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Durable complete response of metastatic gastric cancer with anti-Met therapy followed by resistance at recurrence

Daniel V.T. Catenacci¹, Les Henderson¹, Shu-Yuan Xiao², Elicia Penuel³, Premal Patel³, Robert L. Yauch³, Amy Peterson³, and Ravi Salgia¹

¹Department of Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, IL, USA.

²Department of Pathology, University of Chicago, Chicago, IL, USA.

³Genentech, Inc., South San Francisco, CA, USA.

Abstract

A 48 year-old female with chemo-refractory metastatic gastric cancer to the liver was treated on a Phase I clinical trial with MetMAB, a monoclonal antibody targeting the Met tyrosine kinase receptor. The primary tumor had high *MET* gene polysomy and evidence for an autocrine production of HGF, the growth factor ligand of Met. A complete response was obtained lasting two years; the cancer recurred as a peritoneal deposit invading into the transverse colon and a gastrohepatic ligament node. Compassionate use of MetMAB therapy at recurrence achieved a mixed response - a partial response of the two initial lesions, but with development of multiple new foci of carcinomatosis. Tissue and serum studies evaluating the Met signaling pathway did correlate with MetMAB treatment response initially and at the time of recurrence.

Keywords

Gastric adenocarcinoma; Met; HGF; MetMab

INTRODUCTION

A 48 year-old female with a remote history of stage I, right-sided, ER/PR+, HER2–, infiltrating ductal breast cancer, treated with mastectomy and axillary lymph node dissection, followed by four cycles of cyclophosphamide and doxorubicin in 2000, presented with upper gastrointestinal bleeding in February, 2007. A biopsy of an ulcerated lesion located at the gastric incisura was identified as poorly differentiated adenocarcinoma with signet ring features. A CT scan on 03/05/07 revealed marked thickening along the lesser curvature of the stomach with no evidence of metastatic spread (Fig. 1a,b). The patient underwent a total gastrectomy with D2 lymphadenectomy and cholecystectomy in April, 2007. The primary tumor arose in a background of atrophic antral gastritis with intestinal metaplasia consistent with a primary gastric cancer. Four of 21 perigastric lymph nodes were involved. Intraoperatively, a serosal nodule was palpated in the gallbladder, consistent with metastatic disease. The final pathology report was pT3, N1, M1 (Fig. 2a). The margins were free of tumor. Post-operatively, the patient had no evidence of residual disease (Fig. 1c).

Corresponding Author: Daniel Catenacci, University of Chicago Medical Center, 5841 S. Maryland Avenue, MC2115, Chicago, IL 60637, Phone: 773-702-7596, Fax: 773-702-3163, dcatenac@medicine.bsd.uchicago.edu.

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Systemic chemotherapy with 5-FU/leucovorin and oxaliplatin was initiated. Due to her prior exposure to anthracyclines, she did not receive perioperative epirubicin (MAGIC regimen – epirubicin, cisplatin, 5-FU) (1), nor did she receive adjuvant chemoradiotherapy (MacDonald regimen (2)) given the existence of metastasis to the gallbladder.

Following six cycles of biweekly FOLFOX, imaging revealed a new hypodense lesion in the right hepatic lobe measuring 8.7mm × 12.4mm consistent with progressive disease (Fig. 1d). The patient was enrolled on an open-label phase II non-randomized trial evaluating an investigational small molecule receptor tyrosine kinase (RTK) inhibitor. This investigational agent was reported to inhibit Met, (a receptor tyrosine kinase involved in survival, proliferation, migration and metastasis), VEGFR2 and many other tyrosine kinases. The patient received four cycles of this therapy. An unconfirmed partial response was observed after the first two cycles (Fig. 1e), however the lesion progressed by RECIST criteria after the next two cycles (Fig. 1f). After a 4-week wash-out period, the patient was enrolled in a phase I trial evaluating the safety of MetMab (3,4), a monoclonal, monovalent (one-armed) antibody that binds to the extracellular component of the Met transmembrane receptor. The rationale for subsequent Met inhibition was multifactorial. Despite the progression by RECIST criteria, the tumor size was considered to be marginal to the treating clinicians, and there was lack of evidence of new lesions elsewhere, suggesting partial benefit from the RTK inhibitor. Also it appeared that cytotoxic therapy would not be urgently necessary for disease control. Additionally, this patient had previously progressed on oxaliplatin-based chemotherapy. Analysis for *MET* gene copy number from the primary gastric tumor (as well as metastatic lymph nodes and gallbladder deposit) revealed high polysomy and Met protein expression was detectable by IHC (Fig. 2a,b). This last point, combined with the question of specificity for Met versus VEGFR2 inhibition versus other tyrosine kinase domains with the initial RTK inhibitor suggested the possibility that isolated Met inhibition, by an antibody approach, may be active.

