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Original contribution

# *MDM2* amplification and immunohistochemical expression in sarcomatoid renal cell carcinoma☆,☆☆

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**Summary** The sarcomatoid variant of renal cell carcinoma is a highly aggressive tumor with propensity for metastasis and limited therapeutic options. Metastases of sarcomatoid renal cell carcinoma can sometimes be mistaken for a variety of spindle cell sarcomas, particularly at soft tissue sites in the absence of a history of a kidney tumor. Immunoreactivity for markers associated with certain types of soft tissue sarcomas can, therefore, pose a pitfall for diagnosis under such circumstances. We evaluated the immunohistochemical and molecular features of 49 cases of sarcomatoid renal cell carcinoma with special emphasis on the expression of MDM2 by immunohistochemistry and *MDM2* amplification by fluorescence in situ hybridization. Of the 49 sarcomatoid renal cell carcinoma cases evaluated by fluorescence in situ hybridization, 5 (10%) were positive for *MDM2* gene amplification and 5 (10%) contained polysomy 12. Immunohistochemical nuclear expression for MDM2 was also observed in 30/49 (61%) cases; of these, 15/19 (78%) were metastatic and 15/30 (50%) were primary. MDM2 expression by immunohistochemistry has been previously reported in conventional clear cell renal cell carcinoma; however, occurrence of this phenomenon has not yet been properly assessed in the sarcomatoid variant of renal cell carcinoma. Our study demonstrates that alterations of the *MDM2* pathway are relatively frequent in sarcomatoid renal cell carcinoma, and nuclear positivity for MDM2 by immunohistochemistry, as well as *MDM2* amplification by fluorescence in situ hybridization may pose a potential pitfall for diagnosis with dedifferentiated liposarcoma at metastatic sites. A panel approach to immunohistochemical testing is recommended for the diagnosis of these lesions. Also, identification of cases of sarcomatoid renal cell carcinomas harboring *MDM2* copy number gain or gene amplification may also have potential therapeutic implications.


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## 1. Introduction

Sarcomatoid renal cell carcinoma (sRCC) is an aggressive, high-grade histologic variant of renal cell carcinoma with propensity for metastasis and poor prognosis [1]. Median survival after diagnosis is less than one year and cancer-specific survival at 5 years is 15–22% [1,2] as current therapeutic approaches are largely ineffective [3]. Sarcomatoid renal cell carcinoma is usually a biphasic neoplasm harboring both carcinomatous and sarcomatous components. The amount of the sarcomatous component may vary considerably and tumors exhibiting 100% sarcomatoid component may be difficult to diagnose, especially in advanced stages where they may resemble any form of sarcoma [4].

Sarcomatoid transformation may occur in any subtype of renal cell carcinoma as a manifestation of a common loss of differentiation pathway [5]; however, there has been no consensus histopathological definition of sarcomatoid renal cell carcinoma by the International Society of Urological Pathology (ISUP) [4]. Historically, a renal cell carcinoma has been regarded as showing sarcomatoid transformation when it harbors a population of atypical spindle cells that resemble a spindle cell sarcoma [6]. The sarcomatoid component in these tumors most often resembles a fibrosarcoma, a malignant peripheral nerve sheath tumor or several other types of spindle cell sarcomas [1]. For these reasons, accurate diagnosis of sarcomatoid renal cell carcinoma may be challenging as it may be mistaken for a true sarcoma. This is especially true in cases in which a clinical history is not known or in rare cases where a sarcomatous soft tissue mass resembling an *MDM2* positive de-differentiated liposarcoma is the presenting sign of an occult primary renal cell carcinoma [7]. The goal of this study was to evaluate the frequency and spectrum of immunohistochemical and molecular alterations of *MDM2* in sarcomatoid renal cell carcinoma and to address its potential role for rendering an incorrect diagnosis of primary sarcoma at metastatic sites.

## 2. Materials and methods

With institutional review board approval, subjects were identified from three academic hospitals (Beth Israel Deaconess Medical Center, Boston, MA; Medical College of Wisconsin, Milwaukee, WI and Charles University School of Medicine, Plzen, Czech Republic) by a retrospective medical records search for patients with tissue diagnosis of sarcomatoid renal cell carcinoma during nephrectomy procedure and/or at metastatic sites. This search yielded 49 patients with sarcomatoid renal cell carcinoma (30 primary and 19 metastatic). Tissue sections from all cases were fixed in buffered formalin and embedded in paraffin for conventional processing and stained with hematoxylin and eosin (H&E). For immunohistochemical study, three representative 1 mm cores from each case were obtained to create a tissue microarray block. Only the sarcomatoid components of the tumors were targeted for inclusion. The tissue microarray block was constructed with the TMA Grandmaster platform (3DHISTECH LTD, Budapest, Hungary). From the tissue microarray block four micrometer thick sections were cut and deparaffinized in xylene, hydrated in descending dilutions of ethanol, and exposed to heat-induced epitope retrieval.

Immunohistochemical staining was performed using reagents from the Dako Envision FLEX kit and the Dako AutostainerPlus stainer. Following pretreatment with Target Retrieval Solution, tissue was blocked with peroxidase-blocking reagent for 5 minutes and incubated with the primary antibody at room temperature. Signals were detected using the Dako FLEX detection kit. Counterstaining was performed with Envision FLEX hematoxylin for 7 minutes at room temperature. Appropriate positive and negative controls were run concurrently for all antibodies tested, including cytokeratin AE1/3 (Clone AE1/AE3, dilution: ready to use, Dako, Carpinteria, CA, USA), CK18 (Clone DC10, dilution: ready to use, Dako, Carpinteria, CA, USA), Cam5.2 (Clone CAM5.2, dilution: ready to use, BD Biosciences, San Jose, CA), Pax8 (Clone polyclonal, dilution 1:100, Proteintech Group, Rosemont, IL), RCC (Clone SPM314, dilution: ready to use, Dako, Carpinteria, CA), CD10 (Clone 56C6, dilution: ready to use, Dako, Carpinteria, CA, USA), p53 (Clone DO-7, dilution: 1:25, Santa Clara, CA, USA), MDM2 (Clone SMP14, dilution 1:50, Santa Cruz Biotechnology, Santa Cruz, CA), EMA (Clone E29, dilution ready to use, Dako, Carpinteria, CA, USA), p16 (Clone EP435Y-129R, dilution 1:50; Abcam, Cambridge, MA), and CDK4 (Clone D9G3, dilution 1:400, Cell Signaling, Danvers, MA, USA). Antibody staining was evaluated by a semiquantitative method. Altered p53 IHC (mutant type) was assessed by either diffuse, strong positivity in the majority of cells, cytoplasmic staining or complete absence of any staining in tumor cells (null-pattern) as previously validated in other tumor types [8].

