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(54) Benævnelse: **ANTITUMORMIDDEL OG FREMGANGSMÅDE TIL FORUDSIGELSE AF TERAPEUTISK EFFEKT FOR PATIENTER MED KRAS-MUTERET KOLOREKTAL CANCER**

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TAS-102 in patients with solid tumors' CANCER vol. 107, no. ISS.6, 2006, pages 1383 - 1390, XP055144969

DESCRIPTION

Technical Field

[0001] The present invention relates to a method for predicting a therapeutic effect of chemotherapy that uses an antitumor agent (hereinafter referred to as TAS-102) containing α,α,α-trifluorothymidine (FTD) and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride (TPI) at a molar ratio of 1:0.5, and also relates to an antitumor agent to be administered to a patient who is predicted to sufficiently respond to the chemotherapy using the antitumor agent.

Background Art

[0002] The standard therapy for treating colorectal cancer patients has been performed, typically, with chemotherapy using fluoropyrimidine-based antitumor agent (e.g., a combination of 5-fluorouracil (5-FU) and leucovorin (LV)), and optionally, with multidrug chemotherapy (FOLFIRI, FOLFOX, or the like) that additionally uses irinotecan or oxaliplatin. Such methods have achieved a certain therapeutic effect (Non-Patent Document 1).

[0003] However, when a colorectal cancer patient becomes refractory or intolerant to these standard therapies using 5-FU, irinotecan, or oxaliplatin, the choice of antitumor agent that can significantly prolong their survival is very limited. Further, although cetuximab, which is a chimeric antibody targeting the epithelial growth factor receptor (EGFR), and panitumumab, which is a fully human monoclonal antibody, are often selected for such colorectal cancer patients who are refractory or intolerant to standard therapy, it has been reported that these antitumor agents had no effects when the patients have colorectal cancer with KRAS gene mutation (Non-Patent Documents 2 and 3).

[0004] As explained above, despite the vigorous development of chemotherapies for colorectal cancer patients, their therapeutic effects are still insufficient. In particular, effective chemotherapies have not substantially been established for colorectal cancer patients with KRAS gene mutation. Further, since the effects of chemotherapies greatly depend on the genetic factors of the patients, there is no way to estimate the effects of the antitumor agents before the actual administration.

Citation List

- **Non-patent Documents**

[0005]

Non-Patent Document: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™); Colon Cancer (Version 3, 2011), Rectal Cancer (Version 4, 2011)

Non-Patent Document 2: N Engl J Med. 2008; 359 (17):1757-65.

Non-Patent Document 3: J Clin Oncol. 2008; 26 (10):1626-34.

[0006] Overman Michael J et al., Cancer Investigation, Marcel Dekker Inc., US, vol. 36, no. 8, 1 January 2008 (2008-01-01), pages 794-799 describe a Phase I clinical study of three times a day oral administration of TAS-102 in patients with solid tumors. A total of 15 patients with different types of tumors were enrolled.

[0007] Yamazaki, Kentaro et al., The 9th Annual Meeting of Japanese Society of Medical Oncology, Program-Shorokushu, 1 August 2011 (2011-08-01), page 170, describe a multicenter, randomized, double-blind, phase II study of TAS-102 plus best supportive care (BSC) (A) versus placebo plus BSC(P) in patients with chemotherapy-refractory metastatic colorectal cancer (mCRC).

Summary of Invention

Technical Problem

[0008] An object of the present invention is to provide chemotherapy for colorectal cancer patients that ensure a significant survival-prolongation effect and fewer side effects.

Solution to Problem

[0009] The present inventors conducted extensive research on various chemotherapies for colorectal cancer patients, and found that colorectal cancer patients with KRAS gene mutation are more likely to respond to TAS-102 than wild-type patients; and that, therefore, it becomes possible to estimate the adequacy of the therapeutic effect of chemotherapy using TAS-102 on a patient by detecting the presence/absence of KRAS gene mutation as an indicator. Based on this finding, the inventor completed the present invention.

[0010] Specifically, the present invention provides the following methods and antitumor agents.

