



# Improving the management of immune adverse events

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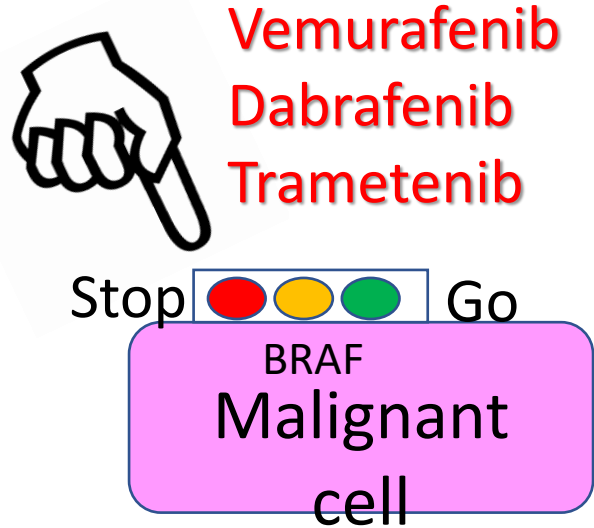
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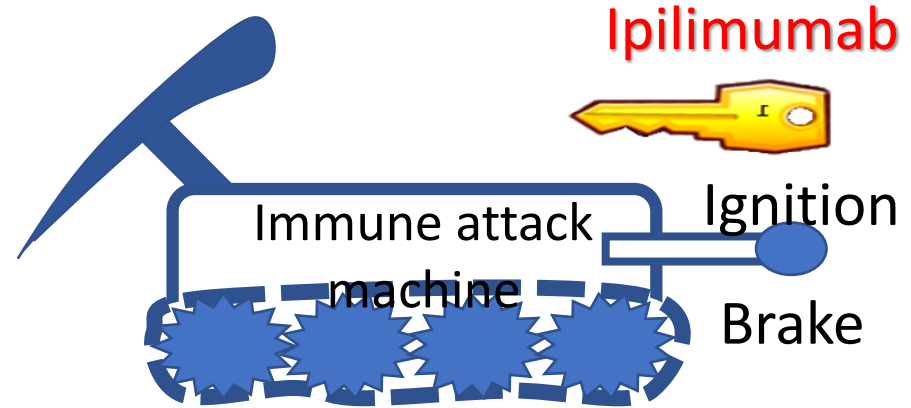
University of Birmingham



