11 of 53). CD47-high tumors were most frequently type AB (57.1% in CD47-high versus 13.2% in CD47-low tumors) followed by type A (28.6% versus 7.5%). Tumors of the worst prognostic type C (n = 4) were exclusively CD47-low. A multivariate analysis adjusting for age, sex, performance status, stage, and resection status confirmed the significant correlation between CD47-high status and a more favorable WHO type ($p = 0.0275$).

Type A and AB tumors had nearly equal proportions of CD47-high and CD47-low tumors: type A (50.0% CD47-high, n = 4 of 8) and type AB (53.3%, n = 8 of 15). Types B1 to C were almost exclusively CD47-low (B1: 7.1% CD47-high, n = 1 of 14; B2: 0%, n = 0 of 19; B3: 14.3%, n = 1 of 7; C: 0%, n = 0 of 4; Table 1).

As expected, EFS and OS were both worse for WHO types B3 to C in this cohort compared with the other histologies. Median EFS was 1.7 years versus 7.7 years (hazard ratio [HR] = 3.39, 95% confidence interval [CI]: 1.03–11.15, $p = 0.0023$), whereas OS was 5.25 years versus 22.2 years (HR = 4.06, 95% CI: 1.08–15.27, $p = 0.0017$). EFS and OS were not significantly different between patients with CD47-high tumors and those with CD47-low (EFS HR = 0.54, 95% CI: 0.17–1.71, $p = 0.39$; OS HR = 0.83, 95% CI: 0.27–2.51, $p = 0.73$). Multivariate survival analysis adjusting for age, sex, performance status, WHO type, and resection status did not reveal any significant correlation between CD47 and these survival outcomes, EFS ($p = 0.81$) and OS ($p = 0.33$).

Just more than a third of patients in the cohort had a PNS (37.3%), with most (64%) having myasthenia gravis. Other PNS included pure red cell aplasia, Guillain-Barré syndrome, autoimmune enteropathy, and lymphocytic myocarditis. Tumors that were $CD47^{low}$, when compared with $CD47^{high}$, more often had a PNS (52.4% versus 12.0%). Nevertheless, multivariate analysis adjusted for WHO type did not reveal an independent association between CD47 status and PNS ($p = 0.0948$). $CD47^{low}$ tumors were most often WHO types B2 and B3, which in this cohort had the highest frequency of PNS.

Discussion

To our knowledge, this study is the first report of CD47 expression levels in TETs. CD47 expression predicts worse outcomes in hematological and solid malignancies.[7,16] We found that most TETs were CD47 positive and expressed significantly higher levels of CD47 compared with the normal thymus. TETs, which tended to have higher CD47 expression, were those with a more favorable WHO histology, but this did not correlate with improved EFS or OS. This may have been limited by the sample size of the cohort. Prior studies in other cancer types have similarly failed to find a clear relationship between CD47 expression and survival outcomes, and further studies with larger cohorts remain to be done.[17–20]

The vast majority (85.7%) of tumors with high CD47 expression were WHO types A and AB, which, unlike other types, are difficult to distinguish apart as they share a common histologic appearance (the occurrence of spindle epithelial cells) and specific genetic alterations.[21] It is yet unclear how their common tumor microenvironment selectively promotes higher CD47 expression.

Preclinical data have revealed that targeting CD47 leads to inhibition of tumoral growth and metastasis in a number of cancer types, including breast and NSCLCs.[22,23] In the clinical setting, anti-CD47 monoclonal therapy has not been tested in TETs, although in a phase 1/2 trial of a peptide compound designed to achieve downstream inhibition of CD47, the only response was found in a patient with thymoma, who also had high levels of CD47 expression.[11]

For patients with TETs who develop resistance to chemotherapy, and who already have a high incidence of autoimmune events, anti-CD47 therapy may be worth exploring as a novel immunotherapy given the different side effect profile when compared to anti-PD(L)1 antibodies. Owing to the high expression of CD47 on TET tumor cells, we have initiated a clinical trial to test anti-CD47 blockade in TETs.

Credit Authorship Contribution Statement

Thomas Yang Sun: Writing—original draft preparation and subsequent revisions, Data gathering, Data analysis, Investigation.

Brandon Nguyen: Data analysis, Data gathering.

Simon B. Chen: Pathology review, Manuscript review.

Yasodha Natkunam: Pathology review, Tissue microarray creation, Manuscript review.

Sukhmani Padda: Database curation, Manuscript review.

Matt van de Rijn: Tissue microarray creation.

Robert West: Tissue microarray creation.

Joel W. Neal: Data gathering, Manuscript review.

Heather Wakelee: Manuscript review, Supervision.

Jonathan W. Riess: Conception, Supervision, Manuscript review, Data analysis.

