QCGC research

QCGC Research Symposium

Prof Andreas Obermair
& Dr Jeffrey Goh

We research & develop the best standard of care for women experiencing gynaecological cancer

Cherish Base Camp Trek

QLD Centre for Gynaecological Cancer Research

An entity within The University of Queensland

Housed on Herston campus (next to RBWH) in UQCCR

Chair: Prof. A Obermair; less than 10 research staff; supported by all gynae-oncologists

Budget approximately $600,000 per annum

- Revenue: Competitive grants*^, Cherish & other donations
- Outgoings: Salaries, direct research costs

*Shortfall: Development of grants, writing of grant applications, admin costs are not covered by grants;
^Success rate is < 10%

Media hype

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DAILY EXPRESS

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WEATHER: SHOWERS

FRIDAY AUGUST 1, 2014 55p

3 MEMBERS OF BRITISH FAMILY DIE IN HOLIDAY CAR TRAGEDY

SEE PAGE 4

Richard Hughes riding winner, Ivawood

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NEW HOPE FOR CANCER CURE

£300m boost to fight against killer disease

By Macer Hall Political Editor

THE NHS is set to become a world leader in the fight against cancer, David Cameron will predict today.

Britain will drive cutting-edge research as a result of a £300million funding boost to be unveiled by the Prime Minister.

The spin-offs are likely to transform the way cancer and other life-threatening conditions are diagnosed and treated, bringing new hope to families across the country.

A deal has been agreed to significantly increase investment in a project to map 100,000 complete genetic DNA code sequences, Mr Cameron will confirm.

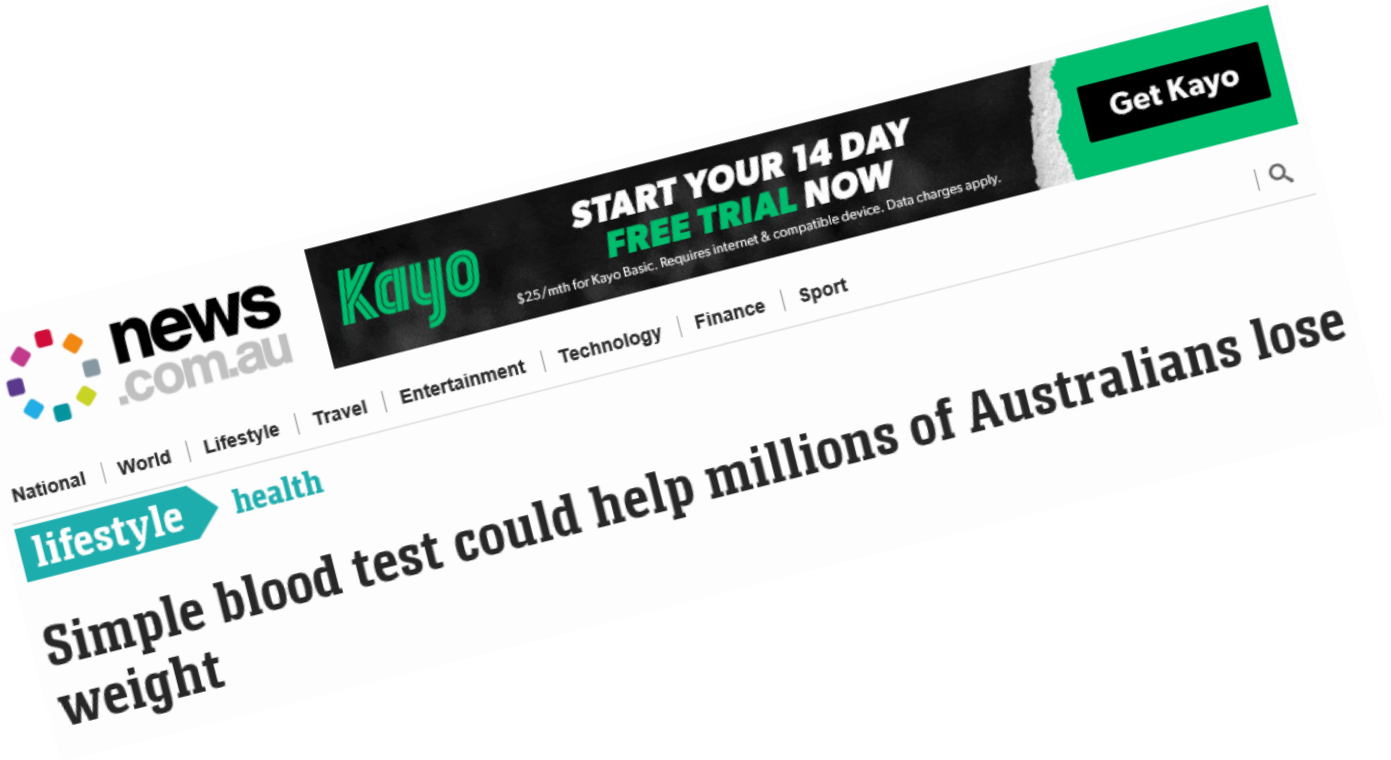
Ahead of today's announcement, he said: "This agreement will see the UK lead the world in genetic research within years.