# Treatment for advanced melanoma



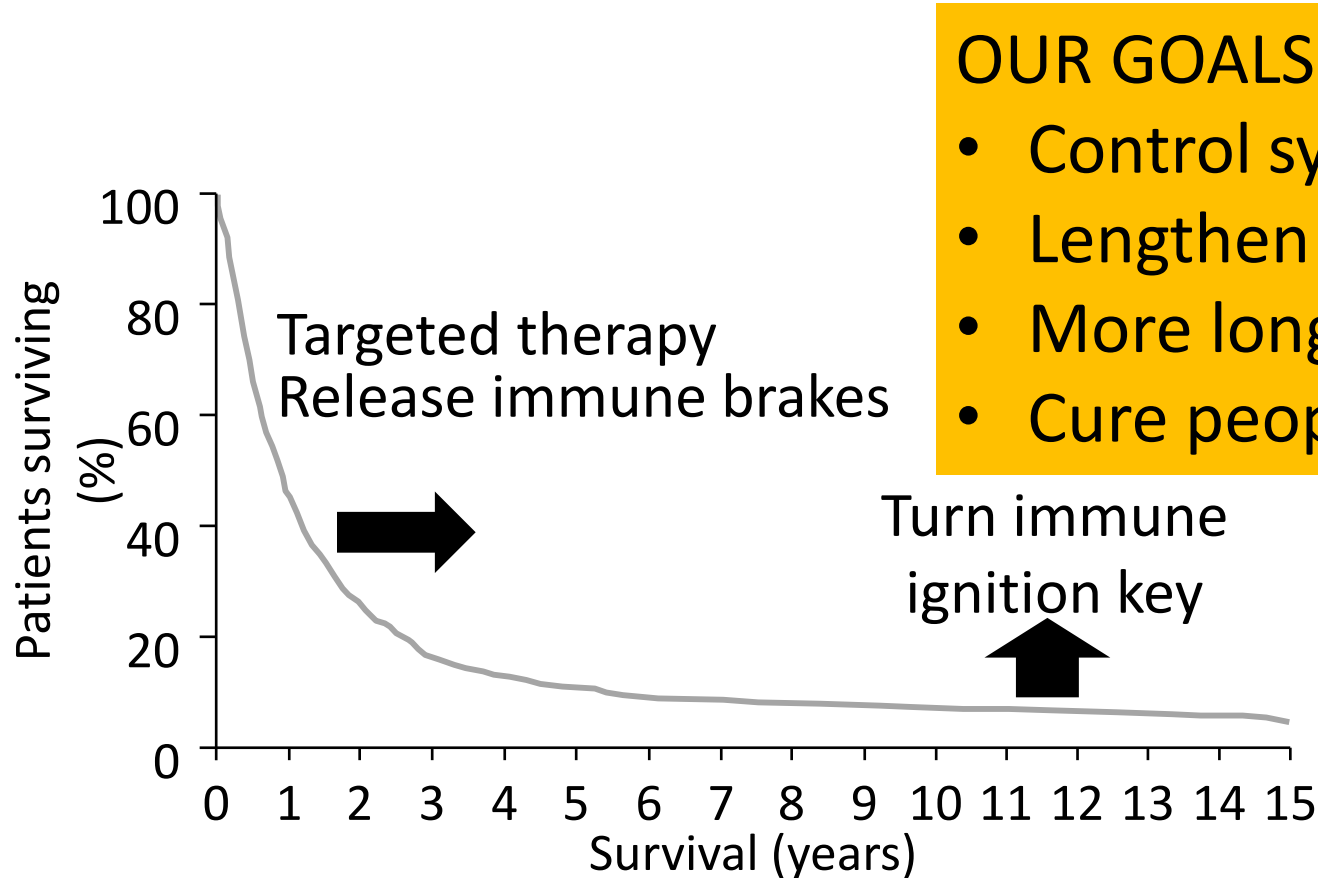
Molecularly targeted therapy



Immune checkpoint inhibitors

Nivolumab  
Pembrolizumab

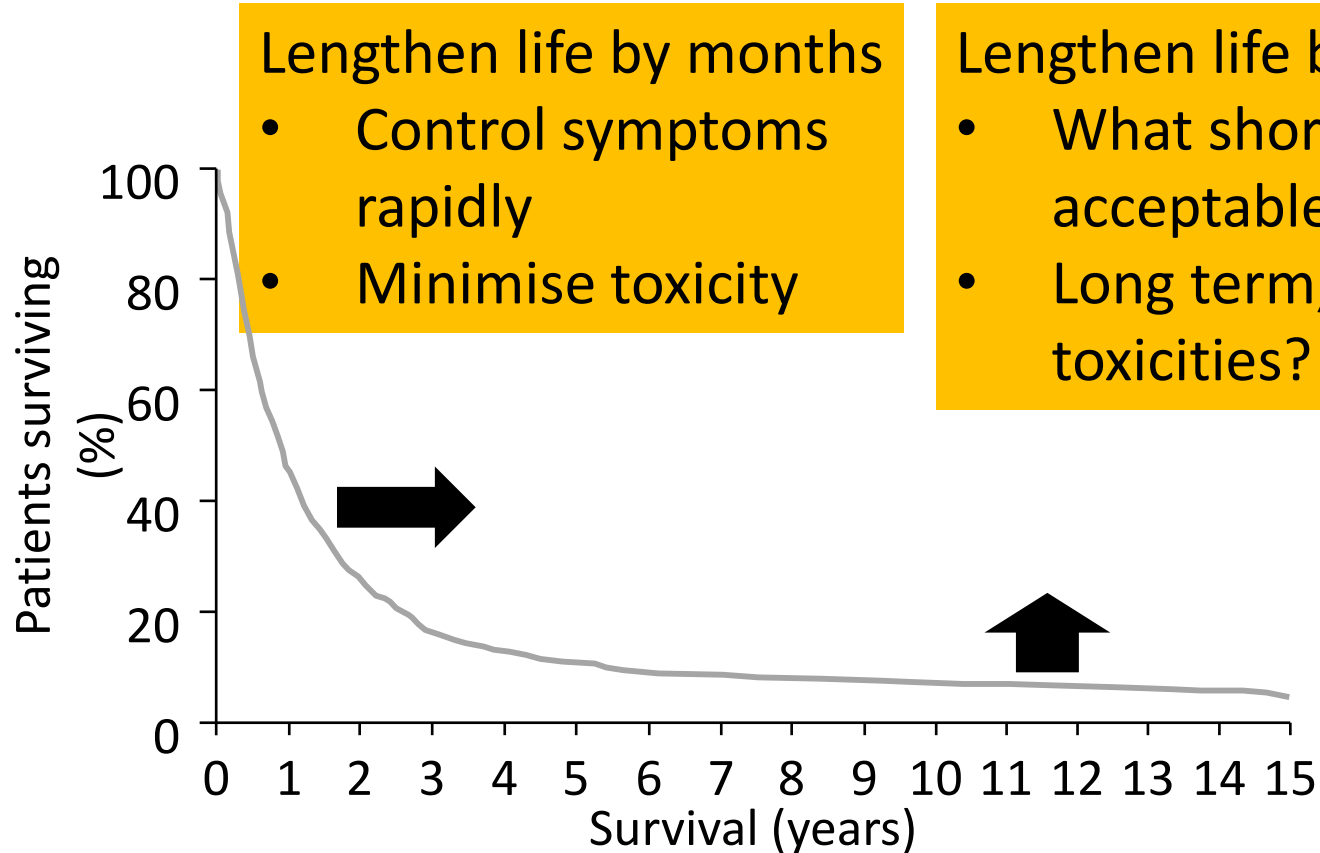
# Benefits of treatment



## OUR GOALS

- Control symptoms
- Lengthen life
- More long-lived survivors
- Cure people after surgery

