Mark schemes

- (a) 1. Methylation prevents transcription of gene; 1 2. Protein not produced that prevents cell division / causes cell death / apoptosis;3. No control of mitosis. 3 (b) 1. Scatter graph; 2. Fat on x axis and death rate on y axis; (Because) looking at relationship between two discrete / independent variables. 3. 3 (c) (Trend) shows positive correlation / shows the more fat in diet, the higher deathrate 1. from breast cancer; But number of points off line / anomalies. 2. 2 [8] (a) 1. Rank all STs in ascending order; 2 2. Find value with same number (of people) above and below. Accept find middle value 2 (b) Not ethical to fail to treat cancer. 1 Yes since with ipilimumab: (C) 1. Median ST increased by 2.1 months; 2. Percentage of patients showing reduction in tumours increased from 10.3% to15.2%; No because: No standard errors shown / no (Student) t- test / no statistical test carried out; 3. 4. (So) not able to tell if differences are (statistically) significant / due to chance(alone); 5. Improvement might only be evident in some patients / no improvement in somepatients; Quality of (extra) time alive not reported; 6. If answers relate only to 'Yes' or 'No', award 2 marks max 4 max (d) 1. Faulty protein recognised as an antigen / as a 'foreign' protein; T cells will bind to faulty protein / to (this) 'foreign' protein; 2. 3. (Sensitised) T cells will stimulate clonal selection of B cells;4.
 - (Resulting in) release of antibodies against faulty protein.

3 max

- [10]
- (a) 1. Binding (of interferon gamma) changes shape/tertiary structure of receptor (protein);

- 2. This activates/switches on the enzyme;
- 3. Use of ATP (to phosphorylate STAT1);
 - 1. Accept reference to second messenger mechanism/process3. Context is important

2 max

2

2

- (b) 1. Phosphorylated STAT1;
 - 2. IRF (protein);
 - Accept in either order
 - 1. Must be phosphorylated but accept STAT1P
 - 2. Ignore references to phosphorylated
- (c) 1. Causes more helper T cells to form;
 - 2. (So) more interferon (gamma) production (by helper T cells);
 - 1. and 2. require idea of more
- (d) 1. (Tumour suppressor gene) slows cell division/causes death ofdamaged/tumour/cancer cells;
 - 2. *IRF* gene leads to formation of IRF (protein) that binds to gene B;
 - 3. (Gene B protein) causes death of damaged/mutated cells ORslows division;
 - 2. 'It' means IRF gene
 - 3. Context is important
 - 3. If clearly stated **and** includes the protein, scores 2 marks because it subsumes point 1

3

[9]

- (a) 1. Removes (main / largest) source of oestrogen / (different) mice produce different
- 4

amounts of oestrogen;

Accept: so oestrogen from ovaries not a confounding variable – idea of.

2. (Allows) oestrogen to be controlled / oestrogen to be made by aromatase only /only oestrogen made in lungs to be involved.

Reject: references to injection of aromatase.

2

- (b) 1. (Anastrozole) prevents / reduces oestrogen production;
 - 2. (Fulvestrant) stops remaining oestrogen binding / less oestrogen binds toreceptors.

Note: brackets around drug names.

(c) (Yes for Group T)

1. Least tumours per animal (from fig. 1);

Accept: 'mean values' for tumour area.

- 2. Lowest (mean) tumour area / size (from fig. 2);
- 3. Lowest top of range;

(But)

4. Means (tumour area) are similar;

Where candidates confuse range and standard deviation, do not give credit.

5. Ranges overlap / share values <u>so</u> differences may not be real / treatments may be just effective in reducing tumour;

Ignore significance

- 6. Range affected by outliers / SD's would be better;
- 7. Done on mice / not done on women / humans;
- 8. Only 10 mice used per group / small sample size <u>so</u> may not be representative / reliable;
- 9. Might be side effects;
- 10. Only did for 15 weeks so maximum effect of drugs may not have been seen.

5 max

(d) 1. Tumours may be different depths / area does not take depth into account /tumours are 3-D / are not 2-D;

Neutral: different sizes Accept: height / thickness for depth

- 2. (Measure) tumour volume / mass / weight.
- (e) 1. Allows tumours to grow / develop / form; Neutral: gives drug more time to work.
 - 2. (So) can investigate treatment rather than prevention (of tumours) / when tumour / cancer is more advanced.