"I am determined to do all I can to support the health and scientific sector to unlock the power of DNA, turning an important scientific breakthrough into something that will help

TURN TO PAGE 7

Hollywood star Tom Cruise joined VIPs including Zara Phillips for the racing at Goodwood yesterday SEE PAGE 8

Tom Cruise and Zara's glorious day at the races



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lifestyle health

Simple blood test could help millions of Australians lose weight

What is credible information?

1. Research on humans?
   - Mice
   - Cell cultures
2. Research published?
   - A study to begin?
   - Pubmed
3. Published in peer-reviewed paper?
   - Everyone can publish on the internet
   - Peer review gives assurance

What are clinical trials?

Clinical trials are research investigations in which people volunteer to test new interventions to prevent, detect, treat or manage medical conditions

- Is a new intervention feasible?
  - Can it be done?
- Is it safe?
  - Side effects, recovery from surgery
- Is it effective?
  - Is it better for patients than the existing treatment
  - Most QCGC Research trials are on effectiveness

How clinical trials develop

- Unsatisfactory current treatments, diagnosis, tests, … or accidental advantage
- Literature review
- Principle Investigator (PI) proposes a trial
- Minimise risk to patients
  - “New intervention is possibly better”
  - One group versus two or more groups of patients (randomly allocated to an intervention)
- Human Research Ethics Committees for review + approval
- Governance + institutional review
- Seek funding
  - Minimize the possibility that the funder(s) of the trial can influence outcomes

QLD Centre for Gyn Cancer Research

Research portfolio including clinical trials in

- Ovarian: ECHO, Image
- Uterine: FeMMe, ENDO-3
- Cervix: LACC
- Training: Imagine trial

Aim of QCGC Research to develop the best standard of care for women affected by gynaecological cancer

Clinically focused on patients' needs; not primary lab-based research

Research News

2018/2019

We research & develop the best standard of care for women experiencing gynaecological cancer