[0011] Item 1. A method for predicting a therapeutic effect of chemotherapy that uses an antitumor agent comprising α,α,α-trifluorothymidine and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride at a molar ratio of 1:0.5 on a colorectal cancer patient,

the method comprising the steps of:

1. (1) detecting the presence or absence of KRAS gene mutation in a biological sample obtained from the patient; and
2. (2) predicting that the patient is likely to sufficiently respond to the chemotherapy, when KRAS gene mutation is detected in Step (1).

[0012] Item 2. The method according to Item 1, wherein the KRAS gene mutation is a mutation of codon 12 and/or codon 13.

[0013] Item 3. The method according to Item 1 or 2, wherein the colorectal cancer patient is a colorectal cancer patient who is refractory or intolerant to standard therapy.

[0014] Item 4. An antitumor agent for use in the treatment of a colorectal cancer patient with KRAS gene mutation, the antitumor agent comprising α,α,α-trifluorothymidine and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride at a molar ratio of 1:0.5.

Advantageous Effects of Invention

[0015] By using the prediction method of the present invention, it becomes possible to provide chemotherapy that ensures more significant survival-prolongation effects with respect to colorectal cancer patients (in particular, with respect to colorectal cancer patients who are refractory or intolerant to standard therapy, i.e., patients that antitumor agents had little effect on, and thus those that had few choices regarding antitumor agents for significantly prolonging their survival).

[0016] In addition, although it has been reported that TAS-102 has a therapeutic effect on solid cancers including colorectal cancers (Cancer Invest. 2008; 26(8):794-9.), the superior therapeutic effect of TAS-102, particularly on KRAS gene mutation-type colorectal cancer patients, has not been recognized. Moreover, since it was known that the survival of KRAS gene mutation-type colorectal cancer patients is shorter than that of wild-type colorectal cancer patients, the significant survival-prolongation effect of TAS-102 on the KRAS gene mutation-type colorectal cancer patients is an unexpected effect.

Brief Description of Drawings

[0017]

Fig. 1 shows Kaplan-Meier survival curves of KRAS gene wild-type patients.

Fig. 2 shows Kaplan-Meier survival curves of KRAS gene mutation-type patients.

Fig. 3 is a graph showing relative tumor volumes of several nude mice groups implanted with a colorectal cancer strain and administered with different agents.
TAS-102: p.o., Days 1-14 (b.i.d.)
Cetuximab: i.p., Days 1, 5, 8, 12

Description of Embodiments

[0018] The prediction method of the present invention predicts whether chemotherapy using TAS-102 has a sufficient therapeutic effect on a colorectal cancer patient, based on the presence or absence of KRAS gene mutation in the patient.

[0019] The protein of KRAS gene, which is used as an indicator in the present invention, is a type of G protein having a molecular weight of 21,000 localized inside the cell membrane, and that is known to be involved in cell proliferation by transmitting epidermal growth factor signals to the nucleus. In addition, there are reports that mutation of codon 12 and/or 13 in KRAS gene causes persistent transmission of EGFR signals.

[0020] The target patients of the present invention are colorectal cancer patients. In the present invention, "colorectal cancer" refers to a malignant tumor generated in colon or rectum, including primary colorectal cancers, locally recurrent colorectal cancers, and metastatic colorectal cancers that have spread to other tissue (e.g., liver). The "colorectal cancer patients" include not only patients currently having colorectal cancer tumor tissues, but also patients who have undergone resection of colorectal cancer tumor tissues. Therefore, in this specification, the therapeutic effect of chemotherapy encompasses shrinkage of colorectal cancers, suppression of proliferation, survival prolongation, as well as suppression of recurrence of colorectal cancers after resection of tumor tissues.