Fluorescence in situ hybridization to detect amplification of the *MDM2* gene was performed on all cases with fluorescently-labeled probes using a chromosome 12 centromere-specific (CEP12) and *MDM2* locus-specific probe set (Abbott Molecular Inc, Des Plaines, IL). A minimum of 50 interphase cells were analyzed per case by one of two technologists certified in cytogenetics by the American Society for Clinical Pathology. *MDM2* amplification in our study was defined as *MDM2*/CEP12 ratio of $\geq 2$, while polysomy 12 was defined as gains of *MDM2*/CEP12 in equal ratio while not exceeding six total copies per cell. Non-amplified cases were defined as *MDM2*/CEP12 ratio of $<2$. All fluorescence in situ hybridization procedures were performed per manufacturer protocols and analysis was completed using an Olympus BX41 microscope (Melville, NY). Image capture was performed using Cytovision software (Leica Biosystems, Buffalo Grove, IL).

In addition, an observational retrospective secondary data analysis of clinically-annotated multi-platform cancer –omics datasets from the Cancer Genome Atlas Project (TCGA) and MSK IMPACT study via online data mining tools (cbio portal) was performed. Clinicopathological and molecular data

from TCGA clear cell renal cell carcinoma (n = 418) [9], TCGA chromophobe renal cell carcinoma (n = 65) [10], TCGA papillary renal cell carcinoma (n = 280) [11] and MSK IMPACT advanced renal cell carcinoma (n = 323) [12] was analyzed with respect to *MDM2* amplification via the cBio Cancer Genomics Portal (http://cbioportal.org; Memorial Sloan Kettering Cancer Center, New York, NY) [13,14]. The cohorts were queried for *MDM2* gene amplification in the cbio portal by using the advanced onco query language (*MDM2*: AMP) [13,14]. In the cBio portal, copy number gain was defined as gain of one gene copy number, while amplification was defined as gain of 2 or more gene copy numbers.

## 3. Results

### 3.1. Sarcomatoid renal cell carcinoma cohort and morphological features

A total of 49 cases were reviewed. Minimal histomorphological criteria for diagnosis of sarcomatoid renal cell carcinoma consisted of identifying atypical or malignant-appearing spindle cell elements resembling any specific type of sarcoma or a sarcoma not otherwise specified. With this criterion, 49 cases with intersecting fascicles of malignant spindle cells, or cases with pleomorphic malignant spindle cells were identified. In some tumors, renal carcinoma origin was supported by the presence of sharp transitions between the sarcomatoid components and pre-existing conventional, non-sarcomatoid renal cell carcinoma (Fig. 1A-C). The non-sarcomatoid component in nearly all cases in which it was present was a conventional clear cell renal cell carcinoma except for one case with a type II papillary renal cell carcinoma. The percent sarcomatoid component could be evaluated in 25/30 cases in the primary kidney tumors and ranged from 3% to 95% with an average of 42% of the tumor displaying sarcomatous transformation. The histomorphology of all the cases at metastatic sites was exclusively of sarcomatoid type except for two cases; one case metastatic to the lung showed a focal (<20%) component of conventional clear cell renal cell carcinoma, and a second case metastatic to the left parietal skull showed an equal admixture of conventional renal cell carcinoma with the sarcomatoid component.