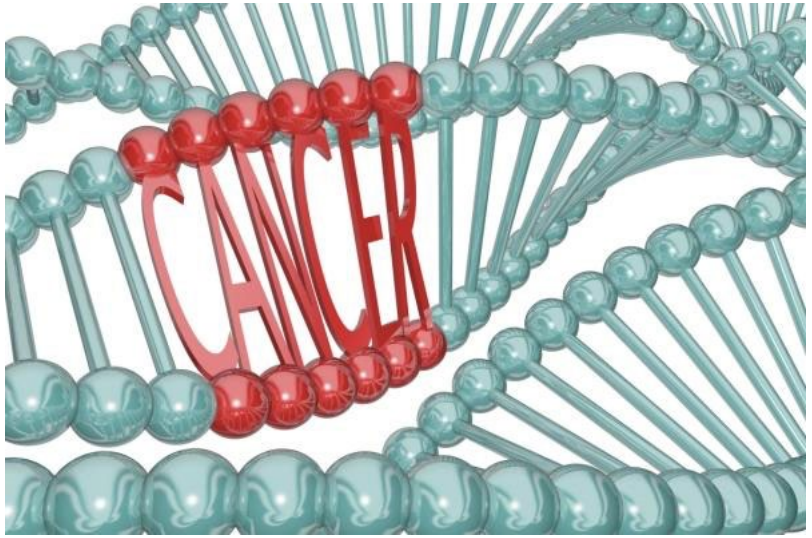
HPV vaccination

- Gardasil – the human papillomavirus (**HPV) vaccine** against 9 HPV strains
- In Australia, Gardasil is Government funded for
  - People > 9 years
    - People between 12 and 13 years are offered vaccination for free at schools
  - Men who have sex with men
  - People > 9 years with immune deficiencies
- The United States FDA expanded the approval of **Gardasil** 9 to include men and women ages 27 to 45 years in October 2018

Genetic testing

Tumours can develop

- Genetic (15%): Mutations are in the genes are inherited from father or mother (one each). If one gene is mutated, it causes cancer
  - Genes can not be modified
  - At IVF genetic mutations can be identified and affected eggs can be discarded
- Spontaneous (85%): Risk factors (obesity) change environment; cells mutate (change their DNA); start uncontrolled growth
  - Risk factors can be modified

