

# Highly expressed Claudin18.2 as a potential therapeutic target in advanced gastric signet-ring cell carcinoma (SRCC)

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**Background:** Advanced gastric signet-ring cell carcinoma (SRCC) is a specific type of malignant gastric cancer (GC) with distinct poorer survival. Claudin18.2 (CLDN18.2) is a promising neo-biomarker for the treatment of GC. Clinical trials of CLDN18.2-targeted antibody and T cell-based immunotherapy providing promising prospects for the treatment of GC. The effect of antibody therapy depended on the expression rate of CLDN18.2 has been found in clinical trials. This study aimed to determine the prevalence and the therapeutic value of CLDN18.2 in advanced gastric SRCC.

**Methods:** Expression of CLDN18.2 in 105 formalin-fixed, paraffin-embedded (FFPE) tumor tissues was detected by immunohistochemistry (IHC) and evaluated according to FAST criteria. Next-generation sequencing (NGS) using 416 pan-cancer genes panel was performed to characterize the genomic landscape in 61 advanced gastric SRCC patients. Fisher's exact test was used to determine gene differences in different CLDN18.2 expression levels.

**Results:** A total number of 105 advanced gastric SRCC samples were analyzed, of which 95.2% (100/105) were positive stained. Moderate-to-strong CLDN18.2 expression was observed in 64.8% (68/105) of all samples. In particularly, 21.0% (22/105) samples had positive staining in more than 90% tumor cells. No significance was found between CLDN18.2 expression and overall survival (OS). NGS results showed that single nucleotide variations (SNVs) could be frequently found in TP53 (26.2%), CDH1 (19.7%), MED12 (18.0%), PKHD1 (18.0%) and ARID1A (11.5%), besides, copy number variations (CNVs) were rich in NOTCH1 (18.0%) and FLT4 (9.8%) in SRCC samples. Moreover, SNVs in GRIN2A was found in 20% of the patients who had CLDN18.2 staining in <40% of tumor cells (P=0.043), indicating CLDN18.2 expression might be related to the aberration of GRIN2A in advanced gastric SRCC.

**Conclusions:** The highly expressed CLDN18.2 among advanced gastric SRCC patients that we found certified the value of CLDN18.2-targeted therapy in this specific type of GC. In addition, Analyses between CLDN18.2 expression and genetic abnormalities provided novel therapeutic options for advanced gastric SRCC.

Keywords: Gastric signet-ring cell carcinoma (gastric SRCC); CLDN18.2; next-generation sequencing (NGS)

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# Introduction

Gastric signet-ring cell carcinoma (SRCC) is an exceptional subtype of gastric adenocarcinoma which has abundant intracellular mucin accumulation and the crescentshaped nucleus are displaced toward one side of the tumor cells (1). According to World Health Organization (WHO) classification: gastric cancer (GC) pathologic specimen with at least 50% of signet-ring cell is defined as SRCC. In recent decades, the overall morbidity of GC decreased worldwide, however, the decline is mainly caused by the decrease of intestinal type, while for diffuse type, especially gastric SRCC, is on the rise (2-4). Usually, SRCC is more prone to invasion and metastasis and have unique chemosensitivities, which led to a worse prognosis (3,5,6). However, SRCC treatment regimen are still controversial as SRCC is not specifically identified in most studies. For diffuse type GC, targeted therapies including anti-HER2 (7) and anti-VEGFR2 (8) provide few benefit in overall survival (OS). Immunotherapy may be a promising treatment as PD-L1 is overexpressed in about 23% of gastric SRCC (5).

CLDN18.2 is a splice variant of the membrane epithelial tight junctions protein Claudin18 (CLDN18) and has been identified as a promising biomarker for targeted therapy (9). CLDN18.2 has a restricted expression profile in normal tissues, it physiologically expresses only in the tight junction supramolecular complex of gastric mucosa. While upon malignant transformation, the changes in cell polarity lead to the exposure of CLDN18.2 epitopes (10), which are suitable for targeted therapy. Prior evidence demonstrates that except for GC, CLDN18.2 is aberrantly expressed in various primary tumors and metastases, including pancreatic, biliary, ovarian, and lung adenocarcinomas (11-14), which makes CLDN18.2 a pan-cancer target. At present, antibody [zolbetuximab (10,15-18), formerly called IMAB362] and chimeric antigen receptor engineered T cells (CAR-T) (19,20) targeting CLDN18.2 has been applied in clinical trials with promising results achieved. Correlation between higher CLDN18.2 expression and better therapeutic benefits has been found through antibody-based clinical trials. Previous studies have reported a relatively high expression rate of CLDN18.2 in diffuse type GC (9,21), however, no study on advanced gastric SRCC has been conducted. Therefore, this study aimed to establish the prevalence of CLDN18.2 expression in advanced gastric SRCC, and to determine the therapeutic value of CLDN18.2 in this specific type of GC.

In this study, we identified, for the first time, that the

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expression rate of CLDN18.2 in advanced gastric SRCC patients was relatively high. The survival analyses based on CLDN18.2 expression were performed. We also conducted next-generation sequencing (NGS) in 61 advanced gastric SRCC samples, genetic abnormalities in advanced gastric SRCC were profiled and the relation between CLDN18.2 expression and GRIN2A mutation was discovered.

We present the following article in accordance with the MDAR reporting checklist. (available at: http://dx.doi. org/10.21037/jgo-20-344).

# Methods

### Tissue specimens and ethical statement

A total of 105 formalin-fixed, paraffin-embedded (FFPE) tissue specimens with histology of advanced gastric SRCC for the testing of CLDN18.2 expression were collected at Nanjing Drum Tower Hospital. Patients at stage III were all administrated first-line 5-FU-based adjuvant chemotherapy after D2 gastrectomy, while patients at stage IV were treated by first-line 5-FU-based palliative chemotherapy. None of the patients had radiotherapy, chemotherapy or other medical intervention before specimen collection. Samples from stage III patients were curative surgical specimens, while samples from stage IV patients were palliative surgical specimens or gastroscope specimens. OS data was available in 86 cases; 61 of the tissues were selected for NGS.

### Immunohistochemistry (IHC) and histologic assessment

All tissue samples were stained using rabbit monoclonal anti-CLDN18.2 antibody (Abcam, 222512) at 1/800 dilution. This antibody was designed to recognize human CLDN18.2 aa 1–100. After diluted antibody was added to the whole tissue surface, the slides were incubated at 4 °C overnight. Slides were then rewarmed at room temperature for 10 minutes and sufficiently washed with PBS for three times. Goat Anti-Rabbit IgG H&L (HRP) (Abcam, 205718) were used as secondary antibody, when the slides were dry, secondary antibody were dropped to cover the whole tissue and incubate in a 37 °C incubator for 30 minutes. Nuclear were stained with hematoxylin; 3% hydrogen peroxide were used to block endogenous peroxidases. Each patient's slides were tested twice.

To determine CLDN18.2 expression status, tissue samples were analyzed according to the intensity of staining and the percentage of stained tumor cells. The intensity

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was classified into 4 grades: no membrane or cytoplasmic reactivity as 0, weak membrane or cytoplasmic reactivity as 1+, moderate membrane or cytoplasmic reactivity as 2+, and strong membrane or cytoplasmic reactivity as 3+. Samples showing any specific staining with  $\geq$ 1+ intensity were defined as CLDN18.2 positive. According to FAST criterion, more than 40% of tumor tissues specific staining with  $\geq$ 2+ intensity were defined as moderate-to-strong expression (21). Percentage of overall CLDN18.2 positive cells was considered by the estimated number of CLDN18.2 positive cells divided by the estimated overall number of tumor cells in each sample.

The pathological diagnosis of SRCC in our study were confirmed by two independent pathologists. The interpretation of IHC results were performed according to the FAST criterion.

# NGS and data processing

61 out of 105 samples which had enough tumor tissue were selected for NGS. 15 had CLDN18.2 positive staining in <40% of tumor cells, 46 had CLDN18.2 positive staining in  $\geq$ 40% of tumor cells. Genomic DNA from FFPE tissue specimens were extracted using QIAamp DNA FFPE Tissue Kit (Qiagen, Catalog no.56404) according to the manufacturer's protocols. Hybridization-based enrichment was carried out with GeneseeqOne<sup>TM</sup> pan-cancer gene panel (416 cancer-relevant genes). Captured libraries by Dynabeads M-270 (Life Technologies, MA, USA) were amplified in KAPA HiFi HotStart ReadyMix (KAPA Biosystems, MA, USA) and quantified by qPCR using the KAPA Library Quantification kit (KAPA Biosystems, MA, USA) for sequencing. The libraries were pairedend sequenced on Illumina HiSeq4000 NGS platforms (Illumina, CA, USA) according to the manufacturer's instructions. VarScan2 was employed for the detection of single nucleotide variations (SNVs). Copy number variations (CNVs) were detected by ADTEx.

# Statistical analysis

SPSS was used for all statistical analysis. GraphPad Prism 7.0 (GraphPad Software) was used for presenting the statistical result graphs. Survival analysis were obtained using the Kaplan-Meier method and compared with the log-rank test. Fisher's exact test were used to determine NGS results. A P value of less than 0.05 was considered significant.

### Ethical statement

The study was approved by the Ethics Committee of Nanjing Drum Tower Hospital (No. 2016-196-01). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Because of the retrospective nature of the study, the requirement for informed consent was waived.

### **Results**

# CLDN18.2 highly expressed in advanced gastric SRCC

Tissue samples from 105 advanced gastric SRCC patients were collected and stained with anti-CLDN18.2 antibody. Positive staining was detected in 95.2% (100/105) of all SRCC tumor tissues, which is much higher than general gastric adenocarcinoma (77%) (9). In accordance with the FAST clinical trial (NCT01630083),  $\geq$ 2+ membrane staining intensity in  $\geq$ 40% tumor cells was defined as moderate-to-strong CLDN18.2 expression. In our study, moderate-to-strong CLDN18.2 expression was observed in 64.8% (68/105) of all samples (*Table 1*). In particularly, 21.0% (22/105) samples had CLDN18.2 staining in  $\geq$ 90% tumor cells (*Table 1*). There is no connection of CLDN18.2 expression with gender or stage (*Table 1* and Table S1). However, staining intensity  $\geq$ 2+ in  $\geq$ 90% of tumor cells often occurred in younger patients (<60 years old) (P=0.042).

Micrographs of representative stained tissues were shown in *Figure 1A* according to the 0–3+ staining intensity classification, of all samples, 5 (4.8%) were 0+, 22 (21.0%) were 1+, 33 (31.4%) were 2+ and 45 (42.9%) were 3+. The percentage distributions of overall CLDN18.2 positive cells in the 105 samples were as follows: 24 (22.9%) had 0–25% CLDN18.2 positive tumor cells; 21 (20.0%) had 26–50%; 16 (15.2%) had 51–75% and 44 (41.9%) had 76–100% (*Figure 1B*). The increased proportion of 3+ samples were observed as the percentage level went up (*Figure 1B*), which indicated that there might be a positive correlation between staining intensity and the percentage of positive cells.

# *Relationship of OS and CLDN18.2 expression in advanced gastric SRCC patients*

OS was analyzed by the Kaplan-Meier method in 86 cases whose survival time were available. Different grouping patterns were set up according to previous studies (9,21) by different percentage of overall CLDN18.2 positive cells. The correlation between OS and CLDN18.2 expression

Factors		Staining intensity ≥2+ in ≥40% of cells		Staining intensity ≥2+ in ≥90% of cells	
Factors	Total cases (%)	N (%)	P value	N (%)	P value
All samples	105 (100.0)	68 (64.8)	-	22 (21.0)	_
Gender					
Male	71 (67.6)	50 (70.4)	0.079	17 (23.9)	0.276
Female	34 (32.4)	18 (52.9)		5 (14.7)	
Age					
≥60	38 (36.2)	22 (57.9)	0.267	4 (10.5)	0.042*
<60	67 (63.8)	46 (68.7)		18 (26.9)	
Stage					
III	92 (87.6)	59 (64.1)	0.719	19 (20.7)	0.841
IV	13 (12.4)	9 (69.2)		3 (23.1)	

 Table 1 CLDN18.2 expression in advanced gastric SRCC

\*, represent for P<0.05. SRCC, signet-ring cell carcinoma.

were shown in *Figure 2*. There were no significant differences of OS by different CLDN18.2 expression levels in advanced gastric SRCC (log-rank test). This result indicated that CLDN18.2 expression was not a prognostic risk factor in advanced gastric SRCC patients.