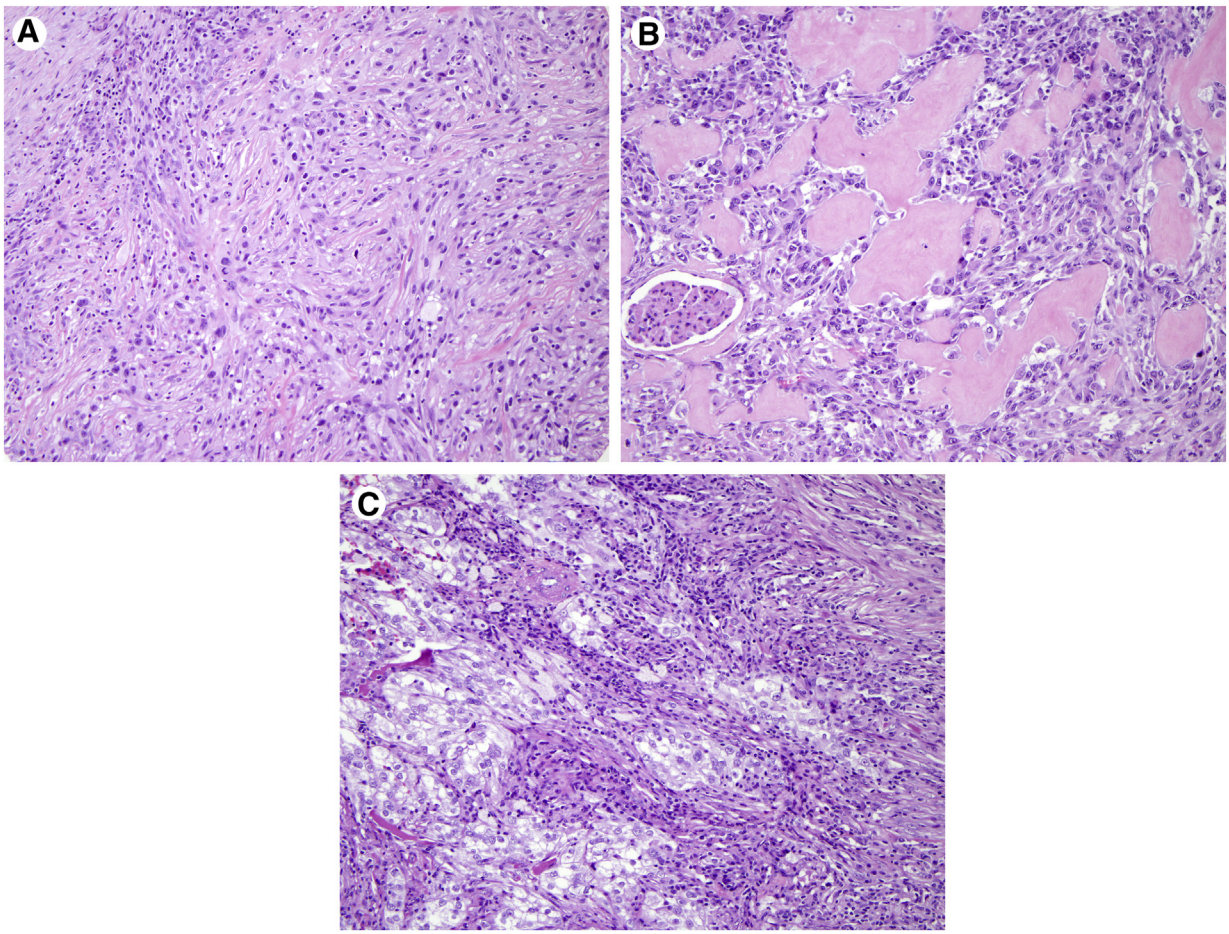


**Fig. 1** A, Metastatic sRCC mimicking a primary soft tissue spindle cell sarcoma (H&E, x100). B, Primary sRCC showing high grade spindle cell morphology and an entrapped glomerulus (H&E, X100). C, Conventional clear cell renal cell carcinoma (left) showing sharp transition to sRCC (right) (H&E, X100).

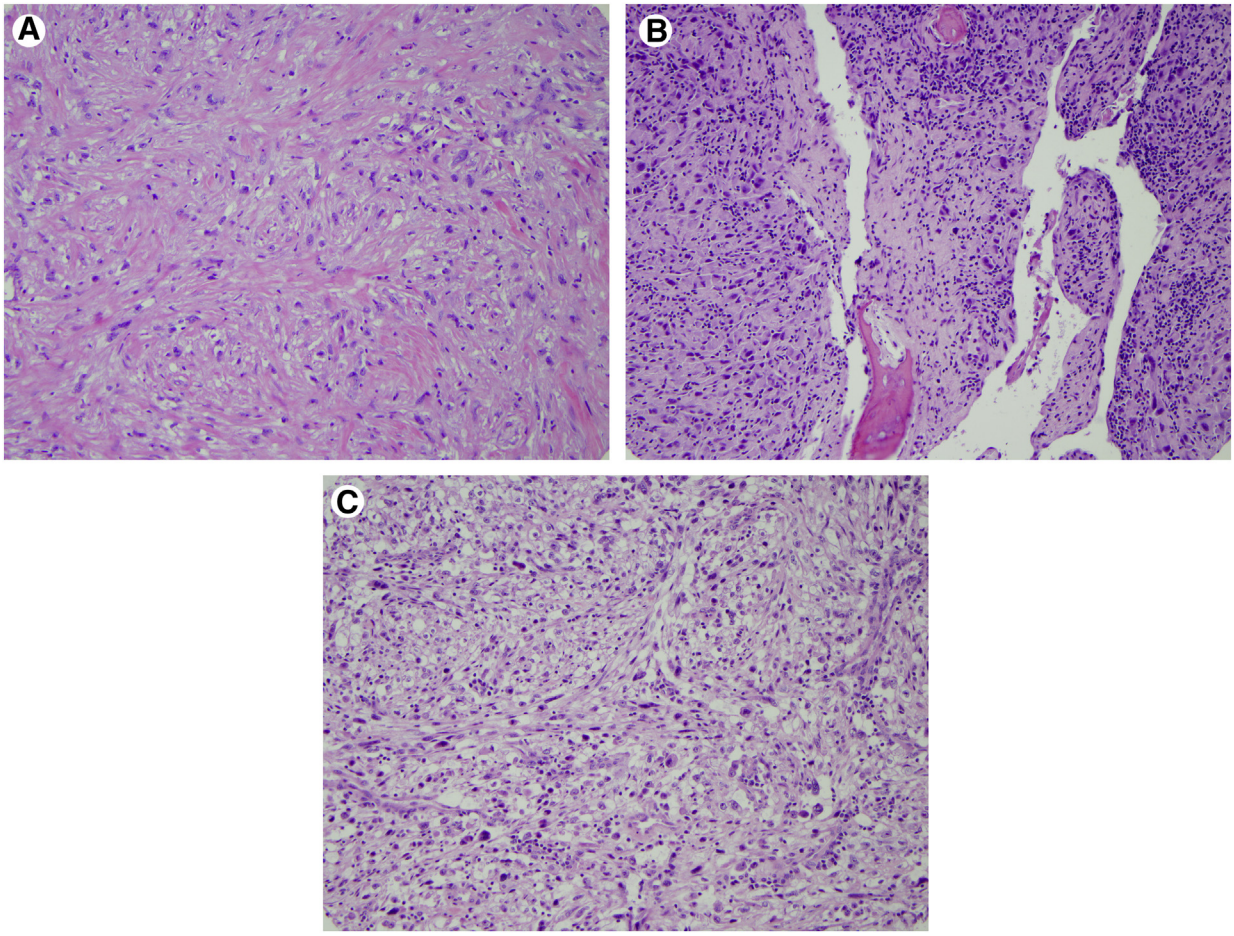


**Fig. 2** A, Soft tissue (anterior abdominal wall) metastasis of sRCC showing stromal sclerosis (H&E, X100). B, Metastasis of sRCC to bone with focal rhabdoid features (H&E, X40). C, Soft tissue (right back) metastasis of sRCC showing fascicular growth pattern and highly atypical rhabdoid appearing cells (H&E, X100).