Accept: to see whether it can destroy / treat / stop growth of a tumour (that already exists) / to allow / assess treatment of a tumour

2

2

(f) 1. Unethical (not to treat patients) / may increase probability of patients dying /getting more ill;

Reject: references to giving people tumours

2. Use normal cancer drugs / treatment. Accept: named type of cancer treatment, e.g. chemotherapy

[15]

2

(a) 1. Sugar-phosphate (backbone) / double stranded / helix **so** provides strength / stability

/ protects bases / protects hydrogen bonds; Must be a direct link / obvious to get the mark Neutral: reference to histones

- 2. Long / large molecule **so** can store lots of information;
- Helix / coiled so compact;
 Accept: can store in a small amount of space for 'compact'
- Base sequence allows information to be stored / base sequence codes foramino acids / protein;

Accept: base sequence allows transcription

- Double stranded so replication can occur semi-conservatively / strands can act as templates / complementary base pairing / A-T and G-C so accurate replication / identical copies can be made;
- (Weak) hydrogen bonds for replication / unzipping / strand separation / many hydrogen bonds so stable / strong; Accept: 'H-bonds' for 'hydrogen bonds'
- (b) 1. (Mutation) in **E** produces highest risk / 1.78;
 - 2. (Mutation) in **D** produces next highest risk / 1.45;
 - 3. (Mutation) in **C** produces least risk / 1.30; *Must be stated directly and not implied*

E > *D* > *C* = 3 marks Accept: values of 0.78, 0.45 and 0.30 for MP1, MP2 and MP3 respectively If no mark is awarded, a principle mark can be given for the idea that all mutant alleles increase the risk

(c) **180**;

1

3

6

(d) (Similarities):

- 1. Same / similar pattern / both decrease, stay the same then increase;
- 2. Number of cells stays the same for same length of time; *Ignore: wrong days stated*

(Differences):

(Per unit volume of blood)

- 3. Greater / faster decrease in number of healthy cells / more healthy cells killed /healthy cells killed faster; Accept: converse for cancer cells Accept: greater percentage decrease in number of cancer cells / greater proportion of cancer cells killed 4. Greater / faster increase in number of healthy cells / more healthy cellsreplaced / divide / healthy cells replaced / divide faster; Accept: converse for cancer cells For differences, statements made must be comparative 3 max (e) 1. More / too many healthy cells killed; (So) will take time to replace / increase in number; Neutral: will take 2. time to 'repair' 3. Person may die / have side effects; 2 max [15] (a) (i) 1. (Tumour suppressor) gene inactivated / not able to control / slow down cell division; Ignore: references to growth 2. Rate of cell division too fast / out of control. 1 and 2 Accept: mitosis 1 and 2 Reject: meiosis 2 (ii) 1. (Genetic) code degenerate; Accept: codon for triplet Accept description of degenerate code, e.g. another triplet codes for the same amino acid 2. Mutation in intron. Accept: mutation in non-coding DNA 1 max (b) Antibody has specific tertiary structure / binding site / variable region; 1. Do not accept explanations involving undefined antigen Complementary (shape / fit) to receptor protein / GF / binds to receptor protein /to 2. GF; Ignore: same shape as receptor protein / GF
 - 3. Prevents GF binding (to receptor).

		2.	Lifestyle; Stress, smoking, diet etc are examples of lifestyle.	
		3. 2	Body mass; Allow weight for mark point 3	
		3. 4.	Health; Reject: height.	
		5.	Ethnicity;	
		6.	Genetic factors / family history;	2 max
	(ii)	1.	Large sample / number / 410 000; <i>Reject: random</i>	
		2.	Long time period / 8.5 / many years;	
		3.	Different countries / more than one country;	2
(b)	Cor	rect ar	nswer of 209 / 209.1 = 2 marks; Answer of 210 = one mark	
	Inco	rrect a	answer but multiplies by 8.5 = 1 mark;	2
(c)	Age	affect	ts risk of cancer; Must relate to cancer not just to illness	1
(d)	1. 1.	Corr Reje	relation does not mean causal relationship; ect casual for point 1. Reference to 'due to other factors' on its own is not enough for a mark	
	2.	Tea /estii	/ coffee contains other substances / different amounts of caffeine mated intake (of tea / coffee);	
	3.	No c	control group;	
	4.	Only onei	one type of cancer studied / further studies required / only nvestigation / study / group;	4
(e)	(i)	1.	Treated the same; 2. Accept decaffeinated	