The patient was enrolled into the 20mg/kg cohort in the phase I study (OAM4224g) testing MetMab monotherapy in patients with solid tumors refractory to standard treatment (phase I manuscript in preparation). MetMab was administered intravenously every three weeks beginning March 2008, for ten doses. A complete response (CR) was observed in June 2008, following four MetMab doses (Fig. 1g) and confirmed by MRI in September 2008. Toxicities reported included grade 2 anasarca, and grade 2 hypoalbuminemia. No other patient enrolled into the phase I study had a response to single agent MetMab (5). In November 2008, despite a sustained CR, the patient discontinued MetMab. This was due to drug-related side effects and treatment fatigue combined with an ongoing CR, calling into question the benefit from additional infusions. The hypoalbuminemia and anasarca resolved within four weeks following cessation of MetMab and the patient underwent serial surveillance imaging and physician visits every three months for approximately two years. In October 2010, an asymptomatic lesion on the transverse colon was found (Fig. 1h), along with a new metastatic deposit at the gastrohepatic ligament (Fig. 1i). Biopsy of the colon confirmed poorly differentiated adenocarcinoma along with signet ring cell type and HER2 negativity by immunohistochemistry, consistent with the original gastric cancer pathology (Fig 2a).

Given the previous CR to MetMab, a single-patient IND for compassionate use was approved by the FDA and the Study Sponsor-(IND 105303). MetMab was given at a dose of 15mg/kg, the recommended phase II dose found to be active in patients with NSCLC (6). Following three cycles, CT imaging in December 2010 revealed that the transverse colonic metastatic lesion partially responded to therapy, decreasing from 54.1mm × 37.4mm to 38.7mm × 35.9mm (Fig. 1j). The gastrohepatic ligament node also decreased, measuring 21.9mm × 13.3 mm decreased from 24.5mm × 25.1 mm previously (Fig. 1k thick arrow).

Unfortunately, multiple new foci of carcinomatosis developed (Fig. 1k thin arrow, I). Given this mixed response, MetMab was discontinued, and the patient was treated with salvage irinotecan chemotherapy - the carcinomatosis progressed after four cycles.

RESULTS

Tissue and Serum Correlates

Primary Tumor – prior to anti-Met therapy 2007—To further explain the durable complete radiologic response observed after treatment with MetMab, additional correlative studies were conducted. Analysis of *MET* gene copy number by *fluorescence in situ hybridization* (FISH) was performed as previously described (7) on the primary tumor, metastatic lymph node and metastatic gallbladder of the surgical specimen obtained from 2007. There was no evidence for high-level, focal *MET* gene amplification, which has been identified in approximately 5–10% of gastro-esophageal adenocarcinomas (8,9). However, in these samples, the poorly differentiated non-signet ring cells showed 4 *MET* copies/cell in 60% of the tumor cells, consistent with high polysomy/FISH+ as scored by the Go method (10) or high polysomy/FISH- as scored by the Cappuzo method (11), and FISH- by *MET/CEP7* ratio which was 1.04, using cutoff of 2 (Fig 2b, Table 1). The mean copy of *MET*/cell was 3.7. The most common cell type was 4*MET*: 4*CEP7* found in 41.67% of nuclei. The increased gene copy correlated with Met moderate to high expression (2+) observed by immunohistochemistry (IHC) (Fig. 2a). These gene copy number scores were similar in the signet ring cells as well as both the lymph node and gallbladder metastases (Table 1). Sequencing of the *MET* open reading frame did not reveal a coding mutation, nor was there evidence for expression of the *MET* exon 14 oncogenic splice variant.