Of the 19 metastatic sarcomatoid renal cell carcinomas, 4 (21%) were metastasis to soft tissue, 4 (21%) were metastasis to bone, and 2 (11%) were located within the perirenal soft tissues in the retroperitoneum separate from the primary renal mass. The remaining metastatic lesions were identified within lungs (4), lymph nodes (2), pancreas (1), pleura (1), and brain (1) (Fig. 2A-C).

### 3.2. Immunohistochemical findings

Immunohistochemical findings are presented in Fig. 3. Immunohistochemistry performed for MDM2 showed nuclear expression in 30/49 (61%) cases; 21 (70%) of these cases showed strong nuclear expression while 9 (30%) cases showed weak or patchy staining (Fig. 4A). Of the metastatic sarcomatoid renal cell carcinomas 15/19 (78%) showed some degree of MDM2 expression, whereas only 15/30 (50%) primary sarcomatoid renal cell carcinomas were positive for MDM2. An altered p53 immunostaining pattern was observed in 18/49 (37%) cases; MDM2 positive cases showed concurrent altered p53 immunostaining in 13/30 (33%) cases, 7 of which were metastatic and 6 of which were primary. CDK4 was expressed in 11/49 (22%) cases; 7 metastatic and 4 primary tumors. Of the CDK4 positive cases only one metastatic and one primary case showed strong diffuse staining while the rest showed weak or patchy positivity (Fig. 4B). Immunohistochemistry was also performed for the following epithelial markers: cytokeratin CK18, AE1/AE3, Cam5.2 and EMA to determine sensitivity of these markers for diagnosis of sarcomatoid carcinoma. Overall, the tumors expressed CK18, cytokeratin AE1/AE3, EMA and Cam5.2 in 46/49 (94%), 44/49 (90%), 36/49 (73%) and 27/49 (55%) cases, respectively. In the metastatic group; CK18, AE1/AE3, EMA and CAM5.2 showed some degree of positivity in 17/19 (89%), 16/19 (84%), 13/19 (68%) and 11/19 (57%) cases, respectively. Of these cases, only weak or patchy positivity was seen for AE1/AE3 in 6/16 (38%) tumors, CK18 in 4/17 (23%), and CAM5.2 in 4/11 (36%) positive tumors (Fig. 4C). All the metastatic tumors which stained with EMA showed a strong and diffuse staining pattern. In the primary group, CK18, AE1/AE3, EMA and CAM5.2 showed positivity in 29/30 (96%), 28/30 (93%), 23/30 (76%) and 16/30 (53%) cases, respectively. In this

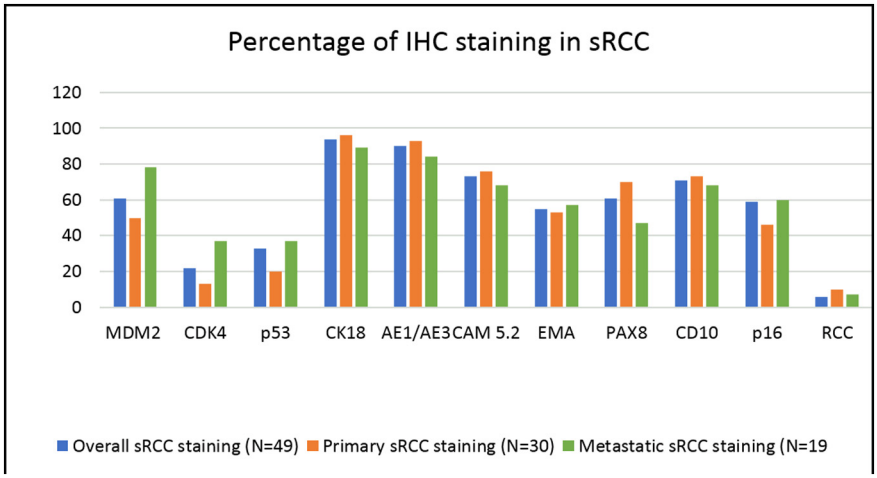


**Fig. 3** Summary of immunohistochemical findings in sarcomatoid renal cell carcinoma. IHC = immunohistochemistry, sRCC = sarcomatoid renal cell carcinoma.

group, only weak and patchy positivity was observed for AE1/AE3 in 3/28 (10%) cases, CK18 in 3/29 (10%), CAM5.2 in 6/16 (37%) cases, and EMA in 6/23 (26%) cases. Markers supporting renal origin such as PAX8, CD10 and RCC were also tested. PAX8 expression could be identified in 30/49 (61%) cases and CD10 was positive in 35/49 (71%) cases. In the metastatic group; PAX8 and CD10 were positive in 9/19 (47%) and 13/19 (68%) cases. PAX8 showed only weak or patchy