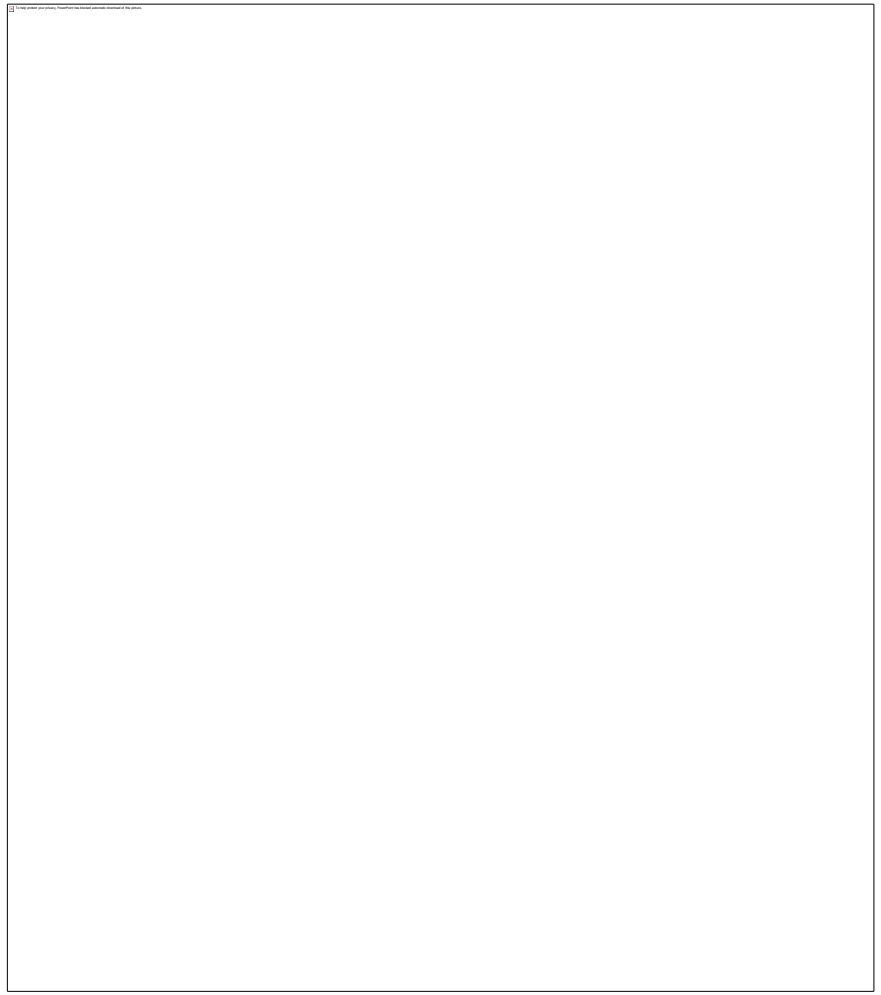


Impact of genetic mutation

- Causes cancer in multiple family members, younger ages, in people who don’t display the usual risk factors
- Causes multiple cancer types
  - BRCA: breast, ovary, pancreas, …
  - Lynch: bowel, uterus, stomach, bladder, ..
  - Peutz-Jeghers: cervix, ovary, …
- Can be inherited
  - First degree family members have a 50% chance of having inherited the mutation
  - Males and females
- Respond extremely well to certain treatments

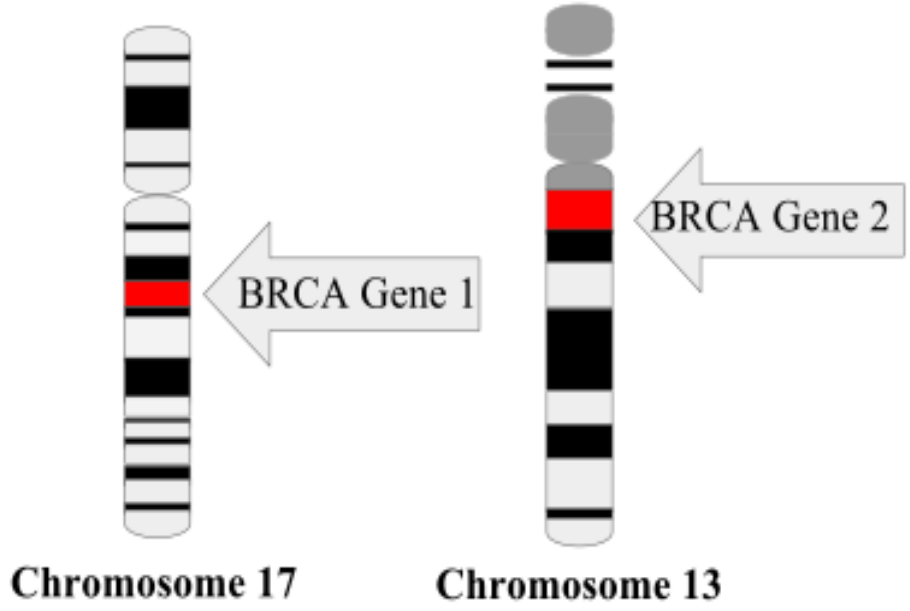
BRCA, BRIP, …

- BRCA is a tumour suppressor gene
- If it is mutated (changed) it is unable to suppress tumour growth
- Inherited: autosomal dominant
  - Males + females
  - High “show” rate
  - 1st degree relatives (siblings/offspring) have a 50% risk of BRCA
- Risk of ovarian/breast cancer is increased ten to thirty times
- No screening is effective



Impact of genetic testing

- Patient
  - Can develop other cancers also
    - BRCA, BRIP: breast, ovarian, pancreatic cancer (and others)
    - Lynch: Uterine, bowel (and others)
  - Affects choice of cancer medication
- First degree relatives (sons, daughters, siblings) – they have a 50% chance of being affected if the patient has a mutated gene



How can genetic testing be done

Through your doctors (over the counter tests are inaccurate; e.g. 23andMe)

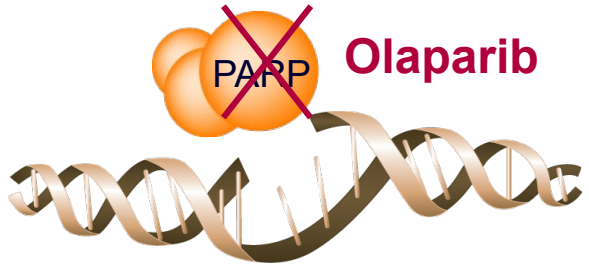
- Uterine cancers
  - Tissue test
    - Negative – makes Lynch unlikely
    - Abnormal test result requires confirmatory testing
  - Blood, sputum