### GRIN2A mutation was related to CLDN18.2 expression

To explore the relation between CLDN18.2 expression and genetic abnormalities, 61 specimens were examined using a gene panel that covers entire exons in 416 cancerrelevant genes (Table S2). Genetic aberrations identified in all 61 samples revealed several common SNVs and CNVs in advanced gastric SRCC (Table S3 and Table S4). Briefly, the top 5 genes with the highest SNVs rate were TP53 (26.2%), CDH1 (19.7%), MED12 (18.0%), PKHD1 (18.0%) and ARID1A (11.5%). The top 2 genes with the highest CNVs rate were NOTCH1 (18.0%) and FLT4 (9.8%). Furthermore, specimens for NGS were divided into two groups based on CLDN18.2 expression. Of them, 15 were CLDN18.2 expressed in <40% of tumor cells, 46 were CLDN18.2 expressed in  $\geq 40\%$  of tumor cells. After the analyses of genetic aberrations in these two groups, one gene named GRIN2A were found significantly different between the two groups (Figure 3, Table S5 and Table S6). Three (20.0%) of the 15 samples that had CLDN18.2 expression in <40% of tumor cells harboring GRIN2A mutation, while only 1 (2.2%) of the 46 moderate-to-strong CLDN18.2 expression samples had GRIN2A mutation (P=0.043), indicating GRIN2A variation was more likely to occur in patients who had lower CLDN18.2 staining. Since anti-CLDN18.2 antibody was not effective enough in CLDN18.2 low expression patients, mutant GRIN2A might be a potential therapeutic target in those patients. Other detected SNVs (MED12, TOP2A, EZH2, RNF43, WRN, STAG2, CDK6, CYLD and GATA6) or CNVs (CDK12, CCNE1, ERBB3, FGFR4 and MED12) were not statistically significant (*Figure 3*, Table S5 and Table S6).

### Discussion

In this study, we first tested CLDN18.2 expression in 105 FFPE tumor tissues from advanced SRCC patients by IHC method. The results demonstrated that CLDN18.2 was highly expressed in gastric SRCC, which made a promising prospect for the clinical use of zolbetuximab in advanced gastric SRCC. Survival analyses based on different grouping patterns showed no significance between CLDN18.2 expression and OS. In addition, NGS found that GRIN2A mutation was related to CLDN18.2 expression level.

CLDN18.2 had been identified as a highly selective cell lineage marker since its expression in normal tissues was strictly confined to differentiated epithelial of the gastric mucosa. Besides, the retained expression of CLDN18.2 had been found in a significant proportion of primary GCs (any positive 77%,  $\geq$ 2+ in  $\geq$ 60% of cells 56%) and its metastases (lymph node 66%, ovarian 96%), which made CLDN18.2 become one of the most notable targets in GC studies (9).

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**Figure 1** Expression of CLDN18.2 in advanced gastric SRCC. (A) Micrographs of representative stained tissues: 0+, 1+, 2+ and 3+ staining intensity. The magnification was 200×. (B) The graph depicted the distribution of CLDN18.2 staining percentages and intensities in tumor cells from advanced gastric SRCC patient samples. N, total number of cases; N1, number of cases that had 0–25% CLDN18.2 positive tumor cells; N2, number of cases that had 26–50% CLDN18.2 positive tumor cells; N3, number of cases that had 51–75% CLDN18.2 positive tumor cells; N4, number of cases that had 76–100% CLDN18.2 positive tumor cells. SRCC, signet-ring cell carcinoma.

Zolbetuximab (IMAB362) was a first-in-class monoclonal antibody specific targeted to CLDN18.2, recently, a multicentre phase II clinical study of zolbetuximab found that all responders had  $\geq$ 70% CLDN18.2 expression in tumor cells, which suggested the correlation between higher CLDN18.2 expression and better therapeutic benefit (17). Besides, another phase II trial (FAST; NCT01630083) had shown that patients with  $\geq$ 2+ membrane staining intensity in  $\geq$ 40% tumor cells could get benefits from zolbetuximab therapy (15). In this study, high expression rate of CLDN18.2 in advanced gastric SRCC patients had been found for the first time. Significant difference of CLDN18.2 expression between primary GCs and advanced gastric SRCC (77% vs. 95.24%) hinted that CLDN18.2based targeted therapy had great potential in the treatment of advanced gastric SRCC. Moreover, since PD-L1 overexpressed in gastric SRCC (5), antibodies targeting PD-1/PD-L1 combined with CLDN18.2 antibody zolbetuximab might be an effective treatment for advanced gastric SRCC.

In the survival analyses, 4 grouping patterns were set up according to the percentage of overall CLDN18.2 positive



Figure 2 OS was irrelated with CLDN18.2 expression. (A) OS in CLDN18.2 positive patients and negative patients, median OS (mOS) was 17.0 months compared to 9.0 months, P=0.107. (B) mOS was 15.9 months in patients who had CLDN18.2 expression in  $\geq$ 40% of tumor cells and 20.3 months in patients who had CLDN18.2 expression in <40% of tumor cells, P=0.128. (C) mOS was 16.0 months in patients who had CLDN18.2 expression in  $\geq$ 70% of tumor cells and 17.5 months in patients who had CLDN18.2 expression in <70% of tumor cells, P=0.694. (D) mOS was 16.9 months in patients who had CLDN18.2 expression in  $\geq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\geq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\geq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\geq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\geq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\geq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\geq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\geq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\geq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\leq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\leq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\leq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\leq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\leq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\leq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\leq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\leq$ 90% of tumor cells and 17.0 months in patients who had CLDN18.2 expression in  $\leq$ 90% of tumor cells and 17.0 months in patients who had CLDN18

cells. However, no relationship had been found between OS and CLDN18.2 expression, which exactly indicated that the high expression of CLDN18.2 was irrelevant to a poor prognosis in advanced gastric SRCC. No survival analysis of CLDN18.2 expression in advanced gastric SRCC has been reported before, however, some previous studies on general GC suggested that as disease progressing, the expression of CLDN18.2 decreasing, which contributed to the increased invasive potential of the tumor cells (22,23). However, according to FAST clinical trial and other studies (9,21), no significant correlation between the expression of CLDN18.2 and the progression or prognosis of GC had been found, which consisted with our findings. According to TCGA database (Figure S1), no statistical difference

in OS was discovered between CLDN18.2 high and low expression groups as well (P=0.14), however, disease free survival (DFS) was statistically significant in those two groups (P=0.0062), which indicating CLDN18.2 high expression might be related with the progression of the disease. Further studies were needed for clarifying the role of CLDN18.2 in the prognosis of GC.

NGS was performed to explore the genomic landscape for advanced gastric SRCC and to discover the correlated genes in different CLDN18.2 expression groups. Our results confirmed several common gene abnormalities in advanced gastric SRCC, such as *TP53*, *CDH1*, *MED12*, *PKHD1*, *ARID1A* and *NOTCH1*. We also found that CLDN18.2 expression might have some relation with

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Figure 3 A representative genomic landscape in different CLDN18.2 expression levels. Each row represented one gene, and each column represented one sample. A P value of less than 0.05 was considered significant. SNV, single nucleotide variation; CNV, copy number variation.

GRIN2A mutation. GRIN2A was the encoding gene of GluN2A, which was a subunit of the N-methyl-D-aspartate receptor (NMDAR) (24), and participated in the transport of calcium ions. GRIN2A was one of the key genes in epilepsy researches, however, only a few researches had been done on GRIN2A in cancer field. The existing studies had shown that GRIN2A mutation was frequently found in melanoma (25) and induced the loss of tumor suppressor function (26,27). Besides, NMDAR signal had been found to be related with brain metastasis of breast cancer (28). Here, in our study, we found for the first time that GRIN2A mutation had some potential relation with CLDN18.2 expression in advanced gastric SRCC. GRIN2A mutation was enriched in patients with lower CLDN18.2 expression, indicating NMDAR inhibitors were probably useful in those patients. However, supporting evidence seems relatively weak due to the small sample size of GRIN2A mutation in our study, further and more comprehensive researches were

needed to clarify the relevant mechanism.

In summary, the objective of this study was to assess the expression status of CLDN18.2 in advanced gastric SRCC patients, and to determine the therapeutic value of CLDN18.2 in this particular GC subtype. The high expression rate of CLDN18.2 in advanced gastric SRCC that we found provided the basic information for the CLDN18.2-based targeted therapy in advanced gastric SRCC patients. NGS results revealed the relation between GRIN2A mutation and CLDN18.2 expression, which provided possible innovative targeted therapy direction in advanced gastric SRCC.

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# Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All experimental methods were carried out in accordance with the approved guidelines. This study was conducted with the approval of the Ethics Committee of Nanjing Drum Tower Hospital (No. 2016-196-01). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Because of the retrospective nature of the study, the requirement for informed consent was waived.

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# References

1. Shu Y, Zhang W, Hou Q, et al. Prognostic significance of frequent CLDN18-ARHGAP26/6 fusion in gastric signet-

ring cell cancer. Nat Commun 2018;9:2447.

- Lu M, Yang Z, Feng Q, et al. The characteristics and prognostic value of signet ring cell histology in gastric cancer: A retrospective cohort study of 2199 consecutive patients. Medicine (Baltimore) 2016;95:e4052.
- Liu X, Cai H, Sheng W, et al. Clinicopathological Characteristics and Survival Outcomes of Primary Signet Ring Cell Carcinoma in the Stomach: Retrospective Analysis of Single Center Database. PLoS One 2015;10:e0144420.
- Bamboat ZM, Tang LH, Vinuela E, et al. Stage-stratified prognosis of signet ring cell histology in patients undergoing curative resection for gastric adenocarcinoma. Ann Surg Oncol 2014;21:1678-85.
- Pernot S, Voron T, Perkins G, et al. Signet-ring cell carcinoma of the stomach: Impact on prognosis and specific therapeutic challenge. World J Gastroenterol 2015;21:11428-38.
- Taghavi S, Jayarajan SN, Davey A, et al. Prognostic significance of signet ring gastric cancer. J Clin Oncol 2012;30:3493-8.
- Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-97.
- Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224-35.
- Sahin U, Koslowski M, Dhaene K, et al. Claudin-18 splice variant 2 is a pan-cancer target suitable for therapeutic antibody development. Clin Cancer Res 2008;14:7624-34.
- Sahin U, Schuler M, Richly H, et al. A phase I doseescalation study of IMAB362 (Zolbetuximab) in patients with advanced gastric and gastro-oesophageal junction cancer. Eur J Cancer 2018;100:17-26.
- 11. Micke P, Mattsson JS, Edlund K, et al. Aberrantly activated claudin 6 and 18.2 as potential therapy targets in non-small-cell lung cancer. Int J Cancer 2014;135:2206-14.
- Wöll S, Schlitter AM, Dhaene K, et al. Claudin 18.2 is a target for IMAB362 antibody in pancreatic neoplasms. Int J Cancer 2014;134:731-9.
- Keira Y, Takasawa A, Murata M, et al. An immunohistochemical marker panel including claudin-18, maspin, and p53 improves diagnostic accuracy of bile duct

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neoplasms in surgical and presurgical biopsy specimens. Virchows Arch 2015;466:265-77.

- Shinozaki A, Shibahara J, Noda N, et al. Claudin-18 in biliary neoplasms. Its significance in the classification of intrahepatic cholangiocarcinoma. Virchows Arch 2011;459:73-80.
- 15. Dudov A, Pecheniy A, Rusyn A, et al. Final results of the FAST study, an international, multicenter, randomized, phase II trial of epirubicin, oxaliplatin, and capecitabine (EOX) with or without the anti-CLDN18.2 antibody IMAB362 as first-line therapy in patients with advanced CLDN18.2+ gastric and gastroesophageal junction (GEJ) adenocarcinoma. Ann Oncol 2016;27:vi207-42.
- Singh P, Toom S, Huang Y. Anti-claudin 18.2 antibody as new targeted therapy for advanced gastric cancer. J Hematol Oncol 2017;10:105.
- Türeci O, Sahin U, Schulze-Bergkamen H, et al. A multicentre, phase IIa study of zolbetuximab as a single agent in patients with recurrent or refractory advanced adenocarcinoma of the stomach or lower oesophagus: the MONO study. Ann Oncol 2019;30:1487-95.
- Türeci Ö, Mitnacht-Kraus R, Wöll S, et al. Characterization of zolbetuximab in pancreatic cancer models. Oncoimmunology 2018;8:e1523096.
- Zhan XB, Wang B, Li ZH, et al. Phase I trial of Claudin 18.2-specific chimeric antigen receptor T cells for advanced gastric and pancreatic adenocarcinoma. J Clin Oncol 2019;37:abstr 509.
- 20. Jiang H, Shi Z, Wang P, et al. Claudin18.2-Specific Chimeric Antigen Receptor Engineered T Cells for

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the Treatment of Gastric Cancer. J Natl Cancer Inst 2019;111:409-18.

