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What if our immune systems could fight cancer?

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Hannover Re



Overview of the presentation

- Cancer and the history of cancer immunotherapy
- Cancer immunotherapy – the current view
- Future trends in immunotherapy

Ben Willcox

- Impact of immunotherapy on insurance
- Conclusions and Q&A

Nay Wynn



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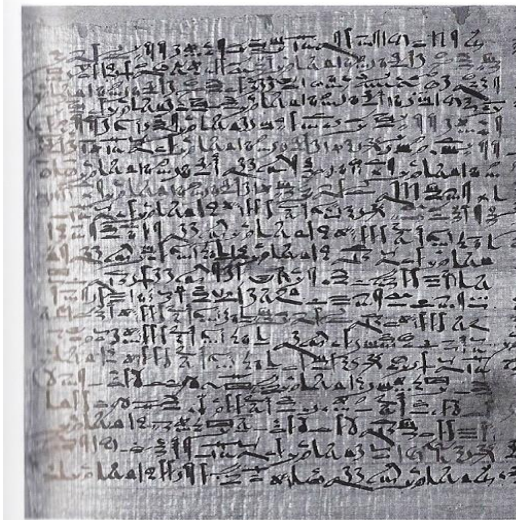
Cancer and the history of cancer immunotherapy



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Cancer – ancient disease, modern trend

- Cancer – uncontrolled growth of our own cells
- Many different types
- First described ~ 2500 years ago, in papyri
- But generally rare in historical record: infectious disease dwarfs cancer as cause of death in western world – until recently



Edwin Smith papyrus



Victorian slums

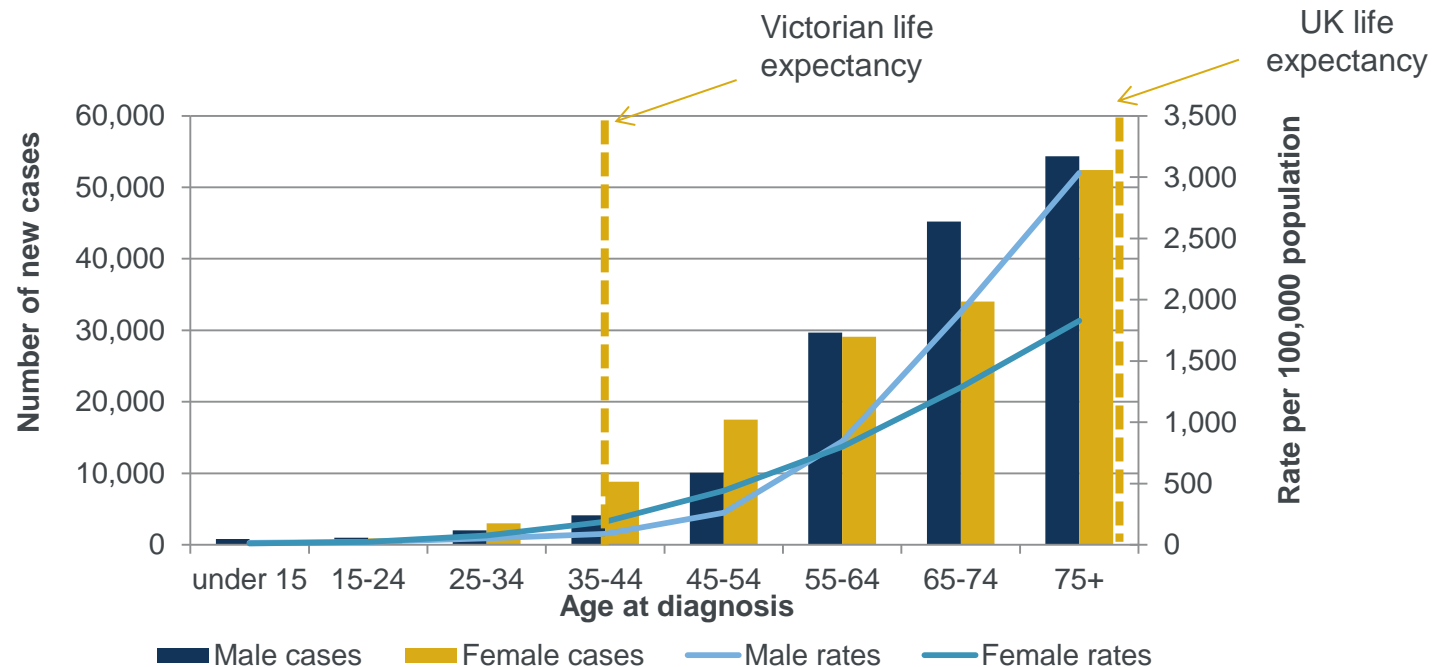
Life expectancy:
1871: ~ 40 years



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Cancer – ancient disease, modern trend

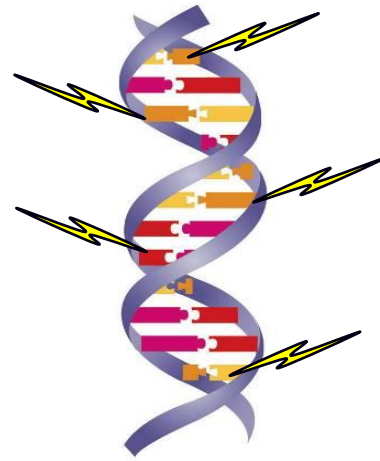
- Cancer increases after ~ 40 years
- Victorian life expectancy ~ 40 years
- Cancer therefore becomes more evident as life expectancy increases
- Advances in hygiene, childbirth healthcare, antibiotics, **vaccination**



What causes cells to divide out of control?

- Accumulation of faults in our DNA

Environmental carcinogens
e.g. tobacco, UV light



Inheritance

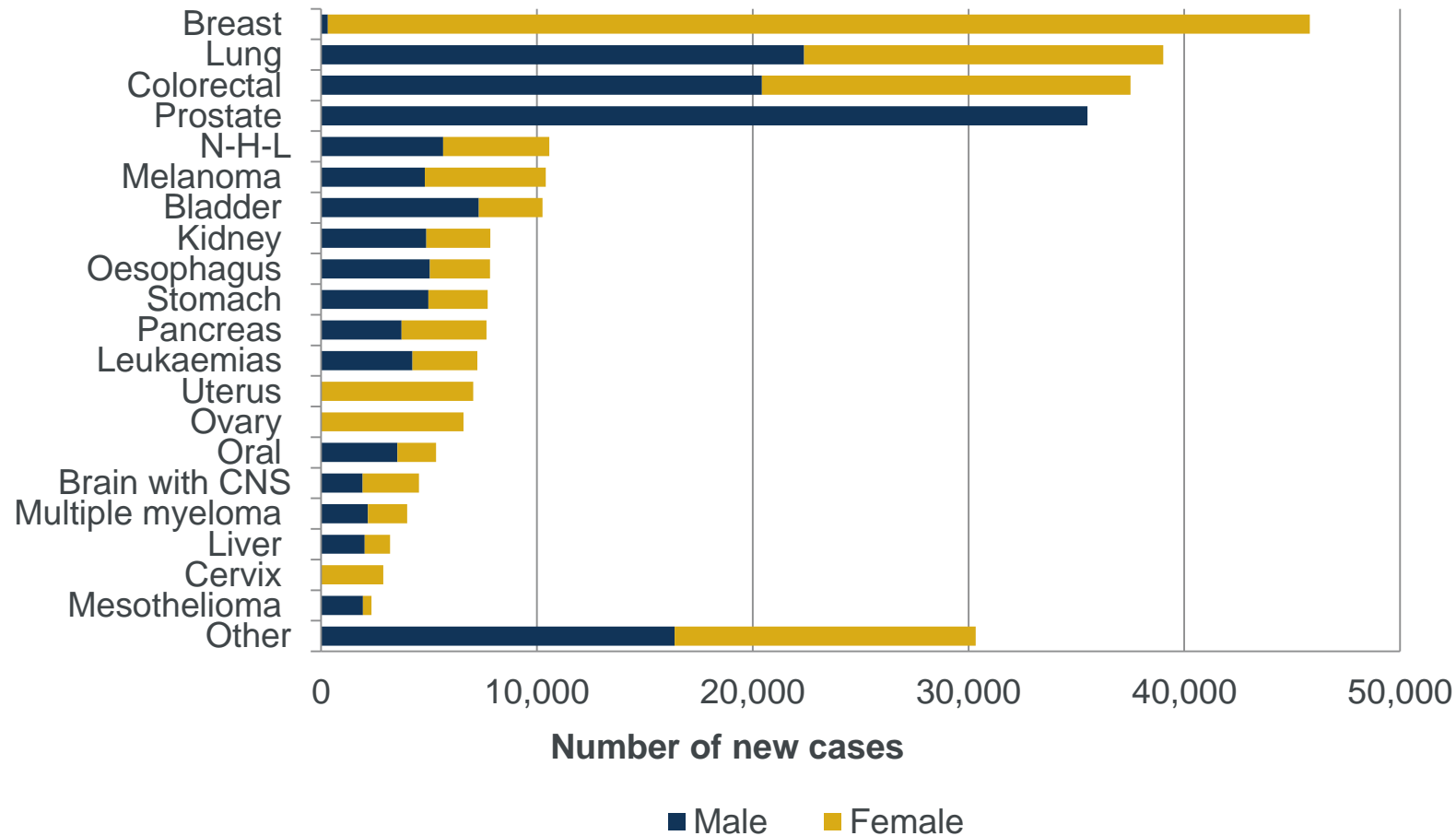


Natural cell processes



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The 20 most common cancers in the UK