# Harms of treatment



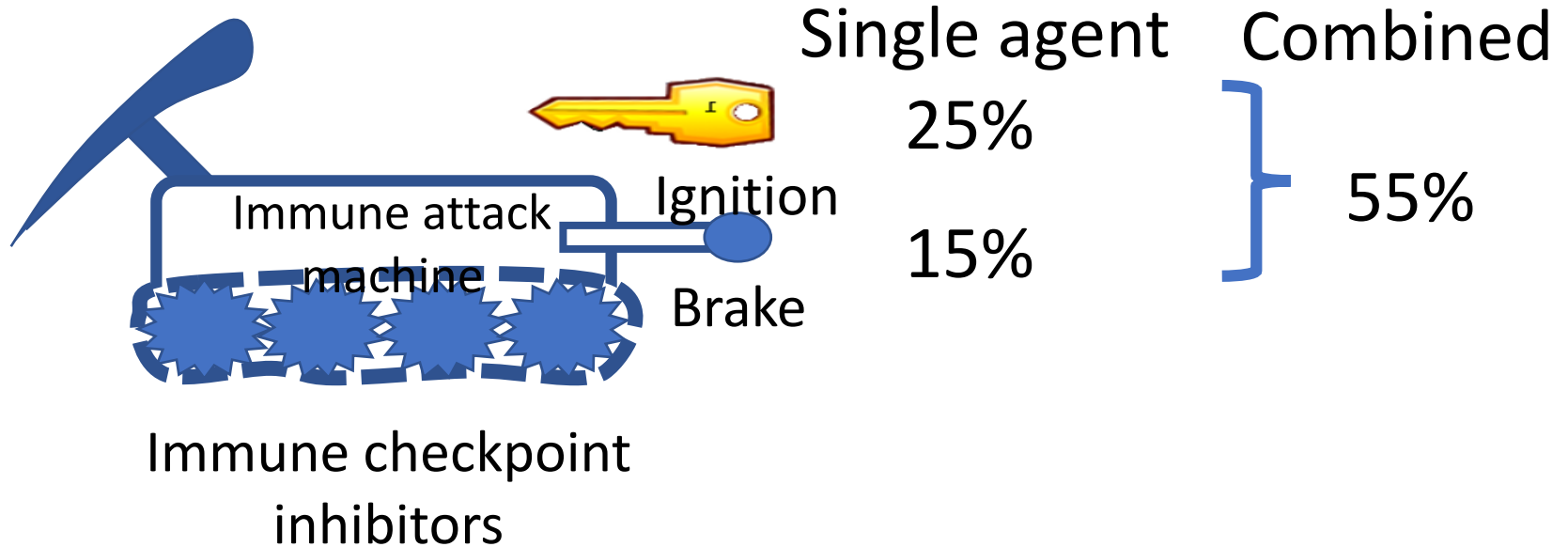
Lengthen life by months

- Control symptoms rapidly
- Minimise toxicity

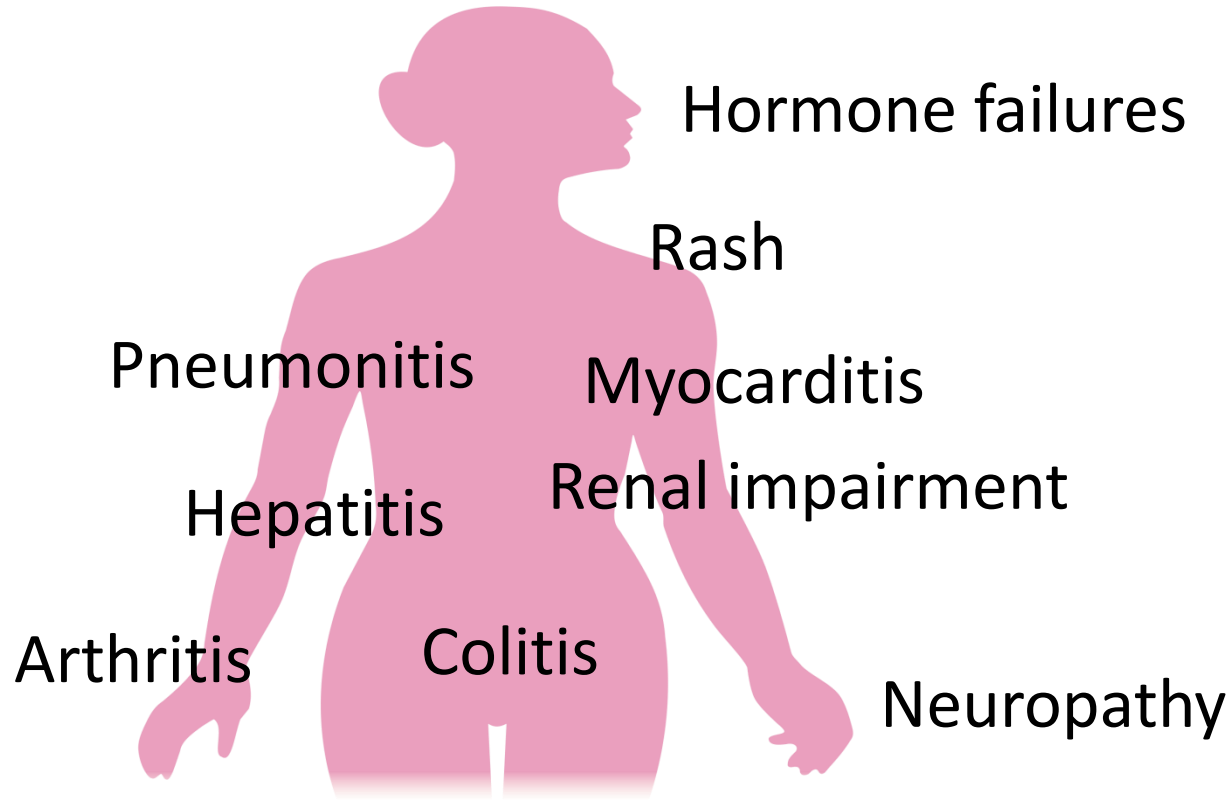
Lengthen life by years (decades?)

- What short term toxicity is acceptable?
- Long term, chronic and late toxicities?

# Risk of major side effects (requiring hospitalisation and/or high dose steroids)



# Diverse side effects affecting any organ



# Late onset colitis after pembrolizumab

Patient 382. late 70s male

Stage IVc – primary 2011, stage IV lung and brain 2012, excision brain metastasis 2015

Dacarbazine 2012 discontinued progression in brain,

ipilimumab x4 Feb-May 2013

Grade 3 diarrhoea, CRP 199, no pathogens or CD, colitis on CT and sigmoid biopsy

Inflammatory poly-arthritis



pembrolizumab  
4 cycles



Low dose prednisolone



Sulphasalazine



High dose steroids

# Hepatitis as part of multiple IrAE

UID 408 – middle aged male, cutaneous melanoma 2013, nodal, liver, lung, bowel, spleen metastases 2013, good response dabrafenib+trametenib, elective switch to immune therapy

severe headache, fever,  
low cortisol, pituitary

enlargement  
ALT 315 ALT  
~8xILN normal

Inflammatory polyarthrits

Transient rise  
ALT 7xULN

Ongoing CR

1-20

21-40

41-60

61-80

81-100

weeks

ipilimumab

pembrolizumab

Dexamethasone  
started 12mg/d

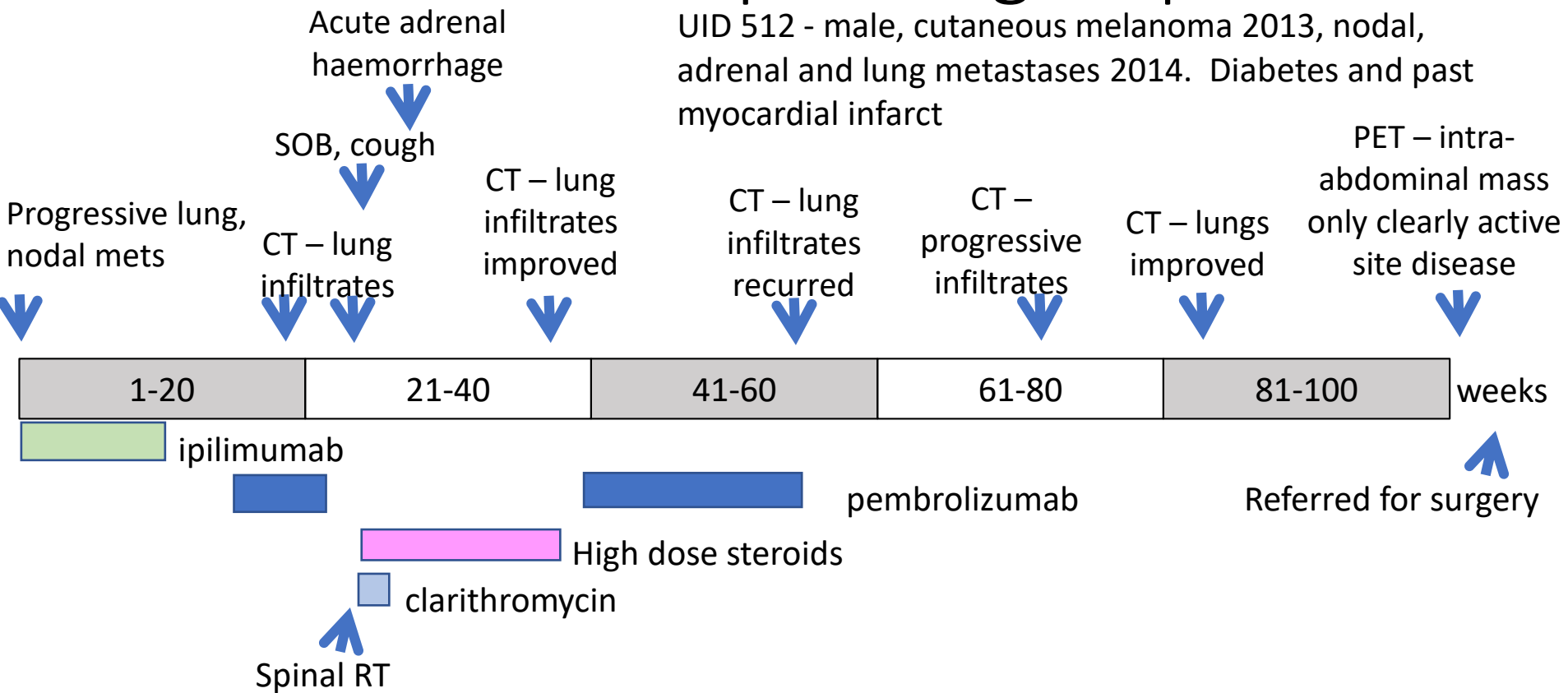
Prednisolone  
40mg/g tapered  
to 7.5mg/d