- Ovarian cancers (high-grade serous cancers)
  - Tissue test
    - Captures BRCA gene + BRCA'ness (subsidized by Astra Zeneca)
  - Blood, sputum
    - Some test for 30 genes

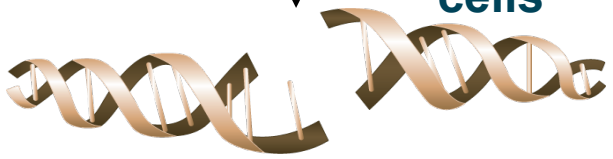
Ovarian cancer
PARP inhibitors: Olaparib (AZD 2281)

DNA SSBs occur all the time in cells and PARP detects and repairs them

During the replication process unrepaired SSBs are converted into DSBs



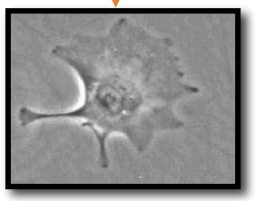
Replicating cells



Normal cell

Repair by Homologous Recombination

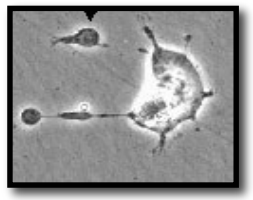
Survival



Tumour specific killing by Olaparib

Cancer cell with HRD

No effective repair (No HR pathway)



Cell death

Ovarian cancer
PARP inhibitors: Olaparib (AZD 2281)

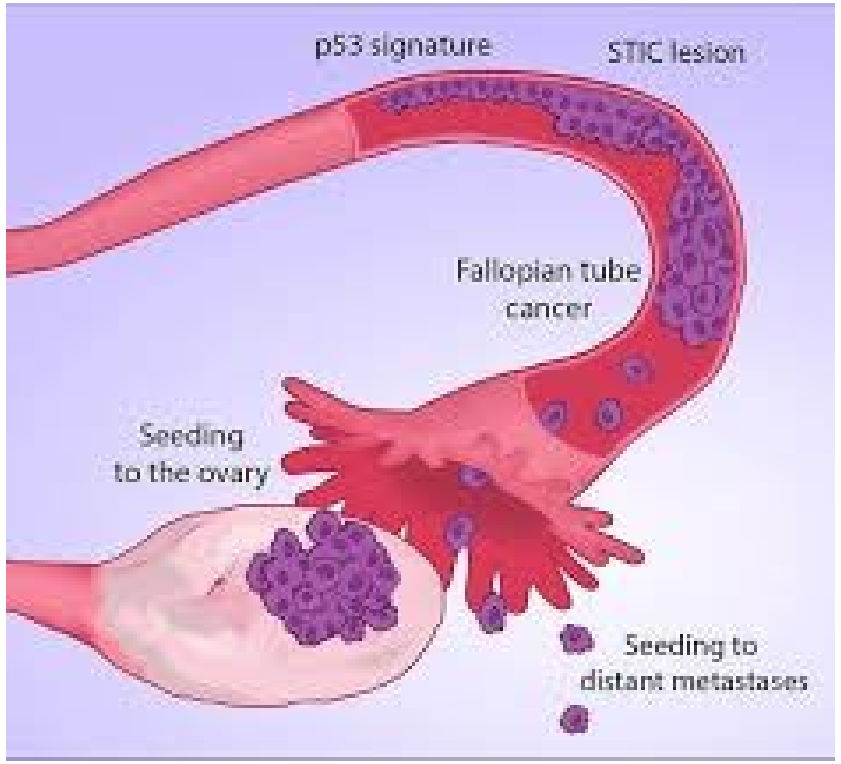
[1]Lynparza™ Approved Product Information 7th January 2016.

Genetic testing for general population?