- Rohde C, Yamaguchi R, Mukhina S, et al. Comparison of Claudin 18.2 expression in primary tumors and lymph node metastases in Japanese patients with gastric adenocarcinoma. Jpn J Clin Oncol 2019;49:870-6.
- 22. Oshima T, Shan J, Okugawa T, et al. Down-regulation of claudin-18 is associated with the proliferative and invasive potential of gastric cancer at the invasive front. PLoS One 2013;8:e74757.
- Jun KH, Kim JH, Jung JH, et al. Expression of claudin-7 and loss of claudin-18 correlate with poor prognosis in gastric cancer. Int J Surg 2014;12:156-62.
- 24. Traynelis SF, Wollmuth LP, McBain CJ, et al. Glutamate receptor ion channels: structure, regulation, and function. Pharmacol Rev 2010;62:405-96.
- Wei X, Walia V, Lin JC, et al. Exome sequencing identifies GRIN2A as frequently mutated in melanoma. Nat Genet 2011;43:442-6.
- Prickett TD, Zerlanko BJ, Hill VK, et al. Somatic mutation of GRIN2A in malignant melanoma results in loss of tumor suppressor activity via aberrant NMDAR complex formation. J Invest Dermatol 2014;134:2390-8.
- D'mello SA, Flanagan JU, Green TN, et al. Evidence That GRIN2A Mutations in Melanoma Correlate with Decreased Survival. Front Oncol 2014;3:333.
- Zeng Q, Michael IP, Zhang P, et al. Synaptic proximity enables NMDAR signalling to promote brain metastasis. Nature 2019;573:526-31.



**Figure S1** Relation of OS/DFS and CLDN18.2 expression in GC according to TCGA. (A) OS was irrelated with CLDN18.2 expression. (B) DFS was related with CLDN18.2 expression. HR, hazard ratio; n, number of cases.

				CLDN18.2 expression				
Stage	TNM		Total cases (%)	Staining intensity ≥2+ in ≥40% of cells (%)	P value	Staining intensity ≥2+ in ≥90% of cells (%)	P value	
III	Т	Т3	62 (67.4)	40 (64.5)	0.674	15 (24.2)	0.108	
		T4	30 (32.6)	18 (60.0)		3 (10.0)		
	Ν	N1	6 (6.5)	2 (33.3)	0.293	0 (0.0)	0.326	
		N2	18 (19.6)	12 (66.7)		5 (27.8)		
		N3	68 (73.9)	44 (64.7)		13 (19.1)		
	Ν	T4 N1 N2 N3	30 (32.6) 6 (6.5) 18 (19.6) 68 (73.9)	18 (60.0) 2 (33.3) 12 (66.7) 44 (64.7)	0.293	3 (10.0) 0 (0.0) 5 (27.8) 13 (19.1)	0.326	

Table S1 The relation between CLDN18.2 expression and TNM stage in stage III patients

 $\label{eq:Table S2} Table \ S2 \ The \ summary \ information \ of \ the \ sequenced \ patients$ 