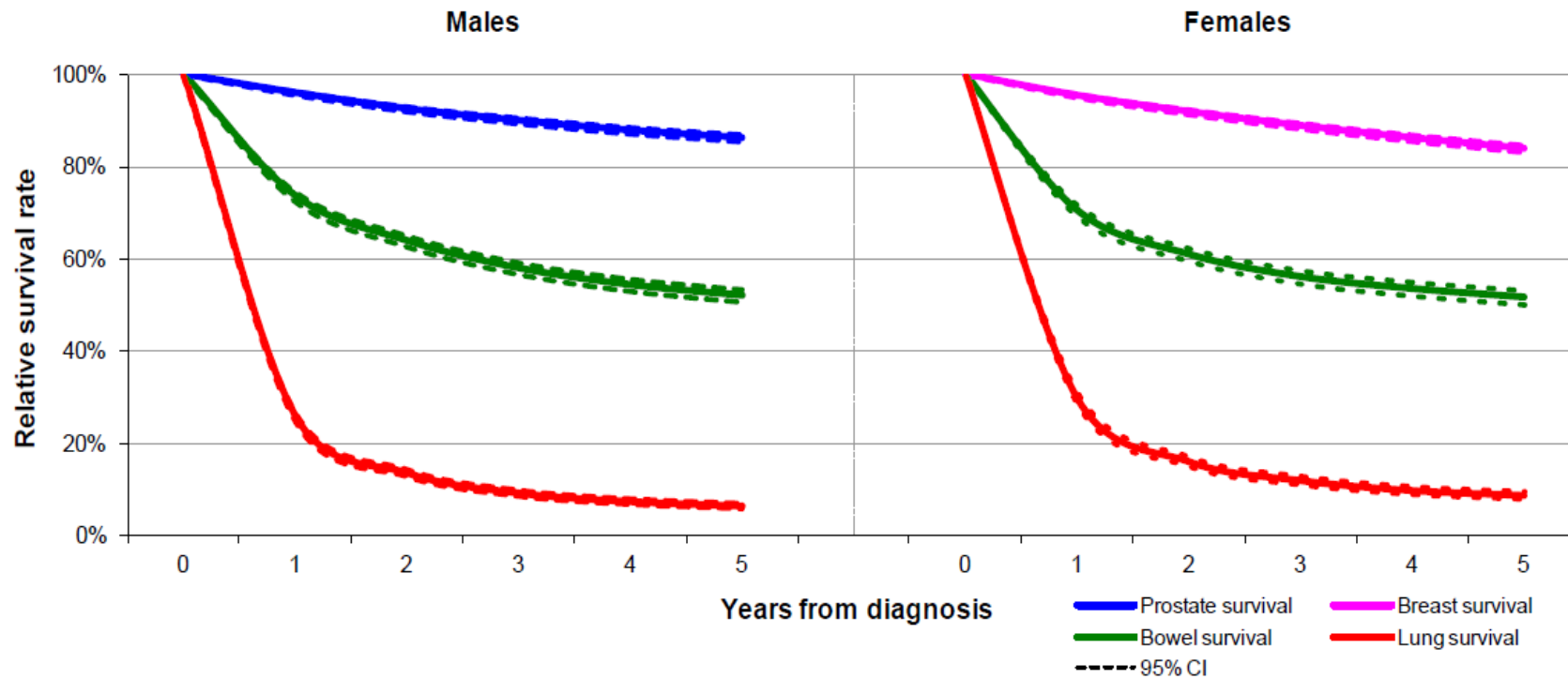


The current cancer treatment landscape

- Chemotherapy – eg Hodgkin's Lymphoma (~80% 5-year survival due partly to chemotherapy); also testicular cancer
 - disadvantages: non-specific; infection; often resistance means effects are short-lived
- Radiotherapy – eg prostate cancer (60% of men with early stage prostate cancer cured with radiotherapy)
 - disadvantages: non-specific; not so effective for metastases
- Surgery – eg breast cancer, where surgery contributes to high 5-year survival rates
 - disadvantages: ineffective for metastases; may not be curative in advanced settings



Many diseases, different prognoses



- Some cancers still have a very poor prognosis: 'cancers of unmet need'
- Treatment for late-stage disease is largely ineffective
- New treatment approaches required: cancer immunotherapy?



Your immune system: vital and exploitable



“Boy in the bubble”
syndrome



Smallpox virus (Variola virus)



Edward Jenner
1796, vaccination
1979, eradication

- A precedent from infectious disease
- Can we harness the incredible power of the immune system to cure cancer?

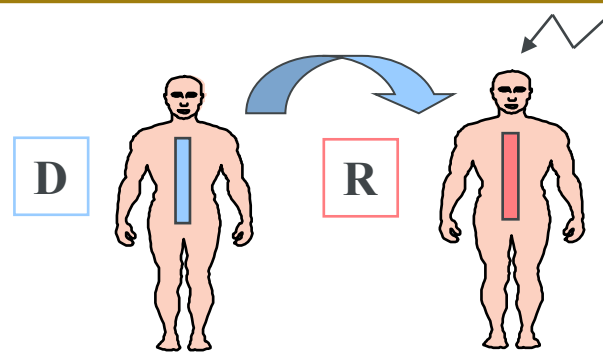


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Evidence for an immune response to cancer

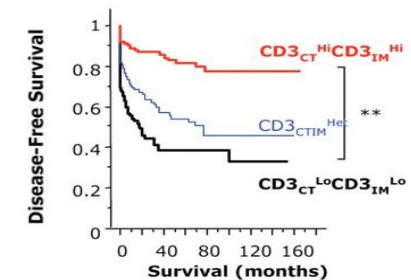
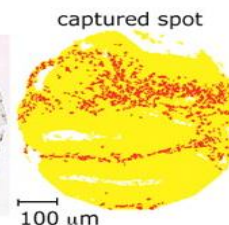
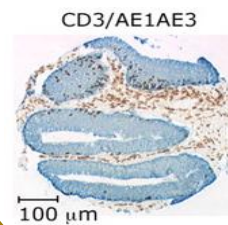
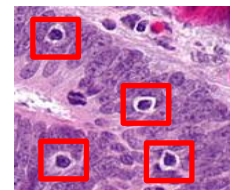
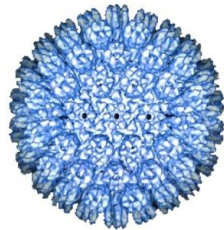


William B. Coley, 1893
Bacterial immunotherapy



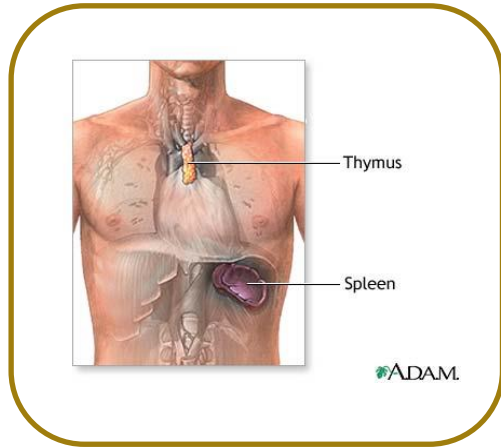
Stem Cell Transplantation: curative, due to 'GvL' effect

Immuno-suppression
(organ transplant,
HIV/AIDS)

