Developing a cancer vaccine, and challenges in performing clinical trials of experimental therapies

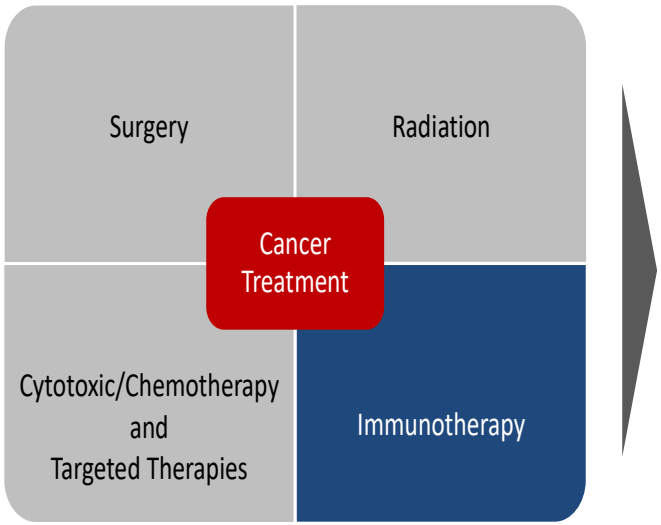
Steinar Aamdal

Professor emeritus in Oncology

University of Oslo

Cancer treatment

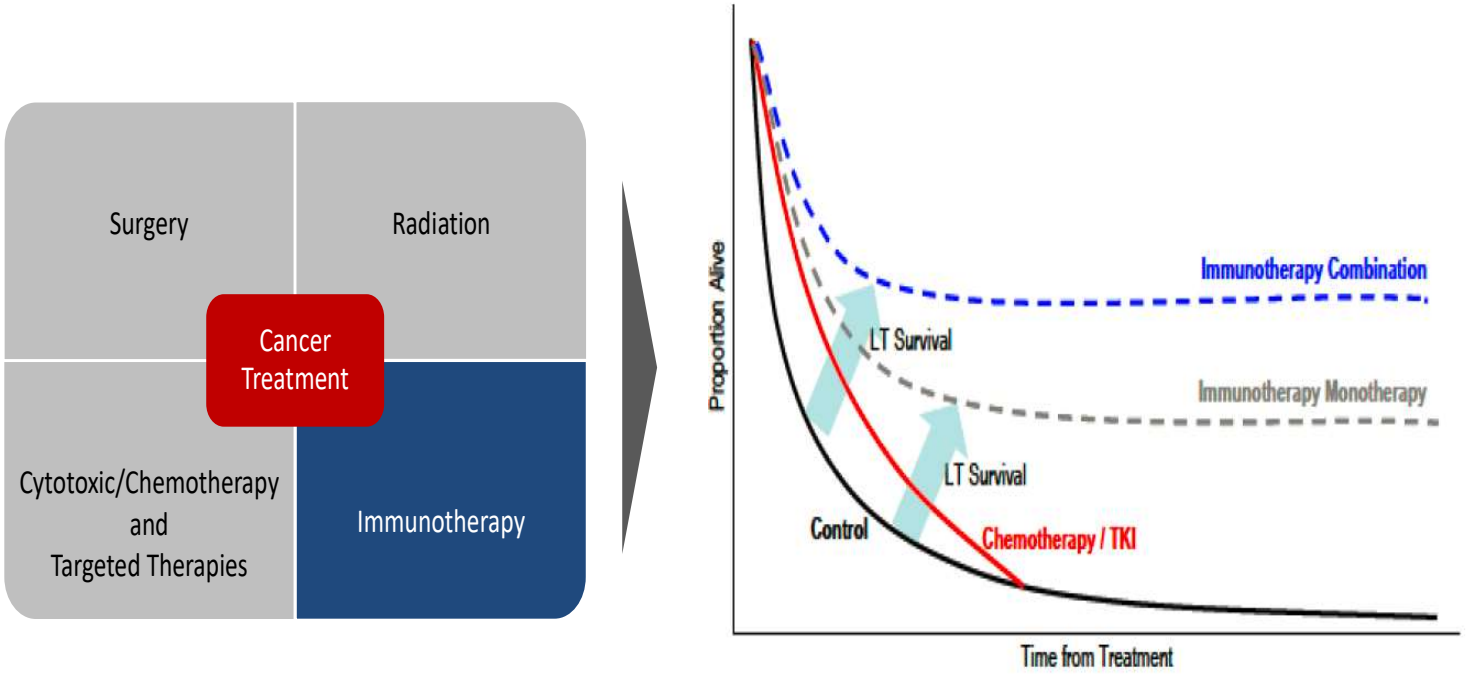
A paradigm shift



*Citi – opinion article November 19th 2013

Cancer treatment

A paradigm shift



*Citi – opinion article November 19th 2013

ARTICLE IN PRESS

EUROPEAN JOURNAL OF CANCER XXX (2011) XXX–XXX

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journal homepage: www.ejconline.com