[0021] Further, the treatment history of the colorectal cancer patients of the present invention is not particularly limited insofar as the patients can endure administration of TAS-102; however, the target patients are preferably colorectal cancer patients who are refractory or intolerant to standard therapy, in terms of prediction accuracy of the present invention. In the present invention, "standard therapy" refers to chemotherapy that uses a fluoropyrimidine-based antitumor agent (e.g., a combination of 5-fluorouracil (5-FU) and leucovorin (LV)) or combination chemotherapy (FOLFIRI, FOLFOX, or the like) that uses irinotecan or oxaliplatin, in addition to the fluoropyrimidine-based antitumor agent. Herein, the condition "refractory or intolerant to standard therapy" refers to a state in which the patient is not responsive to the

standard therapy (including the cases where progression (PD) is observed during the standard therapy, the cases where cancer recurrence is found during or within 6 months after the standard therapy conducted as postoperative adjuvant chemotherapy, and the like), a state in which the patient is unable to withstand the administration of a standard amount of the antitumor agent due to aggravation of disease or side effects, or the like.

[0022] In the present invention, "TAS-102" refers to an antitumor agent containing α,α,α-trifluorothymidine and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride at a molar ratio of 1:0.5. The antitumor agent is known for its antitumor effect mainly on solid cancers, such as colorectal cancers, through oral administration (pamphlet of WO96/30346).

[0023] "α,α,α-trifluorothymidine" is a known nucleic acid derivative in which a methyl group at 5-position of thymidine is substituted with a trifluoromethyl group, and is known for its antitumor effect due to DNA synthesis inhibitory activity (J. Am. Chem. Soc. 84:3597-3598, 1962; J. Med. Chem., 7:1-5, 1964; Biochemistry, 33:15086-15094, 1994).

[0024] "5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride" is a known compound having an activity for inhibiting thymidine phosphorylase activity, and is known for its effect of enhancing an antitumor effect (pamphlet of WO96/30346), metastasis inhibition effect (pamphlet of WO98/13045), effect of alleviating gastrointestinal side effects of antitumor agents (pamphlet of WO00/56337), anti-HIV effect (pamphlet of WO01/34162), effect of enhancing radial ray treatment (pamphlet of WO2008/001502), and therapeutic effect on inflammatory bowel disease (pamphlet of WO2009/047904).

[0025] TAS-102 may be provided as a combination drug (a preparation containing a plurality of active ingredients) obtained by formulating α,α,α-trifluorothymidine and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride into a single dosage form (single-formulation type), or may be provided as single active ingredient preparations by formulating each of the active ingredients into a plurality of dosage forms. Of these, a combination drug of α,α,α-trifluorothymidine and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride is preferable.

[0026] The dosage form of the antitumor agents is not particularly limited, and can be suitably selected depending on the purpose of the treatment. Specific examples thereof include oral preparations (such as tablets, coated tablets, powders, granules, capsules, and fluids), injections, suppositories, patches, and ointments. Of these, the combination drug containing α,α,α-trifluorothymidine and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride is preferably in the form of an oral preparation. Each antitumor agent can be prepared by a commonly known method, using one or more pharmacologically acceptable carriers in accordance with each dosage form. Examples of the carriers include those that are widely used in common drugs, such as excipients, binders, disintegrators, lubricants, diluents, solubilizing agents, suspending agents, tonicity adjusting agents, pH adjusters, buffers, stabilizers, colorants, sweetening agents, and flavoring agents.

[0027] "Chemotherapy in which an antitumor agent containing α,α,α-trifluorothymidine and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride at a molar ratio of 1:0.5" refers to chemotherapy in which at least TAS-102 is administered; this includes chemotherapy using TAS-102 alone, and chemotherapy using TAS-102 and other antitumor agents.

[0028] The administration schedule of the chemotherapy is suitably selected according to conditions such as the patient's age, sex, stage of disease, presence or absence of metastasis, and history of treatment. For example, it is preferable to repeat the following 4-week administration course. In each course, TAS-102 is administered from Day 1 to Day 5, and from Day 8 to Day 12, 2 to 4 times a day in an FTD (α,α,α-trifluorothymidine) amount of 20 to 80 mg/m^2 (per body surface area)/day, preferably 2 to 3 times a day in an FTD amount of 50 to 70 mg/m^2 (per body surface area) /day, more preferably 2 times a day in an FTD amount of 70 mg/m^2 (per body surface area)/day.