sulphasalazine

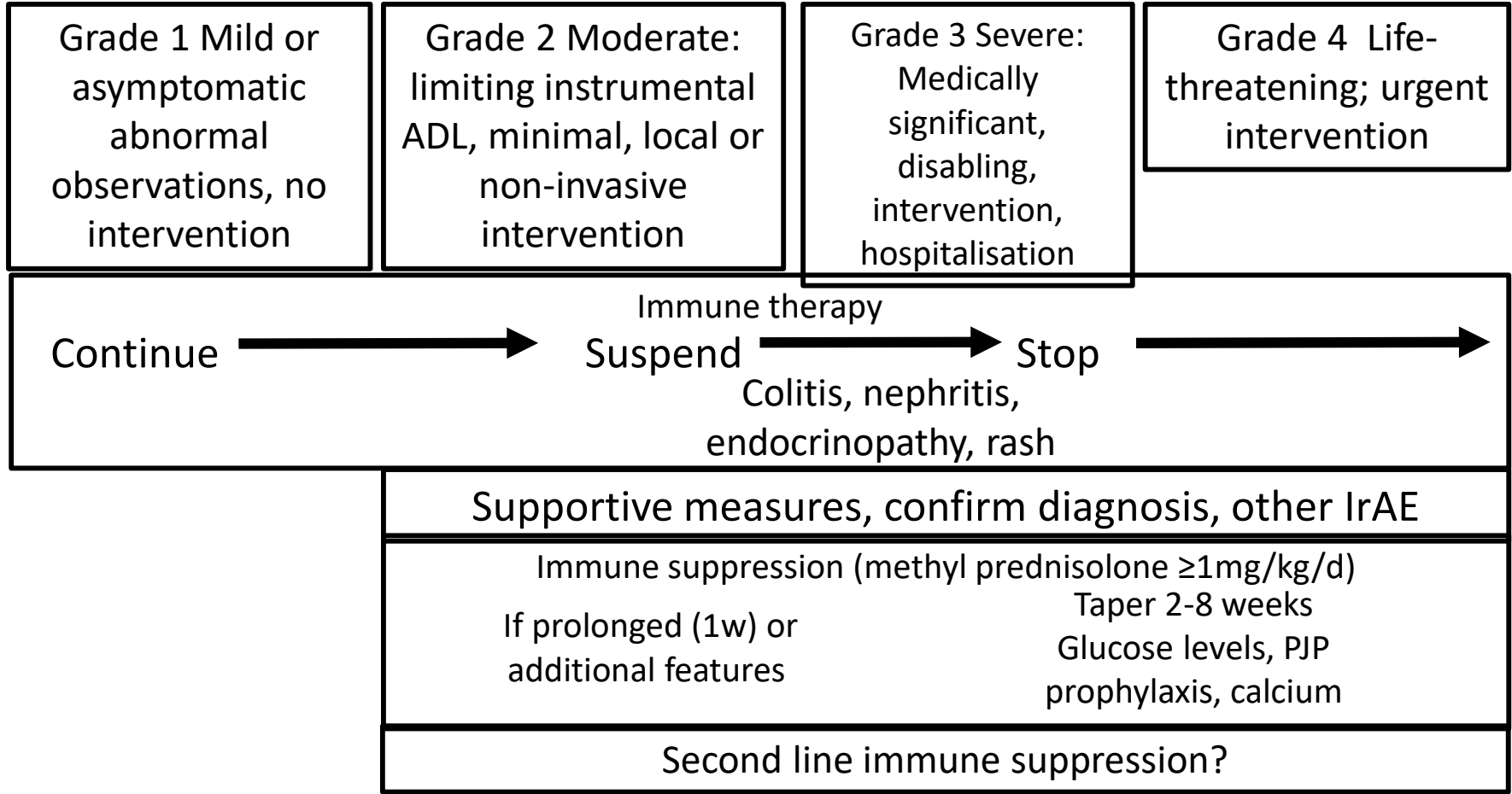


# Pneumonitis complicating response

UID 512 - male, cutaneous melanoma 2013, nodal, adrenal and lung metastases 2014. Diabetes and past myocardial infarct



# Simple algorithm



# Overview from melanoma trials

	Reference	N	Regimen
1	Larkin NEJM 2015;373: 23	313	Nivolumab 3mg/kg Q14/7
		313	Niv 1mg/kg + Ipi 3mg/kg Q21/7 x4 → Niv 3mg/kg Q14/7
		311	Ipilimumab 3mg/kg Q21/7 x4
2	Postow NEJM 2015;372: 2006	95	Niv 1mg/kg + Ipi 3mg/kg Q21/7 x4 → Niv 3mg/kg Q14/7
		47	Ipilimumab 3mg/kg Q21/7 x4
3	Robert NEJM 2015;372: 2521	278	Pembrolizumab 10mg/kg Q14/7
		277	Pembrolizumab 10mg/kg Q21/7
		256	Ipilimumab 3mg/kg Q21/7 x4