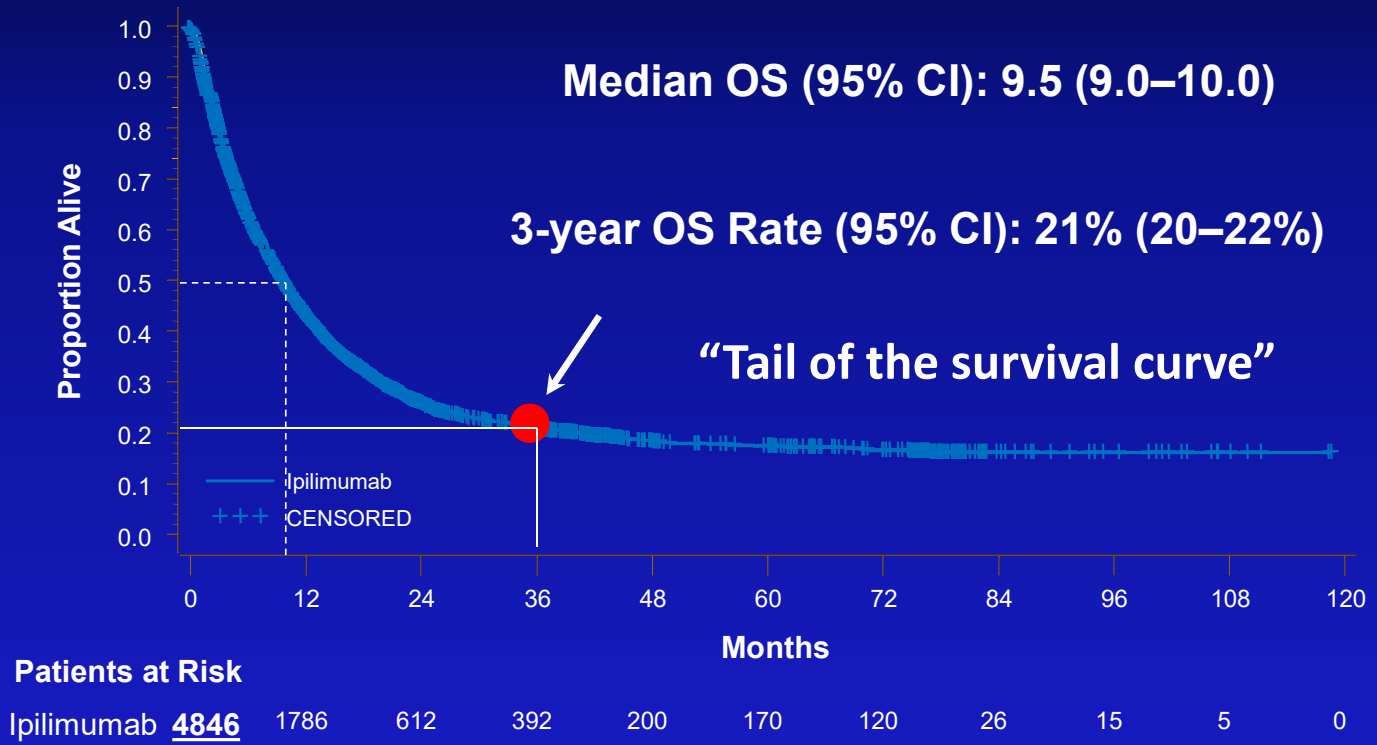
Review

New drugs in melanoma: It's a whole new world

Alexander M.M. Eggermont *, *Caroline Robert*

Institut de Cancérologie Gustave Roussy, Villejuif, Paris-Sud, France

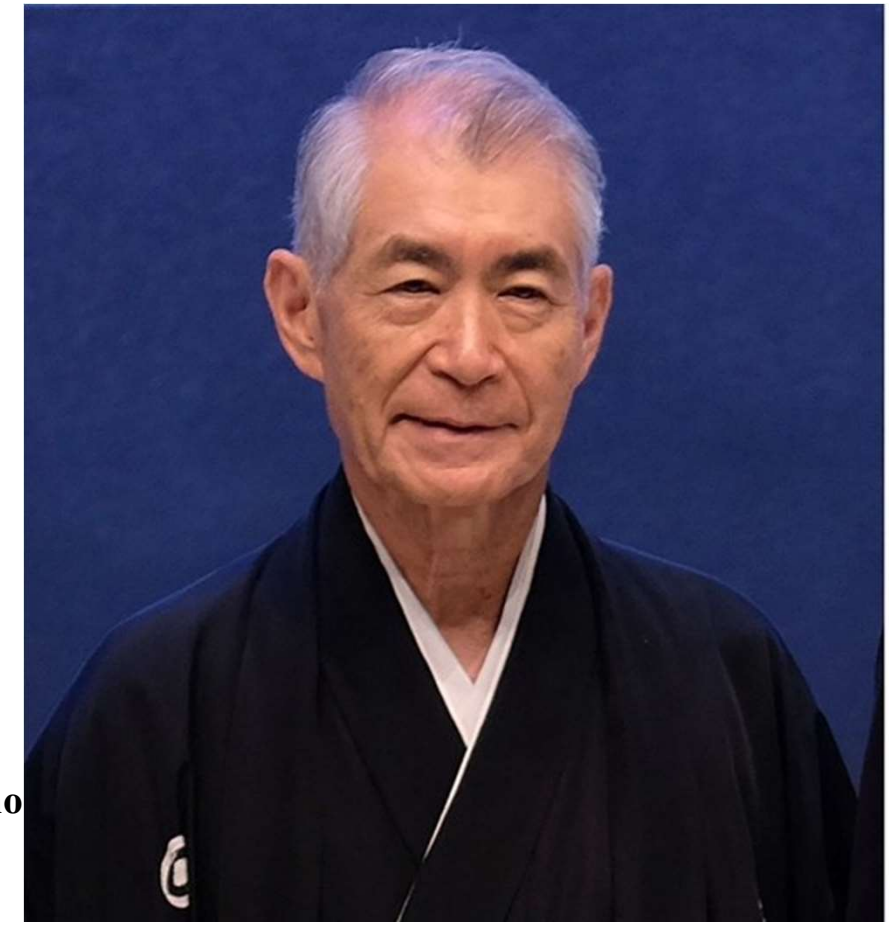
Ipilimumab (Anti CTLA4) leads to durable anti tumor responses with a plateau at 3 years in OS in malignant melanoma



Schadendorf D 2015

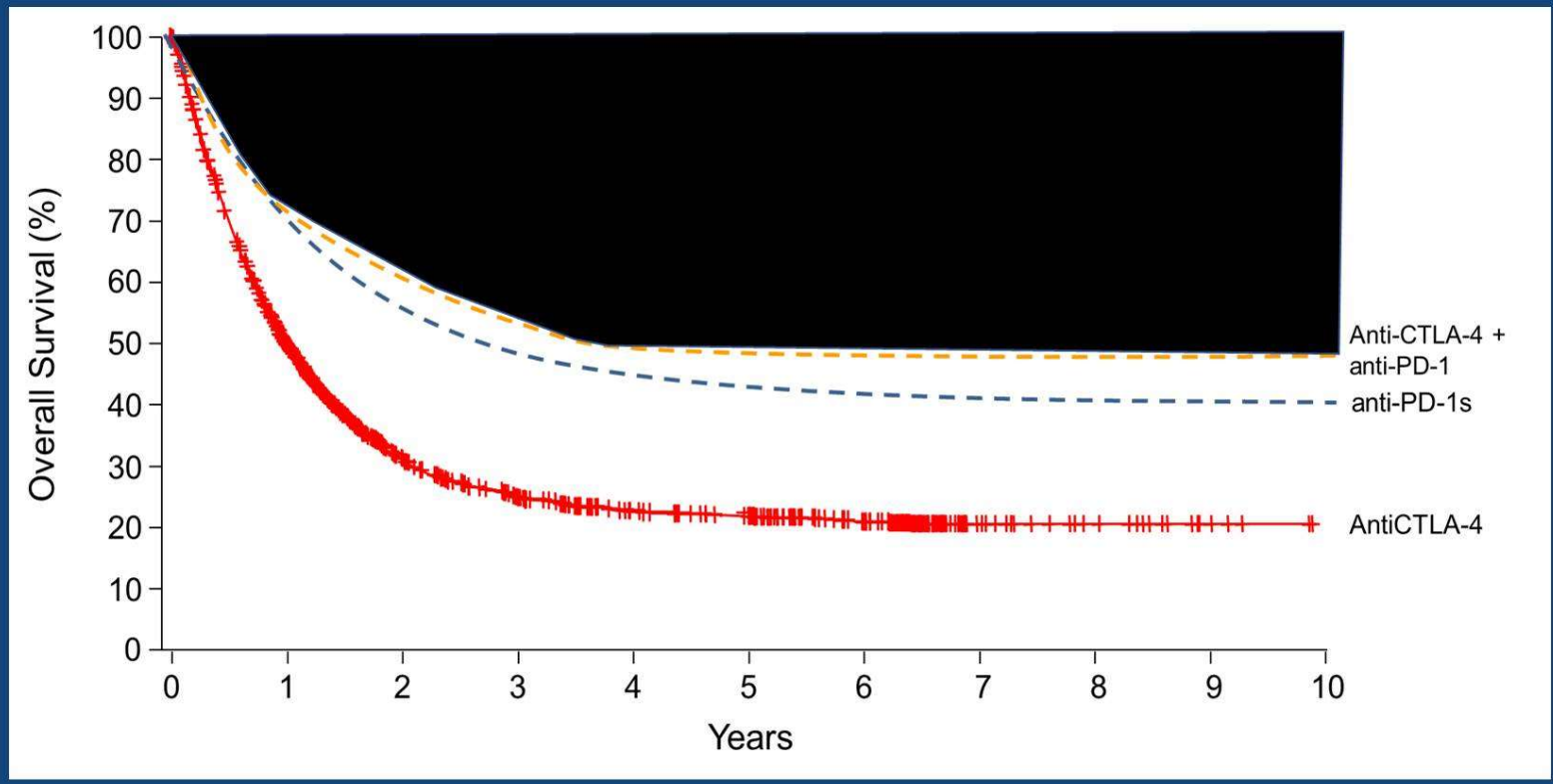
Nobel Price in Medicine 2018

Tasuku Honjo for anti PD-1 and James P. Allison for Anti-CTLA



Forskning.no

But do not work in all patients

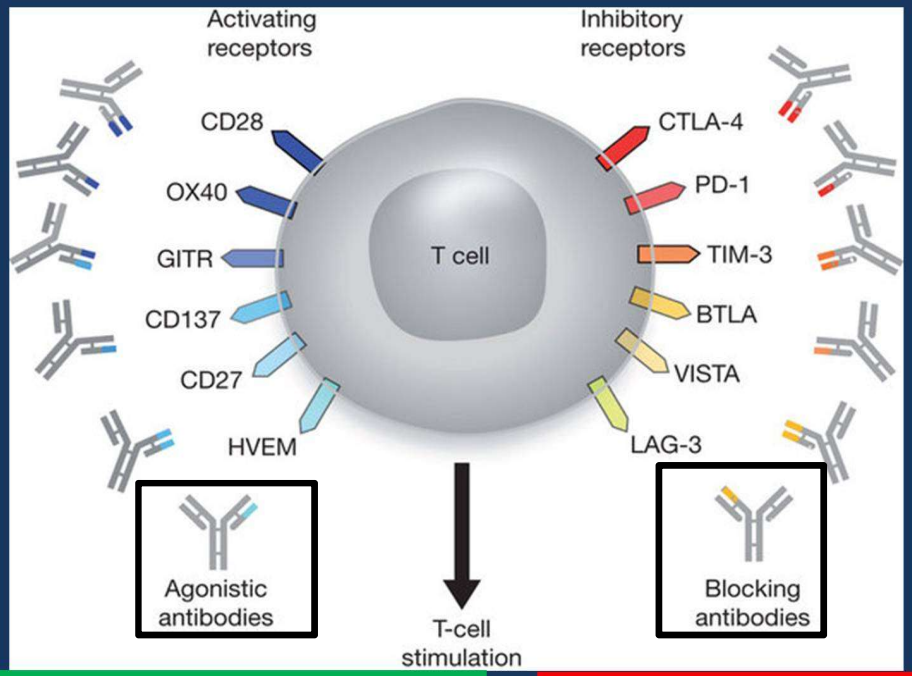


Presented By Paolo Ascierto at 2018 ASCO Annual Meeting

Ways of Improving Immunotherapy

- **Determine optimal dose and schedule of the checkpoint inhibitors: 1mg/kg, 3mg/kg, 10mg/kg ; Q2 week, Q 3 week, 4 week, Q 3 month ?**
- **Treat the «right» patients**
  - ***Biomarkers***
- **New combinations of checkpoint inhibitors**
- **Co-stimulation rather than inhibiting the inhibitors**
- **Break the «PD-1 ceiling» - combinations recruiting novel T- cells clones:**
  - **Cancer vaccines**
  - **Long peptide vaccines**
  - **Oncolytic virus**
  - **CAR-T**
- **..**