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NEGRE ADM 10         Deck Adm 1000000000000000000000000000000000000
No.000000000000000000000000000000000000
Production         Product
FISD22802FTES, RHORT, TRUE, RAM, RUT, NOTA, LUD, JANZ, CATER, FORTA, MARE, RUTA, LUD, JANZ, CATER, SARD, RUTA, LUD, JANZ, CATER, SARD, RUTA, LUDTA, LUTA, LUTA, KUTA, KUTA, LUTA, LUTA, LUTA, KUTA, LUTA, LUTA, LUTA, KUTA, 
PHS11, PET, PRI2H, NAMP, NAMPS, CORO, UGTAN, UGTAN, UGTAN, UGTAN, UGTAN, UGTAN, UGTAN, UGTAN, UGTAN, UGTAN, UGTAN, UGTAN, UGTAN, UGTAN, UGTAN       PK       M       IIC         PK1222010       Nome       RUT, NMA, NUMPA, UGTAN, UGTAN       Nome       37       M       IIC         PK1222011       PMOREN, NUTOR, PMCA, UMA, PMA, PMAN, UGTAN       Nome       37       M       IIC         PK1222011       PMOREN, NUTOR, PMCA, UMAT, PMS1, PMORN, DMOREN, NUTOR, PMCA, UMAT, PMS1, PMORN, DMORAN, SETZI, ZPCTIA, INPERI-       Nome       37       M       IIC         PK1222011       PMOREN, NUTOR, PMCA, UMAT, PMS1, PMORN, DMORAN, SETZI, PCTIA, INPER-       Nome       36       M       IIC         PK12220201       PKTAN, UGTAN, MURAN, DMOREN, GUTAN, TORNE, DMORAN, AME, TOGEN, PMS1, NUTOR, DMORAN, DMOREN, DMOREN
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Distribution         Distribution<
Fait23011NomeFAIT230114NomeALT2, CANL (MAC)NomeALT2, CANL (MAC)Nom
F1612281114       PE050FB, MCAQ, AKI, MARDIN, None       37       M       IIC         F161228115       RASALI, MA, LATZ, PRSS, PACH, None       57       M       IIE         F161228115       RASALI, MA, LATZ, PRSS, PACH, None       57       M       IIE         F161228111       REGIP, MAR, EBCJE       F16122812       M       IIE         F161228110       THSA, PTEN       F0671       M       IIE         F161228111       REGIP, MAR, GETL, MEGL       M       IIE       IIE         F1612281201       MEGP, MAR, MCH, MEDIZ, PROM, None       M       IIE       IIE         F1612282831       MEGP, MAR, MCH, MEDIZ, PROM, None       MAR       IIE       IIE         F1612282831       MEGP, MAR, MCH, MEDIZ, PROM, NARSAN, DANNE, MAR, MCH, MEDIZ, PROM, NARSAN, DANNE, MCR, MCR, MCR, MCR, MCR, MCR, MCR, MCR
AMAGE 115 PARAME DECIGA         Norma         ST         M         IIIB           P151229115         MAGE XGD X, CANDAL CHALL TAGERRAR, MADDY, AMARCAN, GETTA PARAMENI, CGSTR, SCHIL, PARACI, TGC, RAMON, PIROA         Norma         90         M         IIID           F1512291016         TTT, ILGRER, VAS, ULTAL, COBMIC, MEDIZ, MICHAN         FIGHT         90         M         IIID           F1512291016         TTT, ILGRER, VAS, ULTAL, COBMIC, MEDIZ, MICHAN         FIGHT         90         M         IIID           F1512290130         NTT, TLGRER, MEDIZ, MICHAN, LODRIN, MADT, COBMIC, MEDIZ, MICHAN         FIGHT         90         M         IIID           F1512290130         NTT, TLGRER, MEDIZ, MICHAN         RODRIN, MICHAN, MI
F151223115WAS, ASCI, YAC, KTZ, PRASP, PRADIN, COSTA, RODA, PACOT, KOLON, CARDA, CANDAN, CARDAN, STR, SOHB, PACOL, COL, ADDA, TANPI, COS, SOL, PICAN, STR, SOHB, PACAD, COS, MARCI, MEDIZ, HIST, GERB, CHI, HANS, HIST, GERB, CHI, HANS, HIST, GERB, CHI, HANS, HIDE, F1512200312MEGR, WAS, MASL, COSMA, CORD, HIDE, F1512200312MEGR, WAS, MASL, COSMA, COSMA, HIDE, F1512200312MEGR, WASL, SOL, MEDIZ, PACOL, MIDR, FANCA, ROD, MEDIZ, PACOL, NATA, NATA, NERS, SEY, FUENTI, ATT, FSFRA, HIDE, FANCA, ROD, MEDIZ, PACOL, SOL, MARCH, PTEN, SCHOL, FANCA, SOL, MARCH, PTEN, HIDE, RACAL, ROD, MEDIZ, PACOL, SOL, MARCH, PTEN, HIDE, RACAL, ROD, MARCH, PACO, MEDIZ, PACOL, SOL, MARCH, PTEN, HIDE, RACAL, RODA, MARCH, PACON, MARCH, PTEN, HIDE, RACAL, RODA, MARCH, PACON, MARCH, PTEN, HIDE, RODA, RODA, MARCH, PERA, MARCH, HIDE, RACAL, RODA, MARCH, PTEN, HIDE, RACAL, RODA, MARCH, RODA, MARCH, PTEN, HIDE, RACAL, RODA, MARCH, RODA, MARCH, PTEN, HIDE, RACAL, RODA, MARCH, RODA, MARCH, PTEN, HIDE, RODA, RODA, MARCH, PTEN, MARCH, HIDE, RODA, RODA, MARCH, PTEN, MARCH, HIDE, RODA, RODA, MARCH, PTEN, MARCH, 
MEDIZ, ANDA, FAXODO, CHAJ, MINIT, CSPIT, SDBB, PARAC, TEGZ, BAO, PIROA         VIN         J
CARE IN SPRING TRACE, TRACE, SING, FROM.         VM         def         M         III C           F15122280130         TTTP, FGP2, NTP. MOG         FGGFT         S0         M         IIIC           F15122280130         TTTP, FGP2, NTP. MOG         FGGFT         S0         M         IIIC           F1512280130         MTOR, FANGA, PKOT, MEDT, PARINT, NAT, CRIMA, S0, PKOT, MEDT, PARINT, ART, FGERA, MARCA, PKOT, MART, PORTA, BARDT, CRIMA, MAY, POGFA, MART, MART, CRIMA, MAY, POGFA, MART, MART, MART, CRIMA, MAY, POGFA, MART, M
F151228030         MEGRE WASS, UDTAL, COMIN, MEDIZ,         WINH         49         M.         IIIC           F1512220110         TP35, PTEN         F04PT         50         M.         IIIC           F1512280330         TP31, TUBARA, ESTI, GSTP1, ATT         None         None         S5         F         IIIC           F1512280330         TP31, TUBARA, ESTI, GSTP1, ATT, FORDAR, MEDIZ, PRIVID, CONTA, TRAVAD, SGKT, NATL, CONTAN, ATT, FORDAR, MEDIZ, PRIVID, CONTA, TEX, MOTORE, MULE, FERA, TSC, TEX, MOTORE, MULE, MOTORE, MULE, TEX, MOTORE, MULE, TEX, MOTORE, M
TIFL FORE, NF1, PAK3         FORM         FORM         FORM         S0         M         IIIC           F151228103         MF1, TUBBA, ESR1, GSTP1, ATRX         None         S8         F.8         IIIC           F151228103         MF0R, PARCA, PR01, MED1, PARCD, PR01, NDT, CMR01, NDT, NDT, NDT, CMR01,
F15/2289110     TPS, TURN     F0F1     S0     F     IIIC       F15/228932     MTOR, FANCA, PEDT, MEDT, PRIOT, NATZ, NENA, SEN, TENT, ATT, FORRA, TANDA, NTRIS, IRAN, TEN, KAN, PABI, NENA, PEDLO, FANCO, SON, NAT, CONTAN, NATZ, NENA, SEN, PEDRIT, AUT, FORRA, TANDA, NTRIS, IRAN, PEDRI, MADDI, PERBLE, SDHB, DOYD, JAKS, TEO, ANNO, PERBLE, SDHB, DOYD, TER, SDHB, TEN, PERBLE, SDHB, DOYD, TER, SDHB, TEN, PERBLE, SDHB, DOYD, TER, SDHB, TEN, PERBLE, SDHB, TEN, PERBLE, ANDT, HEDTE, PERBLE, SDHB, TEN, PERBLE, ANDT, HED
F151228833     MP1, TUBBA, ESR1, GSTP1, ATRX     Name     S6     F     IIC       F151228832     MDC, FNACP, KPOL, POLD,     Name     S6     M     IIE       F151228832     MDC, FNACP, KPOL, POLD,     Name     S6     M     IIE       F1512289130     REG, AL, TEN, KAR, BRI, REEK,     Name     S6     M     IIE       F151229111     REG, AL, TEN, KAR, BRI, REEK,     Name     S63     M     IIE       F151229112     REG, CA, HOLD, CHAN, LEP, MAC, REEK, CARDER,     Name     S63     M     IIE       F151229113     REFAD, SRM, TEN, FAR, BRI, SRM, CREEK,     Name     48     M     IIE       F151229131     REFAD, SRM, TEN, FAR, SRM, SRM, CREEK,     Name     48     M     IIE       F151229132     REFAD, SRM, TEN, FAR, SRM, SRM, SRM, SRM, SRM, SRM, SRM, SR
F151228832       MTOR, RMACA, PROJ., MEDJ, ZMEDJ, MARZ, SMRJ, KAT, CERMA, MARZ, MBN, SRY, FUPHTI, ATT, FERA, MARZ, MBN, SRY, FUPHTI, ATT, FERA, MARZ, MBN, SRY, FUPHTI, STAT, FERA, MARZ, MBN, SRY, FUPHTI, STAT, PARCH, SETDS, KOMSA, MAXI, POEPA, BARDY, CERCH, PARCI LPANS, TOCZ, TOMA, SETDS, KOMSA, MAXI, POEPA, BARDY, CERCH, PARCI LPANS, TOCZ, TOMA, SETDS, KOMSA, MAXI, POEPA, BARDY, CERCHA, PARCI LPANS, TOCZ, TOMA, SETDS, KOMSA, MAXI, POEPA, BARDY, CERCHA, PARCI LPANS, TOCZ, TOMA, SETDS, KOMSA, MAXI, POEPA, BARDY, CERCHA, PARCI LPANS, TOKZ, TOMA SETDS, KOMSA, MAXI, POEPA, BARDY, CERCHA, PARCI LPANS, TOKZ, TOMA SETDS, KOMSA, MAXI, POEPA, BARDY, CERCHA, PARCI LPANS, TOKZ, TOMA SETDS, KOMSA, MAXI, PARCH, TAY, MARCH, PARCHA, BARDY, TOKZ, TAY, MARCH, SETDS, KOR, PROJ. AND, ATT, MARCH, POES, MARIZ, FANCA, PARCH, TOKA SETDS, KOR, PROJ. AND, ATT, MARCH, POES, MARIZ, FANCA, CREEBP LACGR, NOL TOKI, AND, SETDS, SOL, MILLO, ENDS, MARIZ, FANCA, CREEDP LENDS, BARDY, MCMAR, BRACH, MEDIZ, MARY, MARKA, BRACH, MEDIZ, MARY, MARKA, BRACH, MEDIZ, MARY, MARKA, MARKA, BRACH, PEIST2289128       MCD12, TEK       None       48       M       IIB 11612289129         F1512289129       MCD12, TEK       NOTCH, FLT, HNETA, RAPTOR, FORFR, GOM, MORE, MARIZ, MARKA, MARKH, PIST2289129       POMIZ, TIFL, BUM, NF1       FLT, REPTOR, GARAZ, NOTCH1       68       M       IIB 11612289129         F1512289129       MCD12, TANCA, ERCOL, ACCHI, FUT, HIEL, MARKA, BRACH       NOTCH1, FLT, HNETA, REPCOL, ACCHI, MARKA, BRACH, CPC2D6       None       47       FL       IIB 1161228910       MCD12, TANCA, ACCHI, MARKA, MAR
NAZZ, NAN, SRY, PTPHI1, SKT, AKT, EDGRA, THADA, NTRY, IGK, TAN, REI, IKRKE, ROST, ALL, TEK, NOTCHZ, MUSL, PTEN, SETTOZ, KUMAS, AKI, POGRA, BADD, COKYZ, PDETIA, PMAS, POL, POLH, EFREDZ, SDNA, MET, IGETIP, MASS, SRACE, GARZA, MET, IGETIP, MASS, RAD, C. MACZ, GARZA, MET, IGETIP, MASS, RAD, C. MACZ, GARZA, MET, IGETIP, MASS, RAD, C. MACZ, GARZA, MET, IGETIP, MASS, RAD, C. MEDDZ, BRCAT, KOMAS, REDA, CHEIBBR LUCCR, NGOT, TPOTI, APO, TETZ, GMAS SNARDACA, EZA, MOTO, MET, GARZA, MARCH, LUCCR, NGOT, TOTI, MAP, TETZ, GMAS SNARDACA, EZA, MOTO, MARCH, CARL, RADS, NARD, FI 512289335       SS       SS       M       IIB         F1 512289355       CHELO, RRAT, KOMAS, REDA, CHEIBBR SNARDACA, EZA, MOTO, META, COMAS, META, TEK, KT, ECAMA, FGRZ, BLM, LURAR RADZ, SARDA, FARZ, BLM, META       Nane       AS       M       IIB         F1 512289355       CHELO, RRAT, KOMAS, BRCA, COREIZ       Nane       AS       M       IIB         F1 512289355       CHELO, RRAT, KOMAS, BRCA, COREIZ       Nane       AS       M       IIB         F1 512289355       CHELO, RRAT, KOMAS, BRCA       Nane       AS       M       IIB         F1 512289357       TPSO, KOR, PROSCA, COXIZ, GERRA       Nane       AS       M       IIB         F1 512289358       CHELO, RM, KICO, COLITI       NOTCH1, BAPT       51       M       IIB         F1 512289129       MEDIZ, INKACO, RECOLITI       NOTCH1, BAPT       AS       M       IIB      <
THADA, NTEKI, BTK, ATM, RBJ, IKRKE, BSTD2, KOMBA, LAKI, POCEA, LBAPD, SETD2, KOMBA, LAKI, POCEA, LBAPD, BETD2, KOMBA, LAKI, POCEA, BAPD, BETD2, KOMBA, LAKI, POCEA, BAPD, BETD2, RADI, DENNDIA, KOM BEGO2, FACI, DENNDIA, KOM BEGO2, FACI, DENNDIA, KOM BEGO2, FACI, DENNDIA, KOMA BEGO2, RADI, PAUSA, REI, STAN, RAACE, TEK, KIT, EPCAM, FORTE, BUM, LIZR, KARTZA, GERRAS, DEOTES, CONA, CEEDBR LICCG, REIO, FTCH, FACI, REI, CARDA, SIA, NETI, TEK, KIT, EPCAM, FORTE, BUM, LIZR, KARTZA, GERRAS, DEOTES, CONA, CEEDBR LICCG, REIO, FTCH, MARSA       Nane       48       M       IIB         F1512289357       TPS3, KOR, PIKSCA, COK12, FGFRB       None       48       M       IIB         F1512289128       MEDIZ, TEK       Nane       48       M       IIB         F151289127       TPS3, KOR, PIKSCA, COK12, FGFRB       NOTCH1, RATA, RPTOR, GAZO, NOTCH1       68       M       IIB         F151289128       TUBBAA, TSHR, CYP2D6       None       47       F       IIB         F151289128       TUBBAA, TSHR, CYP2D6       NOTCH1, RAPT, RECO, RAZO, NOTCH1       63       M       IIC         F151289129       MEDIZ, FANCDO, PCOL11Y       NOTCH1, RAPT, RECOLA, RECOL
SPETC2 (KINGA, LAKI, POPCA, JAK2), COKIV2, PECH A, MSI, TOCE, AXIN2, EROCZ, RACI, LMSI, TOCE, AXIN2, EROCZ, RACI, LMSI, TOCE, AXIN2, EROCZ, RACI, LMSI, TOCE, AXIN2, CREDENIDA KOPE AGATA, MET (JORNI)A KOPE BACCZ, RACI, LMSI, PARS, BAD, PALLD, JAK2, CATA2, LMSI, RABD, PALLD, LHCGR, NBC1, TPCH, JACE, TER, GRMA, MARACA, EZH, MOTCH L, GLMS, NF1, TKC, KT, ECACA, CALV, AKER, RABDI, COHI, METD2, KMT7A, GRIRAZ, POG-RID, METD2, KMT7A, GRIRAZ, COKI, MED12, AMETI NORG, MED2, STK11, XPC NOTCH METD2, STK11, XPC NOTCH MED2, STK11, XPC NOT