To determine a possible autocrine/paracrine phenomenon, evaluation of HGF (hepatocyte growth factor), the sole ligand for Met, was observed to be expressed in the cytoplasm of tumor cells by IHC (3+) and not localized solely to the cell membrane, consistent with an autocrine loop (5). (Fig. 2a).

Transverse Colon Metastasis - at tumor recurrence 2010—Tissue from the transverse colonic metastasis was analyzed for potential resistant mechanisms to Met directed therapy, including *MET* gene copy by FISH, as well as Met and HGF expression (Fig 2, Table 1). *MET* FISH analysis revealed a similar scoring pattern with a slightly lower mean *MET* copy/cell of 2.99 in the non-signet ring cells (Fig 2b). The most common cell type was now 2*MET*:2*CEP7* found in 28% of nuclei, and the second most common was 4*MET*:4*CEP7* found in 22% of nuclei. Met expression was determined to be slightly higher in this specimen (3+) when compared to expression from the 2007 specimens (Fig 2a), while HGF expression was significantly lower than in the earlier tissue samples (0–1+). Unfortunately, it was not possible to obtain tissue representing the multiple new foci of carcinomatosis observed after the three recent doses of MetMab, nor of the original transverse colon lesion after partial response to rechallenge with MetMab treatment.

Serum HGF—Serum HGF levels were evaluated in all phase I patients at baseline and throughout treatment at regular intervals. This patient exhibited one of the highest baseline plasma HGF levels (3441pg/mL +/- 301.8pg/ml) (Fig 3). Moreover, this was the only patient on the phase I study to experience a post-treatment rapid and sustained decrease in serum HGF (526.8pg/mL +/- 91.98pg/mL). HGF serum levels at recurrence were similar to levels post-MetMab initially (346pg/mL +/- 30.08ng/mL) (Fig 3) (5).

DISCUSSION

We present an intriguing case of chemotherapy refractory gastric cancer with metastasis to the liver that achieved a durable complete response to MetMab, a monovalent antibody that inhibits the receptor Met. Salient points of the original case include **i)** that the primary gastric tumor that was resected in 2007 was determined to have *MET* gene high polysomy; **ii)** that both Met and HGF were expressed by IHC in the primary tumor and expression increased with histologic progression to the gallbladder metastasis; and **iii)** that the HGF serum level was extremely high prior to treatment with MetMab and precipitously fell immediately after drug exposure and remained low, even at the time of widespread recurrence of disease.

The detection of a strong Met and HGF expression restricted to the tumor epithelium in the primary tumor is particularly relevant, and in preclinical models is consistent with autocrine Met signaling. In addition, our patient had one of the highest baseline HGF levels on the phase I trial (median=1104 pg/mL, n=29) (5). Importantly, this was the only patient on the phase I study to experience a post-treatment rapid decrease which persisted throughout the remaining evaluated time-points. The drop in HGF levels is difficult to explain, given that interruption of a presumed dependence on a HGF/Met autocrine loop may be expected to lead to a reflexive *increase* in circulating HGF.