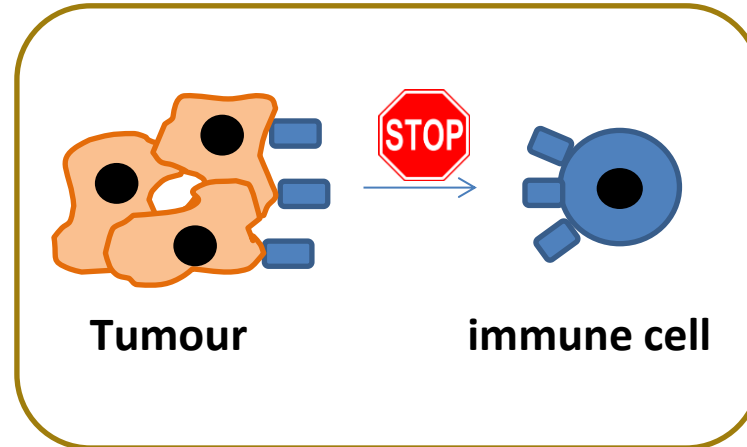


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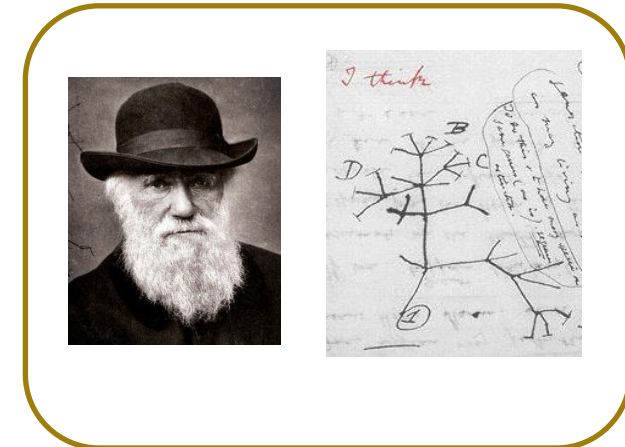
Immune recognition of cancer: the challenge



Immune tolerance to self



Tumour immunosuppression

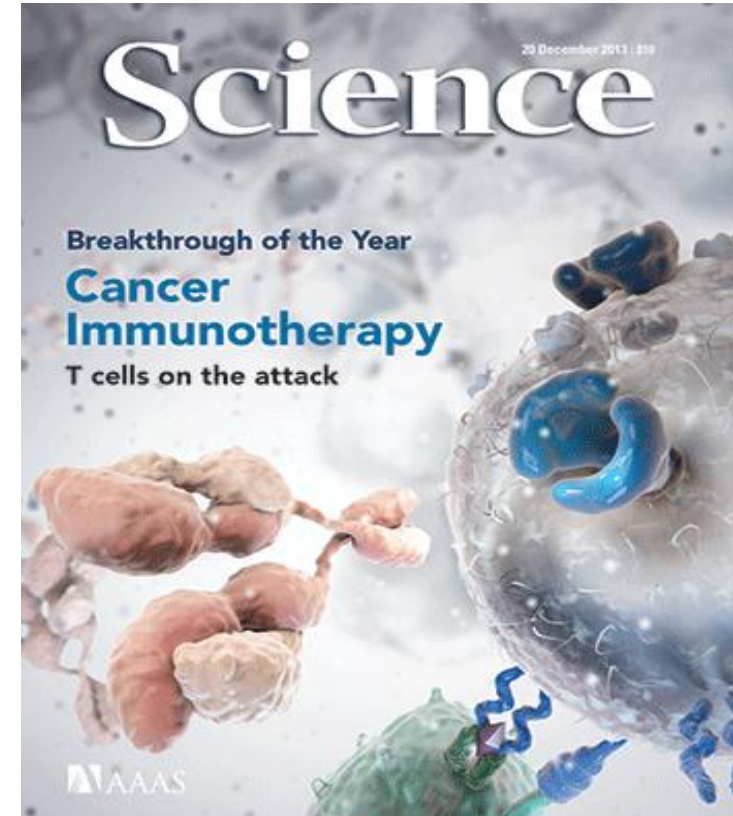


Tumour evolution to evade the immune system



Immunotherapy: a game-changer?

- “Tumour immunology has long had a bright future”
- “For those mice in the audience, it’s good news...”
- “Immunotherapy earns its spot in the ranks of cancer therapy”
- “...a tipping point in the fight against cancer”



Cancer immunotherapy – the current view



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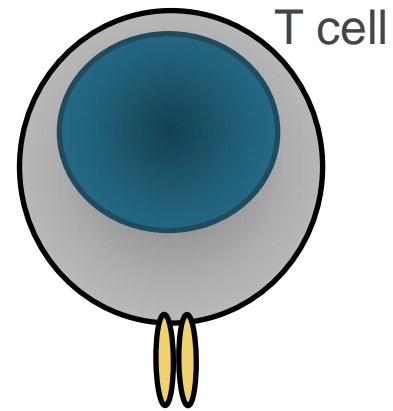
Two game-changing approaches

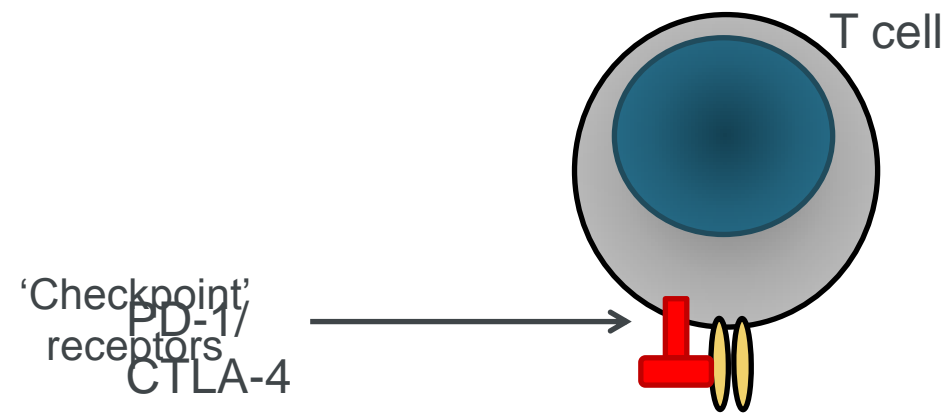
- (i) Removing the brakes on the immune system
- (ii) Engineering 'smarter' immune cells