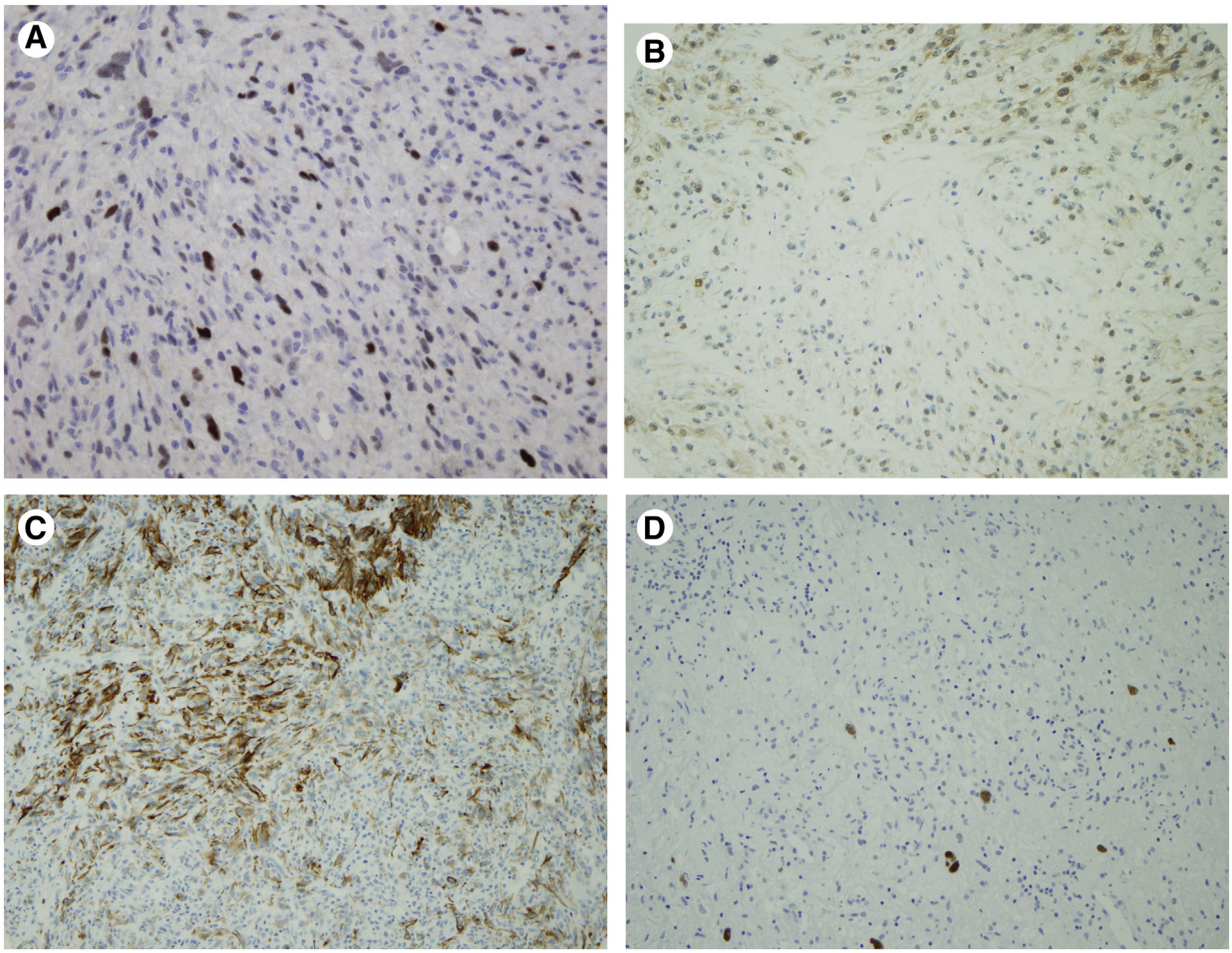


**Fig. 4** A, Strong MDM2 nuclear and cytoplasmic expression within spindle cells (MDM2 X200). B, Patchy CDK4 staining in metastatic sRCC (CDK4 X200). C, Focal keratin positivity in metastatic sRCC (KER, X100). D, Focal PAX8 positivity highlighting only few cells (PAX8, X100).

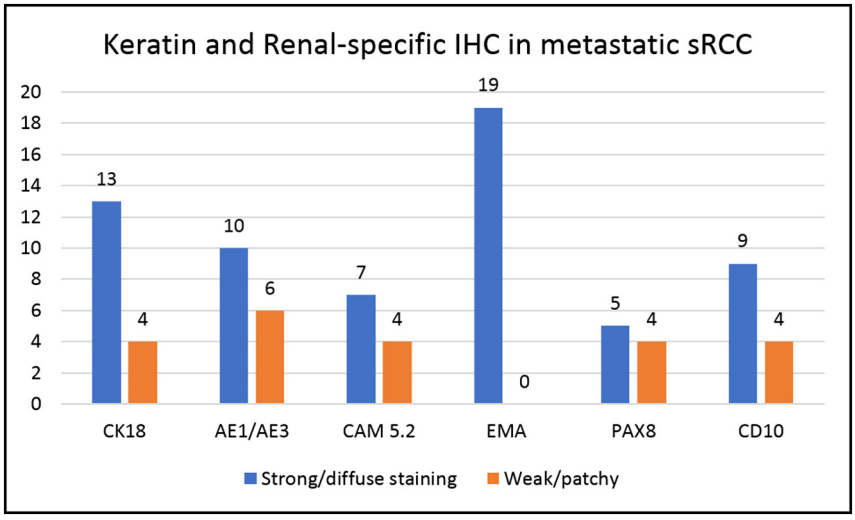


**Fig. 5** Summary of differential expression patterns in the metastatic cohort of sRCC for epithelial and renal-specific IHC. IHC = immunohistochemistry, sRCC = sarcomatoid renal cell carcinoma.

positivity in 4/9 (44%) cases, while CD10 showed weak or patchy positivity in 4/13 (30%) cases. In the primary group; PAX8 and CD10 were positive in 21/30 (70%) and 22/30 (73%) cases. In this group PAX8 showed weak or patchy positivity in 6/21 (29%) cases, while CD10 showed weak or patchy positivity in 5/22 (23%) cases (Fig. 4D). The staining pattern (strong *vs.* weak) is summarized in Fig. 5. RCC was expressed in only 4/49 (6%) cases. Finally, p16 was expressed in 23/39 (59%) cases.