CDR12, PDE11A, PMSI, PDE1, PDL, PDL, PDL, PDL, PDL, PDL, PDL, PDL
ERGC2, RAC1, DENNIDA, KOR         TIMPAR3, EGFR         63         M         IIB           PI6102, RM, IPTPN11, STAT3, FAACE, QARDA, MET, IMPA, RUE, RUMD, IND         TIMPAR3, EGFR         63         M         IIB           PI6102, RM, IMP, RUE, RUMD, RUMD, RUMD, IMPARA, CPEEBR LHOGR, NSD, IPTOHI, APC, TET2, GRMD, SMARCA, EZEN, ROTCHC, CWAS, RIM, TETE, GRMD, SMARCA, EZEN, ROTCHC, CWAS, RIM, TETE, GRMD, SMARCA, EZEN, ROTCHC, CWAS, RIM, TETE, GRMD, FI51228835         MED12, TEK         None         48         M         IIB           F151228835         CHD2, TEK, KIT, EPCAM, FGRTR, SMA, MARENT, ROS, RAILO, FANCOZ, SET02         None         48         M         IIB           F151228835         CHD2, TEK         None         48         M         IIB           F151228835         CHD2, TEK, CAC, CK12, FGRD         None         48         M         IIB           F1512289312         PRDM12, TTF1, BLM, NF1         FLT4, RPTOR, GAT2, NOTCH         63         M         IIB           F1512289132         MED12, FANCD2, PCD111Y         NOTCH1, FLT4, INF1A, RPTOR, KORA, CK13, GORA         M         IIB           F1512289133         RIKGA, REOCL4         MED1         GCIA         M         IIC           F1512289134         NORE, REOCL4         MORE         GCIA         M         IIC           F1512289149         NORE, SCH11,
F151223319PHOLP, REM, PTPMINI, TATAT, STAT, FANCE, GATAS, MET, IGFR, PANS, BALO, KOYEB, JAKZ, GATAZ, JAKS, RADD, FMST, PAPEP, IPOETA, PABE, RADD, FMST, METAZ, GRINZA, POERBR, COH I, MEDIZ, FIS12289335None88MIIBF1512289356MEDIZ, TRADC, SKIDZ PEDIA, TETANone88MIIBF1512289357TPSA, NDR, PKICAC, COKIZ, FGRASNOTCHI, FLT, HINFIA, RPTOR, FGRASMIIBF1512289372PRDM12, TTF1, BLM, NF1FGRI, SMO, MVDB8MMIIBF1512289373PRDM12, TFA, DCD, POETAFGRI, SMO, MVDB8MMIIBF1512289128MEDIZ, FANCDZ, PCOH1YNOTCHI, BAP1G1MIICF1512289129MEDIZ, FANCDZ, PCOH1YNOTCHI, BAP1G2MIIBF1512289130MEDIZ, FANCDZ, PCOH1YNOTCHI, BAP1G2MIIBF1512289131NORAS, BRCA1CDKN2B, CDKN2A, CDKS, CCND1G2MIIBF1512289140NORECDKN2B, CDKN2A, CDKS, CCND1G2MIIBF1512289141NORECDKN2B, CDKN2A, CDKS, CCND1G2MIIBF1512289141NORECDKN2B, CDKN2A, CDKS, CDKN2A, CDKS, CDKN2A, NOTCH1G3MIIBF1512289141NOREMEDIZ, STK11, XPCCDKN2B, CDKN2A, NOTCH1G3M<
GARAS, MET, IGFIR, PAKS, REI, CYV286, PAPER, IPOETA, PALED, BARDI, PALLD, FLRCGS, BRCA, KOMAS, REAC, CARBER, LHCGR, NBCJ, FTCHT, APC, TET2, GRMS, STATUS, GRNAA, POSTBL, COT-14, BURS, NET1, TKYT25, GRNAA, POSTBL, COT-14, BURS, NET1, TKYT25, GRNAA, POSTBL, COT-14, BURS, NET1, TKYT25, GRNAA, POSTBL, COT-14, MEDIZ, ROST, ARDZ, FANCACE, SETDZ       None       48       M       III         F151228335       MEDIZ, TEX       None       48       M       III         F151228335       MEDIZ, TEX       None       48       M       III         F151228335       CHD4, PDKI, NRAS       None       48       M       III         F1512283123       PDKN12, TTF1, BLM, NF1       PLT4, HPT0R, GARZ, MCT0H       68       M       III         F1512283123       PUBM12, TTF1, BLM, NF1       PLT4, HPT0R, GARZ, MCT0H       68       M       III         F1512283123       TUBB4A, TSHR, CYP2D6       None       47       F       III         F1512283123       MEDIZ, FANCEZ, PCDH1Y       NOTCH1, BZ1, MARS, CDH, MUEIZ, MARS       M       III         F151228313       MEDIZ, FANCEZ, PCDH1Y       NOTCH1, BZ1, HMF1A, RECOLA, RPTOR, AR       M       III         F151228314       None       CORNER, CDKN2A, CDKR, CDKN2A, CDKR, CMDN       62       F       IV         F151228314       None       CORNER, CDKN2A, CDKR, CM, FMAS, CM       NO<
PAPE1, PDE114, PUL82, RAND1, PALLD.         ERGCS, BRCAC, JONAS, BRCAC, CIEEBBR, LHCGR, NSD1, PTCH1, APC, TET2, GMM3, SMAGCA, PLR, NDTCH, CONS, NF1, TKK, KTT, EPCAM, FOFFA, BLM, L/TR.         KMTCA, GMM3, PDG7B, CONS, NF1, MERI, ROTS, ALMICA, PAPCA, ROCH, MED12, KDC, PKOL, STAG2, FANCA, FAT1, MERI, ROSS, ALMICE, FANCO, SET02         None         48         M         IIA           F1512289335         MED12, TEK         None         48         M         IIB           F1512289337         MED12, TEK         None         48         M         IIB           F1512289337         TP53, KDR, PKGGA, CDK12, FGFR3         NOTCH1, FLT4, HNF1A, RPTOR, GATA2, NOTCH1         66         M         IIB           F1512289317         TP50, KDH 1, TF1, BLM, NF1         FGTR1, SMO, MYD88         48         M         IIB           F1512289132         PDBM, TDH, CDH1         FGTR1, SMO, MYD88         48         M         IIB           F1512289143         MED12, FAROD2, PCDH11Y         FOTH1, BD11         M         IIC           F1512289143         None         CONT01H, BD12         AIM         IIB           F1512289143         None         CONT01H, MED12, AIMEN         None         M         IIC           F1512289143         None         CONT01H, MED12, AIMEN         NOTCH1, HED12, AIMEN         M         IIC           F1512289
BRCA1, KDMAA, BRCA2, CREBBR, LHCGR, NOTCH2, GNAS, INT, TRE, KIT, ECAA, FGF78, LUK, LI7R, KMT2A, GINXA, POGCH8, CDH1, MED12, KOR, PKCD3, STAG2, FANCA, CNT, AMER1, ROS1, ARID2, FANCD2, SETD2         None         48         M         IIA           F1512289353         MED12, TEK         None         48         M         IIB           F1512289357         TPS3, KDR, PIK3CA, CDK12, FGFR3         None         48         M         IIB           F151229123         PIDM17, TTF1, ILM, NF1         FLT4, RPTOR, GAT2, NOTCH1         68         M         IIB           F151229132         TUBB4A, TSHR, CYP2D6         None         47         F         IIB           F151229313         MED12, FANCD2, PCDH11Y         NOTCH1, BAP1         64         M         IIC           F1512289343         None         CRED12, FMK18, CDKN28, CDKN2A, CDK6, CCND1         62         M         IIB           F1512289343         None         CRED12, FMC2, HOK28, CDKN2A, CDK6, CDK12, CDK12, CDK18, CDKN2A, CDK6, CDK12, FFC2, PLC1, FANCA, CDK2, CDK12, CDK18, CDKN2A, NOTCH1
SMARCAL E242, NOTCHE, GNAS, NFT, TKE, KIT, PCAM, FGFZE, BUM, LT/R.         None         48         M         III           KITZA, GRINZA, PODERB, COH1, MED12, KIDR, PCOL STAGZ, FANCAZ, SETD2         None         48         M         III           F1512289335         CH0J, PCK1, INAS         None         48         M         III           F1512289337         TP53, KOR, PIK3CA, CDK12, FGFR3         NOTCH1, FLT4, HNF1A, PFTOR, FGFR3         66         M         III           F1512289127         PT9D, CDH1         FGFR1, SMO, MYD68         48         M         III           F1512239127         PT9D, CDH1         FGFR1, SMO, MYD68         47         M         III           F1512239127         PT9D, CDH1         FGFR1, SMO, MYD68         48         M         III           F1512239129         MED12, FANCD2, PCDH11Y         Nore         61         M         III           F151228934         MNone         CCND1         64         M         III           F151228934         None         CKN28, COKN2A, COKA2, CCM4, CKN2         M         III           F151228934         None         CCND1         63         M         III           F151228934         None         CCNN1, MED12, AMER1         NOR         CCNN2A, CCN6, CCN12, CCN1
TEK, KIT, EPCAM, FOFR2, BLM, ILTR, KMT2A, CRIMA, POCTRA, COHT, MEDI2, KNDR, PKD1, STRAG2, FANCA, FAT1, AMKER1, ROST, ARD2, FANCA, SET1, MAKER1, TARS, SET1, SET2, SET1, SE
NOR. PKD1, STAG2, FANCA, FAT1, AMERT, NOS1, ARID2, FANCD2, SETD2         None         48         M         IIA           F1512289335         MED12, TEK         None         48         M         IIB           F1512289336         CHD4, PDK1, NRAS         None         48         M         IIB           F1512289312         PRDM12, TF1, BLM, NF1         FLT4, RPT0R, GAT2, NOTCH1, FLT4, HNF1A, RPT0R, FGFR3         66         M         IIB           F1512239128         TUBBAA, TSHR, CYP2D6         None         47         F         IIB           F1512239129         MED12, FANCD2, PCD111Y         NOTCH1, BAP1         51         M         IIC           F1512289144         None         COKIN2E, COKIN2A, CDK6, CCND1         62         F         IV           F1512289134         NKGCA, RECOL4         MET         None         62         F         IV           F1512289134         None         COKIN2E, CDKN2A, CDK6, CCND1         62         M         IIB           F1512289134         NORC         NOTCH1, KTAS, CDH1, MED12, AMERT         None         IIB         IIIC           F1512289134         None         CDK12, INMM2         S         F         IIIB           F1512289139         NONE         NOTCH1         NO
F151228935         MED12, TEK         None         48         M         IIA           F151228936         CH0A, PDX1, NRAS         None         48         M         IIB           F151228937         TPS3, KDR, PIK3CA, CDK12, FGFR3         NOTCH1, FLT4, HNF1A, RPTOR, GATA2, NOTCH1         68         M         IIB           F1512289123         PRDM12, TTF1, BLM, NF1         FL4, RPTOR, GATA2, NOTCH1         68         M         IIB           F1512289123         PUBBA, TSHR, CVP2D6         None         47         F         IIB           F1512289129         MED12, FANCD2, PCDH11Y         NOTCH1, BAP1         51         M         IIC           F1512289129         MED12, FANCD2, PCDH11Y         NOTCH1, BAP1         62         M         IIB           F1512289134         None         CDK12B, CDK12A, CDK8, CCND1         62         M         IIB           F1512289345         BCL2L11, KPAS, CDH1, MED12, AMER1         None         0         IIC         IIB           F1512289349         NTRK1, CDH1         PADM1         48         M         IIB           F1512289331         JAK1, DDR2, ABCGA, MCO1, MGN1, OCH1, FL74, HNF1A, RECC2, FLON, FANCA, CREBB, TSO2         F         IIB           F1512289134         None         CDK12, MDM2
P1512289335     MELDI2, TEK     None     48     M     IIIA       F1512289337     TPS3, KDR, PIK3CA, CDK12, FGFR3     NOTCH1, FLT4, HNF1A, RPTOR, FGFR3     66     M     IIIB       F1512289123     PRDM12, TTF1, BLM, NF1     FLT4, RPTOR, GATA2, NOTCH1     68     M     IIIB       F1512289123     PRDM12, TTF1, BLM, NF1     FLT4, RPTOR, GATA2, NOTCH1     68     M     IIIB       F1512239127     PTFRD, CDH1     FGFR1, SMO, MYDB8     48     M     IIIB       F1512239128     TUBB4A, TSHR, CYP2D6     None     47     F     IIIB       F1512289134     ATM, GNAS, BRCA1     CCND1     64     M     IIC       F1512289343     ATM, GNAS, BRCA1     CCND1     62     M     IIB       F1512289344     None     CDKN28, CDKN2A, CDK6, CCND1     62     M     IIB       F1512289343     DILL1, KRAS, CDH1, MED12, AMER1     None     62     F     IV       F1512289343     None     CDKN28, CDKN2A, CDK6, CCND1     63     M     IIC       F1512289344     None     NOTCH1, FLT4, HNF1A, RECOL4, RPTOR, RA     M     IIC       F1512289134     None     NOTCH1, FLT4, HNF1A, RECOL4, RPTOR, RA     M     IIC       F16020411109     MED12, STK11, XPC     NOTCH1, FLT4, HNF1A, RECOL4, RPTOR, RA