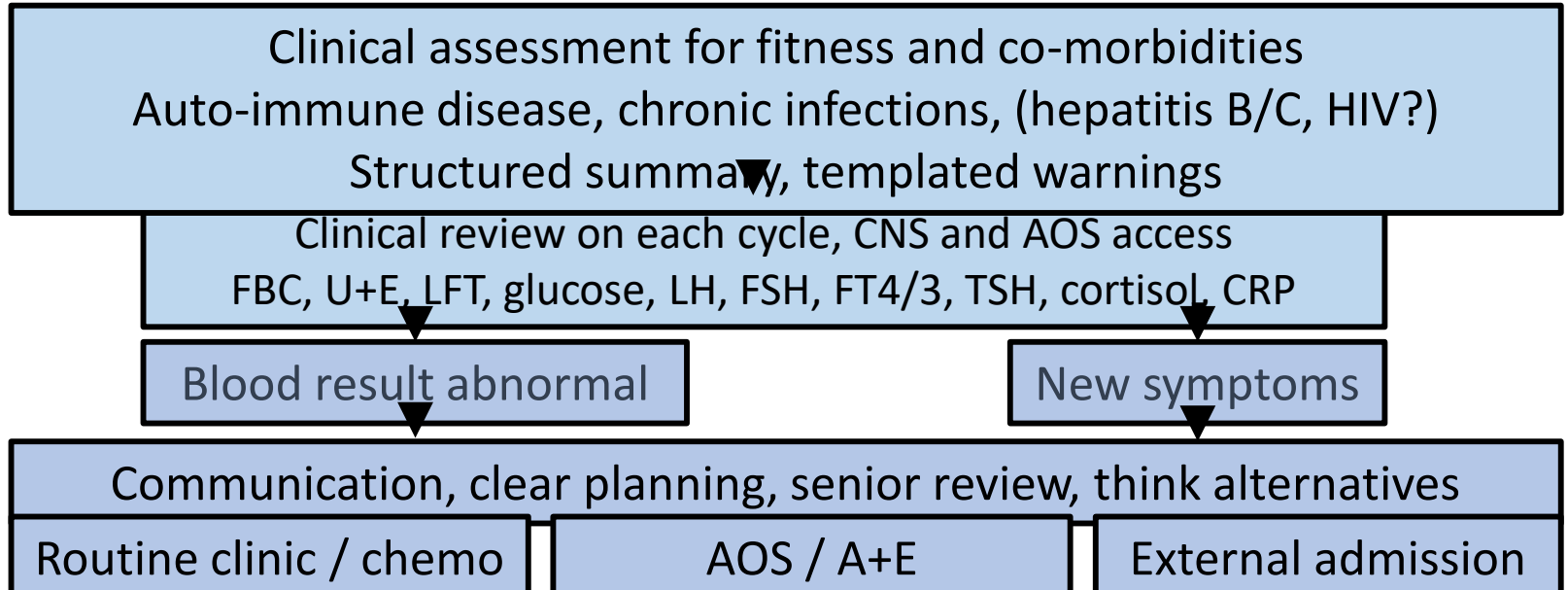
# Summary of adverse events (all%, G3+4%)

IrAE	1. Niv	3. P2	3. P3	1. N+I	2. N+I	1. Ipi	2. Ipi	3. Ipi
Any related	82, 16	80, 13	73, 10	96, 55	91, 54	86, 27	93, 24	73, 20
Headache	7, 0			10, <1		8, <1		
Pyrexia	6, 0			19, <1	20, 3	7, <1	15, 0	
Fatigue		21, 0	19, <1		39, 5		43, 0	15, 1
Asthenia		12, <1	11, 0					6, <1
Arthralgia	8, 0	9, 0	12, <1	11, <1	11, 0	6, 0	9, 0	5, <1
Myalgia					10, 0		13, 0	
Nausea		10, 0	11, <1		22, 1		24, 2	9, <1
Anorexia					15, 0		9, 0	
Vomiting					14, 1		11, 0	
Diarrhoea	19, 2	17, 3	14, 1	44, 9	45, 11	33, 6	37, 11	23, 3
Colitis	1, <1	2, 1	4, 3	12, 8	23, 17	12, 9	13, 7	8, 7
Abd. Pain					11, 0		9, 2	
Constipation					11, 1		9, 0	
Lipase ↑					13, 9		4, 2	

# Summary of adverse events (all%, G3+4%)

IrAE	1. Niv	3. P2	3. P3	1. N+I	2. N+I	1. Ipi	2. Ipi	3. Ipi
ALT ↑	4, 1			18, 8	22, 11	4, 2	4, 0	
AST ↑	4, 1			15, 6	21, 7	4, <1	4, 0	
Hepatitis		1, 1	2, 2					1, <1
Renal		0, 0	<1, 0		3, 1		2, 0	<1, <1
Dyspnoea	5, <1			10, 1	10, 3	4, 0	11, 0	
Pneumonitis		<1, 0	2, <1		11, 2		4, 2	<1, <1
Rash	26, <1	15, 0	13, 0	40, 5	41, 5	33, 2	26, 0	15, <1
Pruritis	19, 0	14, 0	14, 0	33, 2	35, 1	35, <1	28, 0	25, <1
Vitiligo		9, 0	11, 0		11, 0		9, 0	2, 0
Hypothyroid	9, 0	10, <1	9, 0	15, <1	16, 0	4, 0	15, 0	2, 0
Hypopituitary		<1, <1	<1, <1		12, 2		7, 4	2, 2
Hyperthyroid		7, 0	3, 0					2, <1
T1 diabetes		<1, <1	<1, <1					0, 0
Uveitis		<1, 0	1, 0					0, 0

# The general clinical algorithm



## Triage

- ❖ Acute oncology nurse
- ❖ Cancer specialist nurse
- ❖ Chemotherapy nurse

## Assessment

- ❖ Acute oncology doctor
- ❖ Oncology SPR on call
- ❖ Medical SPR on call

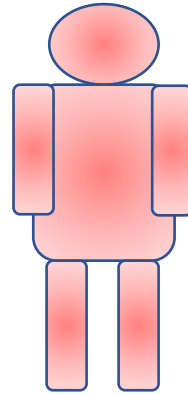
## Admission

- ❖ Ward SPR
- ❖ Onc. SPR - own team
- ❖ Oncology consultant
- ❖ Other specialities

# Must knows ...



Diarrhoea



Rash



## Non-specific

Out of the ordinary

- Generally unwell
- Exhausted
- Weakness
- Headache
- Breathless
- Nausea, vomiting
- Dizziness
- Numbness



Acute oncology  
24 hour hotline

# The response



## Triage

### ASK

- ❖ Immune treatment in last year?
- ❖ Unwell?
- ❖ Symptom?
- ❖ Red flag features

### ACTION

- ❖ Assess if grade  $\geq 2$ , or red flag features and immune treatment within year

### ADVISE

- ❖ Further contact
- ❖ Out patient review
- ❖ Patient admitted afar



## Assessment

### ASSESS

- ❖ Vital signs
- ❖ Red flag signs
- ❖ Blood tests – kidney, liver, hormone

### ACTION

- ❖ Admit if grade 3 and / or red flag
- ❖ Admit if unclear

### ADVISE

- ❖ Supportive measures
- ❖ Oral steroids
- ❖ Further contact
- ❖ Out patient review