[0029] The chemotherapy of the present invention may be preoperative adjuvant chemotherapy in which the chemotherapy is performed before resection of tumor, or postoperative adjuvant chemotherapy in which the chemotherapy is performed after resection of tumor.

[0030] In the present invention, "therapeutic effect" can be evaluated based on a tumor-shrinking effect, an effect of suppressing recurrence, an effect of prolonging survival, etc. The effect of suppressing recurrence can be represented by extension of progression-free survival or the degree of improvement in recurrence rate. "Survival" can be represented by the degree of extension of the median of overall survival or progression-free survival. "Sufficiently respond to chemotherapy using an antitumor agent containing α,α,α-trifluorothymidine and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride at a molar ratio of 1:0.5" means a superior therapeutic effect by the administration of TAS-102, including a significant extension of survival, and a significant suppression of recurrence, compared with a treatment without the administration of TAS-102.

[0031] The prediction method of the present invention comprises Steps (1) and (2) described below.

[0032] Step (1) is a step of detecting the presence or absence of KRAS gene mutation in a biological sample obtained from a patient.

[0033] The biological sample is not particularly limited, as long as it is obtained from a cancer patient and contains cancer cells. Examples thereof include body fluid (such as blood and urine), tissue, extracts thereof, and cultures of obtained tissue. The method for obtaining the biological sample can be suitably selected according to the type of biological sample.

[0034] In the present invention, examples of "KRAS gene mutation" include mutations of codons 12, 13, and 61. In terms of accuracy in the prediction of the present invention, the

mutations of codons 12 and 13 are preferable. More specifically, examples includes a mutation in which glycine of codon 12 is converted to serine, aspartic acid, valine, cysteine, alanine or arginine due to point mutation of the first or second base of codon 12 of KRAS gene, and a mutation in which glycine of codon 13 is converted to aspartic acid due to point mutation of the second base of codon 13 of KRAS gene (Clin Cancer Res. 17(14):4901-4914, 2011; J Mol Diagn. 12(1):43-50, 2010).

[0035] The method for detecting KRAS gene mutation of the present invention is not particularly limited insofar as the above mutations can be found, and a known detection method can be used. Examples of detection methods include the direct sequence method, and the Scorpion-ARMS method (RT-PCR) (Nature Biotech 17:804-807, 1999). The Scorpion-ARMS method is preferable in terms of the detection sensitivity. Further, commercially available detection kits, such as TheraScreen: KRAS (produced by DxS Limited may be used.

[0036] The biological sample is prepared through suitable treatment according to these measurement methods. Further, the reagents containing one or more primers or probes used for the detection may be prepared through a common method according to these measurement methods.

[0037] Step (2) is a step of predicting that the patient is likely to sufficiently respond to chemotherapy that uses TAS-102, when KRAS gene mutation is detected in Step (1).

Examples

[0038] Examples are given below to illustrate the present invention in more detail. Needless to say, the present invention is not limited to these Examples.

Example 1

[0039] Progressive recurring colorectal cancer patients (169 cases) who are refractory or intolerant to standard therapy including 5-FU, irinotecan, and oxaliplatin, and who have a treatment history of at least 2 regimens, are divided into a TAS-102 administration group (112 cases) and a placebo group (57 cases). There was no significant background difference between these two groups (including percentage of male patients (TAS-102 administration group, 57.1%; placebo group, 49.1%), average age (TAS-102 administration group, 63; placebo group, 62), ECOG PS 0 (TAS-102 administration group, 64.3%; placebo group, 61.4%), and percentage of the patients having a treatment history of 3 or more regimens (TAS-102 administration group, 84.8%; placebo group, 77.2%)). In the TAS-102 administration group, during the 4-week administration course, TAS-102 was administered twice a day in an FTD amount of 70 mg/m^2 (per body surface area)/day from Day 1 to Day 5 and from Day 8 to Day 12. This administration schedule was regarded as one course, and the course was

repeatedly performed. On the other hand, no antitumor agent, including TAS-102, was given to the placebo group.