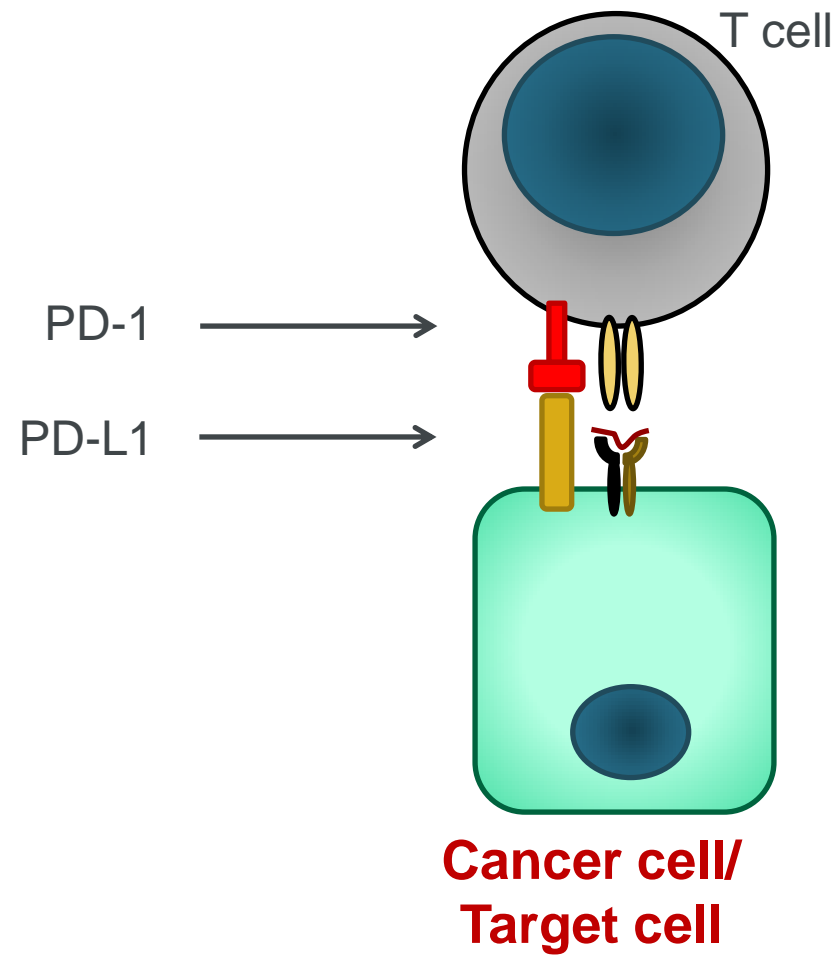


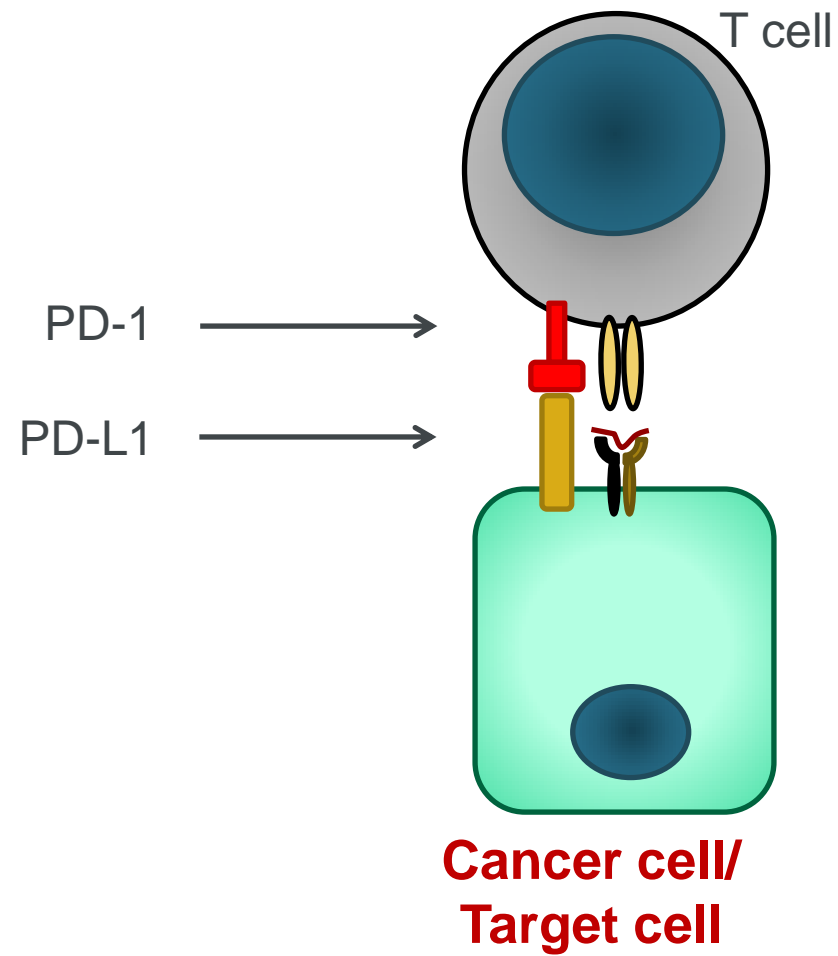
Checkpoint blockade: 'removing the brakes'