		2.	No caffeine; 2. <i>Reject placebo.</i>	
	(ii)	1.	Absorb different amounts; <i>Reject: Different body masses</i>	
		2.	Broken down by enzymes / digested;	
		3.	Different blood volumes;	
		4.	Differences in metabolism;	
		5.	Caffeine from a different source; 1 max	
	(iii)	1.	Less oxygen / glucose to (cancer) cells; 'Reduces cell division' on its own should not be credited.	
		2.	Less carcinogens;	
		3.	Reduces spread of cancer (cells);	
			I max [15] (a) 1. To allow comparis	son;
	2.	Beca num	ause different number of cells in samples / different times for incubation / nbers become easier to manipulate;	
(b)	203	.7(%);		
			Allow 1 mark for 21.8 / 10.7 Allow 1 mark for correct answer (203.74) but not correctly to 1 dp 204 = 1 mark	
			2	
(c)	(i)	1.	(At every concentration) uptake is faster at 37°C / at higher temperature;	
		2.	Due to faster respiration / ATP production; 2	
	(ii)	1.	Uptake at 37°C only small increase / levelling off / almost constant as carrier proteins full; Accept 'no (significant) change' Ignore use of numbers	
		2.	Concentration of imatinib is not the limiting factor;	
			[8] (a) Given only sa	line;

Otherwise treated exactly the same way;
(b) Ethical consideration, e.g., leads to death / suffering of mice; Large number to improve reliability / reduce sampling error; Number of mice related to cost / space available / animal husbandry;
(c) Vary in shape / do not grow uniformly; *Q* Allow descriptions of variation in shape.
(d) 7.44 and 1.74;; 7.42 and 1.72;; (Ratio) 4.28 : 1;;

(Ratio) 4.31 : 1;;

(Percentage decrease) 76.6%;;

(Percentage decrease) 76.8%;;

Any of the answers shown gain two marks. An answer of 23.4% or 23.2% Percentage decrease gains one mark. Correct method of calculating rate / ratio / percentage increase with an incorrect answer gains one mark.

2 max

3

1

(e) Reference to Mitosis;

As chromosomes cannot attach (to spindle) / chromatids cannot separate (on spindle);

Q Do not penalise confusion between chromosomes and chromatids in second marking point

Cell division / cell cycle slows down;

Q Mitosis slows down = 2 marks
Q Mitosis stopped = 1 mark
Q Mitosis must be spelt correctly

(f) (i) (Degree of) spread / variation from the mean;

(ii) Both chemicals (on their own) slow down growth / are effective;

2 max

Taxol is more effective than OGF;

Combined treatment (seems) most effective;

<u>SD overlap</u> for OGF with taxol and taxol (on its own) so not conclusive / could be chance / both treatments could be equally effective;

Q Ignore all references to significance

[15] (a) Will replace themselves / keep dividing / replicate;

10

Undifferentiated / can differentiate / develop into other cells / totipotent / multipotent / pluripotent;

Accept tissues

- (b) Reverse transcriptase; Allow phonetic spelling
- (c) (i) Alters base / nucleotide sequence / causes frame shift;

Different sequence of amino acids in polypeptide / protein / primary structure alters the tertiary structure;

Accept any reference, such as adding bases, to changing the base sequence of the gene. Reject deletion / substitution. Idea of sequence essential so not makes different amino acids. Accept answers involving stop / start codons and effect on protein.

(ii) Affects tumour suppressor gene;

Inactivates (tumour suppressor) gene;

Rate of cell division increased / tumour cells continue to divide; Ignore answers relating to oncogenes. May gain third point.