A confounding aspect of this case was the previous treatment with the RTK inhibitor for four months, leading to a transient partial response after two months, and then ensuing disease progression after the next two months. One may speculate that the effect observed after MetMab therapy was attributable to an essential concomitant ‘dual’ or synergistic ‘vertical’ Met inhibition with an intracellular TKI and an extracellular monoclonal antibody blockade. Evidence against this possibility is that a four week washout period of the RTK inhibitor (which in general has at ½ clearance on the order of hours to days) was required prior to commencing MetMab. A similar concept, albeit reciprocal to our case, of ‘vertical’ inhibition of receptor tyrosine kinases has been described with the efficacy of RTK inhibitor lapatinib (targeting Her1/Her2) in patients who progressed following treatment with trastuzumab, a Her2 directed antibody (12,13). It is also a possibility that the RTK inhibitor ‘primed’ the tumor in an undetermined manner, which resulted in extreme sensitivity to subsequent MetMab. An alternate hypothesis is that a transient response due to inhibition of non-Met tyrosine kinases cannot be ruled out. In fact, the phase II RTK inhibitor potently inhibits VEGFR2 with much more affinity than Met. Regardless, the addition of MetMab seemed to overcome an acquired resistance that occurred while on the RTK inhibitor. Given that the clearance of MetMab is in the range of 6.7–8.3 mL/day/kg, it is not likely that the duration of response of two years resulted as a function the lower clearance rate as compared to a small molecule TKI.

Two years after the CR from MetMab therapy, the patient had a recurrence of her tumor at two locations on radiographic imaging. Salient points of this most recent treatment course with MetMab were **i)** that the transverse colon tumor exhibited higher Met expression; **ii)** that HGF levels were relatively low in the tumor and the serum at recurrence compared to intratumoral levels at diagnosis and serum levels just prior to treatment with MetMab originally; and **iii)** that the colonic lesion and the gastrohepatic ligament node both had partial responses to repeat MetMab therapy, while multiple new peritoneal lesions led to an overall mixed response and therefore overall disease progression by RECIST criteria.

The partial response of the transverse colon lesion can potentially be explained by the high levels of Met protein expression, higher than in the 2007 surgical specimens. It appeared that this colonic metastasis, and presumably the gastrohepatic ligament node that also

partially responded, became ‘HGF’ independent due to Met overexpression and thus no longer depended on HGF autocrine signaling. A shift in disease biology is supported by the low serum and tumor HGF levels at the time of recurrence versus serum and tumor HGF levels prior to original MetMab treatment. In an attempt to determine a mechanism of the observed higher Met expression, *MET* FISH was conducted to evaluate for clonal evolution by selection of a higher gene copy number population. However, *MET* copy number was similar to the 2007 samples (Table 1). Regardless, MetMab maintained a partial inhibitory effect on this lesion, suggesting the tumor may have retained some responsiveness to HGF ligand, or more likely, that MetMab may partially abrogate Met activation in Met over-expressed cells by interfering with homodimerization, despite lower levels of HGF (14,15). However, given that there was not a complete response on this second treatment cycle, this suggests that a population of the cells in these two recurrent lesions were resistant to the MetMab therapy.

Given that tumor recurrence occurred long after discontinuing the original MetMab treatment, one might expect that the recurrent tumor would have retained complete sensitivity when re-challenged with MetMab. However, after three doses, there were multiple new peritoneal lesions, and the original recurrent lesions had only partially responded (the majority of tumor remained). It has been reported that treatment of HGF/Met driven tumors with a low concentration of Met inhibitors leads to selection of higher *MET* gene amplified clones *in vitro* and *in vivo* as a mechanism of resistance (16). In this case we discovered that ‘resistance’ after original MetMab was not through clonal evolution to higher *MET* gene amplification. However, one may speculate that this patient’s tumor evolved an increased Met expression, to sustain the addiction to the MET signaling pathway, through mechanisms other than gene amplification (such as increased transcription and/or increased mRNA and protein stability) (17) as a resistance mechanism to being exposed to anti-Met therapies. Importantly, Cepero and colleagues also reported that higher concentrations of Met inhibitors can lead to *KRAS* gene amplification and over-expression of the protein (16). However, we evaluated *KRAS* copy number by FISH, and found a mean copy number of 2.52/cell and only 2% of cells with ≥ 4 copies/cell in the recurrent metastatic lesion which was similar to the primary tumor (Table 1). This suggests that clonal selection or evolution to *KRAS* gene amplification was not present at the time of recurrence and did not play a significant role in the acquired anti-Met resistance of the 2010 tumor biopsied in this case. However, it is possible that *KRAS* became gene amplified in a small subset of cells to overcome the initial MetMab treatment in 2008, and then reverted back to non-gene amplified status during the long period between CR and recurrence. This is plausible since Cepero and colleagues demonstrated this phenomenon of transient *KRAS* amplification during active exposure to a Met inhibitor, which was reversible to non-*KRAS* amplified status after withdrawal of drug. Tumor tissue was not obtained immediately following MetMab exposure originally in 2008 (there was nothing to biopsy!) nor after rechallenge in 2010, and therefore we cannot confirm or refute this hypothesis. Further investigation is underway to determine novel biomarkers that may be predictive of resistance to Met targeted therapy, such as RON (*MST1R*) the other member of the Met RTK family (7).