P1512289336     CHD4, PUK1, NHAS     None     48     M     IIB       P1512289337     TP53, KOR, PIK3CA, CDK12, FGFR3     NOTCH1, FL14, HNF1A, RPTOR, GFR3     66     M     IIB       P1512239123     PTDM12, TTF1, BLM, NF1     FL74, RPTOR, GATA2, NOTCH1     68     M     IIB       P1512239127     PTPRD, CDH1     FGFR1, SMO, MYD88     48     M     IIB       P1512239128     TUBB4A, TSHR, CYP2D6     None     47     F     IIB       P1512289344     None     CCND1     64     M     IIC       P1512289344     None     CCND1     64     M     IIC       P1512289344     None     CCND1     62     F     IV       P1512289344     None     CCND1     62     F     IV       P1512289344     None     CCND1     62     F     IV       P1512289345     BCL2111, KPAS, CDH1, MED12, AMER1     None     62     F     IV       P1512289345     BCL2111, KPAS, CDH1, MED12, AMER1     None     62     F     IIB       P1512289346     None     CDK14, FL74, HNF1A, RECOL4, RPTOR, GAS, GAS, GAS, GAS, GAS, GAS, GAS, GAS
F1512239337       IP33, KDR, PRGAR, CURIZ, FARSA       NOICHT, FLI4, INFO, FAEHS       66       M       IIIG         F1512239127       PTPRO, CDH1       FGFR1, SQG, QATAZ, NOTCH1       68       M       IIIG         F1512239127       PTPRO, CDH1       FGFR1, SQG, MYDB8       48       M       IIIG         F1512239128       TUBB4A, TSHR, CYP2D6       None       47       F       IIB         F1512239129       MED12, FANCD2, PCDH11Y       NOTCH1, BAP1       51       M       IIIC         F151228943       ATM, GNAS, BECA1       COKN12A, CDK, CACK, COND1       62       M       IIB         F151228944       None       CDKN2B, CDKN2A, CDK, CACK, CCND1       62       F       IV         F151228945       BCL2L11, KRAS, CDH1, MED12, AMER1       None       62       F       IV         F151228944       None       NOTCH1, FLT4, HNF1A, RECOL4, RPTOR, 48       M       IIIG         F151228945       BCL2L11, KRAS, CDH1, MED12, AMER1       None       63       M       IIIC         F151228945       BCL2L11, KRAS, CDH1, MED12, AMER1       None       60       M       IIIC         F151228945       BCL2L11, KRAS, CDH1       PRDM1       48       M       IIIC         F1512289108
F1512239123       FH2M, P171, ELM, PF10, MARA, NOTCH1       68       M       IID         F1512239127       PTPRD, CDH1       FGF1, SMO, MARA, NOTCH1       68       M       IID         F1512239128       TUBBAA, TSHR, CYP2D6       None       51       M       IID         F1512239129       MED12, FANCD2, PCDH11Y       NOTCH1, BAP1       51       M       IID         F1512289343       ATM, GNAS, BRCA1       CCND1       64       M       IID         F1512289344       None       CDKN2B, CDKN2A, CDK6, CCND1       62       M       IIB         F1512289349       NTRK1, CDH1       MET       49       M       IID         F1512289349       NTRK1, CDH1       PRDM1       48       M       IID         F1512289349       NTRK1, CDH1       PRDM1       48       M       IID         F1512289349       NTRK1, CDH1       PRDM1       48       M       IID         F1512289349       NOR       CDE12, STK11, XPC       NOTCH1, FLT, HUR1, RECOL4, RPTOR, CREDBP, TSC2       48       M       IID         F1512239108       None       COK12, MDM2       32       F       IIB         F1512289108       None       COK14, MDM2, NOTCH1, FLTA, HUR1, RECOL4, APC, RECOL4, APC, FGF
F1512239127       F1FH2, CUT1       FCHT1, SMC, M7D80       40       M       IIB         F1512239128       TUBB4A, TSHR, CYP206       Nonc M1D80       47       F       IIB         F1512239129       MED12, FANCD2, PCDH11Y       NOTCH1, BAP1       64       M       IIC         F1512289343       ATM, GNAS, BRCA1       COND1       62       M       IIB         F1512289344       None       CDKN2B, CDKN2A, CDK6, CCND1       62       M       IIB         F1512289345       BCL2L11, KRAS, CDH1, MED12, AMER1       None       62       F       IV         F1512289349       NTRK1, CDH1       MeT       48       M       IIC         F1512289349       NTRK1, CDH1       None       62       F       IV         F1512239134       None       CONCH1, FLT4, HNF1A, RECQL4, RPTOR, CREBBY, TSCC2, FLCN, FANCA, CREBBY, TSCC2, FLCN, FAN
None         None         47         F         IIB           F1512239129         MED12, FANCD2, PCDH11Y         NOTCH1, BAP1         51         M         IIC           F1512239343         ATM, GNAS, BRCA1         CCND1         64         M         IIC           F1512239344         None         CDN1         64         M         IIC           F1512239131         PIK3CA, RECQL4         MET         49         M         IIB           F1512289344         None         CDL2L11, KRAS, CDH1, MED12, AMER1         None         62         F         IV           F1512289349         NTRK1, CDH1         PRDM1         48         M         IIC           F1512239134         None         SMC, GAPT, ERCC2, FLON, FANCA, CREBBP, TSC2         F         IIB           F16020411109         MED12, STK11, XPC         NOTCH1         63         M         IIC           F1512239108         None         CDN12, MDM2         32         F         IIB           F1512239333         JAK1, DDR2, ABCB4, MYCN, MGMT, MCDA, PCC, FLOR, FANCA         CCND1         45         F         IIB           F1512239108         None         CDK12, MDM2         32         F         IIB           F1512239137
F1512283343       ATM, GNAS, BRCA1       CCND1       64       M       IIIC         F1512283343       ATM, GNAS, BRCA1       CCND1       64       M       IIIC         F1512283343       None       CDKN2B, CDKN2A, CDK6, CCND1       62       M       IIIB         F1512283345       BCL2L11, KRAS, CDH1, MED12, AMER1       None       62       F       IV         F1512283349       NTRK1, CDH1       PRDM1       48       M       IIIC         F1512239134       None       SMCREBP, TSC2       F       IV         F16020411109       MED12, STK11, XPC       NOTCH1, FLT4, HNF1A, RECQL4, RPTOR, S3       M       IIIC         F1512289333       JAK1, DDR2, ABCB4, MYCN, MGMT, CREBP, TSC2       CCND1       63       M       IIIC         F1512289108       None       CDK12, MDM2       32       F       IIIB         F1512289333       JAK1, DDR2, ABCB4, MYCN, MGMT, MCD1, RAD51, POLE, RET, FANCD2, PTCH1, BRCA2, APC, FCFFRE, CH40, BLM, POGFRB, FR1, ATRX, ARD51, POLE, RET, FANCD2, PTCH1, BRCA2, APC, FCFFRE, CH40, BLM, POGFRB, FR1, ATRX, ARD51, PL1, MCD2, KDR, FANCA       70       M       IIIA         F1512239117       STK11, ALK, WRN, EPCAM, CDK12, PDGFB, NF2, TSC1, RAD51, PLC2, RAS3, NF1, CH44, POGFRB, RAT1, ATRX, ARD54, PHD54, MUT, MSH6, MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PDGFBA, TET2, PTEN, EPAS1, PHIC3, MSH6, MUTYH, BRIP1, PIK3C3,
Instruction         Ann, dired, prover         COND1         64         M         IIIC           F1512289344         None         CDKN2B, CDKN2A, CDK6, CCND1         62         M         IIIB           F1512289345         BCL2L11, KRAS, CDH1, MED12, AMER1         None         62         F         IV           F1512289345         BCL2L11, KRAS, CDH1, MED12, AMER1         None         88         M         IIIB           F1512289349         NTRK1, CDH1         PRDM1         48         M         IIIB           F1612289349         NTRK1, CDH1         PRDM1         63         M         IIIC           F16020411109         MED12, STK11, XPC         NOTCH1         63         M         IIIC           F1512289333         JAK1, DDR2, ABC84, MYCN, MGMT, PDCD1, ERC62, PAK3, OKI, RAD51, PDLE, REF, FANC02, PCH, BRCA2, APC, FGFR2, CHD4, BLM, PDGFRB, FAT1, ATRX, ARD51, CEGR, TP53, PKH01, CDH1, MED12, KDR, FANCA         CCND1         70         K         IIIA           F151228917         STK11, ALK, WRN, EPCAM, CDK12, PDC91, ERC62, PKK3, UNC, CYP2C19, PHA3, NF1, CHD4, PDGFRB, FAT1, ATRX, ARD51, PCI, BRCA2, APC, FGFR2, CHD4, BLM, PDGFRB, FAT1, ATRX, ARD10, PIKSTN, FAT1, MTOR, STAG2, FGFR4, PKH01, MSH6, MUTYH, BRIP1, PIKSG3, MYC, CYP2C19, PHMD1         K         M         IIIB           F1512239107         None         MC1         M         IIB </td
Horse         Conversion conversio
F1512289345       BCL2L11, KRAS, CDH1, MED12, AMER1       None       62       F       IV         F1512289345       BCL2L11, KRAS, CDH1, MED12, AMER1       None       62       F       IV         F1512289349       NTRK1, CDH1       PRDM1       48       M       IIIC         F1512239134       None       NOTCH1, FLT4, HNF1A, RECOL4, RPTOR, 48       M       IIIC         F16020411109       MED12, STK11, XPC       NOTCH1       63       M       IIIC         F1512239108       None       CDK12, MDM2       32       F       IIIB         F1512289333       JAK1, DDR2, ABCB4, MYCN, MGMT, CCN1       CCN01       45       F       IIIB         F151228917       STK11, ALK, WRN, EPCAM, CDK12, RCT, RADG1, POLE, RET, FANCD2, PTCH1, BRCA2, APC, FOFR2, CHD4, BLM, POGFRB, FAT1, ATRX, ARID2, AMER1, TOP1, FGFR1, NF2, TSC1, RADD14, PIK3CA, EPHA3, NF1, CHD4, PDGFRB, ARID2, FLT4, ARID14, PIK3CA, EPHA3, MIC4, CDKN1B       80       M       IIB         F1512239100       None       WT1       80       M
F1512289349         NTRK1, CDH1         PRDM1         48         M         IIIC           F1512289349         NTRK1, CDH1         PRDM1         48         M         IIIC           F1512239134         None         NOTCH1, FLT4, HNF1A, RECOL4, RPTOR, AS         M         IIIC           F16020411109         MED12, STK11, XPC         NOTCH1         63         M         IIIC           F1612239108         None         CK12, MDM2         32         F         IIIB           F1512239108         None         CK12, MDM2         32         F         IIIB           F1512289333         JAK1, DDR2, ABCB4, MYCN, MGMT, DCLE, PDCD1, ERC2, PAK3, OKI, RAD51, POLE, RET, FANCD2, PTCH1, BRCA2, APC, FGFR2, CH4, BLM, PDGRBE, FAT1, ATRX, ARID2, ATL, MC, BLM, PDGRBE, FAT1, ATRX, ARID2, AC, BLM, PDGRBE, FAT1, ATRX, ARID2, CDKN24, NOTCH1         70         M         IIIA           F1512239117         STK11, ALK, WRN, EPCAM, CDK12, PDGFRB, ARID2, FLT4, ARID1A, PLC4, ILM, PLC4,
F1512239134       None       NICH, LTM, HITH, HINFLA, RECQLA, RPTOR, 48       M       IIIB         F16020411109       MED12, STK11, XPC       NOTCH1       63       M       IIIC         F16020411109       MED12, STK11, XPC       NOTCH1       63       M       IIIC         F1512239108       None       CDK12, MDM2       32       F       IIIB         F1512289333       JAK1, DDR2, ABCB4, MYCN, MGMT, PDCD1, ERCC2, PAK3, OKI, RAD51, POLE, RCC2, PAK3, OKI, RAD51, POLE, RCC2, PAK3, OKI, RAD51, POLE, RCC4, PAK3, OKI, RAD51, POLE, RCC4, PAK3, OKI, RAD51, POLE, RCC4, PAK3, OKI, RAD51, POLE, RC1, FANCA, PDCFRB, AF11, ATRX, ARID2, AMER1, TOP1, FGFR1, NF2, TSC1, RAD51C, EGFR, TPS3, PKHD1, CDH1, MED12, KDR, FANCA       CDKN2B, CDKN2A, NOTCH1       70       M       IIIA         F1512239117       STK11, ALK, WRN, EPCAM, CDK12, PDGFRB, ARID2, FLT4, ARID14, PIGFR, ATRX, FAT1, MTOR, STAG2, FGFR4, PKHD1, NSH6, MUTYH, BRIP1, PIKSG3, MYC, CYP2C19, PRDM1       CDKN2B, CDKN2A, NOTCH1       70       M       IIIA         F1512239100       None       WT1       80       M       IIIB         F1512239102       ROS1, ARID1A, CDKN1B       None       49       M       IIIB         F1512239106       MED12, GSTM5, ATRX, TOP1       WT1, NFRSF14, EXT2       58       M       IIIB         F1512239109       PDM12       IKBKE, CDKN2B, CDKN2A, CDKN2A       57       M