[0040] The overall survival (OS) was evaluated in all cases. Further, lesional tissues were obtained from 149 cases (TAS-102 administration group: 99 cases, placebo group: 50 cases) out of all cases, and the presence or absence of the mutation of codons 12 and 13 of KRAS gene was detected according to the Scorpion-Arms method using TheraScreen: KRAS (DxS Limited).

[0041] The relationship between the overall survival and the KRAS gene mutation was analyzed in the TAS-102 administration group and the placebo group. Table 1 shows the results. Further, Figs. 1 and 2 show survival curves of KRAS mutation-type and wild-type according to the Kaplan-Meier method.

Table 1

Patients	Group *	N	Median OS (months)	HR	95%CI	P value
All	A	112	9.0	0.56	[0.39, 0.81]	0.0011
	P	57	6.6			
wt	A	54	7.2	0.70	[0.41, 1.20]	0.191
	P	24	7.0			
mt	A	45	13.0	0.44	[0.25, 0.80]	0.006
	P	26	6.9			

*Group; A (TAS-102 Administration Group), P (Placebo Group) HR (Hazard Ratio), 95% CI (95% Confidence Interval), wt (absence of mutation of codons 12 and 13) mt (presence of mutation of codons 12 and/or 13)

[0042] Among the patients with KRAS gene mutation, the median (13.0 months) of the overall survival in the TAS-102 administration group is statistically significantly long compared with that of the placebo group (6.9 months). This confirms the unprecedented superior survival-prolongation effect of TAS-102 on the patients with KRAS gene mutation (HR=0.44, [95% CI: 0.25-0.80], p=0.006).

[0043] It is known that the patients with KRAS gene mutation generally have a shorter survival than the wild-type patients. However, the survival-prolongation effect of TAS-102 is greater in the patients with KRAS mutation than in the patients with wild-type KRAS (mutation-type: 13.0 months, wild-type: 7.2 months). Such an effect is unexpected to a person skilled in the art.

[0044] In an experiment with regard to all cases, i.e., all cases regardless of the type of KRAS gene, the median of the overall survival of the TAS-102 administration group was also significantly statistically long (9.0 months) compared with the placebo group (6.6 months), thus confirming that TAS-102 provides a superior survival-prolongation effect to progressive

recurring colorectal cancer patients who are refractory or intolerant to standard therapy (HR=0.56, [95% CI: 0.39-0.81], p=0.0011).

Example 2

[0045] Next, in order to verify the usability of TAS-102 with respect to the KRAS gene mutation-type colorectal cancer patients, an *in vivo* efficacy test was performed in a nude mouse subcutaneously transplanted with a human colorectal cancer strain.

[0046] TAS-102 was orally administered to nude mice transplanted with human colorectal cancer strain HCT-116, which is known as a KRAS mutation-type, twice a day for 14 consecutive days in an FTD amount of 150 mg/kg/day by an ordinary method (TAS-102 Administration Group). Further, as a comparative group, cetuximab, which is often clinically used for colorectal cancer patients who are refractory or intolerant to standard therapy including 5-FU, irinotecan, and oxaliplatin, was intraperitoneally administered in an amount of 40 mg/kg/day on Day 1, Day 5, Day 8, and Day 12 (this administration amount is confirmed for the antitumor effect in other cancers). In contrast, no drug was administered in the control group. The antitumor effect was evaluated in each of these administration groups.

[0047] The major axis and the minor axis of each tumor were measured twice a week with a digital vernier caliper to find the tumor volume (TV). At the same time, the body weights were measured as an indicator of side effects. According to the tumor volumes thus obtained, a relative tumor volume (RTV) and a tumor growth inhibition rate (IR) were calculated according to the following equations.

$RTV_n = (TV \text{ on Day } n) / (TV \text{ on Day } 0)$

$IR(\%) = [1 - (\text{average } RTV_n \text{ value in the drug administration group}) / (\text{average } RTV_n \text{ value in the control group})] \times 100$

[0048] Fig. 3 shows the results. The tumor growth inhibition rate on the final measurement day (Day 29) for the TAS-102 administration group was 57.7%, showing a statistically significant antitumor effect. On the other hand, the tumor growth inhibition rate in the cetuximab administration group was 1.7%; the antitumor effect was not substantially exhibited. Further, in all groups, severe weight loss was not observed.