Gastroesophageal adenocarcinoma (GEC) remains a challenging problem in oncology. In 2010, there were 21,000 new cases of GC and 10,570 deaths in the US (18). There is an estimated 350% increase in esophageal/GEJ adenocarcinoma in the US in the last three decades (18). Taken together, GEC is third most frequent cancer world-wide, accounting for more than 1 million deaths per year (19). This case is the first reported of a durable complete response of metastatic GC to anti-Met therapy. Laboratory correlatives evaluating the Met pathways assisted in explaining clinical response initially as well as predicting outcomes at the time of recurrence. Further investigation of Met inhibitors in clinical trials for GEC with well-designed laboratory correlatives is warranted (20).

MATERIALS AND METHODS

Immunohistochemistry and Fluorescence in situ hybridization were conducted as previously described (7).

HGF ELISA

Wells of NUNC MaxiSorp microtiter plates were coated (ON, 4°C) with 0.5 µg/ml of affinity purified Goat anti-huHGF polyclonal antibody in 100µl of coating buffer (0.05M sodium carbonate buffer pH 9.6) and were then blocked with 0.5% BSA in assay buffer (PBS /0.5% BSA /0.05% P 20 /0.25%CHAPS /0.35M NaCl /5mM EDTA /10ppm Proclin300, pH 7.4) for 1h at RT. Diluted human HGF controls and plasma samples (100 µl) in assay buffer were loaded in duplicates and incubated for 2 h at room temperature, followed by the addition of 100 µl affinity purified goat anti huHGF-biotin (150 ng/ml) for additional 1 h at room temperature. Avidin-conjugated HRP (40ng/ml) in PBS /0.5% BSA /0.05% P 20 /10ppm Proclin300, pH 7.4 was added (1 h, room temperature) and the reaction was visualized by the addition of 100 µl chromogenic substrate (TMB) for 15 min. The reaction was stopped with 1M phosphoric acid and absorbance at 450 nm was measured with reduction at 630 nm using an ELISA plate reader. Plates were washed three times with washing buffer (0.05% Tween 20/ PBS) after each step. As a reference for quantification, a standard curve was established by a serial dilution of human HGF (CritRS CR67) (2000 pg/ml-15.625 pg/ml).

Statement of Significance

This research brief is the first to describe a durable complete response obtained with a molecularly targeted monoclonal antibody, MetMAb, to the receptor tyrosine kinase, Met, in a patient with chemo-refractory metastatic gastric cancer. It is also the first to report biomarkers that predicted therapeutic response to Met inhibition.