### 3.3. *MDM2* fluorescent in situ hybridization and gene amplification

*MDM2* gene amplification was assessed by fluorescence in situ hybridization on tissue microarray sections. Of the 49 cases, 5 (10%) showed *MDM2* gene amplification (defined as *MDM2*: Centromere 12 ratio> 2) (Fig. 6). Additionally, 5 (10%) contained polysomy 12 (extra *MDM2* and centromere 12 signals in equal ratio and not exceeding 6 total signals per

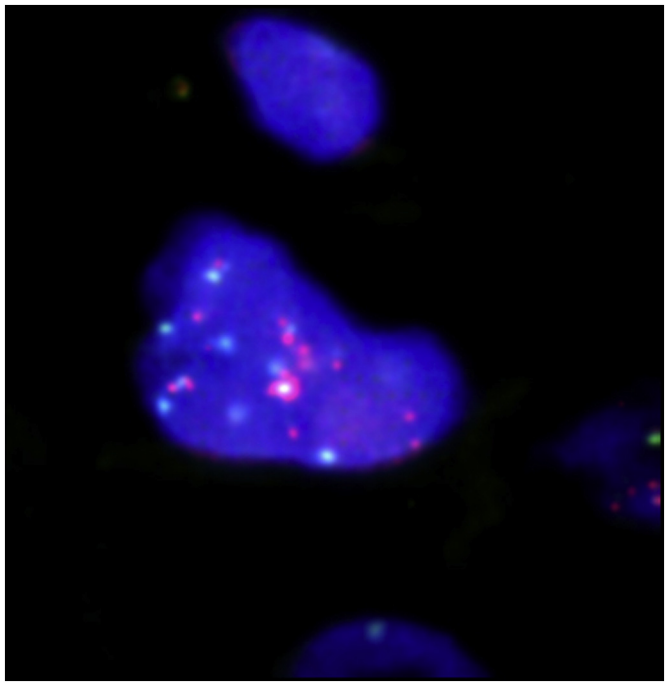

**Fig. 6** *MDM2*/CEP12 FISH showing increased signals consistent with amplification in sRCC.

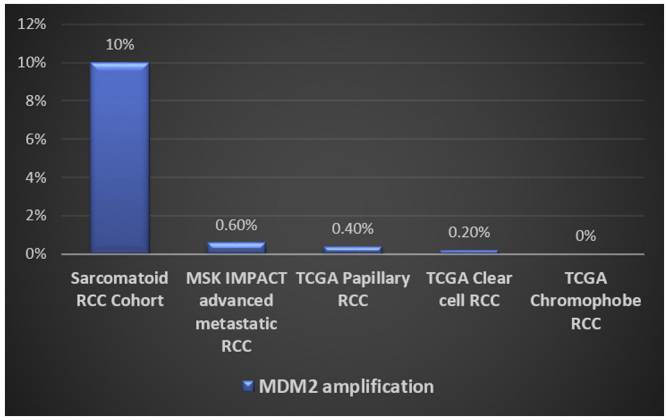


**Fig. 7** *MDM2* amplification frequency in sRCC of this study compared to non-sRCC cohorts (TCGA clear cell RCC, TCGA chromophobe RCC, TCGA papillary RCC and MSK IMPACT advanced RCC).

probe). Of the 49 cases; 3 of 5 cases that contained *MDM2* gene amplification exhibited strong nuclear MDM2 expression by immunohistochemistry and 2 of 5 cases that contained *MDM2* gene amplification had weak nuclear staining for MDM2 by immunohistochemistry. In contrast, 2 of 5 cases that contained polysomy of chromosome 12 exhibited strong nuclear MDM2 expression by immunohistochemistry and 3 of 5 cases had scant or no nuclear MDM2 staining. These results suggest that a subset of sarcomatoid renal cell carcinomas may exhibit MDM2 nuclear protein expression due to *MDM2* gene amplification or copy number gain alterations of chromosome 12.

### 3.4. *MDM2* amplification in non-sarcomatoid renal cell carcinoma Cancer Genome Atlas Project and MSK-IMPACT cohorts

Compared to our *MDM2* amplification frequency of 10%, analysis of Cancer Genome Atlas Project and MSK IMPACT non-sarcomatoid renal cell carcinoma studies revealed extremely low or no *MDM2* gene amplification in conventional clear cell renal cell carcinoma (0.2%, 1/418), chromophobe renal cell carcinoma (0%, 0/65), papillary renal cell carcinoma (0.4%, 1/280), and advanced metastatic non-sarcomatoid renal cell carcinoma (0.6%, 2/323 cases) (Fig. 7).

## 4. Discussion

We have studied 49 cases of renal cell carcinoma showing sarcomatoid transformation with emphasis on immunohistochemical expression and molecular amplification of *MDM2*. Alterations of *MDM2* in these tumors are of importance because of the potential diagnostic pitfalls and emerging clinical and therapeutic implications for targeted therapies [15].

In contrast to clear cell, chromophobe or papillary renal cell carcinoma, the immunohistochemical and molecular features of sarcomatoid renal cell carcinoma have not been well defined. Genetically, sarcomatoid renal cell carcinoma exhibits a complex set of chromosomal gains and losses, with common losses of 13q (75%) and 4q (50%) [16,17]. More recently, comprehensive whole genome sequencing has revealed potential common pathways to sarcomatoid transformation, with recurrent mutations in *VHL*, *PTEN*, *TP53*, *BAP1*, *NF2*, *TMEM97*, *CALML3*, *IL15* and *RELN* [16-19]. In an independent study, sarcomatoid transformation in clear cell renal cell carcinoma exhibited sarcomatoid-specific mutations of *TP53* and *BAP1* only in the sarcomatoid components, as compared with paired carcinomatous elements, thereby implicating *TP53* mutations in the pathogenesis of the sarcomatoid component [20].

The tumor suppressive function of p53 is regulated by *MDM2*, which acts as an E3 ubiquitin ligase for p53 and targets p53 for ubiquitin-mediated proteasome degradation [21]. Amplification and overexpression of both *MDM2* and *CDK4* are characteristic of well-differentiated and de-differentiated liposarcomas, and fluorescence in situ hybridization and immunohistochemistry have become useful tests that are routinely used for confirming the diagnosis of this sarcoma type [22]. De-differentiated liposarcomas may also involve perinephric tissues and the renal parenchyma [23], thereby posing a potential diagnostic pitfall in the differential diagnosis of sarcomatoid renal cell carcinoma. While none of the cases in our study displayed heterologous elements of differentiation, liposarcomatous transformation has been described in renal cell carcinoma further complicating the differential diagnosis [24-26].