[0049] Accordingly, it was proved that TAS-102 is clinically useful for the colorectal cancer patients regardless of the presence/absence of KRAS gene mutation, and that such a therapeutic effect of TAS-102 is particularly significant for patients with KRAS gene mutation.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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Patentkrav

1. Fremgangsmåde til at forudsige en terapeutisk effekt af kemoterapi, der anvender et antitumormiddel omfattende α,α,α-trifluorthymidin og 5-chlor-6-(1-(2-iminopyrrolidinyl)methyl)uracilhydrochlorid ved et molforhold på 1:0,5 på en patient med kolorektal cancer,
hvilken fremgangsmåde omfatter trinnene:

(1) at detektere tilstedeværelsen eller fraværet af KRAS-genmutation i en biologisk prøve taget fra patienten; og

(2) at forudsige, at patienten sandsynligvis vil reagere tilstrækkeligt på kemoterapien, når KRAS-genmutationen detekteres i trin (1).

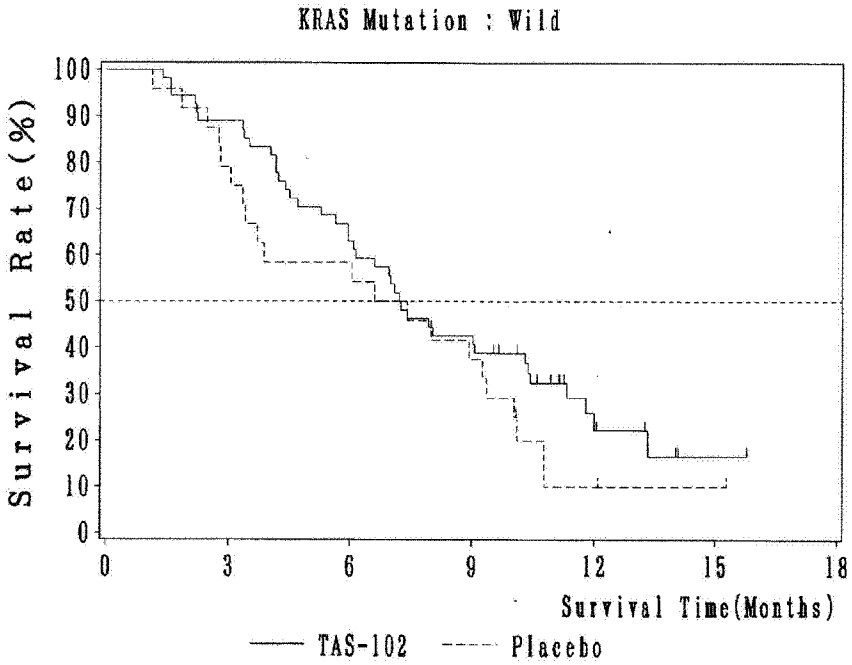
2. Fremgangsmåden ifølge krav 1, hvor KRAS-genmutationen er en mutation af kodon 12 og/eller kodon 13.

3. Fremgangsmåden ifølge krav 1 eller 2, hvor patienten med kolorektal cancer er en patient med kolorektal cancer, der er refraktær eller intolerant over for standardterapi.