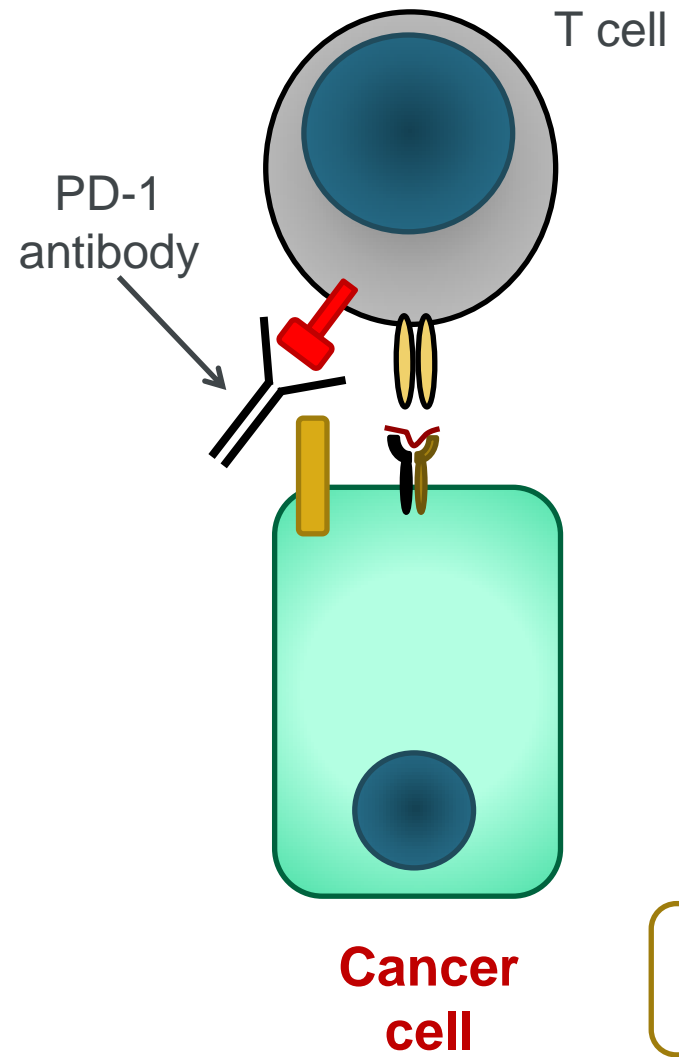
- Unleashing killer T cells



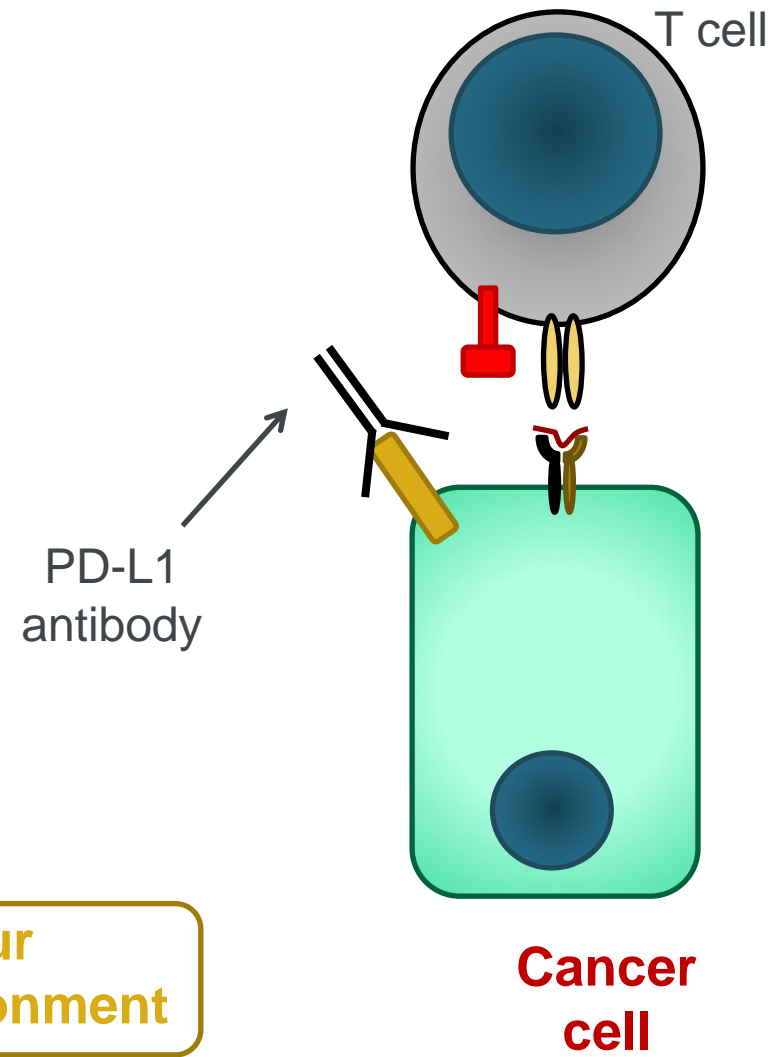


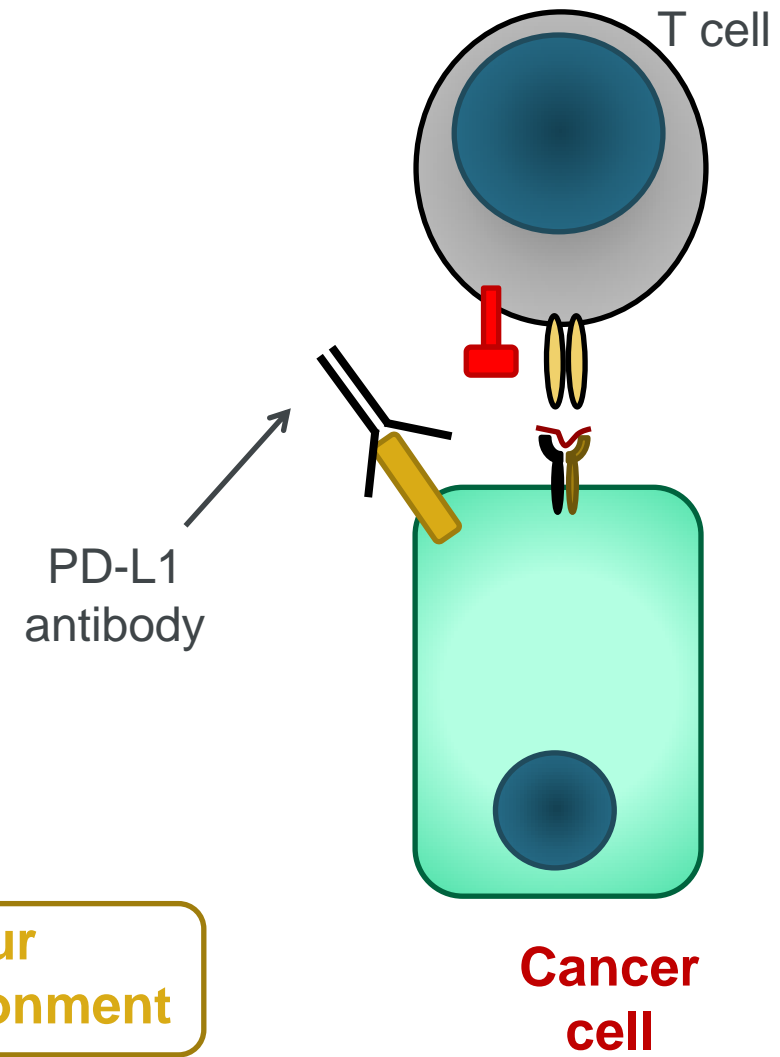
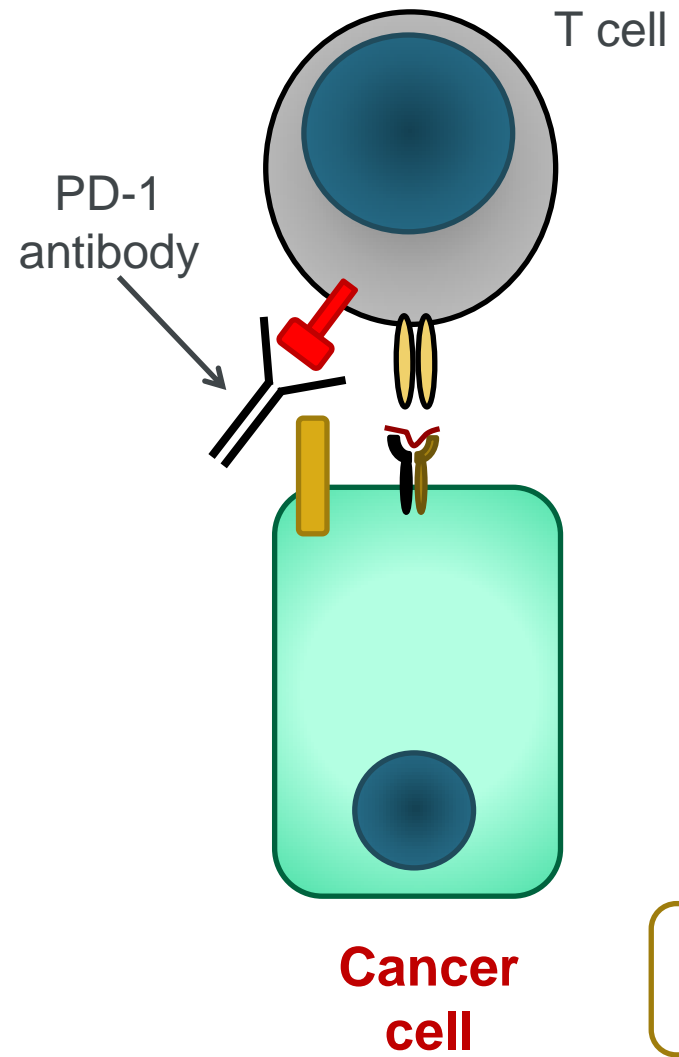




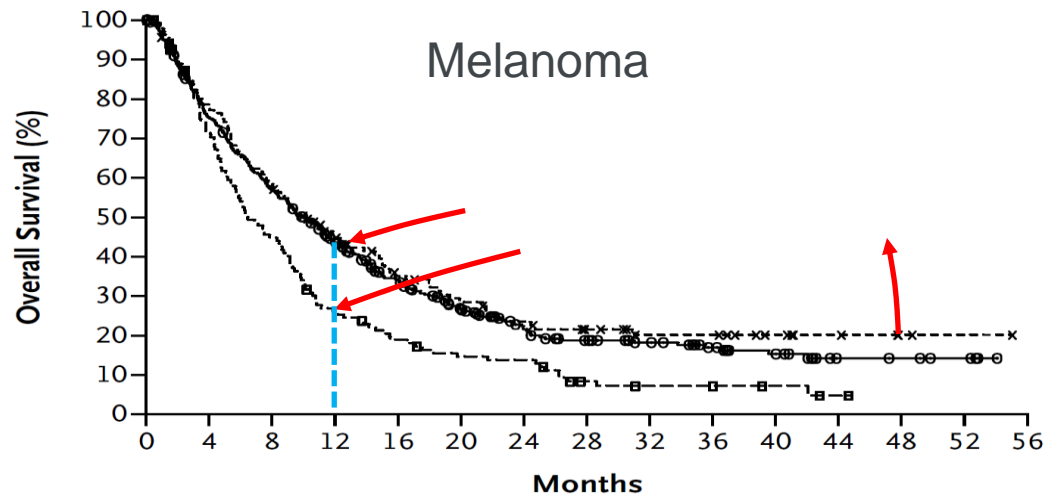


**Tumour
microenvironment**





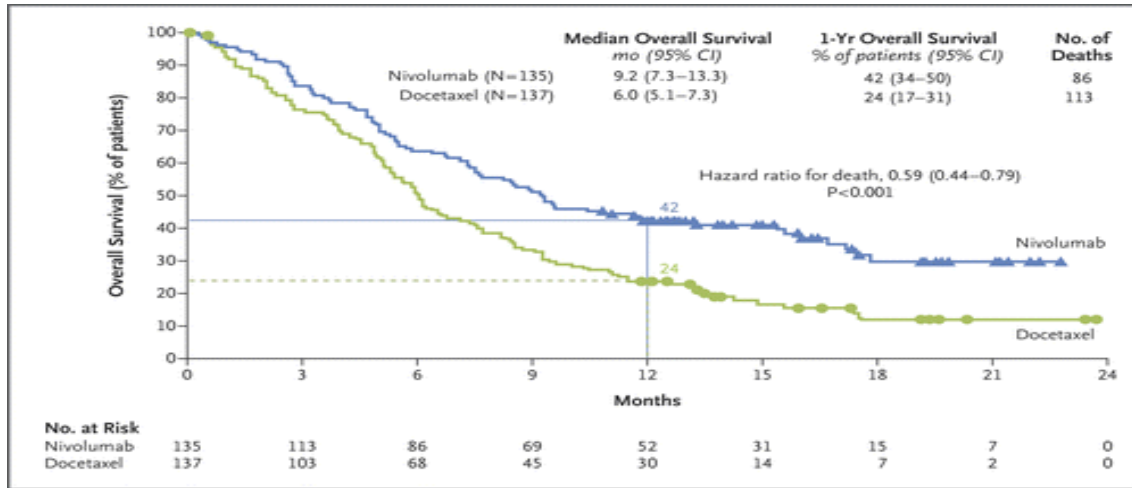
Clinical trials in CB: durability, efficacy in late stage, multiple tumours



- N Engl J Med 2010; 363:711-23
- Patients with metastatic disease, ie previously treated
- Phase 3 study: Ipilimumab
- Improvement in overall survival



Clinical trials in CB: durability, efficacy in late stage, multiple tumours

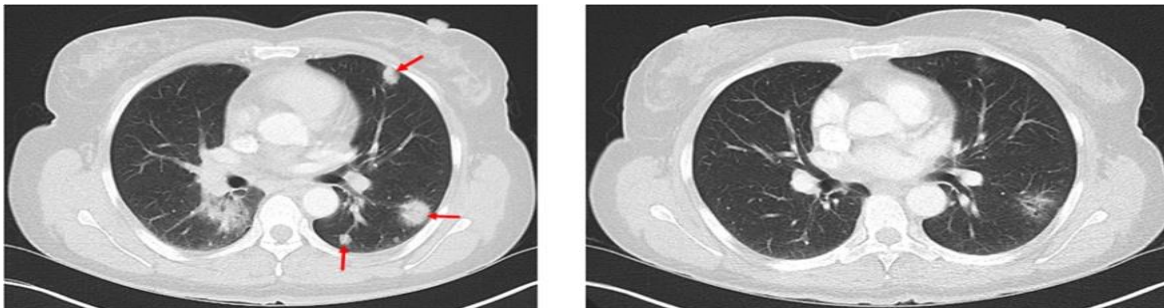


Lung cancer

- Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer
- N Engl J Med 2015; 373:123-135 July 9, 2015 Brahmer *et al.*

Conclusions

- Treatment efficacy in late stage when chemo fails
- Durability of response – increased survival
- Impact in multiple tumours
- Only some patients respond well
- Side effects possible
- Clinical view: “Gobsmacked”



(L) MRI lung scan, 51 year old patient, active tumour progression despite chemo (red arrows = metastases).