In our study, most sarcomatoid renal cell carcinomas expressed epithelial markers, with the most sensitive epithelial marker being CK18 (94%). Other renal cell carcinoma-associated markers, such as PAX8 and CD10 showed a similar pattern of expression as in other previously published studies (60–70%) [27,28]. In most instances, these epithelial and renal lineage specific markers are helpful in supporting an epithelial malignancy over a mesenchymal malignancy. However, in cases with patchy or focal staining for these markers or when an obviously epithelial component is lacking, pathologists should be aware of the potential diagnostic pitfall of MDM2

expression and *MDM2* amplification in sarcomatoid renal cell carcinoma. This is especially true when considering the differential diagnosis of sarcomas with *MDM2* aberrations such as de-differentiated liposarcoma. Because of the increasing awareness of de-differentiated liposarcoma; MDM2 immunohistochemistry and fluorescence in situ hybridization are being increasingly utilized as screening tools in the work up of spindle cell tumors of soft tissue, thus posing a pitfall for diagnosis of the sarcomatoid variant of renal cell carcinoma.

*MDM2* overexpression by immunohistochemistry has been demonstrated in conventional renal cell carcinoma [29]. However, only a single case report has so far called attention to *MDM2* alterations in sarcomatoid renal cell carcinoma, leading to an incorrect initial diagnosis of dedifferentiated liposarcoma [7]. Our study demonstrates that alterations of *MDM2* occur in sarcomatoid renal cell carcinoma which may display nuclear MDM2 expression by immunohistochemistry, *MDM2* gene amplification and polysomy 12, and mutant p53 staining patterns. In our series, overexpression of MDM2 was independent of *MDM2* amplification, suggesting that there is upregulation at the level of transcription or post-translational modification of the *MDM2* protein. Our rate of p53 alterations (37%) by immunohistochemistry is similar to the p53 mutation rate reported by Bi et al of approximately 30% [20]. Our fluorescence in situ hybridization study which demonstrated that 10% of cases displayed polysomy 12 is in keeping with other studies that have demonstrated various chromosomal gains and losses in these tumors [16,17]. Prior studies have demonstrated that altered p53 protein expression and/or direct p53 gene mutation is higher in sarcomatoid cells compared to the parent carcinoma cells in renal cell carcinoma, suggesting that genomic alterations in *TP53* might be involved in triggering the sarcomatoid transformation [18-20].

Sarcomatoid renal cell carcinoma has a dismal prognosis with limited treatment options [30]. The results of this study may have both clinical and therapeutic implications with emerging targeted therapies. Currently, *MDM2*-specific inhibitors, such as SAR405838, are in clinical trials for advanced solid tumors (ie, NCT01636479) [31,32], and *MDM2* antagonists have previously resulted in apoptosis of renal cell carcinoma cells [33]. Similarly, *CDK4*- specific inhibitors, such as Palbociclib (codenamed PD-0332991, trade name Ibrance), are also currently in clinical trials for cancer [34] and may inhibit proliferation of renal carcinoma cells [35]. However, future preclinical and clinical studies are needed to determine the efficacy of *MDM2*- or *CDK4*-specific inhibitors in a subset of advanced sarcomatoid renal cell carcinoma.

Finally, immunotherapy with nivolumab, a monoclonal antibody targeting the programmed cell death receptor has recently been approved for use as second-line option for advanced renal cell carcinoma [36]. Some tumors with *MDM2* amplification have also been shown to be hyper-progressors after immunotherapy, with poorer clinical outcomes and significantly increased rates of tumor growth after single-agent checkpoint (PD-1/PD-L1) inhibitors perhaps indicating that testing for *MDM2* status may be beneficial [37].

In summary, we have demonstrated genetic alterations of *MDM2* by FISH and MDM2 expression by immunohistochemistry in 20% and 61% of our cases, respectively, which may represent a potential diagnostic pitfall in the workup of purely sarcomatoid lesions. Given that even purely sarcomatoid lesions express various keratins we recommend a panel approach to immunohistochemistry including at least one keratin, preferably CK18, which had the highest sensitivity for sarcomatoid RCC in our study. In addition, our results raise the possibility that testing for *MDM2* gene amplification may be useful in determining potential hyper-progressors in patients being considered for immunotherapy. Additional investigations are warranted to determine the effects of immunotherapy in these tumors and whether *MDM2*-altered sarcomatoid renal cell carcinomas are hyper-progressors with worse prognosis following immune checkpoint inhibitors.

## References


[1] de Peralta-Venturina M, Moch H, Amin M, et al. Sarcomatoid differentiation in renal cell carcinoma: a study of 101 cases. Am J Surg Pathol 2001;25:275-84.

[2] Cheville JC, Lohse CM, Zincke H, et al. Sarcomatoid renal cell carcinoma: an examination of underlying histologic subtype and an analysis of associations with patient outcome. Am J Surg Pathol 2004;28:435-41.

[3] El Mouallem N, Smith SC, Paul AK. Sarcomatoid renal cell carcinoma: biology and treatment advances. Urol Oncol Semin Orig Investig 2018; 36:265-71.

[4] Delahunt B, Cheville JC, Martignoni G, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. Am J Surg Pathol 2013;37:1490-504.

[5] Delahunt B. Sarcomatoid renal carcinoma: the final common dedifferentiation pathway of renal epithelial malignancies. Pathology 1999;31:185-90.

[6] Farrow GM, Harrison EG, Utz DC. Sarcomas and sarcomatoid and mixed malignant tumors of the kidney in adults. Cancer 1968;22:556-63.

[7] Logunova V, Sokumbi O, Iczkowski KA. Metastatic sarcomatoid renal cell carcinoma manifesting as a subcutaneous soft tissue mass. J Cutan Pathol 2017;44:874-7.

[8] Lee S, Piskorz AM, Le Page C, et al. Calibration and optimization of p53, WT1, and Napsin a immunohistochemistry ancillary tests for histotyping of ovarian carcinoma. Int J Gynecol Pathol 2016;35:209-21.