References

1. Hsu CH, Chan JK, Yin CH, Lee CC, Chern CU, Liao CI. Trends in the incidence of thymoma, thymic carcinoma, and thymic neuroendocrine tumor in the United States. *PLoS One*. 2019;14:e0227197.
2. Scorsetti M, Leo F, Trama A, et al. Thymoma and thymic carcinomas. *Crit Rev Oncol Hematol*. 2016;99:332–350.
3. Cho J, Kim HS, Ku BM, et al. Pembrolizumab for patients with refractory or relapsed thymic epithelial tumor: an open-label phase II trial. *J Clin Oncol*. 2019;37:2162–2170.
4. Giaccone G, Kim C, Thompson J, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. *Lancet Oncol*. 2018;19:347–355.
5. Weiskopf K. Cancer immunotherapy targeting the CD47/SIRPα axis. *Eur J Cancer*. 2017;76:100–109.
6. Zhao H, Song S, Ma J, et al. CD47 as a promising therapeutic target in oncology. *Front Immunol*. 2022;13:757480.
7. Eladl E, Tremblay-LeMay R, Rastgoo N, et al. Role of CD47 in hematological malignancies. *J Hematol Oncol*. 2020;13:96.
8. Sikic BI, Lakhani N, Patnaik A, et al. First-in-human, first-in-class phase I trial of the anti-CD47 antibody Hu5F9-G4 in patients with advanced cancers. *J Clin Oncol*. 2019;37:946–953.
9. Advani R, Flinn I, Popplewell L, et al. CD47 blockade by Hu5F9-G4 and rituximab in non-Hodgkin's lymphoma. *N Engl J Med*. 2018;379:1711–1721.
10. Sallman DA, Al Malki M, Asch AS, et al. Tolerability and efficacy of the first-in-class anti-CD47 antibody magrolimab combined with azacitidine in MDS and AML patients: phase Ib results. *J Clin Oncol*. 2020;38(suppl 15):7507–7507.
11. Mahalingam D, Harb W, Patnaik A, et al. 374 A first-in-human phase 1/2 open label trial evaluating the safety, pharmacology, and preliminary efficacy of VT1021 in subjects with advanced solid tumors. *J Immunother Cancer*. 2020;8(suppl 3):A399–A399.
12. Weksler B, Lu B. Alterations of the immune system in thymic malignancies. *J Thorac Oncol*. 2014;9(suppl 2):S137–S142.
13. Padda SK, Riess JW, Schwartz EJ, et al. Diffuse high intensity PD-L1 staining in thymic epithelial tumors. *J Thorac Oncol*. 2015;10:500–508.
14. Riess JW, Kong CS, West RB, et al. Increased galectin-1 expression in thymic epithelial tumors. *Clin Lung Cancer*. 2019;20:e356–e361.
15. Chen G, Marx A, Chen WH, et al. New WHO histologic classification predicts prognosis of thymic epithelial tumors: a clinicopathologic study of 200 thymoma cases from China. *Cancer*. 2002;95:420–429.
16. Noblejas-López Mdel M, Baliu-Piqué M, Nieto-Jiménez C, et al. Transcriptomic profiles of CD47 in breast tumors predict outcome and are associated with immune activation. *Int J Mol Sci*. 2021;22:3836.
17. Arrieta O, Aviles-Salas A, Orozco-Morales M, et al. Association between CD47 expression, clinical characteristics and prognosis in patients with advanced non-small cell lung cancer. *Cancer Med*. 2020;9:2390–2402.
18. Shi M, Gu Y, Jin K, et al. CD47 expression in gastric cancer clinical correlates and association with macrophage infiltration. *Cancer Immunol Immunother*. 2021;70:1831–1840.
19. Kim H, Jee S, Kim Y, et al. Correlation of CD47 expression with adverse clinicopathologic features and an unfavorable prognosis in colorectal adenocarcinoma. *Diagnostics (Basel)*. 2021;11:668.
20. Imam R, Chang Q, Black M, Yu C, Cao W. CD47 expression and CD163+ macrophages correlated with prognosis of pancreatic neuroendocrine tumor. *BMC Cancer*. 2021;21:320.
21. Marx A, Chan JKC, Coindre JM, et al. The 2015 WHO classification of tumors of the thymus: continuity and changes. *J Thorac Oncol*. 2015;10:1383–1395.
22. Kaur S, Elkahloun AG, Singh SP, et al. A function-blocking CD47 antibody suppresses stem cell and EGF signaling in triple-negative breast cancer. *Oncotarget*. 2016;7:10133–10152.
23. Zhao H, Wang J, Kong X, et al. CD47 promotes tumor invasion and metastasis in non-small cell lung cancer. *Sci Rep*. 2016;6:29719.