F16020411109         MED12, STK11, XPC         NOTCH1         63         M         IIC           F16020411109         MED12, STK11, XPC         NOTCH1         63         M         IIC           F1512239108         None         CDK12, MDM2         32         F         IIIB           F1512289333         JAK1, DDR2, ABCB4, MYCN, MGMT, PDCD1, ERCC2, PAK3, QKI, RAD51, POLE, RET, FANCD2, PTCH1, BRCA2, APC, FGFR2, CH04, BLM, PDG7B8, FAT1, ATRX, AARD2, AMER1, TOP1, FGFR1, NF2, TSC1, RAD51C, EGFR, TP53, PKHD1, CDH1,         CCND1         45         F         IIIB           F1512239117         STK11, ALK, WRN, EPCAM, CDK12, PDGFR3, NF1, CH04, PDGFR8, FAT1, ATRX, AARD2, AMER1, TOP1, FGFR1, NF2, TSC1, RET, FANC2A         CDKN28, CDKN2A, NOTCH1         70         M         IIIA           F1512239117         STK11, ALK, WRN, EPCAM, CDK12, PDGFR4, TET2, PTEN, LPAS1, PIK3CA, EPHA3, NF1, CH04, PDGFR8, ARID2, FLT4, ARID1A, PIK3R1, AMER1, ATRX, FAT1, MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PRDM1         CDKN28, CDKN2A, NOTCH1         70         M         IIIB           F1512239100         None         WT1         80         M         IIIB           F1512239102         ROS1, ARID1A, CDKN1B         None         49         M         IIIB           F1512239104         TP53         NOTCH1         40         M         IIIB           F1512239106         MED12, GSTM5, ATRX, TOP1
CREBBR, TSC2         CREBBR, TSC2           F16020411109         MED12, STK11, XPC         NOTCH1         63         M         IIIC           F1512239108         None         CDK12, MDM2         32         F         IIIB           F1512289333         JAK1, DDR2, ABCB4, MYCN, MGMT, PDCD1, ERCC2, PAK3, QKI, RAD51, POLE, RET, FANCD2, PTCH1, BRCA2, PAC, FGFR2, CHD4, BLM, PDGFRB, FAT1, ATRX, ARID2, AMER1, TOP1, FGFR1, NF2, TSC1, RAD51C, EGFR, TP53, PKH01, CDH1, MED12, KDR, FANCD2, PTCH1, BRCA2, PAC, FGFR3, TET2, PTEN, EPAS1, PIK3CA, EPHA3, NF1, OHD4, PDGFRB, ARID2, FLT4, PDGFRA, TET2, PTEN, EPAS1, PIK3CA, EPHA3, NF1, OHD4, PDGFRB, ARID2, FLT4, ARID14, PIK3R1, AMER1, ATRX, FAT1, MTOR, STAG2, FGFR4, PKH01, MSH6, MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PRDM1         No         M         IIB           F1512239102         ROS1, ARID1A, CDKN1B         None         M         MI         IIB           F1512239104         MC912, GSTM5, ATRX, TOP1         WT1, TNFRSF14, EXT2         S8         M         IIB           F1512239109         MED12, GSTM5, ATRX, TOP1         WT1, TNFRSF14, EXT2         S8         M         IIB
F1002/0411109         MED12, STK1T, XPC         NOTCH1         63         M         IIIC           F1512239108         None         CDK12, MDM2         32         F         IIIB           F1512289333         JAK1, DDR2, ABCB4, MYCN, MGMT, PDCD1, ERCC2, PAK3, QKI, RAD51, POLE, RET, FANCD2, PTCH1, BRCA2, APC, FGFR2, CHD4, BLM, PDGFRB, FAT1, ATRX, ARID2, AMEB1, TOP1, FGFR1, NF2, TSC1, RAD51C, EGFR, TS53, PKHD1, CDH1, MED12, KDR, FANCA         CCND1         45         F         IIIB           F1512239117         STK11, ALK, WRN, EPCAM, CDK12, PDGFRB, ARID2, FLT4, ARID2, KDR, FANCA         CDKN2B, CDKN2A, NOTCH1         70         M         IIIA           F1512239117         STK11, ALK, WRN, EPCAM, CDK12, PDGFRB, ARID2, FLT4, ARID1A, PIK3R1, AMER1, ATRX, FAT1, MTOR, STAG2, FGFR4, PKHD1, MSH6, MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PRDM1         70         M         IIIA           F1512239102         ROS1, ARID1A, CDKN1B         None         49         M         IIIB           F1512289324         TP53         NOTCH1         40         M         IIIB           F1512239106         MED12, GSTM5, ATRX, TOP1         WT1, TNFRSF14, EXT2         58         M         IIIB           F1512239109         PRDM12         IKBKE, CDKN2B, CDKN2A, CDKN2A, CDKN2A         57         M         IIIB
F1512239106         NORE         CDK12, MDM2         32         F         IIIB           F1512289333         JAK1, DDR2, ABCB4, MYCN, MGMT, PDCD1, ERCC2, PAK3, QKI, RAD51P, C         CCND1         45         F         IIIB           F1512289333         JAK1, DDR2, ABCB4, MYCN, MGMT, PDCD1, ERCC2, PAK3, QKI, RAD51P, C         CCND1         45         F         IIIB           F1512289137         STK11, ALK, WRN, EPCAM, CDK12, RAD51C, EGFR, TP53, PKHD1, CDH1, MED12, KDR, FANCA         CDKN2B, CDKN2A, NOTCH1         70         M         IIIA           F1512239117         STK11, ALK, WRN, EPCAM, CDK12, PDGFRA, TET2, PTEN, EPAS1, PIK3CA, EPHA3, NF1, CH04, PDGFRB, ARID2, FLT4, ARID1A, PIK3R1, AMER1, ATRX, FAT1, MTOR, STAG2, FGFR4, PKHD1, MSH6, MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PRDM1         70         M         IIIB           F1512239100         None         WT1         80         M         IIIB           F1512239102         ROS1, ARID1A, CDKN1B         None         49         M         IIIB           F1512239106         MED12, GSTM5, ATRX, TOP1         WT1, TNFRSF14, EXT2         58         M         IIIB           F1512239106         PRDM12         IKBKE, CDKN2B, CDKN2A, CDKN2A         57         M         IIIB
FIST2289333JAKT, DUP2, ABCB4, MYCN, MGMI, PDCD1, ERCC2, PAK3, QKI, RAD51, POLE, RET, FANCD2, PTCH1, BRCA2, APC, FGFR2, CHD4, BLM, PDGFRB, FAT1, ATRX, ARID2, AMER1, TOP1, FGFR1, NF2, TSC1, RAD512, KDR, FANCA2, MED1, CDH1, MED12, KDR, FANCA2, MED1, CDH1, MED12, KDR, FANCA2, FT1, ARD51, PIC4RA, TET2, PTEN, EPAS1, PIK3CA, EPHA3, NF1, CHD4, PDGFRB, ARID2, FLT4, ARD14, PIK3R1, AMER1, ATRX, FAT1, MTOR, STK22, FGFR4, PKHD1, MSH6, MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PRDM1CDKN2B, CDKN2A, NOTCH170MIIIAF1512239100NoneWT180MIIIBF1512239102ROS1, ARID1A, CDKN1BNone40MIIIBF1512239104MED12, GSTM5, ATRX, TOP1WT1, TNFRSF14, EXT258MIIIBF1512239109PRDM12IKBEK, CDKN2B, CDKN2A, CDKN2A, STMIIIB
RET, FANCD2, PTCH1, BRCA2, APC, FGFR2, CHD4, BLM, PDGFRB, FAT1, ATRX, ARID2, AMER1, TOP1, FGFR1, NF2, TSC1, RAD512, EGFR, TP53, PKHD1, CDH1, MED12, KDR, FANCACDKN2B, CDKN2A, NOTCH170MIIIAF1512239117STK11, ALK, WRN, EPCAM, CDK12, PDGFR4, TET2, PTEN, EPAS1, PIK3CA, EPHA3, NF1, CHD4, PDGFRB, ARID2, FLT4, ARID1A, PIK3R1, AMER1, ATRX, FAT1, MTOR, STAG2, FGFR4, PKHD1, MSH6, MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PRDM170MIIIAF1512239100NoneWT180MIIIBF1512239102ROS1, ARID1A, CDKN1BNone49MIIIBF1512239104TP53NOTCH140MIIIBF1512239105MED12, GSTM5, ATRX, TOP1WT1, TNFRSF14, EXT258MIIIBF1512239109PRDM12IKBKE, CDKN2B, CDKN2A, CDKN2A57MIIIB
FIGHA, CHUA, BLM, PDGHRB, NF2, TSC1, RAD51C, EGFR, TP53, PKHD1, CDH1, MED12, KDR, FANCAF1512239117STK11, ALK, WRN, EPCAM, CDK12, PDGFRA, TET2, PTEN, EPAS1, PIK3CA, EPHA3, NF1, CHD4, PDGFRB, ARID2, FLT4, ARID1A, PIK3R1, AMER1, ATRX, FAT1, MTOR, STAG2, FGFR4, PKHD1, MSH6, MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PRDM170MIIIAF1512239100NoneWT180MIIIBF1512239102ROS1, ARID1A, CDKN1BNone49MIIIBF1512239106MED12, GSTM5, ATRX, TOP1WT1, TNFRSF14, EXT258MIIIBF1512239109PRDM12IKBKE, CDKN2B, CDKN2A, CDKN2A57MIIB
RAD51C, EGFR, TP53, PKHD1, CDH1, MED12, KDR, FANCACDKN2B, CDKN2A, NOTCH170MIIIAF1512239117STK11, ALK, WRN, EPCAM, CDK12, PDGFRA, TET2, PTEN, EPAS1, PIK3CA, EPHA3, NF1, CHD4, PDGFRB, ARID2, FLT4, ARID1A, PIK3R1, AMER1, ATRX, FAT1, MTOR, STAG2, FGFR4, PKHD1, MSH6, MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PRDM170MIIIAF1512239100NoneWT180MIIIBF1512239102ROS1, ARID1A, CDKN1BNone49MIIIBF1512239104TP53NOTCH140MIIIBF1512239105MED12, GSTM5, ATRX, TOP1WT1, TNFRSF14, EXT258MIIIBF1512239109PRDM12IKBKE, CDKN2B, CDKN2A, CDKN2A77MIIIB
F1512239117STK11, ALK, WRN, EPCAM, CDK12, PDGFRA, TET2, PTEN, EPAS1, PIK3CA, EPHA3, NF1, CHD4, PDGFRB, ARID2, FLT4, ARID1A, PIK3R1, AMER1, ATRX, FAT1, MTOR, STAG2, FGFR4, PKHD1, MSH6, MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PRDM1CDKN2B, CDKN2A, NOTCH170MIIIAF1512239100NoneWT180MIIIBF1512239102ROS1, ARID1A, CDKN1BNone49MIIIBF1512239106MED12, GSTM5, ATRX, TOP1WT1, TNFRSF14, EXT258MIIIBF1512239109PRDM12IKBKE, CDKN2B, CDKN2A, CDKN2A57MIIIB
F1512239117STRT1, ALX, WRN, EDAW, ODAT2, PDGFRA, TET2, PTEN, EPAS1, PIK3CA, EPHA3, NF1, CHD4, PDGFRB, ARID2, FLT4, ARID1A, PIK3R1, AMER1, ATRX, FAT1, MTOR, STAG2, FGFR4, PKHD1, MSH6, MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PRDM1WT180MIIIBF1512239100NoneWT180MIIIBF1512239102ROS1, ARID1A, CDKN1BNone49MIIIBF1512289324TP53NOTCH140MIIIBF1512239106MED12, GSTM5, ATRX, TOP1WT1, TNFRSF14, EXT258MIIIBF1512239109PRDM12IKBKE, CDKN2B, CDKN2A57MIIIB
EPHA3, NF1, CHD4, PDGFRB, ARID2, FLT4, ARID1A, PIK3R1, AMER1, ATRX, FAT1, MTOR, STAG2, FGFR4, PKHD1, MSH6, MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PRDM1WT180MIIIBF1512239100NoneWT180MIIIBF1512239102ROS1, ARID1A, CDKN1BNone49MIIIBF1512289324TP53NOTCH140MIIIBF1512239106MED12, GSTM5, ATRX, TOP1WT1, TNFRSF14, EXT258MIIIBF1512239109PRDM12IKBKE, CDKN2B, CDKN2A57MIIIB
MTOR, STAG2, FGFR4, PKHD1, MSH6, MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PRDM1MTOR, STAG2, FGFR4, PKHD1, MSH6, MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PRDM1MITOR80MIIIBF1512239100NoneWT180MIIIBF1512239102ROS1, ARID1A, CDKN1BNone49MIIIBF1512289324TP53NOTCH140MIIIBF1512239106MED12, GSTM5, ATRX, TOP1WT1, TNFRSF14, EXT258MIIIBF1512239109PRDM12IKBKE, CDKN2B, CDKN2A57MIIIB
MUTYH, BRIP1, PIK3C3, MYC, CYP2C19, PRDM1WT180MIIIBF1512239100NoneWT180MIIIBF1512239102ROS1, ARID1A, CDKN1BNone49MIIIBF1512289324TP53NOTCH140MIIIBF1512239106MED12, GSTM5, ATRX, TOP1WT1, TNFRSF14, EXT258MIIIBF1512239109PRDM12IKBKE, CDKN2B, CDKN2A57MIIIB
F1512239100       None       WT1       80       M       IIIB         F1512239102       ROS1, ARID1A, CDKN1B       None       49       M       IIIB         F1512289324       TP53       NOTCH1       40       M       IIIB         F1512239106       MED12, GSTM5, ATRX, TOP1       WT1, TNFRSF14, EXT2       58       M       IIIB         F1512239109       PRDM12       IKBKE, CDKN2B, CDKN2A       57       M       IIIB
F1512239102       ROS1, ARID1A, CDKN1B       None       49       M       IIIB         F1512289324       TP53       NOTCH1       40       M       IIIB         F1512239106       MED12, GSTM5, ATRX, TOP1       WT1, TNFRSF14, EXT2       58       M       IIIB         F1512239109       PRDM12       IKBKE, CDKN2B, CDKN2A       57       M       IIIB
F1512289324     TP53     NOTCH1     40     M     IIIB       F1512239106     MED12, GSTM5, ATRX, TOP1     WT1, TNFRSF14, EXT2     58     M     IIIB       F1512239109     PRDM12     IKBKE, CDKN2B, CDKN2A     57     M     IIIB
F1512239106       MED12, GSTM5, ATRX, TOP1       WT1, TNFRSF14, EXT2       58       M       IIIB         F1512239109       PRDM12       IKBKE, CDKN2B, CDKN2A       57       M       IIIB
F1512239109 PRDM12 IKBKE, CDKN2B, CDKN2A 57 M IIIB
F1512289329 TP53, CDH1, ARID1A, ETV1, FLT4, PTCH1 NOTCH1 57 M IIIB
F1512239120 PRSS3 None 49 M IIIA
F1512239121 ARIH1 XPC 40 M IV
F1512239122 TP53, AXL, RHOA None 44 M IIIA
F1512239124 RNF43, STAG2, TGFBR2, ALK, ERBB2 None 54 F IIIB
F1512289338 CDH1, ROS1, GNAS, ATR, SMAD4, PKD1, None 48 M IIIB
F1512289338 CDH1, ROS1, GNAS, ATR, SMAD4, PKD1, None 48 M IIIB LHCGR
F1512289338       CDH1, ROS1, GNAS, ATR, SMAD4, PKD1, None       48       M       IIIB         LHCGR       F1512239132       CDH1, LZTR1       None       67       M       IIIC
F1512289338       CDH1, ROS1, GNAS, ATR, SMAD4, PKD1, LHCGR       None       48       M       IIIB         F1512239132       CDH1, LZTR1       None       67       M       IIIC         F1512239133       ERBB3, TP53, HNF1A, PKHD1, EPAS1, BARD1       EXT2, TSC1, MITF, NSD1       46       M       IIIC
F1512289338       CDH1, ROS1, GNAS, ATR, SMAD4, PKD1, LHCGR       None       48       M       IIIB         F1512239132       CDH1, LZTR1       None       67       M       IIIC         F1512239133       ERBB3, TP53, HNF1A, PKHD1, EPAS1, BARD1       EXT2, TSC1, MITF, NSD1       46       M       IIIC         F16020411106       ARID1A, ERBB3, TP53, GNAS, CREBBP, KRAS       KRAS       35       F       IV