[9] Cancer Genome Atlas Research Network. Comprehensive molecular characterization of clear cell renal cell carcinoma. Nature 2013;499:43-9.

[10] Davis CF, Ricketts CJ, Wang M, et al. The somatic genomic landscape of Chromophobe renal cell carcinoma. Cancer Cell 2014;26:319-30.

[11] Cancer Genome Atlas Research Network, Linehan WM, Spellman PT, et al. Comprehensive molecular characterization of papillary renal-cell carcinoma. N Engl J Med 2016;374:135-45.

[12] Zehir A, Benayed R, Shah RH, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 2017;23:703-13.

[13] Cerami E, Gao J, Dogrusoz U, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov 2012;2:401-4.

[14] Gao J, Aksoy BA, Dogrusoz U, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 2013;6:l1.

[15] Ball MW, Singer EA, Srinivasan R. Renal cell carcinoma. Curr Opin Oncol 2017;29:201-9.

[16] Brunelli M, Gobbo S, Cossu-Rocca P, et al. Chromosomal gains in the sarcomatoid transformation of chromophobe renal cell carcinoma. Mod Pathol 2007;20:303-9.

[17] Jiang F, Moch H, Richter J, et al. Comparative genomic hybridization reveals frequent chromosome 13q and 4q losses in renal carcinomas with sarcomatoid transformation. J Pathol 1998;185:382-8.
[18] Wang Z, Kim TB, Peng B, et al. Sarcomatoid renal cell carcinoma has a distinct molecular pathogenesis, driver mutation profile, and transcriptional landscape. Clin Cancer Res 2017;23:6686-96.
[19] Bergerot P, Agarwal N, Pal SK, Jones J. Sarcomatoid renal cell carcinoma: the apple Doesn't fall far from the tree. Clin Cancer Res 2017;23:6381-3.
[20] Bi M, Zhao S, Said JW, et al. Genomic characterization of sarcomatoid transformation in clear cell renal cell carcinoma. Proc Natl Acad Sci 2016;113:2170-5.
[21] Kubbutat MH, Jones SN, Vousden KH. Regulation of p53 stability by Mdm2. Nature 1997;387:299-303.
[22] Binh MBN, Sastre-Garau X, Guillou L, et al. MDM2 and CDK4 immunostainings are useful adjuncts in diagnosing well-differentiated and dedifferentiated liposarcoma subtypes: a comparative analysis of 559 soft tissue neoplasms with genetic data. Am J Surg Pathol 2005;29:1340-7.
[23] Manini C, Pedalino M, Di Primio OG, et al. Renal liposarcoma clinical and pathological aspects. Case report and literature review. Urologia 2010;77:25-7.
[24] Petersson F, Michal M, Franco M, et al. Chromophobe renal cell carcinoma with liposarcomatous dedifferentiation - report of a unique case. Int J Clin Exp Pathol 2010;3(5):534-40.
[25] Handoo A, Pai RR, Rao VS, et al. Sarcomatoid renal cell carcinoma with osteosarcomatous differentiation – a case report. Indian J Pathol Microbiol 2004;47(4):528-9.
[26] Aird JJ, Nic An Riogh AU, Fleming S, et al. Papillary renal cell carcinoma with Osteosarcomatous heterologous differentiation: a case report with molecular genetic analysis and review of the literature. Int J Surg Pathol 2017;25(8):745-50.
[27] Chang A, Brimo F, Montgomery EA, Epstein JI. Use of PAX8 and GATA3 in diagnosing sarcomatoid renal cell carcinoma and sarcomatoid urothelial carcinoma. Hum Pathol 2013;44:1563-8.
[28] Yu W, Wang Y, Jiang Y, Zhang W, Li Y. Distinct immunophenotypes and prognostic factors in renal cell carcinoma with sarcomatoid differentiation: a systematic study of 19 immunohistochemical markers in 42 cases. BMC Cancer 2017;17:293.
[29] Haitel A, Wiener HG, Baethge U, et al. MDM2 expression as a prognostic indicator in clear cell renal cell carcinoma: comparison with p53 overexpression and clinicopathological parameters. Clin Cancer Res 2000;6:1840-4.
[30] Shuch B, Bratslavsky G, Linehan WM, Srinivasan R. Sarcomatoid renal cell carcinoma: a comprehensive review of the biology and current treatment strategies. Oncologist 2012;17:46-54.
[31] Burgess A, Chia KM, Haupt S, et al. Clinical overview of MDM2/X-targeted therapies. Front Oncol 2016;6:7.
[32] de Jonge M, de Weger VA, Dickson MA, et al. A phase I study of SAR405838, a novel human double minute 2 (HDM2) antagonist, in patients with solid tumours. Eur J Cancer 2017;76:144-51.
[33] Liu Q, Shen H, Lin J, et al. Synergistic roles of p53 and HIF1α in human renal cell carcinoma-cell apoptosis responding to the inhibition of mTOR and MDM2 signaling pathways. Drug Des Devel Ther 2016;10:745-55.
[34] Verma S, Bartlett CH, Schnell P, et al. Palbociclib in combination with Fulvestrant in women with hormone receptor-positive/HER2-negative advanced metastatic breast Cancer: detailed safety analysis from a multicenter, randomized, placebo-controlled, phase III study (PALOMA-3). Oncologist 2016;21:1165-75.
[35] Logan JE, Mostofizadeh N, Desai AJ, et al. PD-0332991, a potent and selective inhibitor of cyclin-dependent kinase 4/6, demonstrates inhibition of proliferation in renal cell carcinoma at nanomolar concentrations and molecular markers predict for sensitivity. Anticancer Res 2013;33:2997-3004.
[36] Tannir NM, Pal SK, Atkins MB. Second line treatment landscape for renal cell carcinoma: a comprehensive review. Oncologist 2018;23:540-55.
[37] Kato S, Goodman A, Walavalkar V, Barkauskas DA, Sharabi A, Kurzrock R. Hyperprogressors after immunotherapy: analysis of genomic alterations associated with accelerated growth rate. Clin Cancer Res 2017;23:4242-50.