## Admission

### ASSESS

- ❖ Observation?
- ❖ Investigations as per adverse event

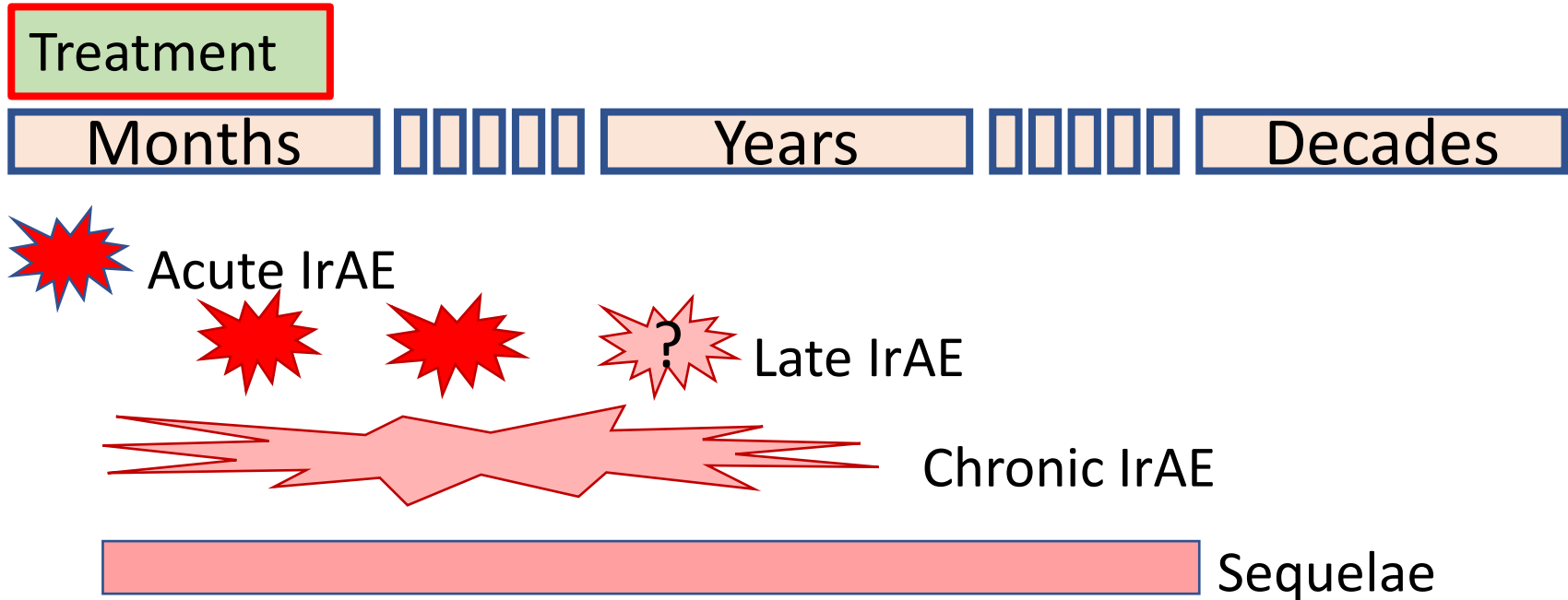
### ACTION

- ❖ Supportive care
- ❖ Methylprednisolone intravenous 1mg/kg
- ❖ Algorithms
- ❖ Specialist input
- ❖ Plan and timeline for escalation
- ❖ Plan and timeline for de-escalation



# Questions on IrAE

1. Describe what happens



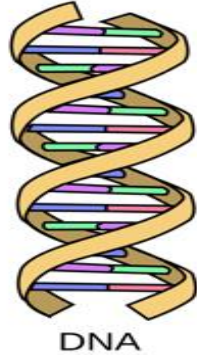
# Questions on IrAE

2. Are some people more likely to get IrAE?

3. Why?

Gene variation?

Variation in gene  
expression?



The cancer?

Environmental  
and lifestyle  
factors?



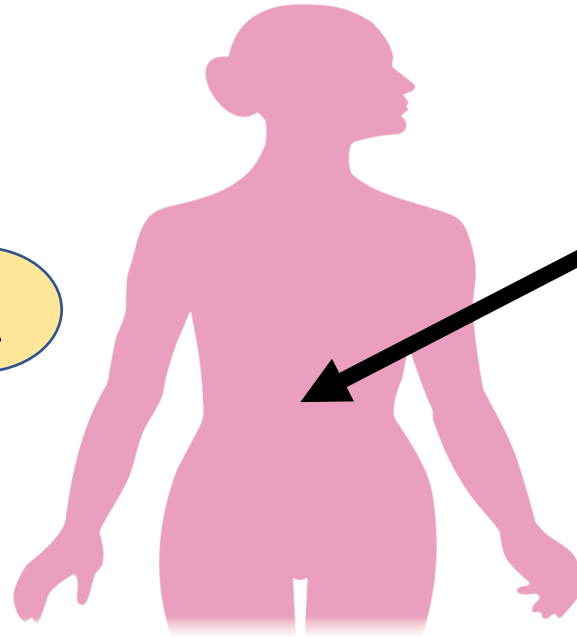
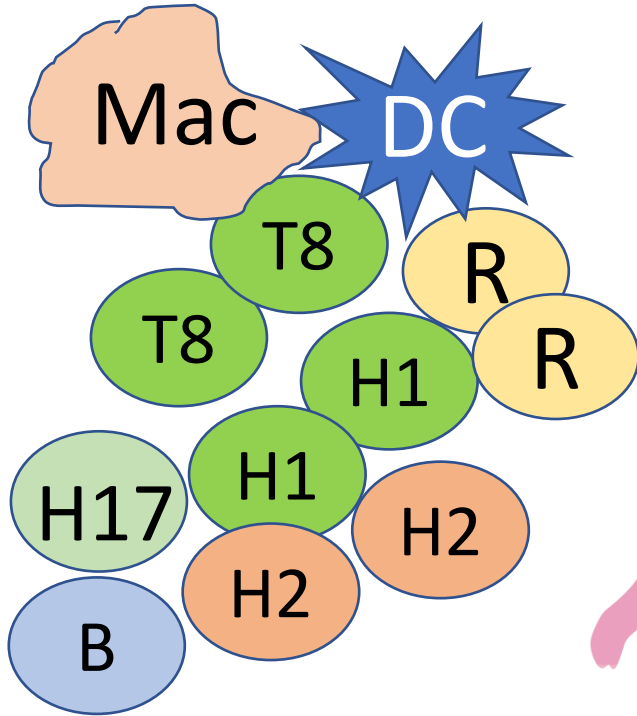
Bacterial flora?

Infections?

Antibiotic exposure?