GSTM5, HDAC2, GATA1

# F16020411107 RAD50, SOX21, ARAF

# NOTCH1, FLT4, FGFR3, RECQL4, 48 F IV TNFRSF14

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SNV_genes_list	SNV_number	SNV_rate
TP53 CDH1	16 12	26.2% 19.7%
MED12 PKHD1	11 11	18.0% 18.0%
ARID1A	7	11.5%
ATRX STAG2	7 6	11.5% 9.8%
ROS1	6	9.8%
ERBB3	ວ 5	o.2% 8.2%
KDR PIK3CA	5 5	8.2% 8.2%
GRIN2A	4	6.6%
EPHA3	4	۵.۵% 6.6%
ERBB2	4	6.6%
BARD1	4	6.6%
BLM CHD4	4	6.6% 6.6%
FANCD2	4	6.6%
GNAS PDE11A	4	6.6% 6.6%
PDGFRB	4	6.6%
PTCH1 PTEN	4	6.6% 6.6%
BRCA1	4	6.6%
FANCA FGFR2	4	6.6% 6.6%
JAK1 PKD1	4	6.6%
PRDM12	4	6.6%
TTF1 EZH2	4 3	6.6% 4.9%
RNF43	3	4.9%
ARID2	3	4.9%
ATM BRCA2	3	4.9% 4 9%
CDK12	3	4.9%
CYP2B6 EPAS1	3	4.9% 4.9%
FAT1	3	4.9%
LHCGR NOTCH2	3 3	4.9% 4.9%
PAK3	3	4.9%
PARP1 POLE	3 3	4.9% 4.9%
SETD2 TFK	3	4.9%
ALK	3	4.9% 4.9%
CREBBP EPCAM	3	4.9% 4.9%
GSTM5	3	4.9%
KDM5A MTOR	3 3	4.9% 4.9%
PDGFRA	3	4.9%
PRSS3	з З	4.9% 4.9%
RAD51 RHOA	3	4.9%
SMARCA4	з З	4.9% 4.9%
TGFBR2 TSC2	3 3	4.9% 4.9%
TOP2A	2	3.3%
AKT1 BRIP1	2 2	3.3% 3.3%
CYP2D6	2	3.3%
טטR2 GRM3	2 2	3.3% 3.3%
IGF1R	2	3.3%
i∟/R MET	2 2	3.3% 3.3%
MLH3	2	3.3%
wi≓∟ MUTYH	2 2	3.3% 3.3%
NSD1	2	3.3%
PCDH11Y	2	3.3 <i>%</i> 3.3%
RAD50 RICTOR	2 2	3.3% 3.3%
RRM1	2	3.3%
SF3B1 ABCB4	2 2	3.3% 3.3%
APC	2	3.3%
Enduz FGFR4	2 2	3.3% 3.3%
FLCN FLT4	2	3.3% 3.3%
GATA2	2	3.3%
JAK2 JAK3	2	3.3% 3.3%
KIT	2	3.3 <i>%</i>
NTRK1 PTPN11	2 2	3.3% 3.3%
RB1	2	3.3%
RET SDHB	2 2	3.3% 3.3%
STK11	2	3.3%
TOP1	2 2	3.3% 3.3%
TUBB4A	2	3.3%
WAS	2 2	3.3% 3.3%
CDK6 CYLD	1	1.6% 1.6%
GATA6	י 1	1.6%
MAP3K1 MDM2	1 1	1.6% 1.6%
NKX2-4	1	1.6%
PARP2 PCDH11X	1 1	1.6% 1.6%
PHOX2B	1	1.6%
runx1 TUBB2B	1 1	1.6% 1.6%
WISP3	1	1.6%
AKT2	ı 1	י.ט% 1.6%
ARAF ARIH1	1	1.6% 1.6%
ASXL1	ı 1	1.6%
	1	1.6%
BCL2L11	1 1	1.6% 1.6%
BTK CDKN1A	1 1	1.6% 1.6%
CDKN1B	1	1.6%
CDKN1C CSF1R	1 1	1.6% 1.6%
CTCF	1	1.6%
DENND1A	י 1	1.6%
DNMT3A DPYD	1 1	1.6% 1.6%
EGFR	1	1.6%
ERCC3 ERCC4	1 1	1.6% 1.6%
ESR1 ETV1	1	1.6%
FANCF	ı 1	1.6%
FANCG FGFR1	1 1	1.6% 1.6%
FGFR3	ı 1	1.6%
FLT3 GATA1	1 1	1.6% 1.6%
GATA3	י 1	1.6%
GNAQ GSTP1	1 1	1.6% 1.6%
HDAC2	1	1.6%
HGF HNF1A	1 1	1.6% 1.6%
IKBKE	1	1.6%
KMT2A KMT2B	1 1	1.6% 1.6%
KRAS	1	1.6%
LZTR1 MEGF9	1 1	1.6% 1.6%
MGMT	1	1.6%
MSH6 MYC	1 1	1.6% 1.6%
MYCN	1	1.6%
NAT1 NAT2	1 1	1.6% 1.6%
NBN	1	1.6%
NRAS	ı 1	1.6%
PALB2 PARK2	1	1.6% 1.6%
PDCD1	1	1.6%
PDK1 PIK3C3	1 1	1.6% 1.6%
PIK3R1	1	1.6%
PMS2 POLD1	1 1	1.6% 1.6%
	1	1.6%
нким1 PRF1	1 1	1.6% 1.6%
PRKACA PTPRD	1	1.6% 1.6%
QKI	י 1	1.6%
RAC1 RAD51C	1 1	1.6% 1.6%
RARA	1	1.6%
RECQL4 SGK1	1 1	1.6% 1.6%
SMAD4	1	1.6%
SMO SOX21	1 1	1.6% 1.6%
SRY	1	1.6%
STAT3 THADA	1 1	1.6% 1.6%
TSC1	1	1.6%
TUBB3	ı 1	۰.۵% 1.6%
UGT1A10 UGT1A3	1 1	1.6% 1.6%
UGT1A4	1	1.6%
UGT1A5 UGT1A6	1	1.6%
UGT1A7	1	1.6%
UGT1A8	1 1 1	1.6% 1.6% 1.6%
UGT1A8 UGT1A9	1 1 1 1	1.6% 1.6% 1.6%
UGT1A8 UGT1A9 VHL XPC	1 1 1 1 1 1	1.6% 1.6% 1.6% 1.6% 1.6%

CNV_genes_list	CNV_number	CNV_rate
NOTCH1	11	18.0%
FLT4	6	9.8%
RECQL4	4	6.6%
CCND1	4	6.6%
CDKN2A	4	6.6%
CDKN2B	4	6.6%
HNF1A	4	6.6%
CDK12	3	4.9%
RPTOR	3	4.9%
FGFR1	3	4.9%
IKBKE	3	4.9%
TNFRSF14	3	4.9%
WT1	3	4.9%
XPC	3	4.9%
CASC3	2	3.3%
CDC6	2	3.3%
CSF3	2	3.3%
ERBB2	2	3.3%
ERCC2	2	3.3%
GATA2	2	3.3%
GRB7	2	3.3%
GSDMA	2	3.3%
GSDMB	2	3.3%
LRRC3C	2	3.3%
MED24	2	3.3%
MSL1	2	3.3%
NR1D1	2	3.3%
ORMDL3	2	3.3%
PSMD3	2	3.3%
RAPGEFL1	2	3.3%
RARA	2	3.3%
WIPF2	2	3.3%
ZPBP2	2	3.3%
BAP1	2	3.3%
CDK6	2	3.3%
EXT2	2	3.3%
FGFR3	2	3.3%
SMO	2	3.3%
CCNE1	1	1.6%
ERBB3	1	1.6%
FGFR4	1	1.6%
MED12	1	1.6%
CREBBP	1	1.6%
EGFR	1	1.6%
FANCA	1	1.6%
FLCN	1	1.6%
EI T1	1	1.6%

IKZF3	1	1.6%
KRAS	1	1.6%
MDM2	1	1.6%
MET	1	1.6%
MIEN1	1	1.6%
MITF	1	1.6%
MUTYH	1	1.6%
MYD88	1	1.6%
NSD1	1	1.6%
PAN3	1	1.6%
PRDM1	1	1.6%
TNFAIP3	1	1.6%
TSC1	1	1.6%
TSC2	1	1.6%
WRN	1	1.6%

1

1.6%

FLT3

Table S5 Relation of SNVs and CLDN18.2 expression

All_genes_list SNV GRIN2A	_and_A SNV_a 3
MED12	0 1
TOP2A EZH2	2 0
RNF43	2
WRN STAG2	3
CDK6	1 (
CYLD GATA6	1 (
MAP3K1	1 (
MDM2	1 (
NKX2-4 PARP2	1 (
PCDH11X	1 (
PHOX2B RUNX1	1 (
TUBB2B	1 (
WISP3	1 (
EPHA3	2 2
ERBB2	2 2
NF1 AKT1	0 £
BRIP1	1 -
CYP2D6	1 -
GRM3	1 -
IGF1R	1
MET	1 -
MLH3	1 -
MPL MUTYH	1 -
NSD1	1 .
PALLD	1
RAD50	1 -
RICTOR	1 -
RRM1 SF3B1	1 -
AMER1	0 4
BARD1	0 4
CHD4	0
FANCD2	0 4
GNAS PDE11A	0 4
PDGFRB	0 4
PTCH1	0 4
ARID2	0 3
ATM	0 3
CDK12	0 3
CYP2B6	0 3
EPAS1 FAT1	0 3
LHCGR	0 3
NOTCH2 PAK3	0 3 0
PARP1	0 3
POLE	0 3
TEK	0 S
ROS1	2
CDH1 ABCB4	2 1 0 -
ADH1C	0 -
AKT2	0 -
APC	0
ARAF	0 -
ARID1A ARIH1	2 5 0
ASXL1	0
ATR	0 -
AXIN2	ء و 0 -
BCL2L11	0 -
BRCA1 BTK	1 3
CDKN1A	0 -
CDKN1B	0
CREBBP	1 2
CSF1R	0
CTCF CYP2C19	0 -
DENND1A	0 -
DNMT3A	0 -
EGFR	0 -
EPCAM	1 2
ERBB3 ERCC2	1 4
ERCC3	0 -
ERCC4	0 -
ETV1	0 -
FANCA	1 3
FANCF FANCG	0 -
FGFR1	0 -
FGFR2	1 3
FGFR4	0 2
FLCN	0 2
FLT3 FLT4	0 2
GATA1	0
GATA2	0 2
GNAQ	0 -
GSTM5	1 2
GSTP1 HDAC2	0 -
HGF	0 -
HNF1A	0 -
JAK1	1 3
JAK2	0 2
JAK3 KDM5A	0 2
KDR	1 4
KIT KMT2A	0 2
KMT2B	0 -
KRAS	0 -
MEGF9	0 -
MGMT	0 -
MSH6 MTOR	ບ - 1 ,
МҮС	0 -
MYCN NAT1	0 · ·
NAT2	
NBN	0 -
NFZ NRAS	u - 0 -
NTRK1	0 2
PALB2 PARK2	υ - Ο -
PDCD1	0 -
PDGFRA PDK1	1 2 0
PIK3C3	0
PIK3CA	1 4
FINONI PKD1	u - 1
PKHD1	3 8
PMS1 PMS2	1 2 0 -
POLD1	0 -
POLH	0 -
PRDM12	u - 1 - 2
PRF1	0 -
PRKACA PRSS3	0 - 1 '
PTPN11	0 2
PTPRD QKI	0 - 0
RAC1	0 -
RAD51	1 2
HAD51C RARA	υ - Ο -
RB1	0 2
RECQL4 RET	0 - 0
RHOA	- 2 1 2
SDHB	0 2
SGK1 SMAD4	0 - 0 -
SMARCA4	1 2
SMO SOX21	0 -
SRY	0 -
STAT3	0 -
STK11 TET2	0 2
TGFBR2	- 2 1 2
THADA	0 -
TP53	u 2 4 1
TSC1	0 -
TSC2	1 2 0 -
TTF1	1 3
TUBB3 TUBB44	0 - 0
UGT1A1	0 2
UGT1A10	0
UGT1A3 UGT1A4	υ - Ο -
UGT1A5	0 -
UGT1A6 UGT1A7	0 - 0 -
UGT1A8	0 -
UGT1A9 VHI	0 - 0
WAS	0 2
YPC	0

A, CLDN18.2 expressed in <40% of tumor cells; B, CLDN18.2 expressed in  $\ge$ 40% of tumor cells.

Table S6 Relation of CNVs and CLDN18.2 expression

All_genes_list	CNV_and_A	CNV_and_B	WT_and_A	WT_and_B	Fisher.test
CDK12	2	1	13	45	0.147
CCNE1	1	0	14	46	0.246
ERBB3	1	0	14	46	0.246
FGFR4	1	0	14	46	0.246
MED12	1	0	14	46	0.246
RECQL4	2	2	13	44	0.251
CASC3	-	-	14	45	0.434
CDC6	1	1	14	45	0.434
0050	1	1	14	45	0.434
	I ,	I	14	45	0.434
ERBB2	1	1	14	45	0.434
ERCC2	1	1	14	45	0.434
GATA2	1	1	14	45	0.434
GRB7	1	1	14	45	0.434
GSDMA	1	1	14	45	0.434
GSDMB	1	1	14	45	0.434
LRRC3C	1	1	14	45	0.434
MED24	1	1	14	45	0.434
MSL1	1	1	14	45	0.434
NR1D1	1	1	14	45	0.434
ORMDI 3	1	1	14	45	0.434
PSMD3	1	1	14	45	0.434
	1	-	14	40	0.494
RAPGEFLI	I	I	14	45	0.434
RARA	1	1	14	45	0.434
WIPF2	1	1	14	45	0.434
ZPBP2	1	1	14	45	0.434
CCND1	0	4	15	42	0.564
RPTOR	0	3	15	43	0.569
FLT4	2	4	13	42	0.630
NOTCH1	2	9	13	37	0.716
BAP1	0	2	15	44	1.000
CDK6	0	2	15	44	1.000
CDKN2A	1	3	14	43	1.000
CDKN2B	1	3	14	43	1 000
	0	1	15	45	1.000
	0	1	15	45	1.000
EGFR	0	1	15	45	1.000
EX12	0	2	15	44	1.000
FANCA	0	1	15	45	1.000
FGFR1	1	2	14	44	1.000
FGFR3	0	2	15	44	1.000
FLCN	0	1	15	45	1.000
FLT1	0	1	15	45	1.000
FLT3	0	1	15	45	1.000
HNF1A	1	3	14	43	1.000
IKBKE	1	2	14	44	1.000
IKZF3	0	1	15	45	1.000
KRAS	0	1	15	45	1.000
MDM2	0	1	15	45	1.000
MFT	n	1	15	45	1 000
	0	1	15	45	1.000
	0	1	15	45	1.000
	U	1	15	45	1.000
MUTYH	0	1	15	45	1.000
MYD88	0	1	15	45	1.000
NSD1	0	1	15	45	1.000
PAN3	0	1	15	45	1.000
PRDM1	0	1	15	45	1.000
SMO	0	2	15	44	1.000
TNFAIP3	0	1	15	45	1.000
TNFRSF14	1	2	14	44	1.000
TSC1	0	1	15	45	1.000
TSC2	0	1	15	45	1.000
WBN	n	1	15	15	1 000
W/T1	-	л О	14	40	1.000
	I	Z	14	44	1.000
AFU	1	2	14	44	1.000

A, CLDN18.2 expressed in <40% of tumor cells; B, CLDN18.2 expressed in ≥40% of tumor cells.