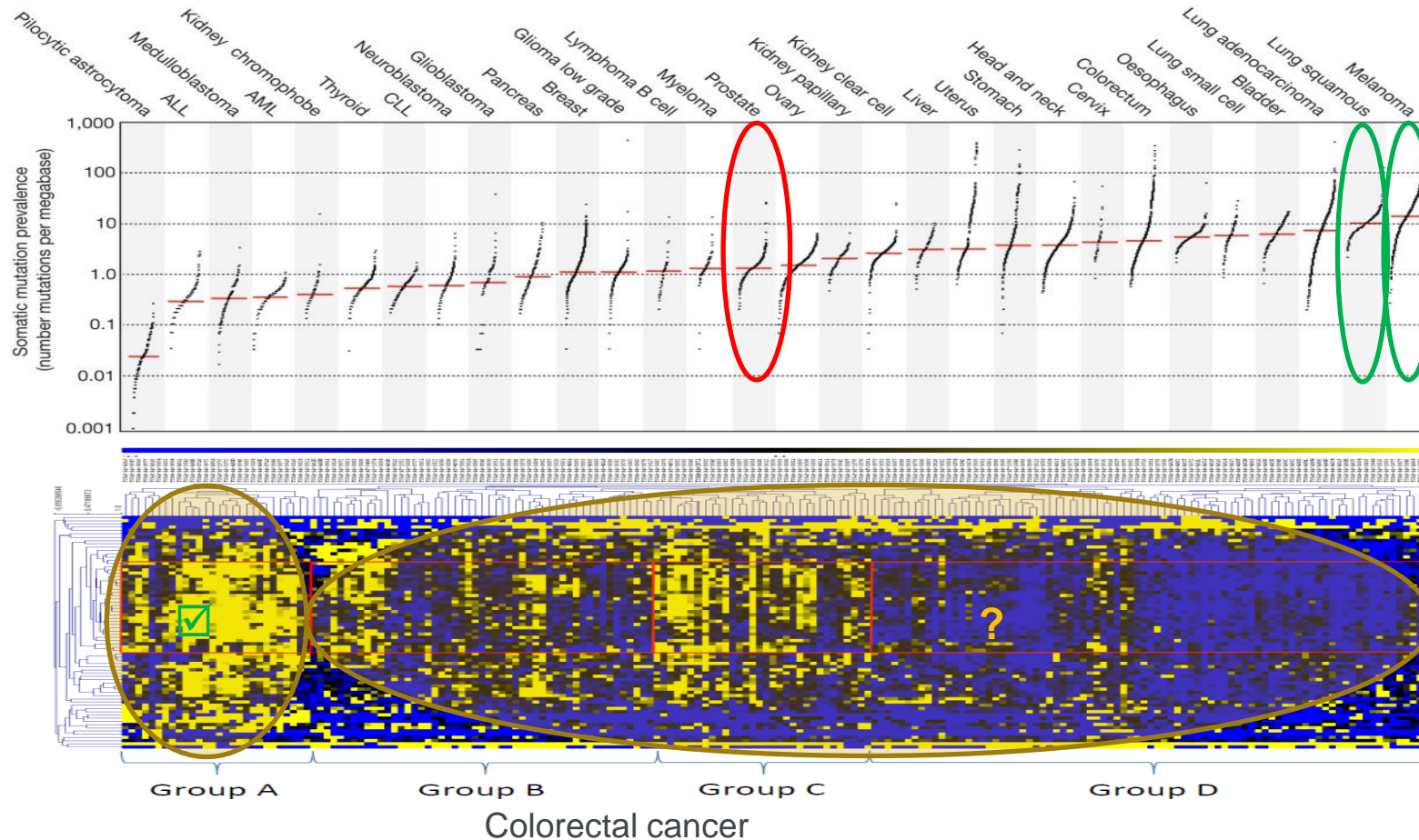
(R) < 3 months of anti-PD1 treatment



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Biological mechanism: recognition of mutated self

- Mutations matter



- The prevalence of somatic mutations across human cancer types.
- Signature of mutational processes in human cancer; Alexandrov et al, Nature 500, 415-21, (2013)

- The more mutated a tumour, the more visible it is to the immune system
- Future scope of identifying likely responders



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Current approvals

- Melanoma - Ipilimumab approved for the treatment of previously-treated metastatic (advanced) melanoma (NICE, 2012)
 - “a major milestone in the treatment of advanced melanoma... a genuine step change in the management of this disease.” Dr Paul Lorigan, Christie NHS Trust.
- Ipi and Nivo combo approved for advanced melanoma (NICE, 2016)
 - “The combination of nivolumab with ipilimumab gives us a glimpse of the future of cancer treatment” Prof Raj Chopra, ICR.
- Lung cancer - strong Nivolumab efficacy data, currently being assessed by NICE



Checkpoint blockade: challenges

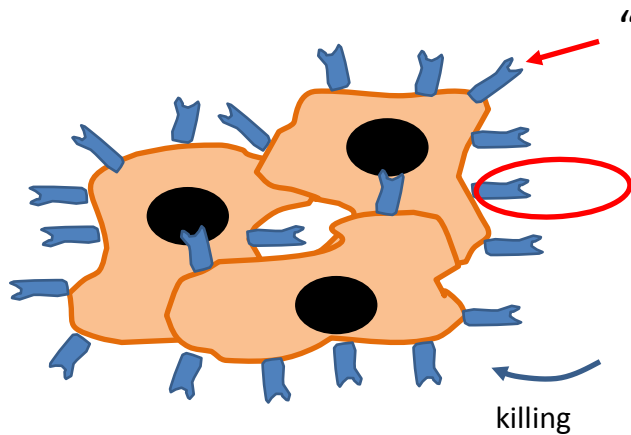
Arguably the most exciting area for pharma oncology research currently, but...

- **Huge expense** - ~ \$100,000 per year per patient – does the NHS have the funds to approve all viable therapies?
- **Only some patients respond well** (durable, complete response) – how to identify these patients?
- **Side effects** – can be severe

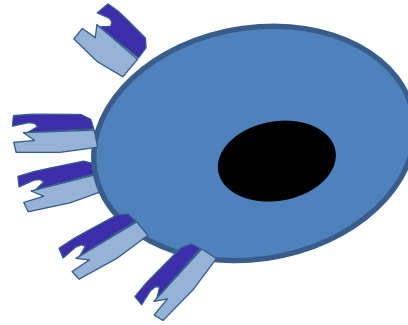


CAR immunotherapy: engineering smarter immune cells

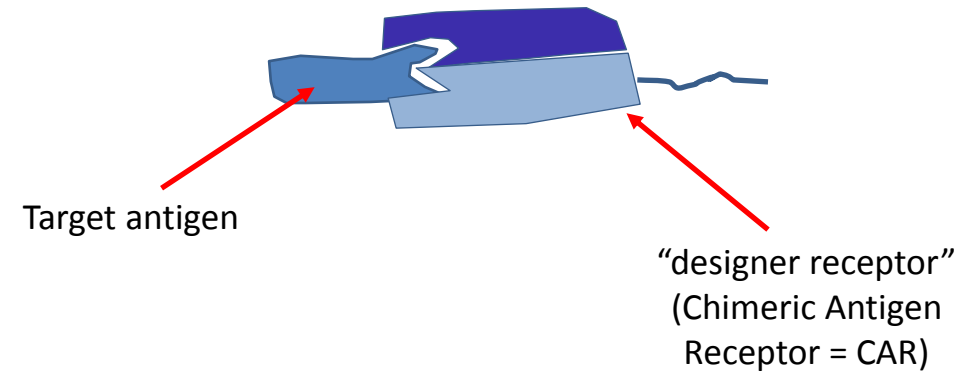
- CAR = Chimeric Antigen Receptor



B cell tumour ALL/CLL



"CAR" T cells



CAR therapy in B cell tumours: game changer



Emily Whitehead - "The girl that lived"

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

NEJM, October 2014



Experimental white blood cell
treatment shows 'remarkable'
promise in leukaemia

CRUK website blog, October 2014

Conclusions

- Relapsed, refractory ALL patients treated
- Complete remission in 90% of patients
- Very effective tumour clearance
- "On target" side effects, can be severe
- Long-lasting responses...potential cures



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CAR immunotherapy: challenges

- Can you expand the success of CAR therapy beyond haematological malignancies?
- What molecular targets will allow safe and specific targeting of tumours?
- Can the cost of a cellular therapy be absorbed into the NHS?



Future trends in immunotherapy



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Trends in checkpoint blockade: 'removing the brakes'

- Combination approaches to increase the proportion of patients who will respond:
 - Ipilimumab + Nivolumab (melanoma) – major improvement in response rate
 - Numerous combinations to test (CB + CB; CB + chemo; CB + targeted therapy; CB + other immunotherapy)
- Improved stratification of likely responders
 - Eg Colorectal cancer – MSI-hi subgroup (15% show high response rate)
 - Improved prediction of where durable responses will be observed – conversion of some conditions from critical to curable

TREND: increasing number of patients/tumours/tumour subgroups where durable responses are observed



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Trends in CAR immunotherapy: 'engineering smarter immune cells'

- More sophisticated CAR targeting approaches
 - A trend away from single targets (eg CD19) towards multiple CAR targets to define tumour and tissue type
 - Different strategies (eg targeting the tumour's 'support structure')
- Extended success of CAR immunotherapy across haematological tumours
 - Adoption in some CD19-positive B cell tumours
 - Application in other tumours eg Myeloma?
- Ongoing CAR trials in multiple solid tumours

TREND: increasing number of patients/tumours/tumour subgroups where CAR therapy can induce durable responses



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New immunotherapy approaches

Personalised vaccines

Generic treatments ineffective ?