# Questions on IrAE

4. What triggers an acute immune event?
5. What cells and other mechanisms are involved?



- Bacterial flora?  
Infections?  
Antibiotic exposure?  
Other drugs?

6. What is the best treatment for IrAE?

# Queen Elizabeth Hospital Birmingham Skin Cancer multidisciplinary team



UNIVERSITY OF  
BIRMINGHAM

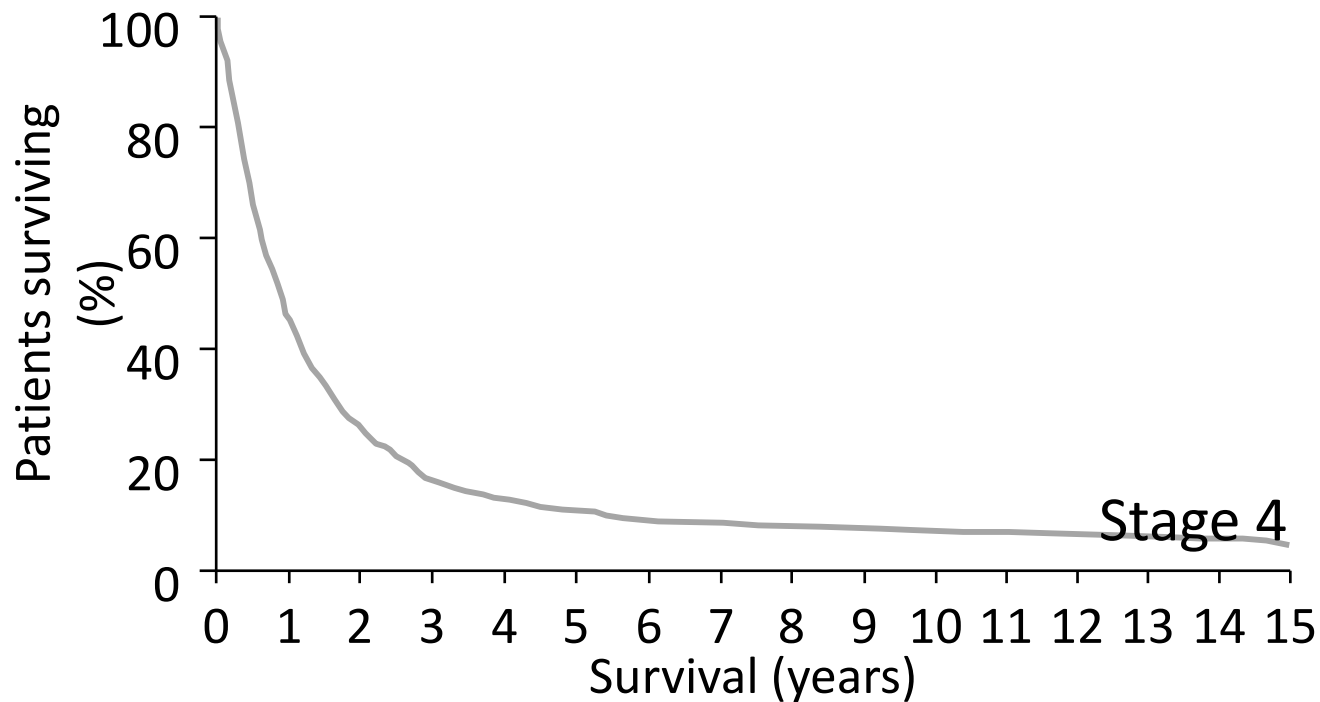