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Figure 1. Radiological assessment

a,b) CT 3/5/07. Primary gastric tumor (white arrows) on the lesser curvature in the axial (a) and frontal (b) views. **c)** CT 5/26/07. Post-operative image showing no radiographic evidence of disease. **d)** CT 8/28/07. Radiographic appearance of a new liver hypodensity after three months of adjuvant chemotherapy with FOLFOX (arrow). **e)** CT Radiographic partial response to treatment with the Met/VEGFR2 inhibitor after 2 cycles in the liver lesion (arrow). **f)** CT 10/4/07. Growth of the liver lesion after six months of the Met/VEGFR2 inhibitor (arrow). **g)** CT 6/12/08. Interval disappearance of the liver lesion after 4 cycles of MetMab monoclonal antibody therapy (arrow). **h,i)** CT 10/22/10. Recurrence of

metastatic gastric cancer on routine surveillance at the (h) transverse colon (arrow) measuring 54.1mm in longest dimension (straight line), and in the (i) gastrohepatic ligament node abutting left lobe of liver (arrow). **j,k,l** CT 2/12/11. Partial regression of the (j) transverse colon lesion (arrow) and the (k) gastrohepatic ligament node (thick arrow) after rechallenging with three cycles of MetMab. However, there were multiple new foci of disease visualized in the peritoneum, some represented in k (thin arrow) and l (arrow). **m,n** PET imaging before rechallenge with MetMab (11/12/10, m) and after three cycles of MetMab (1/20/11, n). However, identified uptake of the transverse colon lesion (m, arrow) had regressed after MetMab therapy (n, arrow) despite progression of disease elsewhere.

Figure 2. Tissue correlates with immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH)

a) IHC. First column, H&E stain; second column, HGF (hepatocyte growth factor); third column, Met; fourth column, activated Met (p-Met). First row, Adjacent paraneoplastic normal mucosa in the proximal stomach (Adj NI); second row, primary tumor (PT) at low power (5×); third row, primary tumor (PT) at medium power (15×); fourth row, primary tumor (PT) at high power (40×); fifth row, metastatic tumor involvement in regional lymph node from surgical specimen 2007 with gland forming cells; sixth row, H&E at 15× and metastatic serosal deposit on the gallbladder (GB) focusing (40×) on a gland forming differentiating region (Diff); seventh row, H&E at 5× and metastatic serosal deposit on the

gallbladder (GB) focusing (40×) on the signet ring (SR) component; eighth (last) row, recurrent colonic invading metastatic lesion (Col Inv) – p-Met and MSP were not conducted due to insufficient tissue remaining from the biopsy. **b)** FISH gene copy number analysis of the primary tumor (left) and the metastatic colon deposit (right) for *MET* in non-signet ring (differentiated cells, left columns) compared to signet ring component (right columns). Blue arrows, poorly differentiated cells; black arrows, signet ring cells.

	2008			2010-recurr
	baseline	C1D2	C2D1	baseline
Number of values	8	8	8	8
Minimum	3002	380	317.3	301.1
25% Percentile	3134	428	352.4	327.8
Median	3471	555.2	396.3	337.6
75% Percentile	3746	595.4	569.5	380.4
Maximum	3761	631.5	636.3	381.8
Mean	3441	526.8	438.6	346.8
Std. Deviation	301.8	91.98	121	30.08
Std. Error	106.7	32.52	42.77	10.63
Lower 95% CI of mean	3189	449.9	337.5	321.7
Upper 95% CI of mean	3694	603.7	539.8	372

Figure 3. Serial HGF serum levels

HGF levels (pg/mL) were drawn at baseline on cycle one day 1 prior to MetMAb, and on cycle 1 day 2 (C1D1) and C2D1 in 2007 while on the phase I trial. Two years later at recurrence, another baseline level was obtained prior to treatment with compassionate use MetMAb.

Table 1

Fluorescence in Situ Hybridization (FISH) analysis of *MET* and *KRAS* gene copy for the primary tumor and metastatic deposit at recurrence in the non-signet ring and signet ring cells