Preventative vaccines

High risk group/known targets ?

Antigens not 'immunogenic' enough ? Add new antigens !

Redirected Viral Immunotherapy

TREND: explosion of new cancer immunotherapy approaches

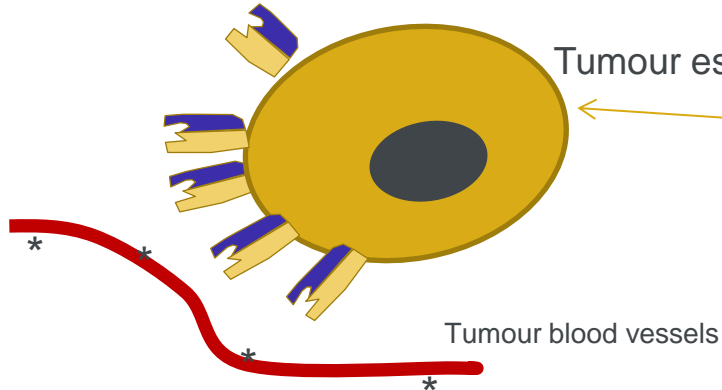
Antigens not 'immunogenic' enough ? Bring in new T cells

Immunocore Ltd
'ImmTAC': Immune mobilising monoclonal TCRs Against Cancer

Tumour escapes ?

Cancer of unmet need

Attacking the tumour's support structure



CAR T cells - CLEC14A

Healthcare provision trends

- Increasing array of expensive, potentially much more effective treatments for cancer
- Challenging regulatory decisions (NICE/NHS) based on efficacy vs cost considerations
- Approved therapies will lag behind availability of effective immunotherapies (e.g. Nivolumab, lung cancer)



Impact of immunotherapy on insurance



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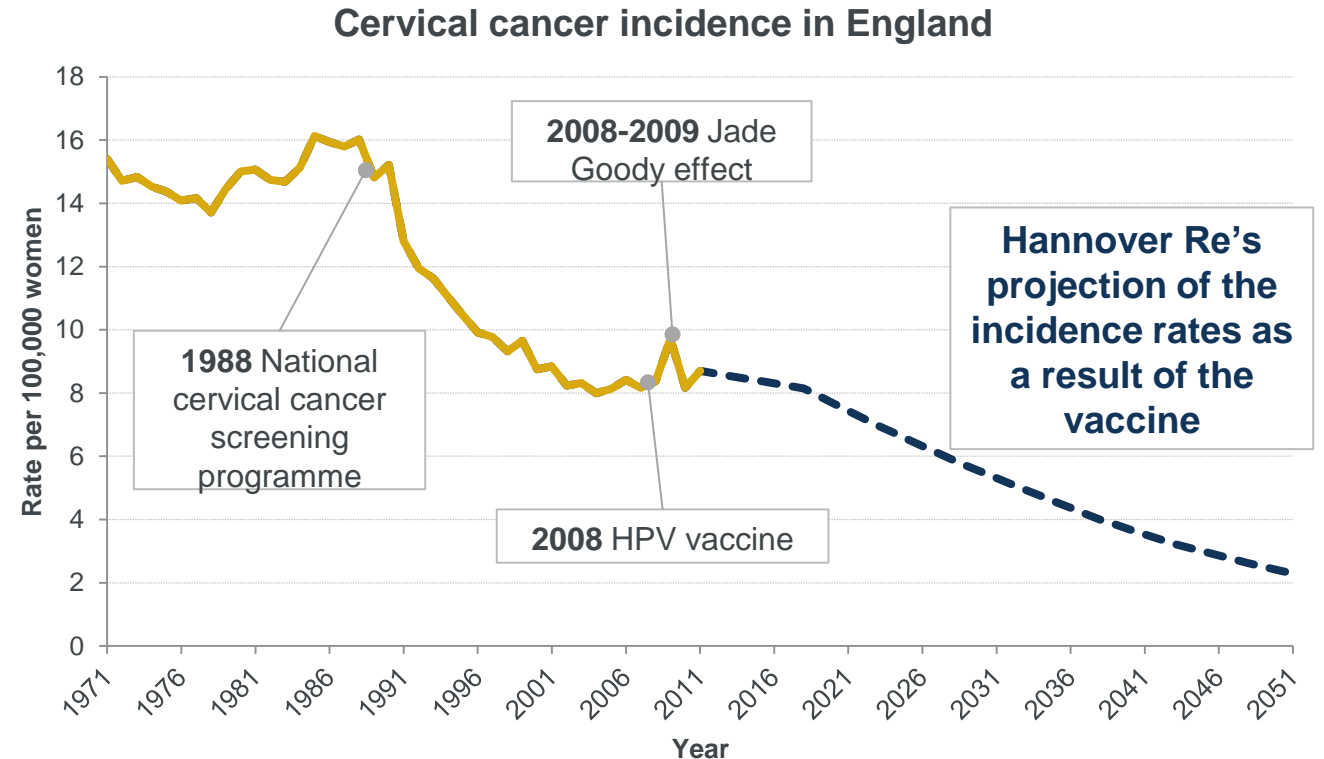
Immunotherapy is a treatment

- Diagnosis of disease required before the treatment is applied
- CI claim payment is likely to be made
- No impact on CI pricing (base rates and trends)



Immunotherapy as a prophylactic treatment

- Immunotherapy needs to:
 - become cheaper
 - lead to better patient outcomes
- “Prevention is better than cure”
- Example: Human Papilloma Virus vaccine – Introduced to all girls aged 12 to 13 in 2008.



Source (excluding the projection)) comes from the Office of National Statistics



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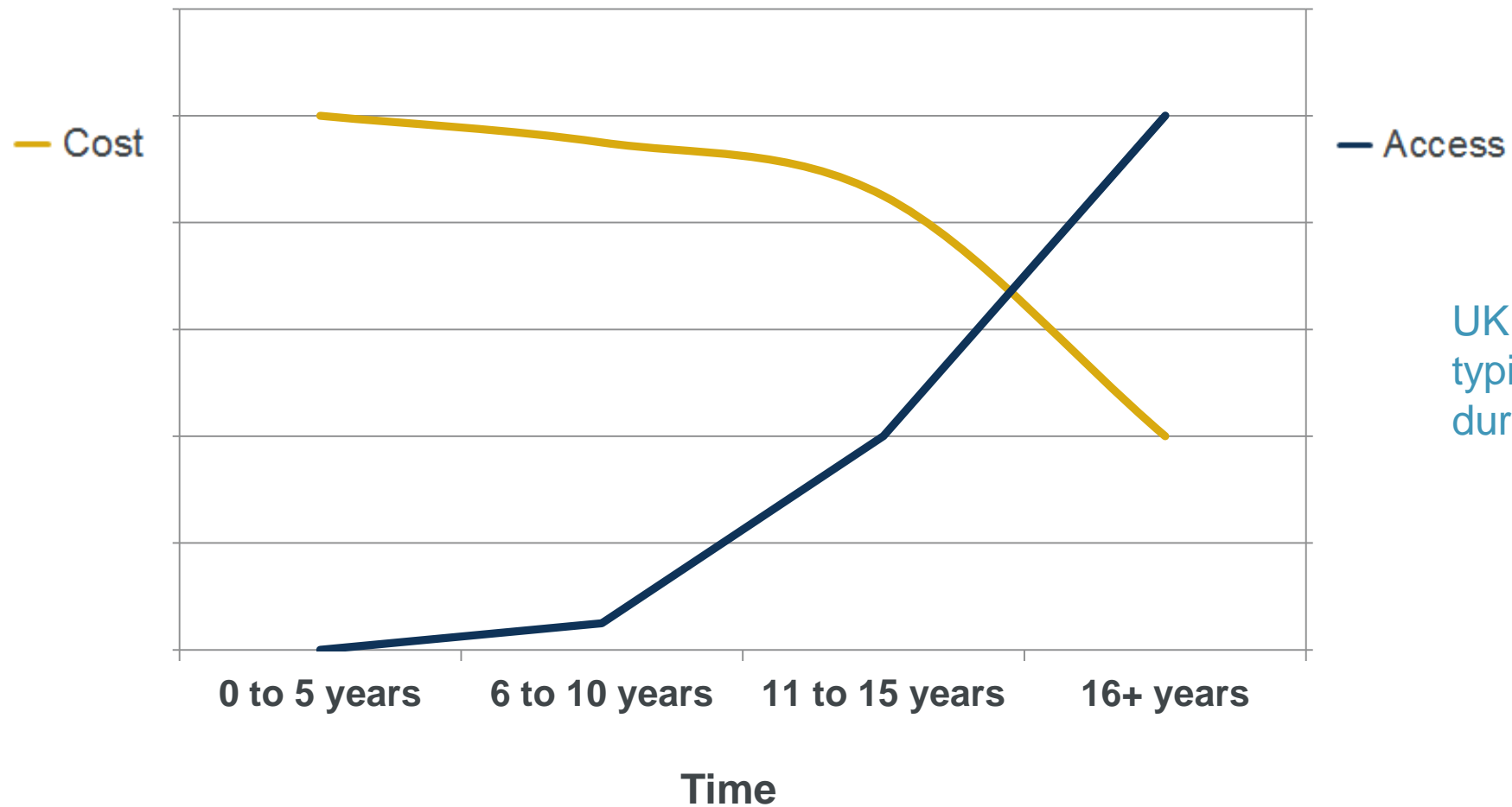
Viruses causing cancer and diseases linked to the immune system