Ways to enhance T cell attack



Turning up The Activating

Blocking the Inhibiting

Mellman et al. *Nature* 2011

Presented By Michael Postow at 2017 ASCO Annual Meeting

Ways of Improving Immunotherapy

- Determine optimal dose and schedule of the checkpoint inhibitors: 1mg/kg, 3mg/kg, 10mg/kg ; Q2 week, Q 3 week, 4 week, Q 3 month ?
- Treat the «right» patients
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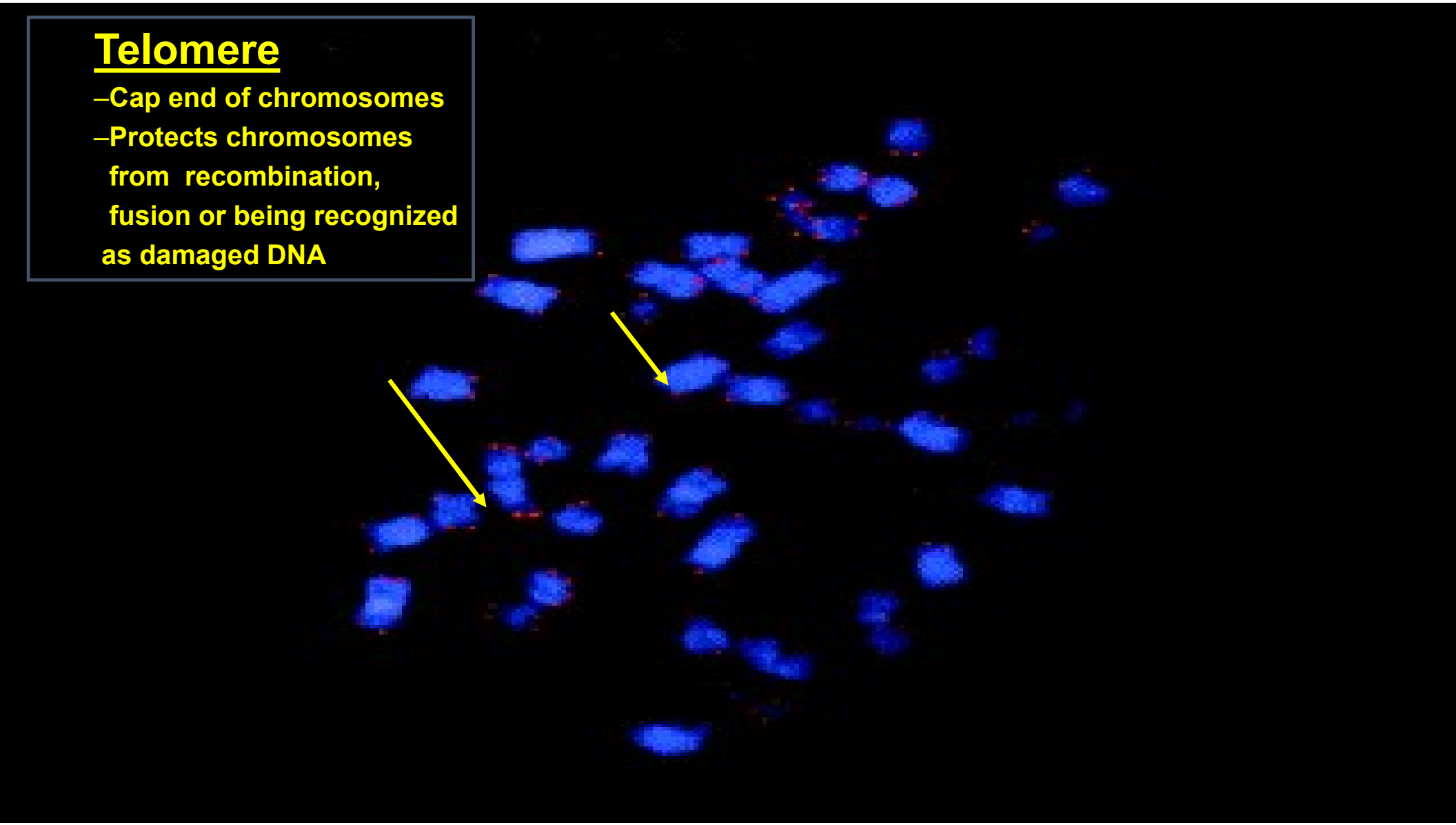
  - **Cancer vaccines**
  - **Long peptide vaccines**
  - **Oncolytic virus**
  - **CAR-T**
- ..

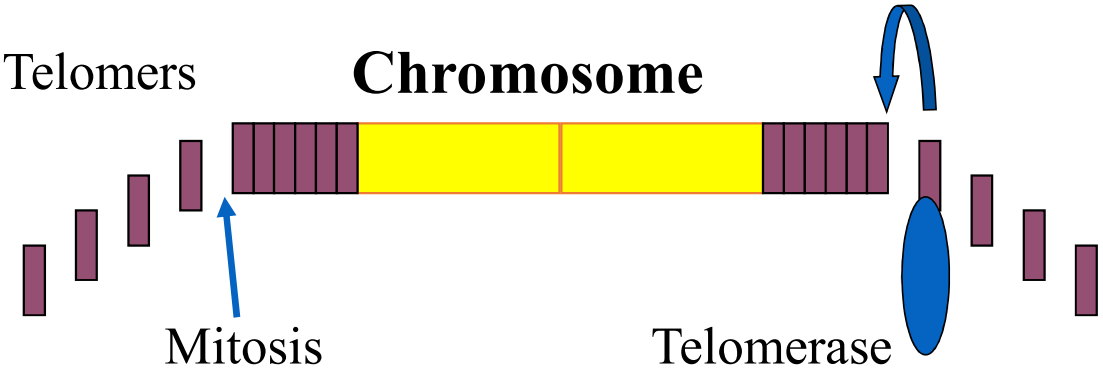
Telomere

–Cap end of chromosomes

–Protects chromosomes from recombination, fusion or being recognized as damaged DNA



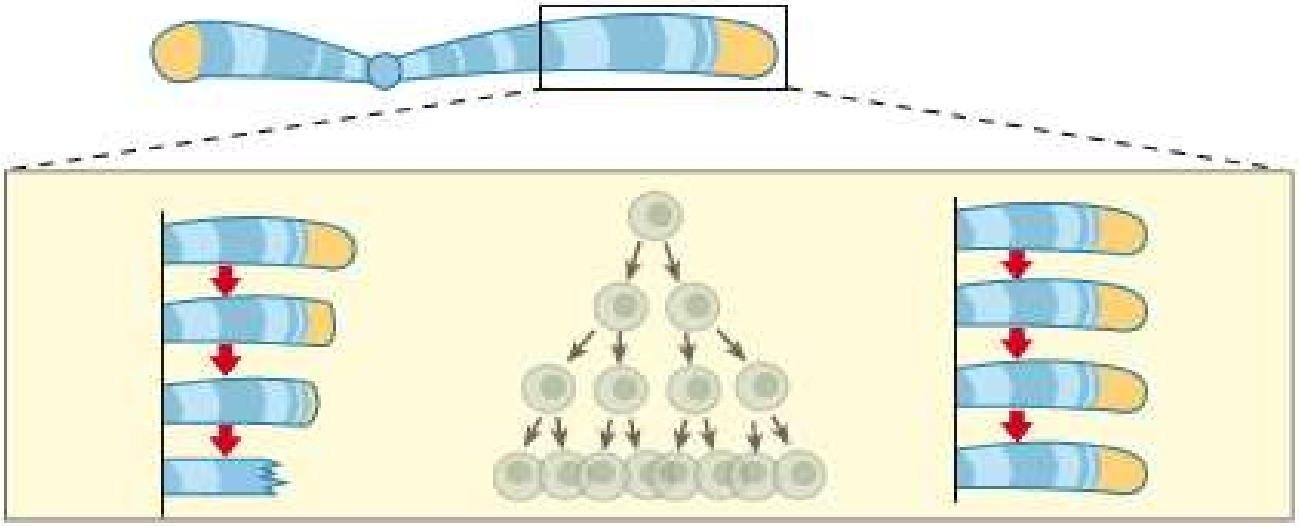
Tumor cells circumvent mitotic clock by expressing telomerase



Somatic cells

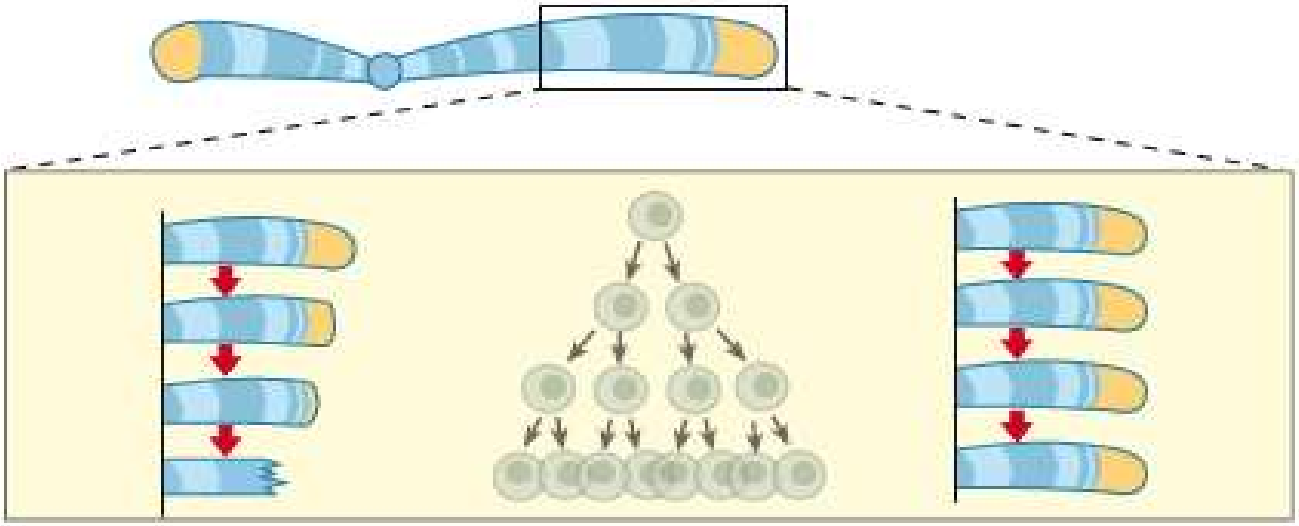
Stem cells & tumor cells

Tumor cells circumvent mitotic clock by expressing telomerase



- **Universal target: ~ 90% of cancer cells express hTERT**
- **Present in cancer stem cells**
- **Essential for unlimited growth and immortality**
- **Most normal cells are telomerase negative**