Primary Tumor		Primary Tumor	
<u>Non-Signet Ring Morphology:</u>		<u>Signet Ring Morphology:</u>	
MET	<p><i>MET</i>/cell: 3.7</p> <p><i>CEP7</i>/cell: 3.53</p> <p><i>MET</i> copy number 4: 60%</p> <p>Ratio <i>MET</i>/<i>CEP7</i>: 1.04</p> <p>Ratio <i>MET</i>/<i>CEP7</i> 2: 0%</p> <p>Most common cell type is 4 <i>MET</i>: 4 <i>CEP7</i> found in 41.67% of nuclei.</p>	MET	<p><i>MET</i>/cell: 3.7</p> <p><i>CEP7</i>/cell: 3.83</p> <p><i>MET</i> copy number 4: 63.33%</p> <p>Ratio <i>MET</i>/<i>CEP7</i>: 0.99</p> <p>Ratio <i>MET</i>/<i>CEP7</i> 2: 0%</p> <p>Most common cell type is 4 <i>MET</i>: 4 <i>CEP7</i> found in 40% of nuclei.</p>
KRAS	<p><i>KRAS</i>/cell: 2.27</p> <p><i>CEP12</i>/cell: 2.17</p> <p><i>KRAS</i> copy number 4: 0%</p> <p>Ratio <i>KRAS</i>/<i>CEP12</i>: 1.05</p> <p>Ratio <i>KRAS</i>/<i>CEP12</i> 2: 0%</p> <p>Most common cell type is 2 <i>KRAS</i>: 2 <i>CEP12</i> found in 46.66% of nuclei.</p>	KRAS	<p><i>KRAS</i>/cell: 2.60</p> <p><i>CEP12</i>/cell: 2.43</p> <p><i>KRAS</i> copy number 4: 5.00%</p> <p>Ratio <i>KRAS</i>/<i>CEP12</i>: 1.07</p> <p>Ratio <i>KRAS</i>/<i>CEP12</i> 2: 0%</p> <p>Most common cell type is 3 <i>KRAS</i>: 3 <i>CEP12</i> found in 40.00% of nuclei.</p>
Transverse Colon Metastasis		Transverse Colon Metastasis	
<u>Non-Signet Ring Morphology:</u>		<u>Signet Ring Morphology:</u>	
MET	<p><i>MET</i>/cell: 3.18</p> <p><i>CEP7</i>/cell: 2.99</p> <p><i>MET</i> copy number 4: 42%</p> <p><i>MET</i>/<i>CEP7</i> ratio: 1.06</p> <p>Ratio <i>MET</i>/<i>CEP7</i> 2: 0%</p> <p>Most common cell type is 2 <i>MET</i>: 2 <i>CEP7</i> found in 28% of nuclei;</p> <p>Second most common is 4 <i>MET</i>: 4 <i>CEP7</i> found in 22% of nuclei.</p>	MET	<p><i>MET</i>/cell: 2.93</p> <p><i>CEP7</i>/cell: 2.76</p> <p><i>MET</i> copy number 4: 36.66%</p> <p><i>MET</i>/<i>CEP7</i> ratio: 1.06</p> <p>Ratio <i>MET</i>/<i>CEP7</i> 2: 5.00%</p> <p>Most common cell type is 2 <i>MET</i>: 2 <i>CEP7</i> found in 23.33% of nuclei;</p> <p>Second most common is 4 <i>MET</i>: 4 <i>CEP7</i> found in 16.66% of nuclei.</p>
KRAS	<p><i>KRAS</i>/cell: 2.52</p> <p><i>CEP12</i>/cell: 2.53</p> <p><i>KRAS</i> copy number 4: 2%</p> <p>Ratio <i>KRAS</i>/<i>CEP12</i>: 1.00</p> <p>Ratio <i>KRAS</i>/<i>CEP12</i> 2: 0%</p> <p>Most common cell type is 3 <i>KRAS</i>: 3 <i>CEP12</i> found in 59.00% of nuclei.</p>	KRAS	<p><i>KRAS</i>/cell: 2.21</p> <p><i>CEP12</i>/cell: 2.26</p> <p><i>KRAS</i> copy number 4: 1.00%</p> <p>Ratio <i>KRAS</i>/<i>CEP12</i>: 0.98</p> <p>Ratio <i>KRAS</i>/<i>CEP12</i> 2: 0%</p> <p>Most common cell type is 2 <i>KRAS</i>: 2 <i>CEP12</i> found in 47.00% of nuclei.</p>