2 max

4

2

1

2

(d) Yes

SCID patients unlikely to survive / quality of life poor unless treated; Cancer that develops is treatable / only affects 25% / five children;

No

Risk of developing cancer is high / 25%; Cancer may recur / may not be treated successfully in future / only short time scale so more may develop cancer;

> No mark for yes or no. Marks are for supporting argument based on biological reasoning. Accept any points

2

1

<u>D</u>NA polymerase is incorrect Ignore references to RNA dependent or DNA dependent Allow phonetic spelling

 (b) (i) (Receptor / transcription factor) binds to promoter which stimulates RNApolymerase / enzyme X;

Transcribes gene / increase transcription;

- (ii) Other cells do not have the / oestrogen / ERα receptors; But do not accept receptors in general.
- (c) Similar shape to oestrogen;

Binds receptor / prevents oestrogen binding;

Receptor not activated / will not attach to promoter / no transcription;

Accept alternative Complementary to oestrogen; Binds to oestrogen; Will not fit receptor;

2 max

Essay Using DNA in science and technology



DNA and classification

- 2.2 Structure of DNA
- 2.3 Differences in DNA lead to genetic diversity
- 2.9 Comparison of DNA base sequences

Genetic engineering and making useful substances

2.5 Plasmids

5.8 The use of recombinant DNA to produce transformed organisms that benefit humans

Other uses of DNA

- 2.5 Cell cycle and treatment of cancer
- 5.8 Gene therapy;

Medical diagnosis and the treatment of human disease;

The use of DNA probes to screen patients for clinically important genes.

(a) (i) Spindle formed / chromosome / centromere / chromatids

13

attaches to spindle;

Chromosomes / chromatids line up / move to middle / equator (of cell);

Do not award second mark for answers referring to chromosomes 'pairing up'. Ignore reference to homologous chromosomes unless context suggests pairing which negates second mark. Neutral: Details on nuclear membrane. Accept: Diagram for second marking point.

- (ii) Chromosome / centromere splits / chromatids / 'chromosomes' separate / pulled apart;
 - To (opposite) sides / poles / centrioles (of cell); *Reject: Homologous chromosomes separate for first marking point. Accept: Diagram for second marking point. Chromatids / 'chromosomes' move to poles / sides / centrioles = 2 marks.*
- (b) (i) Form / replace cells quickly / rapidly / divide / multiply / replicate rapidly;*Neutral: Repair cells.*

Answers must convey idea of 'speed'.

(li) Correct answer = 774 minutes / 12 hours 54mins = 2 marks;;

Incorrect answer but indicates 3 cell cycles involved = one mark;

2

1

2

2

(c) Prevents / slows DNA replication / doubling / prevents / slows mitosis;

New strand not formed / nucleotides (of new strand) not joined together / sugar-phosphate bonds not formed;

First marking point must be in context of DNA replication not cell replication.

Do not negate first marking point if role of DNA polymerase is described incorrectly e.g. Reject: 'joins bases / strands together'. Role of DNA polymerase must be correct for last marking point.

(a) In one country where the percentage of fat (in the diet) is 35%, the death rate (from breast

cancer) is 20 per 100 000; <u>Must</u> have reference to country Accept ... 1 per 5 000 / 0.02%

- (b) 1. No. of deaths from breast cancer divided by total population \times 100 000;
 - 2. No. of deaths from breast cancer divided by all deaths x 100 000;
 - 3. Sample and count deaths from breast cancer in 100 000 people; If sample not 100 000 then must scale appropriately
- 1 max

1

- (c) 1. Positive correlation;
 - But correlation does not show causation / some other (named) factor may beinvolved;
 - 3. Evidence against positive correlation e.g. different death rates at same % fat /similar death rates at different % fat / some countries with higher death rate have lower fat intake;

1. Accept description of positive correlation / directly proportional. Accept positive relationship.

2. Do not accept casual in place of causal.

3. Answer must be consistent with data.

3

2

2

(a) (i) Increases then plateaus / constant / steady / rate does not change;

Neutral: 'peaks' / 'reaches a maximum' / 'stops increasing' / 'no effect' instead of 'plateaus' Reject: rate decreases / reaction stops

Correct reference. to 27 / 28 units; e.g. increases up to / plateaus at 27 / 28

(ii) Substrate concentration / amount of substrate;

As substrate concentration increases, rate increases / positive correlation (between rate and substrate concentration);

 (iii) All <u>active sites</u> occupied / saturated / enzyme limiting (rate of reaction) / maximum number of E-S complexes;

> Reject: enzymes used up Reject: substrate limits rate of reaction

15

 (b) Curve is lower and plateaus at a higher substrate concentration (it must also start at zero);

> Accept: curve lower and joins existing curve at final point (with no plateau) Reject: if curve plateaus before original Reject: if curve plateaus lower than original