Tumor cells circumvent mitotic clock by expressing telomerase



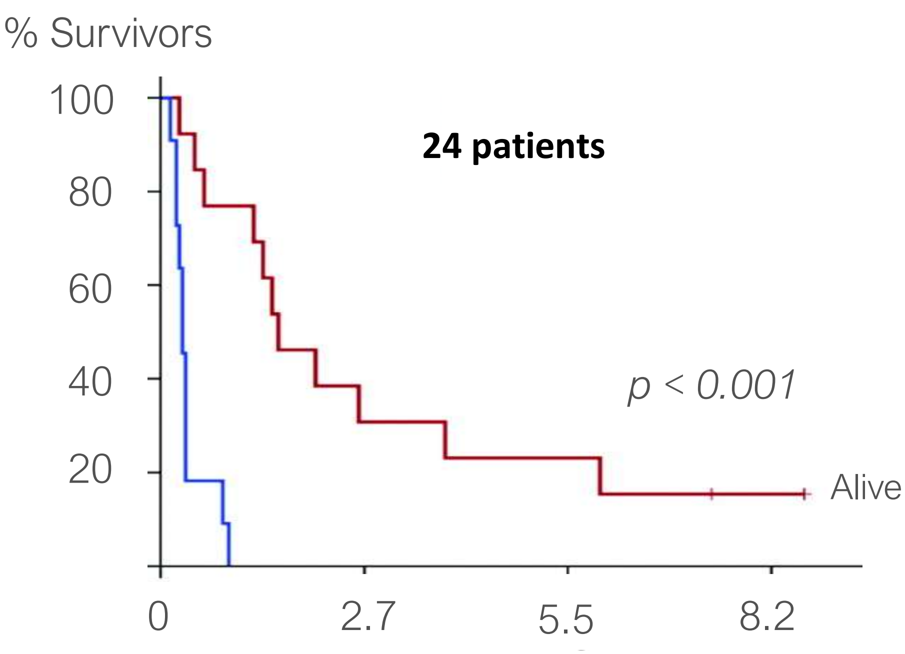
Telomerase (hTERT) an ideal target antigen in cancer therapy

- **Universal target: ~ 90% of cancer cells express hTERT**
- **Present in cancer stem cells**
- **Essential for unlimited growth and immortality**
- **Most normal cells are telomerase negative**

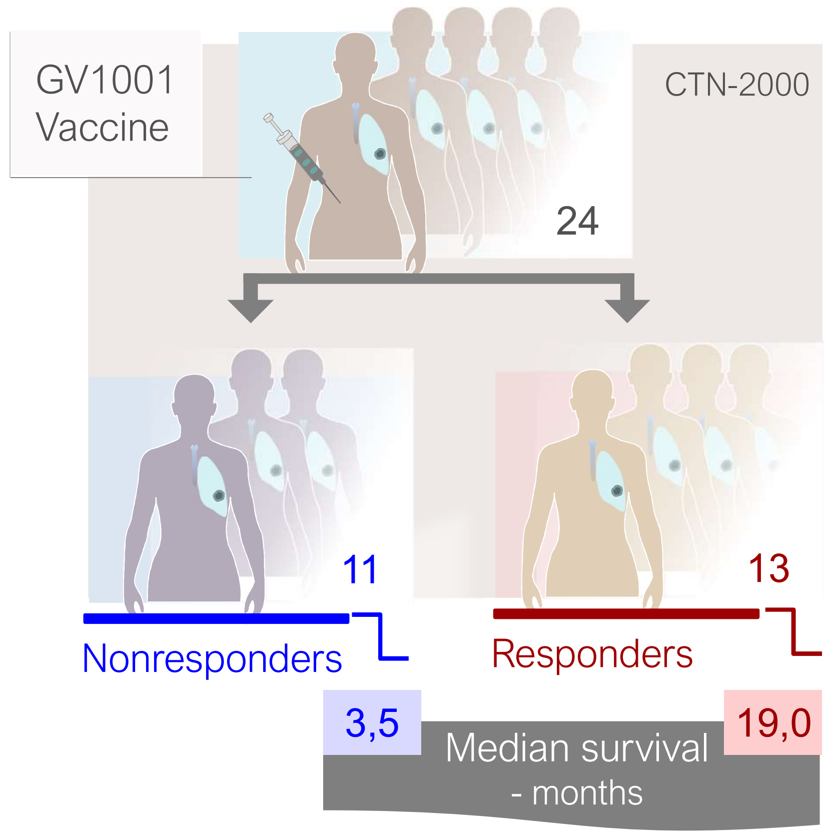
Telomerase peptide vaccine in lung cancer

Trial with first generation telomerase vaccine

NSCLC; non-small cell lung cancer, stage IIIB/IV



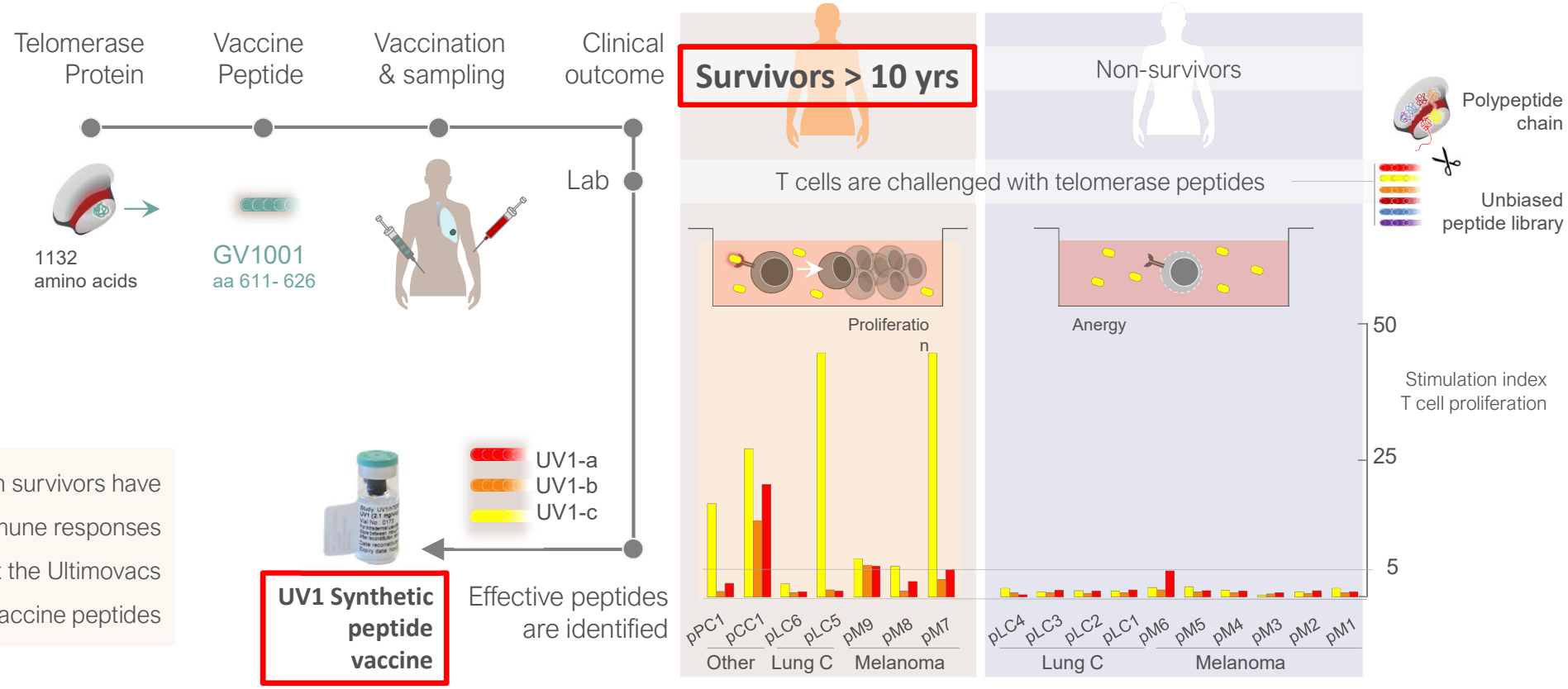
Brunsvig, P. F., J. A. Kyte et al.
Clin Cancer Res 2011; 17:6847-6857