- Human Papilloma Virus
- Hepatitis B and C virus
- Epstein-Barr virus
- HIV
- Aplastic anaemia
- Bacterial meningitis
- Crohn's Disease
- Devic's disease
- Encephalitis
- Major organ transplant
- Multiple Sclerosis
- Rheumatoid Arthritis
- Systemic Lupus Erythmatosus (SLE)

- Impact on CI price from reducing incidence rates to zero over the next:
 - 30 years: **3% reduction**
 - 20 years: **4% reduction**



The development costs & access challenge

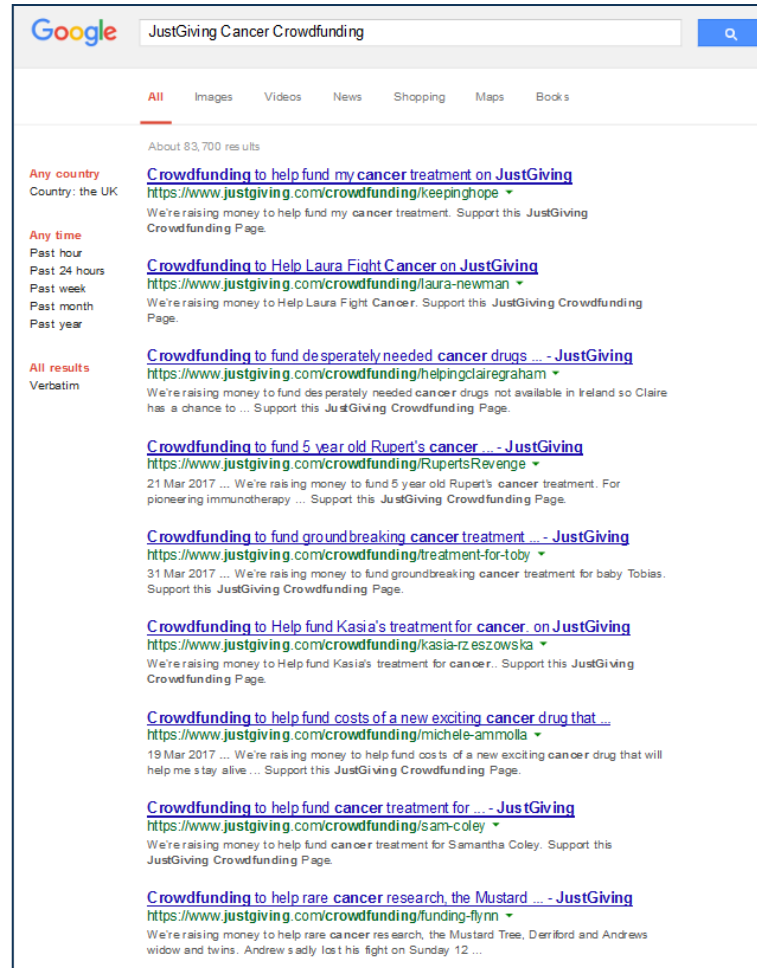
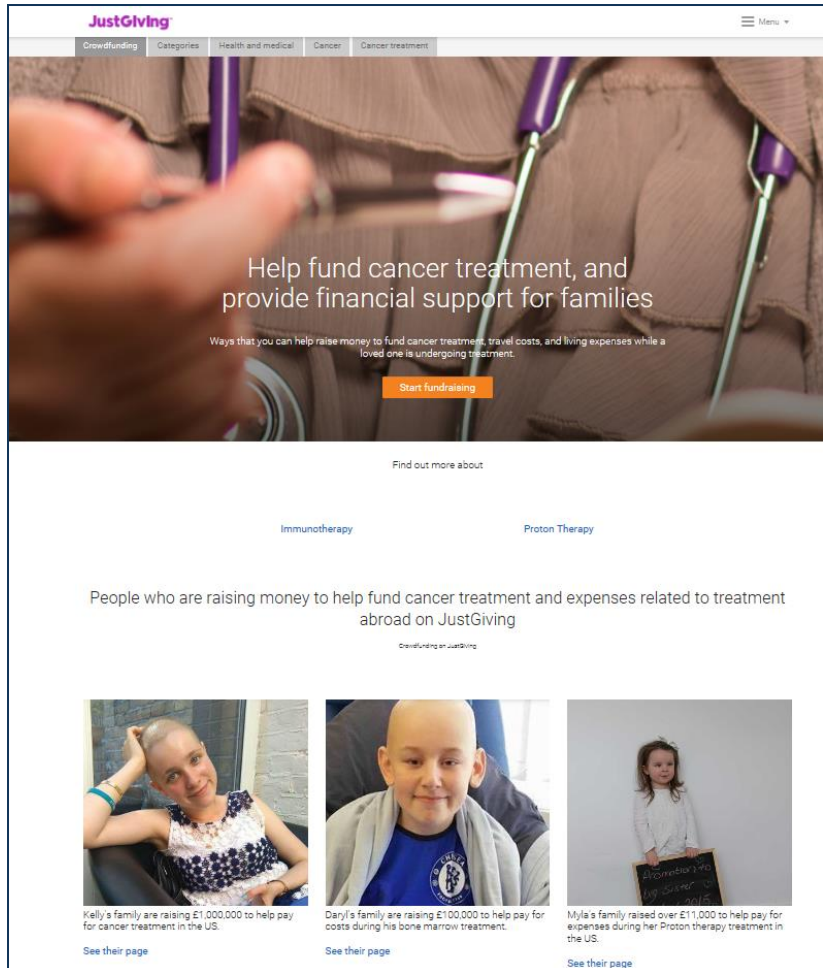


UK Drug Patents:
typically 20 year
duration



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CI Product Considerations: prohibitive costs for individual



- From 2015 to 2016, there was an 8 fold increase in amount of money raised for obtaining cancer treatments abroad
- Travel to USA, Mexico & Germany top 3 treatment destinations
- Immunotherapy most common individual treatment

Source: JustGiving 2017



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CI Product Considerations: meeting hidden cancer costs

- Reduced income

Thirty per cent of people with cancer experience a loss of income as a result of their cancer, with those affected losing, on average, £860 a month.



CI Product Considerations: meeting hidden cancer costs

- Reduced income
- Increased costs
 - Out/In-patient costs

The cost of travel to and from appointments affects 69% of people with cancer and costs them, on average, £170 a month.



CI Product Considerations: meeting hidden cancer costs

- Reduced income
- Increased costs
 - Out/In-patient costs
 - Day to day living costs

Over a quarter (28%) of people with cancer couldn't keep their home adequately warm in winter in the past 12 months because of the cost.



CI Product Considerations: meeting hidden cancer costs

- Reduced income
- Increased costs
 - Out/In-patient costs
 - Day to day living costs
 - Prescription costs

Over a fifth of respondents were affected by costs for over-the-counter or prescription medicines, costing on average £8 a month.

| Costs incurred by respondents to our survey | | |
|---|----------------------|--|
| Cost | % of people affected | Average cost to those affected (£/month) |
| Over-the-counter/prescription medicines | 22% | 8 |
| Dietary supplements | 12% | 16 |
| Dressings | 10% | 7 |
| Private treatment or healthcare | 4% | 112 |
| Dental surgery or care | 11% | 28 |
| Nursing care provided in a person's home | 1% | N/A* |
| Personal care provided in a person's home | 5% | 56 |
| Total | 41% | 41 |

*Sample size too low to report.



CI Product Considerations: meeting hidden cancer costs

- Reduced income
- Increased costs
 - Out/In-patient costs
 - Day to day living costs
 - Prescription costs
 - Clothing and accessories such as wigs

| Costs incurred by respondents to our survey | | |
|---|----------------------|--|
| Cost | % of people affected | Average cost to those affected (£/month) |
| Wigs, hairpieces, head coverings | 10% | 23 |
| Fabric supports | 5% | 14 |
| Clothing | 29% | 31 |
| Modifying the home | 4% | 326 |
| Specialist equipment for home or care provided in a person's home | 6% | 28 |
| Total | 37% | 70 |



CI Product Considerations: hybridisation

- Incorporate benefits provided from other products, such as PMI, major medical expenses and hospital cash style plans to meet the cost of:
 - medical treatments
 - travel expenses
 - non-medical additional costs
 - income replacement costs



Conclusion



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Questions

Comments

Expressions of individual views by members of the Institute and Faculty of Actuaries and its staff are encouraged.

The views expressed in this presentation are those of the presenter.



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