 (c) (i) Methotrexate / drug is a similar shape / structure to substrate so binds to / fits /is complementary to active site;

> **Q** Reject: same structure / shape **Q** Reject: reacts with active site

Less substrate binds / less enzyme-substrate complexes formed;

Accept: substrate cannot bind / enzyme-substrate complex not formed

(ii) Methotrexate / drug is only similar shape to specific substrate / only fits this <u>active site;</u>

Assume that 'it' refers to the drug

OR

Methotrexate / drug is a different shape to other substrates / will not fit other <u>active sites;</u>

[9]

1

1

1

2

(a) To ensure the colour is the same at the start;

	()	
16		1

- Yes curve on graph with bromelain present remains approximately constant / risesvery slightly;
 Would decrease if killing of cells occurred / would increase if cells still dividing;
- 2

- (c) Use of mouse cells (rather than human);
 (Carried out) *in vitro* / not in living organisms;
 Only tested on one type of cancer;
 Not possible to predict effect on humans (as no data collected);
- (d) The faster the rate of division the faster the cancer would grow;By measuring rate of cell division you could see how effective the treatment was;

3 max

(c) Not ethical to replace conventional treatment; As life of patient is at risk (if bromelain not effective);

Nucleus	Number of chromosomes	Mass of DNA / arbitrary units
At telophase of mitosis	26;	30;
From a sperm cell	13;	15;

(b) Cancer cells often have faulty / damaged DNA;

Protein / p53 faulty / not made;

Cell (with faulty / DNA) divides / completes cell cycle;

Uncontrolled division produces cancer;

p53 refers to the protein so do not accept reference to p53 mutating.

- (c) (i) Interphase / S phase / synthesis phase;
 - (ii) Anaphase / A;

Cut gene out of cell / make gene using mRNA / obtain gene with restriction (a) 1 enzymes;

18

- 2 Cut DNA using restriction enzyme / plasmid cut with restriction enzyme;
- 3 Correct reference to sticky ends;
- 4 Join DNA using ligase / insert gene into vector;
- 5 Plasmid / named vector transferred to cell;
- 6 Method of transfer e.g. heat shock;
- 7 Reference to marker gene;
- 8 Select bacteria containing new gene;

4

3

1

1

2

[10] (a)

[9]

max 6

Cells can metastasise / break off / spread to other parts of the body; (b)

	Rem	naining cells continue to divide forming a new tumour / secondary; 2	
(C)	Anti	bodies specific;	
	Norr	mal cells have different antigen / cancer cell has particular antigen;	
	Enzy	yme only present in cancer cells so drug only activated at / near cancer cells; 3	
(d)	All o Wou Stop Nam mad	cells contain DNA; uld stop / inhibit DNA replication in normal cells; os / inhibits cell division; ned example on growth / repair e.g. no new blood cells de / no wound healing;	
		[15] (a) (i) benign does not cause cance	؛r /
		does not invade other tissues causing damage / with benign cancer, pieces which break off do not start new tumours elsewhere in body / metastasis; 1	
	(ii)	may damage organ concerned; may cause blockages / obstructions; may damage / exert pressure on other organs; max 2	
(b)	(i)	because sun's radiation contains ultra violet radiation; this causes mutation of genes which control division; 2	
	(ii)	because fair skin has little melanin which protectsagainst u.v. radiation;	
	(iii)	because cancer has genetic component / may have inherited (onco)gene / gene which gives predisposition to / causes cancer;	
		[7] (a) 1 (DNA altered by) mutation	n;
	2 (n 3 of 4 of 5 ch 6 (tr 8 un 9 m	nutation) changes base sequence; f gene controlling cell growth / oncogene / that monitors cell division; f tumour suppressor gene; hange protein structure / non-functional protein / protein not formed; umour suppressor genes) produce proteins that inhibit cell division;7 mitosis; ncontrolled / rapid / abnormal (cell division); nalignant tumour;	