Clear correlation between Immune responses and overall survival

FROM FIRST GENERATION VACCINE TO THE SECOND

Strategy to select peptides for UV1 vaccine: epitope spreading

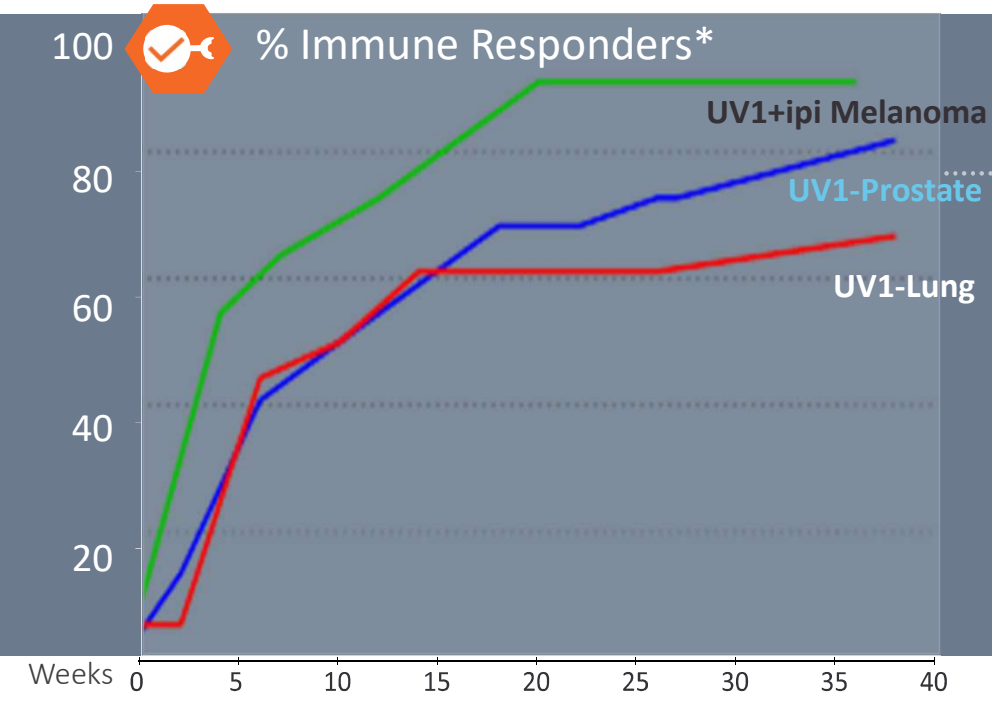


Long term survivors have strong immune responses against the Ultimovacs vaccine peptides

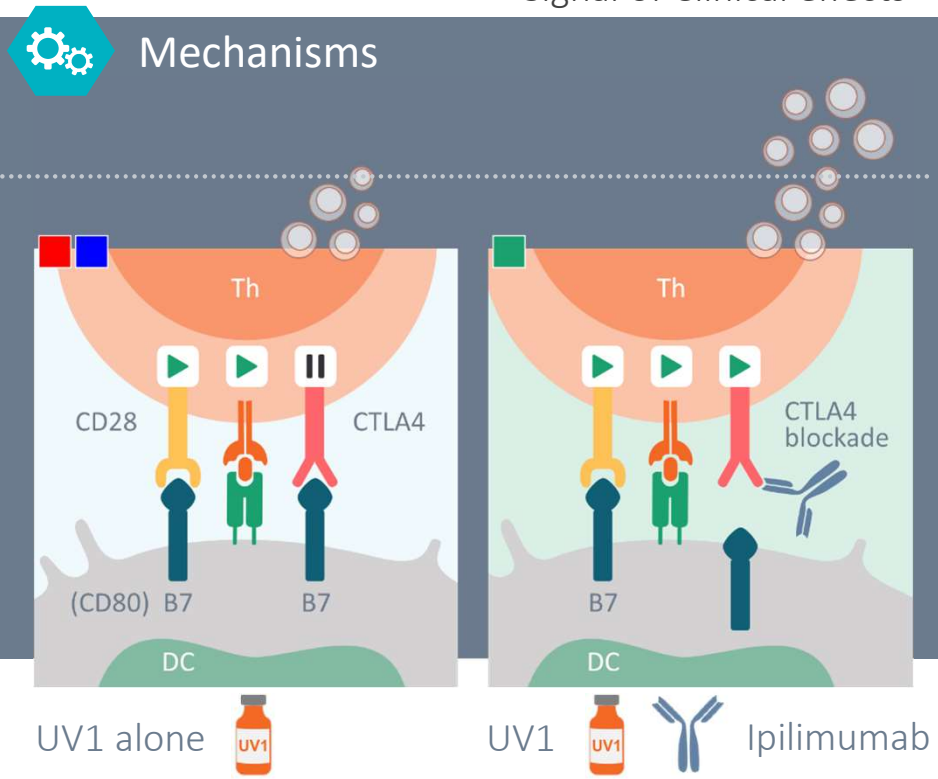
Inderberg-Suso EM et al Oncoimmunology 2012;1: 670-86

Synergistic effect of combination of UV1 and CTLA-4 inhibition

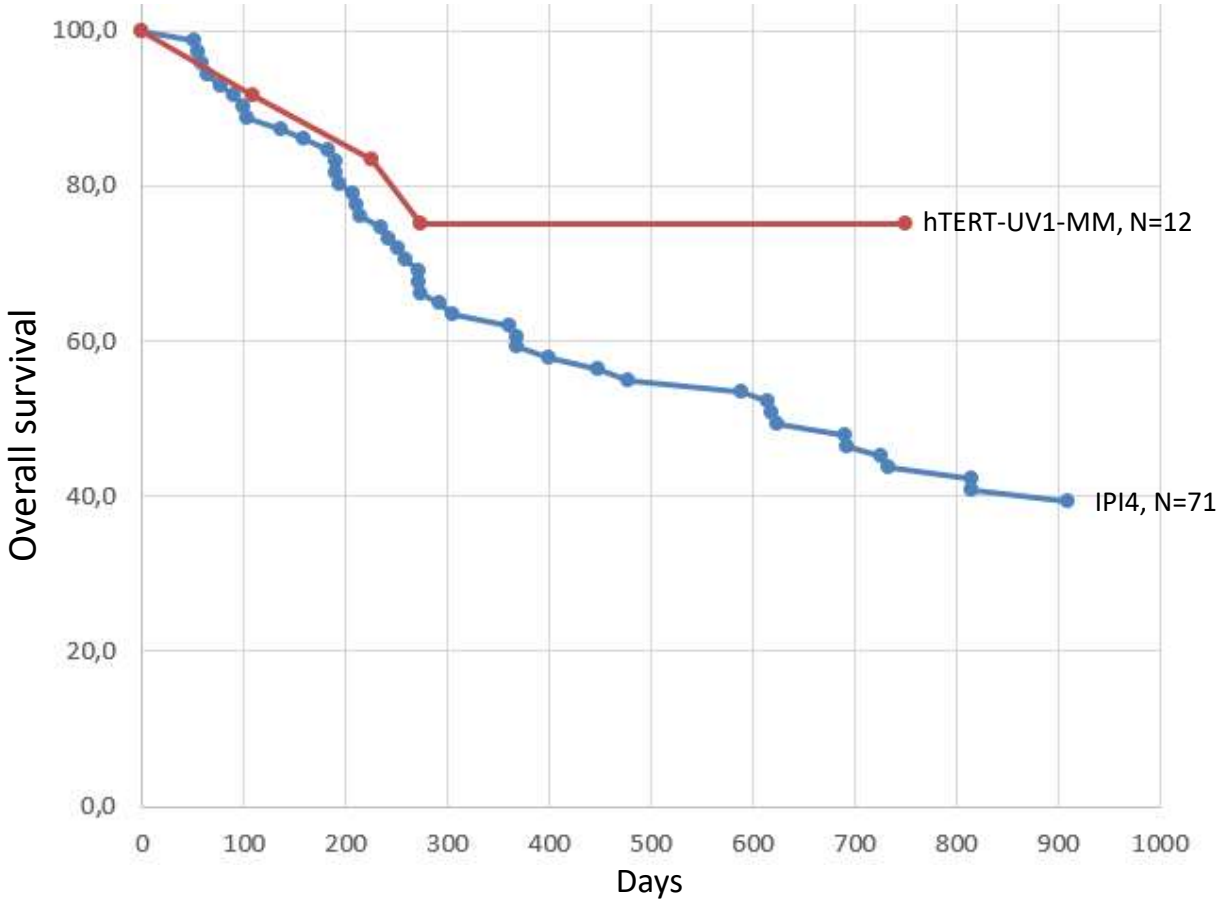
Enlarged Th cell population
Earlier Th cell response
More responders
Signal of Clinical effects



*Accumulated fraction of immune responders



Malignant melanoma – Ipilimumab (IPI4) vs UV1 with Ipilimumab



Study/variable	IPI4	hTERT-UV1-MM	Literature
mOS	20,8 months	Not reached	
OS@1 year	62%	75%	
OS@2 years	42%	75%	20-33,2%*
mPFS	Not available	Verifed to be at least 6,7 months	2,8-3,7 months**

*Hodi, O'Day et al. 2010, Hersh, O'Day et al. 2011, Wilgenhof, Du Four et al. 2013, Ascierto, Simeone et al. 2014, Ahmad, Qian et al. 2015, Ascierto, Del Vecchio et al. 2017