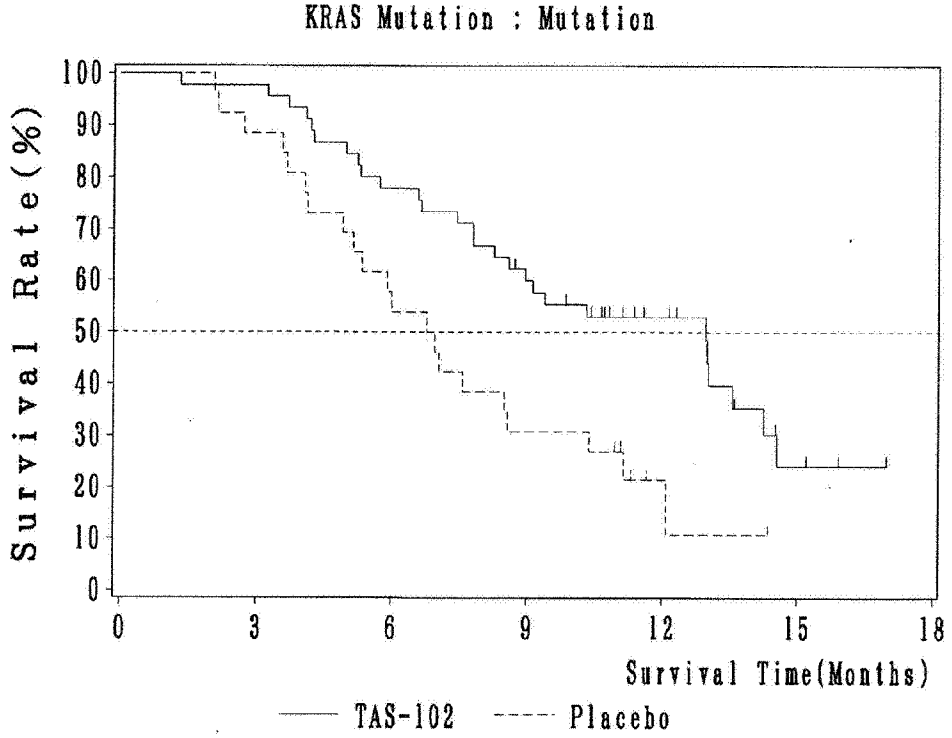
4. Antitumormiddel til anvendelse i behandlingen af en patient med kolorektal cancer med KRAS-genmutationen, hvilket antitumormiddel omfatter α,α,α-trifluorthymidin og 5-chlor-6-(1-(2-iminopyrrolidinyl)methyl)uracilhydrochlorid ved et molforhold på 1:0,5.

DRAWINGS

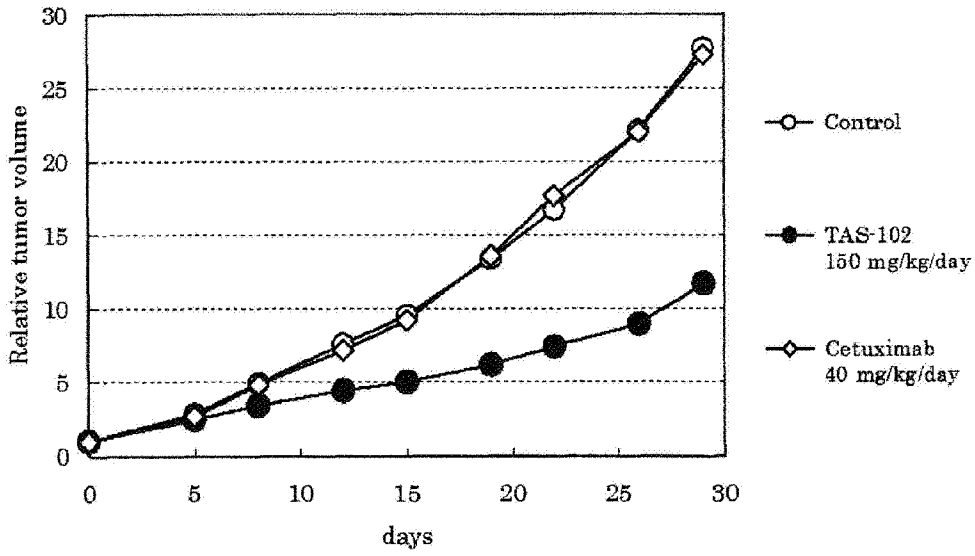
[Fig. 1]



[Fig. 2]



[Fig. 3]


Relative tumor volume
30
25
20
15
10
5
0
0
5
10
15
20
25
30
days
Control
TAS-102
150 mg/kg/day
Cetuximab
40 mg/kg/day