	(b)	cancer cells die / break open;releasing DNA;	2
	(c)	normal DNA and changed DNA have different sequences; DNA only binds to complementary sequence;	2
	(d)	fewer abnormal / cancerous cells / smaller tumours;less cell damage / less spread / fewer locations to treat;	2
	(e)	mRNA base sequence has changed;gene / DNA structure is different / has mutated; cancer gene active / tumour suppressor gene inactive;	-
		[15] (i) Because there are big	3 differences;
21			
		any correct named example e.g. lung cancer / bronchitis much lower in women than in men;	2
	(ii)	easier to compare if sample size effectively the same; different numbers of people in each group;	2
22	(a)	secreted by the liver / storage / release from gall bladder into the duodenum / small	[4]
		intestine; bile passes unchanged from small intestine to colon;	2
	(b)	 (i) chance alone has not caused the difference (between the two patients types);high steroid high bacteria (significantly) high<u>er</u> percentage of cancer patients / low steroids low bacteria (significantly) high<u>er</u> percentage of control patients; 	2
		(ii) some patients with low levels of one / both factor(s) have cancer;	1
	(c)	change in code / base sequence / structure of gene;addition / deletion / substitution; mRNA / transcription changed; gene product / protein structure / amino acid sequence changed / different protein; loss of function; uncontrolled cell division;	4 may
		[9] (a) mass of undifferentiated / unspecialised / toti	potent cells;

23		
		uncontrolled cell division;
		(not 'repeated')
		metastasis / (cells break off and) form new tumours / spread to other parts of body;
		5
	(b)	cancer takes time to develop / exposure when young but cancertriggered later; other organs destroyed before death occurs / metastasis affects other organs; immune system less effective in old people; longer time of exposure to LIV / accumulation of mutagenic effect;
		1 max
	(c)	dark skin / melanin / pigment stops UV light / prevents burning;so less cancer risk in dark skinned people / less likely to develop tumours; <i>(allow converse)</i>
		2 IGI (i) smoking and dripking increase rick:
24		
		risk increases for nonsmokers with more alcohol; 20-40 cigarettes increases risk; at all levels of alcohol consumption; 4 or more drinks increase risk in all groups; worst risk with combination of 40+ cigarettes and 4 or more drinks; smoking and drinking together have a greater effect than either on its own; over 40 cigarettes and no alcohol greater than 1 or 2
		acconolic uninks / valid comment about anomaly, 3 max
	(ii)	other environmental factor / e.g. passive smoking; genetic predisposition / inherited from parents; mutation;
		1 max
		[4] (a) Daughter (C) does not have the condition / one child doesn't have it;
25		
		Accept converse arguments (If candidates see it purely as a genetic cross diagram) D is heterozygous because E is unaffected;
		Parents must have been carriers of normal / healthy recessive/ if recessive then parents homozygous (so all children affected);
		D has cancer, so the cancer allele must be dominant;

(b) Father (A) would pass on X chromosome to daughter; She is not affected;

		Accept that if D's X chromosome carried 'it', then E would be affected.		2
	(-)			2
	(C)	Accept E must be homozygous recessive/have two		
		recessive alleles;		
		Don't know if her father was heterozygous or homozygous;		
		So no chance of cancer / no more chance than rest of the population;		
		If heterozygous, she has a 50% chance of carrying the allele/gene;		
		in homozygous, she has a senous fisk of cancer.	2	max
	(d)	Mutation / mutagen changes DNA of cell;		
		Damaged DNA not repaired / cells not killed / apoptosis doesn't happen: Mutation leads to loss of control / uncontrolled cell division:		
		(Some of these) cells carried to other parts of the body.	2	
			。 [9] (a)	Mo cadmium;
26				
20		Other conditions same as cadmium-treated group;		
				2
	(b)	 As a measure of the effect due to cadmium / to make a comparison: 		
				1
		(ii) Becoming more methylated;		
		Ignore later slight decrease/no change		1
		(iii) Production of more methyltransferase enzyme /increased activity of		
		transferase;		
		Extra incorrect relevant information - cancel		1
	(c)	RNA-polymerase could not bind (to DNA / to promoter);mRNA of p16 cou		
		not be made / no transcription of p16 gene;		2
	(d)	Any four from:		
	(9)	1. Cadmium causes expression of methyltransferase gene / increased		
		activity transferase (from 2 to 3 weeks in); 2. Methyl groups on to promoter / p16 gene / suppressor (gene):		
		3. (p16) normally suppresses tumour growth;		

 p16 protein / p16 expression falls after 4 weeks / <u>after</u> methylation; 5. Tumour formation occurs (after 10 weeks) <u>after</u> p16 falls / <u>after</u> suppressor gene activity falls;

4 max