**Hodi, O'Day et al. 2010, Ascierto, Simeone et al. 2014, Ahmad, Qian et al. 2015, Robert, Schachter et al. 2015, Ascierto, Del Vecchio et al. 2017

Phase I - UV1vaccine in Combination With Anti-PD-1 in melanoma patients Ongoing

Study aimed at documenting the safety and frequency of immune responses of UV1/anti-PD-1 in metastatic malignant melanoma

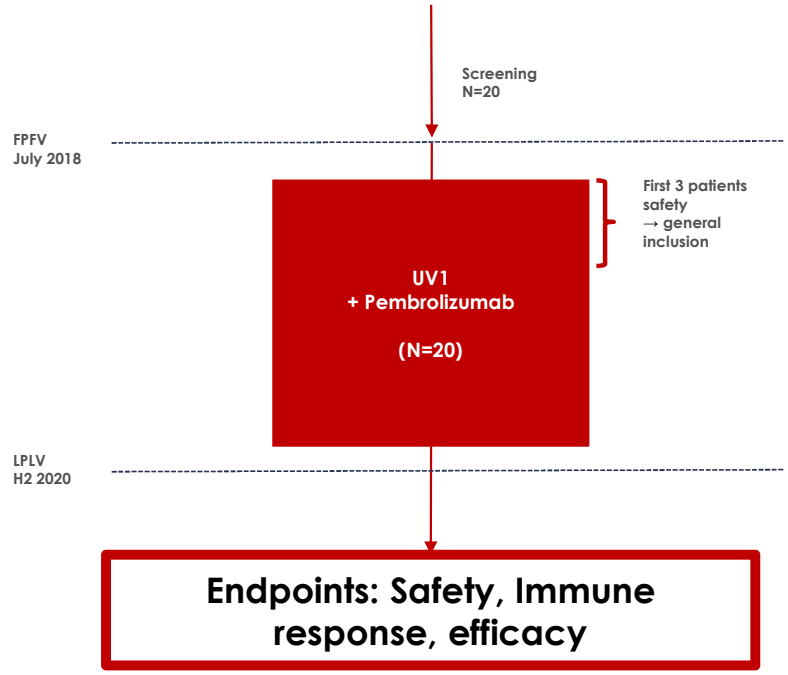
Background and rationale

Background

- Ultimovacs aims to document the safety of the combination therapy prior to launching a larger registration study
- The study is currently ongoing, with the first patient dosed in July 2018
  - **No SAEs reported to date**

Description	▶ **Phase I study evaluating the safety of UV1 + anti-PD-1 in first line metastatic malignant melanoma** ▶ **Territory: US (5 sites)** ▶ Patients (N): 20
Purpose	▶ Document safety and frequency of immune responses of UV1 / anti-PD1 in first-line metastatic malignant melanoma
Goal	▶ Favorable safety profile and number of immune responses
Timetable	▶ First patient in: July 2018 ▶ Last patient out: H2 2020

Study design



Phase I (UV1vaccine in Combination With Anti-PD-1) in melanoma patients

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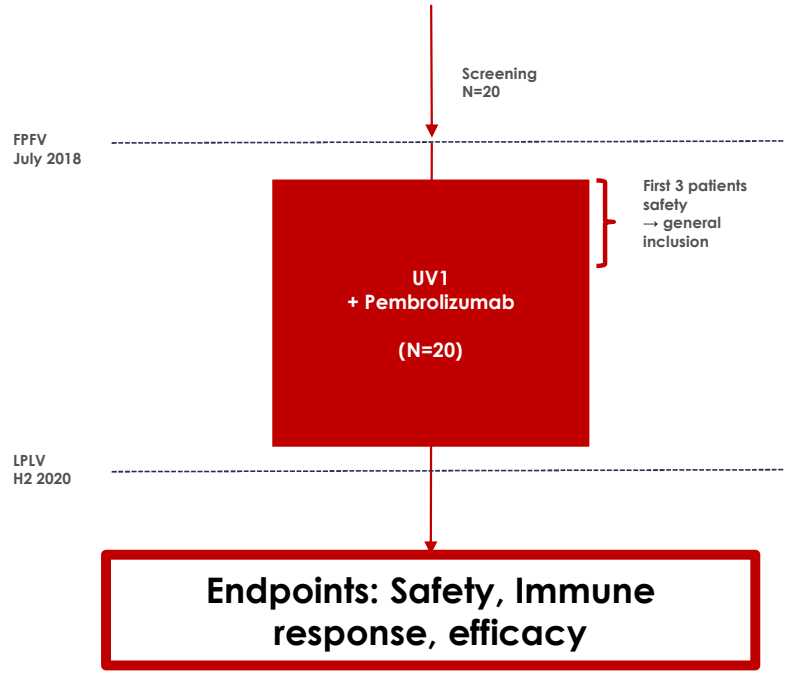


Next step: Randomized Phase II trial: Ipilimumab+ Nivolumab+ UV1 vaccine versus Ipilimumab+ Nivolumab+ UV1 vaccine- in Europe (Nordics) and in the US

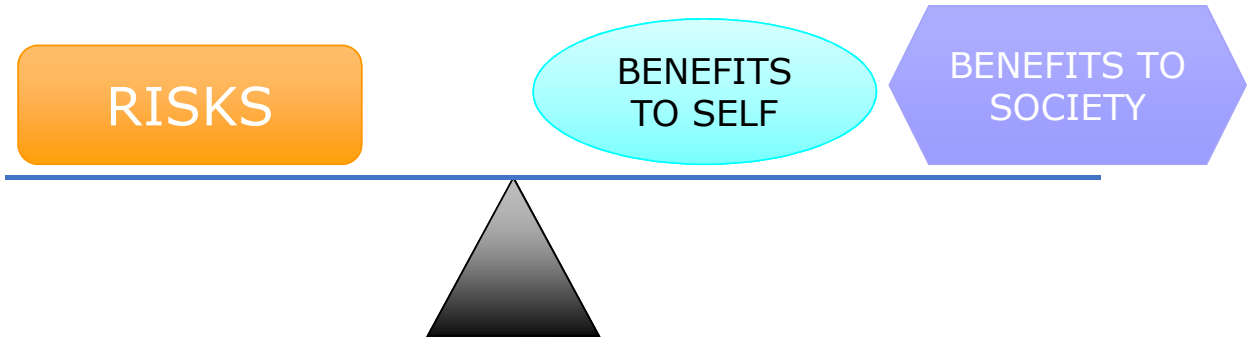
Ethical challenges ?

Ethical Issues

- **Is it really ethical to offer trial participation to patients with life-ending illness?**
  - **Taking away valuable time spend in hospitals, frequent blood sampling, X-ray examinations. travel …**
  - **A therapy with unknown toxicities and unknown anticancer activity**
- **Are seriously ill patients able to make voluntary decisions on trial participation?**
- **Do patients really understand the patient consent information?**
- **Do patients have equal access to clinical trials**

Risk/Benefit Balance

- **Benefits of a clinical trial must justify the risks but the benefits vary**

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don't worry.
I had the same
thing, and they
cured me!

Rates of response to different Phase I treatments

(460 Fase I studier with 11,935 cancer pasienter (NCI study; NEJM 2005; 352:895-904)

Table 1. Rates of Response to Treatment in Phase 1 Oncology Trials.

Trial	No. of Trials	No. of Patients Assessed for Response	Rate of Response			
			Overall Response (Complete and Partial)	Complete Response	Partial Response	Stable Disease and Less-Than-Partial Response
			percent			
Total	460	10,402	10.6	3.1	7.5	34.1*
Cytotoxic chemotherapy						
One investigational agent	92	2,341	4.4	1.5	2.9	40.8
Multiple investigational agents	12	273	11.7	1.5	10.3	27.5
Combination of investigational and FDA-approved agents	88	2,251	16.4	5.6	10.8	31.3†
FDA-approved agents only	29	792	27.4	8.0	19.4	27.2†
Immunomodulator						
One investigational agent	13	203	11.3	3.0	8.4	35.5
Multiple investigational agents	28	651	6.9	2.2	4.8	22.3†
Combination of investigational and FDA-approved agents	19	392	26.0	5.6	20.4	26.7†
Receptor or signal transduction						
One investigational agent	51	1,347	3.2	0.7	2.5	39.3
Multiple investigational agents	7	81	7.4	1.2	6.2	27.2
Combination of investigational and FDA-approved agents	61	935	11.7	2.1	9.5	37.4
Antiangiogenesis						
One investigational agent	15	335	3.9	0.6	3.3	31.0
Combination of investigational and FDA-approved agents	9	135	14.8	5.2	9.6	37.0
Gene transfer						
One investigational agent	7	89	3.4	0	3.4	30.3
Combination of investigational and FDA-approved agents	1	3	0	0	0	0
Vaccine						
One investigational agent	15	265	3.4	3.0	0.4	24.9
Multiple investigational agents	7	198	1.0	1.0	0	35.4
Combination of investigational and FDA-approved agents	6	111	5.4	2.7	2.7	19.8

* For 630 of 10,402 participants, data on stable disease and less-than-partial response are not reported. The percentage was calculated with 9772 as the denominator.

† Percentages were calculated with a denominator adjusted to exclude participants for whom data on stable disease and less-than-partial response were unavailable.