University Hospitals  
Birmingham  
NHS Foundation Trust

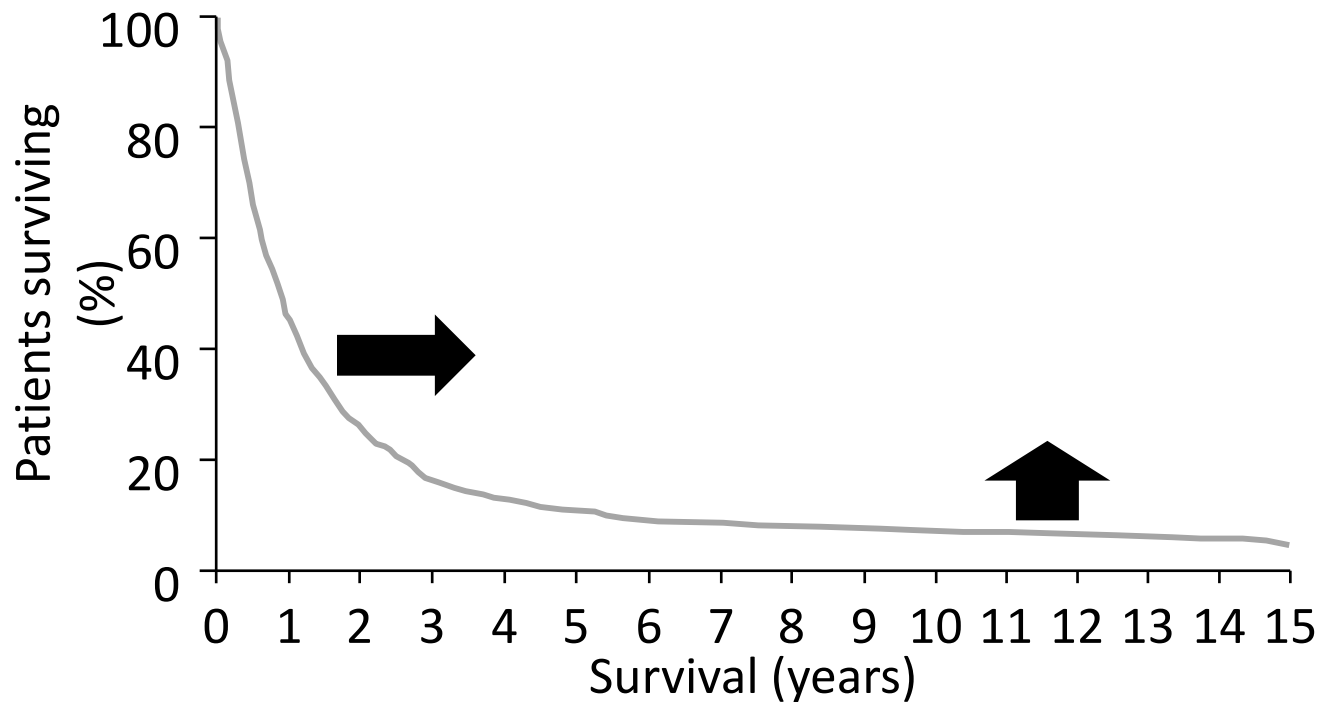




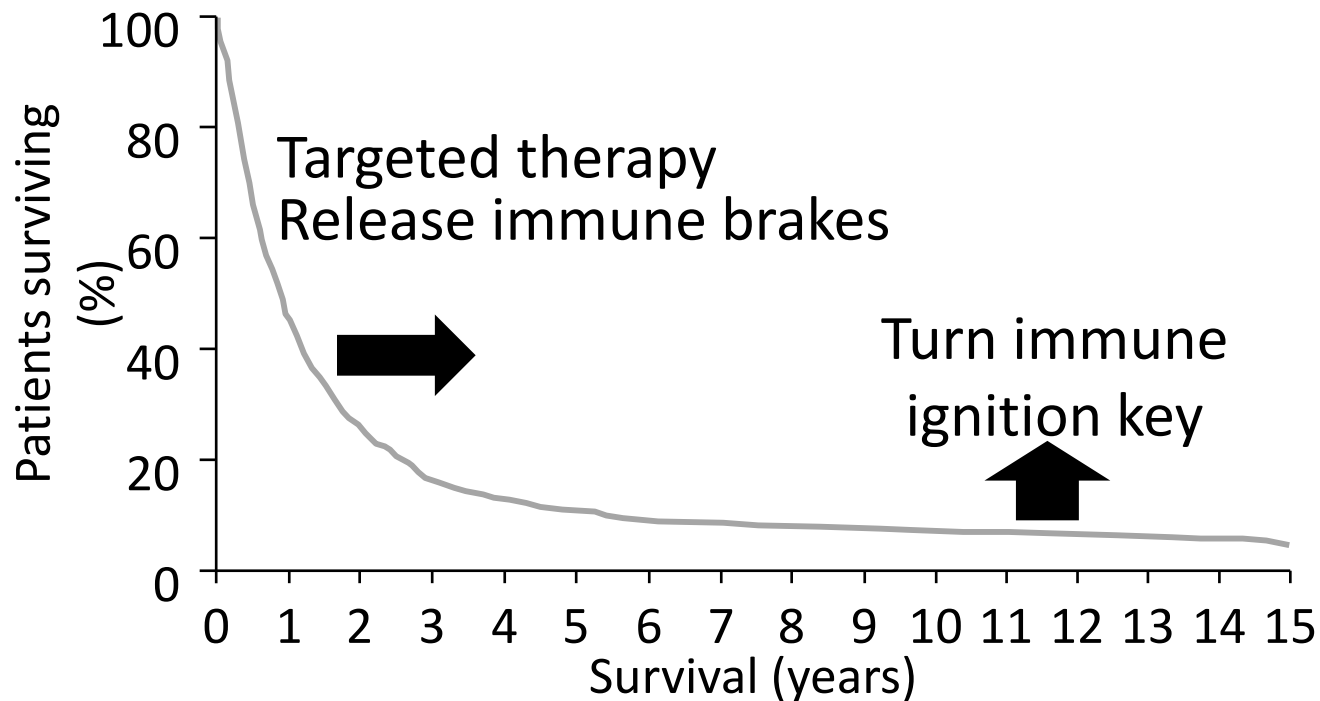
# Benefits of treatment



# Benefits of treatment

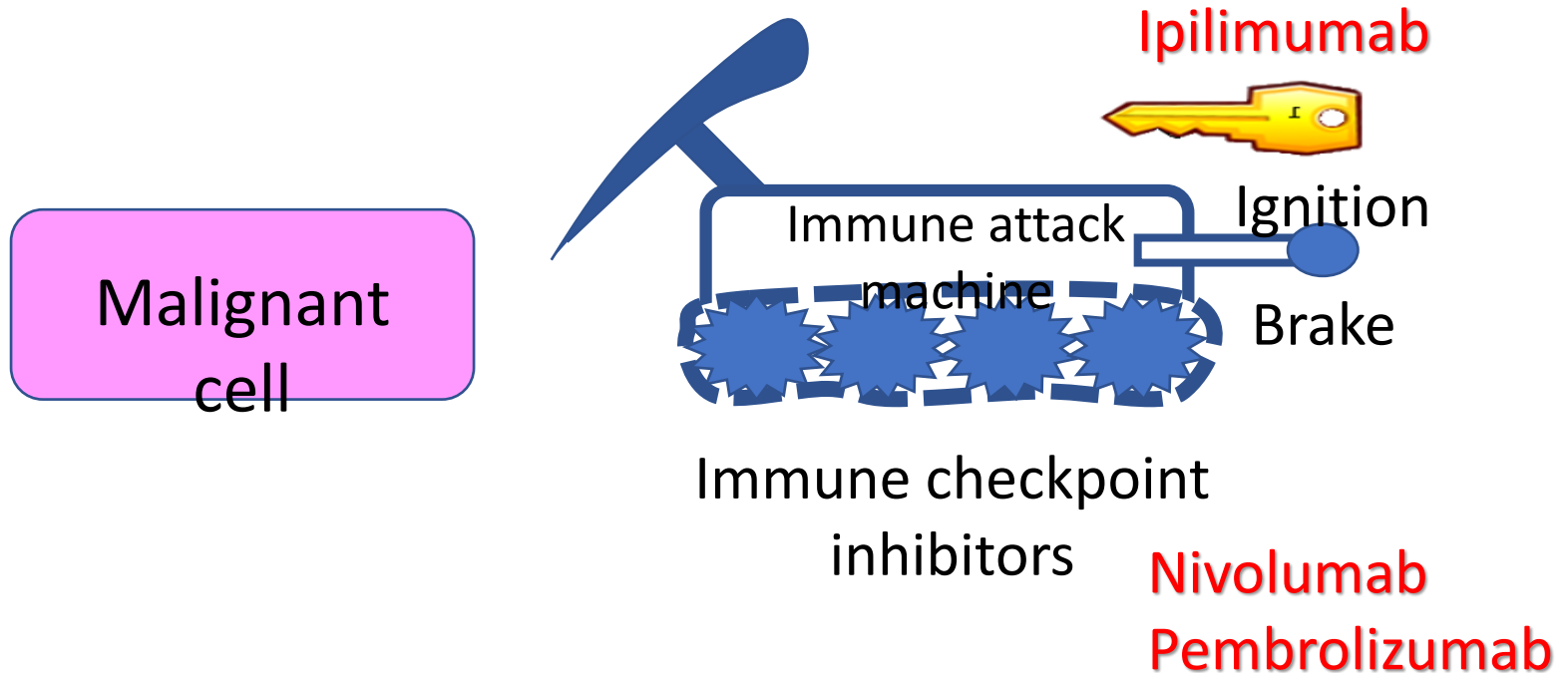


# Benefits of treatment





# Treatment for advanced melanoma



# The immune system has many components