Rates of response to different Phase I treatments

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Table 4. Response Rates and Deaths from Toxic Events in Phase 1 Oncology Trials Involving the First Use of an Agent in Humans

Trial	No. of Trials	No. of Patients Assessed for Response	Overall Response Rate*	No. of Patients Assessed for Toxic Events	Deaths from Toxic Events†
			%		*no. (%)*
Total					
First use of an agent in humans	117	3164	4.8	3498	9 (0.26)
All other trials	343	7238	13.1	8437	49 (0.58)
Cytotoxic chemotherapy					
First use of an agent in humans	43	1298	5.0	1422	7 (0.49)
All other trials	178	4359	15.0	5023	36 (0.72)
Immunomodulator					
First use of an agent in humans	16	404	7.4	431	1 (0.23)
All other trials	44	842	16.6	977	0
Receptor or signal transduction					
First use of an agent in humans	27	742	3.8	853	1 (0.12)
All other trials	92	1621	8.0	1892	12 (0.63)
Antiangiogenesis					
First use of an agent in humans	8	200	7.0	228	0
All other trials	16	270	7.0	345	1 (0.29)
Gene transfer					
First use of an agent in humans	0	0	0	0	0
All other trials	8	92	3.3	112	0
Vaccine					
First use of an agent in humans	23	520	3.1	564	0
All other trials	5	54	1.9	88	0

* The overall response rate includes both complete and partial responses.
† Deaths include all those reported as possibly, probably, or definitely related to the treatment.

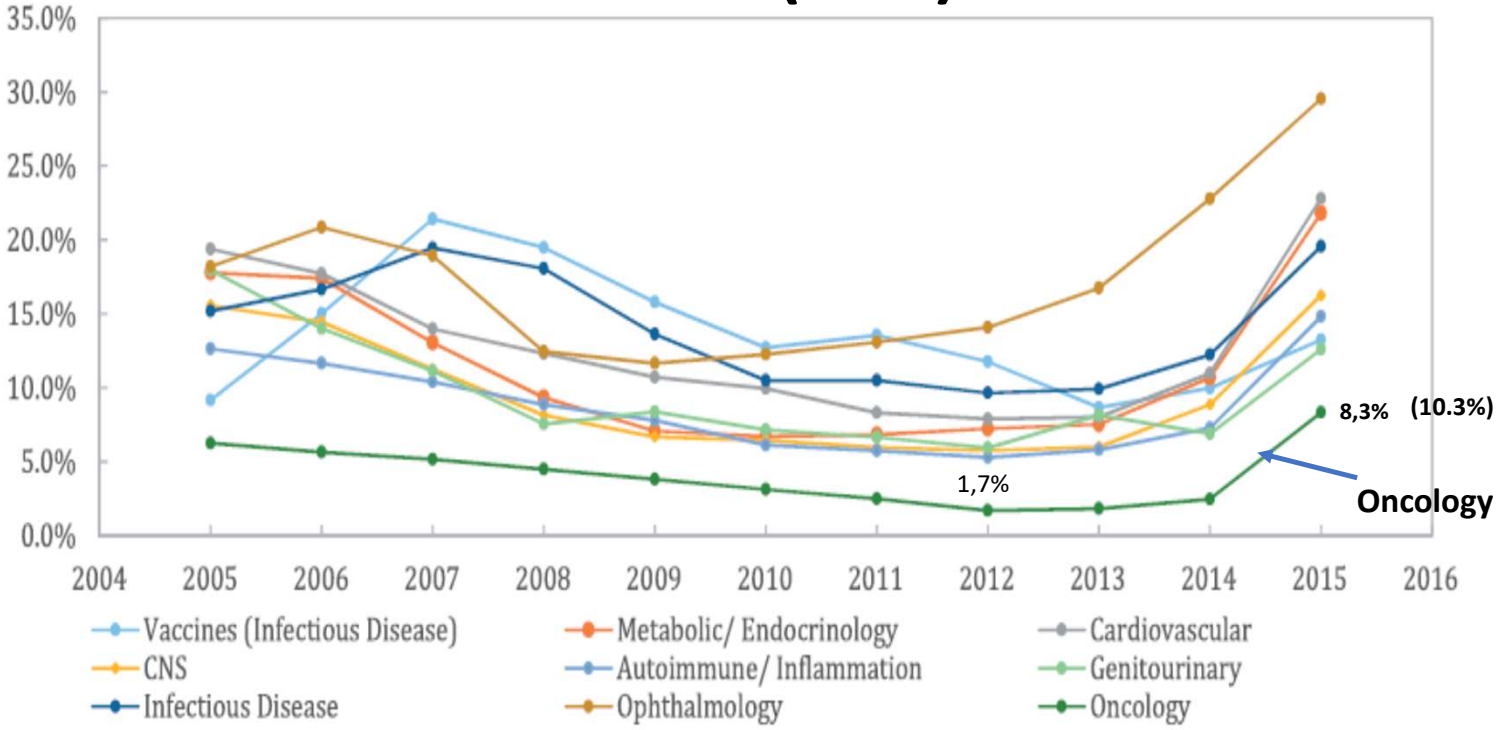
Retrospective study analysing clinical outcome of all consecutive patients treated within a phase I trial at the Drug Development Unit at The Royal Marsden Hospital.

Review of 29 phase-I trials within a 18 months period from 01.01.2005 to 30.06.2006.

Best Response	
Partial Response	19 (9.4%)
Stable Disease at least 2 cycles	88 (43.6%)
Progression Disease	95 (47.0%)
Clinical Benefit	
Stable disease >3months	54 (25.5%)
Clinical Benefit (PR + SD >3months)	73 (36.1%)
Stable disease >6months	36 (17.8%)

Judson 2008

New compounds- Probability Of Success (POS)



Based on 21 143 compounds from Jan. 1 2000-Oct. 2015

Biostatistics (2018) **00**, 00, *pp.* 1–14
doi:10.1093/biostatistics/kxx069

Risk benefit - Who Should decide?

- **Who currently decides a favorable risk-benefit ratio in research?**
  - **Investigators**
  - **Bioethicists**
  - **Lawyers**
  - **Statisticians**
  - **Physicians**
  - **Policymakers**
- **Or Should the people who are facing life-ending illness have some input on whether a risk/benefit ratio is favorable for research studies?**

Patients Have Different Perceptions than Healthy People

- **Substantial data demonstrates that patients facing serious illnesses make very different assessments of their own condition and the risks they are willing to confront compared to healthy individuals (QALY?)**
- **Even families, consistently overestimate symptoms and underestimate patient satisfaction and quality of life**

Patients Willing to Undergo More Risk than Healthy People

- **Patients need very small benefits to find cancer chemotherapy worthwhile.**
- **Nurses needed 50% chance, and doctors needed a 10% chance, general public needed 50% chance of benefit.**
- **Cancer patients only needed only 5% chance of benefit to want an intensive chemotherapy regimen described with many side effects**

Table 5. Patient Considerations of Adverse Effects in Trial Participation

Potential Adverse Effect	Would Still Participate in the Research Trial (%)
Total hair loss	96
Nausea	89
Fatigue	96
10% chance of death	91
Laboratory tests twice a week	90
Bone marrow biopsy	92
Weight gain of 20 pounds	95
Overnight hospitalization	99
Impaired ability to think	76
Cytostatic not cytotoxic experimental treatment	99

Agrawal M, JCO 2006

Phase I trial participation

Typical patient sentiments

- Perhaps this will help someone else”
- This may not work but I can’t cope with doing nothing and just sitting there waiting to die”
- “This is my last chance”
- “My consultant told me there was nothing more but the Phase I unit had some very clever drugs that could help me”
- “It might give me a bit longer…I just want to see my first grandchild born in 4 months/see my child go to school”
- “I am aiming for a cure”

Difference of hope and expectations !

Difference of hope and expectations !

Therapeutic Optimists

Maintaining Hope

A Coping Strategy

Possible patient`s benefit from participating in a trial

- Direct benefit - physiological benefit from the treatment – objective response (PR or CR), disease stabilisation (SD)
  - Toxicity from therapy often perceived as less cumbersome than toxicity from the cancer disease

- Indirect benefit- results from being subject in a trial – physiological and psychological ”inclusion benefit”
  - A number of studies have found that particapating in phase I trials may actually improve patiens quality of life compared to palliative care only
  - Psychological benefit from regular contact with physyscian in a time og great uncertainty, reduses distress
  - Som studies indicate that patients in trials may live longer irrespective of response to treatment?
  - Some also also recieve comfort from knowing they are helping future partients with cancer-altruism

Important ethical Questiones in Phase I trials

- Likelihood that participants will experience benefits- *risk/benefit*
- **Validity of *consent* in critically ill patients**
  - **Are terminally ill patients really able to provide informed consent?**
- **Equal access to trials**

Cannot Label Everyone with Advanced Cancer as Incompetent

- **There will be some people with advanced cancer who are able to and do make rational, reasonable, informed decisions and some who can't just like those without advanced cancer**
- **But cannot conclude that all patients with advanced cancer are unable to give informed consent**

Pressure to participate in trials ?

Table 3. Patient Perception of Pressure to Participate in Phase I Oncology Study

Source of Pressure	No Pressure (%)	Little Pressure (%)	Moderate or a Lot of Pressure (%)
Family	80	11	9
Clinical Researcher	87	6	7
Growing Cancer	17	8	75

Agrawal M, JCO 2006

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Agrawal M, JCO 2006

Equal access to clinical trials ?

Conclusions

- **Patients are understandably driven by the urge for survival**
- **For this reason they require protection, hence the progressive refinement of codes of ethics for clinical trials**
- **Many patients would willingly accept a 5% or less chance of prolonged survival, whatever the toxicity**
- **Need to ensure equal access**
- ***While protecting patients' rights is important, clinical research is the only means by which we can improve patient care***

Right-To-Try Act 2017, passed in May 2017 in the US (already in effect in 38 states)

- **Improved access to new drugs**
- **Limited patient understanding ?**
- ***But***
- **Decrease liability from pharma and physician**
- **Safety consequences (AE reporting)**
- **Expanded Access versus Right-To-Try**

We Don’t Ignore Other Decisions People Make at the End of Life

- **Just facing terminal illness does not invalidate people’s decisions**
- **We accept estate wills and do-not-recuscitate requests made by terminally ill patients as genuine**

  We do not reject the consent of life-saving organ transplants as prima facie invalid because they are made by terminally ill patients who cannot think clearly

Ways of increasing patients`s participation in clinical trial

- **Clinical trials should be defined as *integrated part of patiens treatment***
- **Patients should have the right to be informed about relevant trials**
- **Increase patients awareness – easy accessible information at hospitals, internet....**
- **Equity of access to clinical trials**
- **Invest in clinical trial infrastructure i.e. physicians dedicated to clinical research, study nurses, project managers…**
- **Support clinicians to become *Trial-Friendly***
- ***Access to clinical trials in other countries***

Are patients' expectations realistic?

- Only a small proportion of drugs tested in phase I make it to licensing (~5-10%)
- Response rates (RECIST) in phase I studies are as low as 5%
- The average number of cycles a patient in a phase I study receives = 2 (at least prior to introduction of molecularly targeted therapy)
- The median survival of a phase I patient = 7 months

Ethical issues for the investigator

- **Conflicts of interest**
  - **Best care option for the patient ?**
  - **Patient's family's views**
  - **Intellectual desire to see study succeed**
  - **Desire to be first author**
  - **Financial conflict of interest**
  - **Institutional conflict of interest**

Other challenges

- **Continued therapy in patients responding- before a drug is approved**
- **Staggered inclusion**
- **«Slot times», multiple centers participating**
- **Unequal access to trials**
- **---**

Overall survival Prostate Cancer study

Overall survival, study UV1/hTERT-2012-P

	Dose group			All patients
	100 µg N = 7	300 µg N = 7	700 µg N = 8	N = 22
One-year OS, n (%)	7 (100%)	7 (100%)	7 (87.5%)	21 (95.5%)
Two-year OS, n (%)	7 (100%)	7 (100%)	5 (62.5%)	19 (86.4%)
Median OS, months	51.8	Not reached	Not reached	Not reached

n = number of patients alive
OS = overall survival

PFS not available for the prostate study.

Failure rates in clinical trials

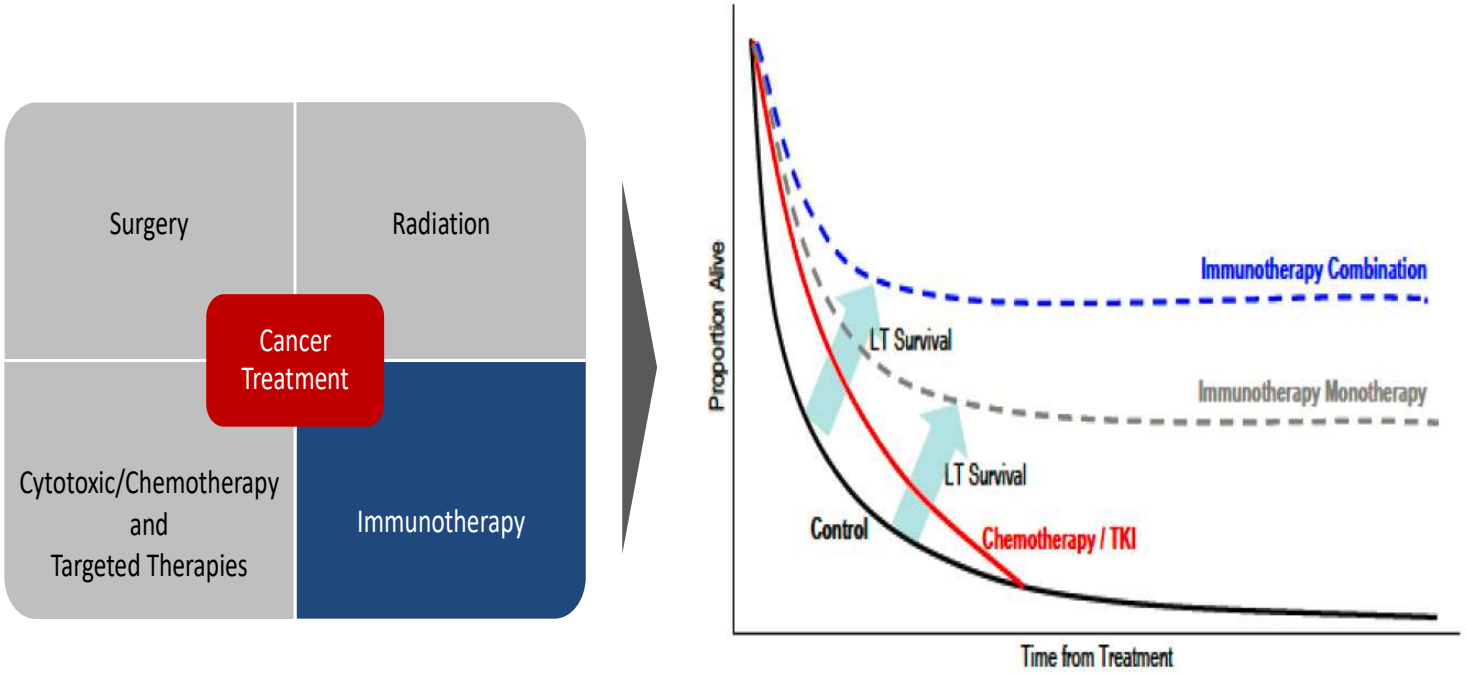
Table 2 Failure rates in clinical trials have soared in the past 20 years

	Attrition rates		Current reasons for failure
	1990	2010	
Phase I	33%	46%	
Phase II	43%	66%	Insufficient efficacy (51%)
			Safety concerns (19%)
			Strategic issues (29%)
Phase III	20%	30%	Insufficient efficacy (66%)
			Safety concerns (21%)

Sources: Fabio Pammolli et al., 'The productivity crisis in pharmaceutical R&D'; Steven M. Paul et al., 'How to improve R&D productivity; and John Arrowsmith, 'Trial watch: Phase II failures: 2008-2010'; 'Trial watch: Phase III and submission failures: 2007-2010'; and 'A decade of change'

Cancer treatment

A paradigm shift



*Citi – opinion article November 19th 2013

UV1 vaccine in prostate cancer patients
overall survival

Overall survival, study UV1/hTERT-2012-P

	Dose group			All patients
	100 µg N = 7	**300 µg N = 7**	**700 µg N = 8**	**N = 22**
One-year OS, n (%)	7 (100%)	7 (100%)	7 (87.5%)	21 (95.5%)
Two-year OS, n (%)	7 (100%)	7 (100%)	5 (62.5%)	19 (86.4%)
Median OS, months	51.8	Not reached	Not reached	Not reached

n = number of patients alive
OS = overall survival

PFS not available for the prostate study.

UV1 cancer vaccine in Non-Small Cell Lung Cancer

Progression free survival, study UV1/hTERT-2012-L

	Dose group			All patients
	100 µg N = 6	300 µg N = 6	700 µg N = 6	N = 18
One-year PFS, n (%)	2 (33.3%)	3 (50.0%)	4 (66.7%)	9 (50.0%)
Two-year PFS, n (%)	0	0	4 (66.7%)	4 (22.2%)
Median PFS, months	11.1	11.3	Not reached	12.3

n = number of patients without progression or death
PFS = progression free survival

Overall survival, study UV1/hTERT-2012-L

	Dose group			All patients
	100 µg N = 6	300 µg N = 6	700 µg N = 6	N = 18
One-year OS, n (%)	2 (33.3%)	5 (83.3%)	6 (100%)	13 (72.2%)
Two-year OS, n (%)	1 (16.7%)	3 (50.0%)	5 (83.3%)	9 (50.0%)
Median OS, months	11.1	26.2	Not reached	28.2

n = number of patients alive
OS = overall survival

Why patients do not participate in clinical trials ?-

- ***Lack of awareness*** **- only a fraction of the patients are aware of clinical trials**
- **---**
- ***Do not think that they qualify*** **- assume that there are not clinical trials that apply to their condition-**
- ***Uncertainty*** **- about effect and side effects. «Will I get placebo rather than active drug ?»**
- ***Inconvenience*****- geographic location- transport, cost**
- ***«Being experimented on»***
- ***Social and economic disadvantages – under-representation of certain populations***
- ***Limited of number of availble clinical trials***