- Should only women with a family history of breast and ovarian cancer be offered genetic BRCA testing? *OR*
- Should the general female population be offered genetic testing?
- ANSWER: It is cost effective to test the entire general female population by a panel of multiple genes (BRCA, RAD, BRIP)
- Testing of the general population saves between 3% and 4% of ovarian cancer and 2% of all breast cancers
- Sequencing of whole genome will become affordable very soon
- Careful about abuse!

Manchanda et al: JNCI 2018

Preventing Ovarian or Fallopian tube cancer?



The majority of ovarian cancers is believed to develop in the fallopian tube;

Opportunity for prevention: Fallopian tubes do not produce hormones;

Fallopian tubes can be removed without adding complications[1] but may increase risk of menopause 1 year after surgery[2];

Incidental finding of fallopian tube cancer: Survival is > 80% (=excellent) much better than ovarian cancer[3]

[1] Hanley et al: J Obstet Gynecol 2018 [2] Collins et al: Am J Obstet Gynecol 2019 [3] Trabert et al.: JNCI 2018

Endometriosis and gynaecology cancer risk

Endometriosis increases the risk of certain subtypes of ovarian cancer:

- Clear cell: 5x
- Endometrioid: 3x
- Serous: 0.3x

Endometriosis does not increase the risk of uterine, cervical or vulval cancer

Should ovarian cancer patients take Aspirin?

- Nurses Health Study an ongoing prospective study enrolled 250,000 US nurses
- Cancer information from large databases; Questionnaires on medications
- This study: Ovarian cancer patients (stage 1 to 3): N = 1143 patients
- Current users of Aspirin (> twice a week) had a 35% improved survival chance
- Recent users had a 55% improved survival rate
- There was no relationship between Aspirin dose and survival
- Other studies previously found no impact of Aspirin on ovarian cancer survival. These studies used prescriber data (possibly unreliable)
- Hesitant to recommend Aspirin widely:
  - Women who took Aspirin prior to ovarian cancer diagnosis had no benefit
  - Observational study (a randomized controlled trial would be needed)
  - Mechanism of action is unknown
  - Risks of aspirin usage

Merritt et al: Lancet Oncol 2018

Endometrial cancer

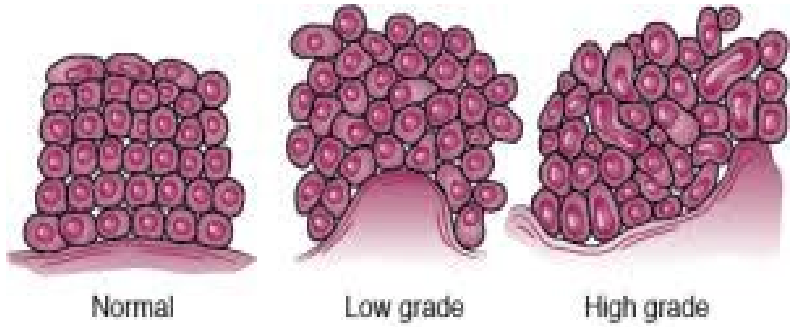
Surgery is cornerstone of treatment

Histopathology: grade, stage, … determine risk of relapse

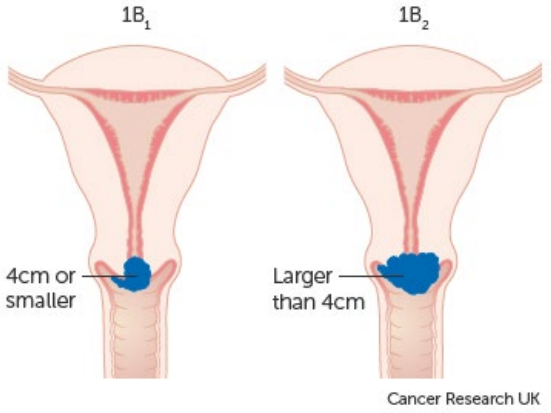
Low risk patients: Survival is so good that it can't be improved any more;
High risk patients: Can postoperative treatment improve outcomes?

Until 2019: Radiation treatment can lower the risk of a relapse but does not affect survival

Grade: How abnormal do tumour cells look under the microscope?



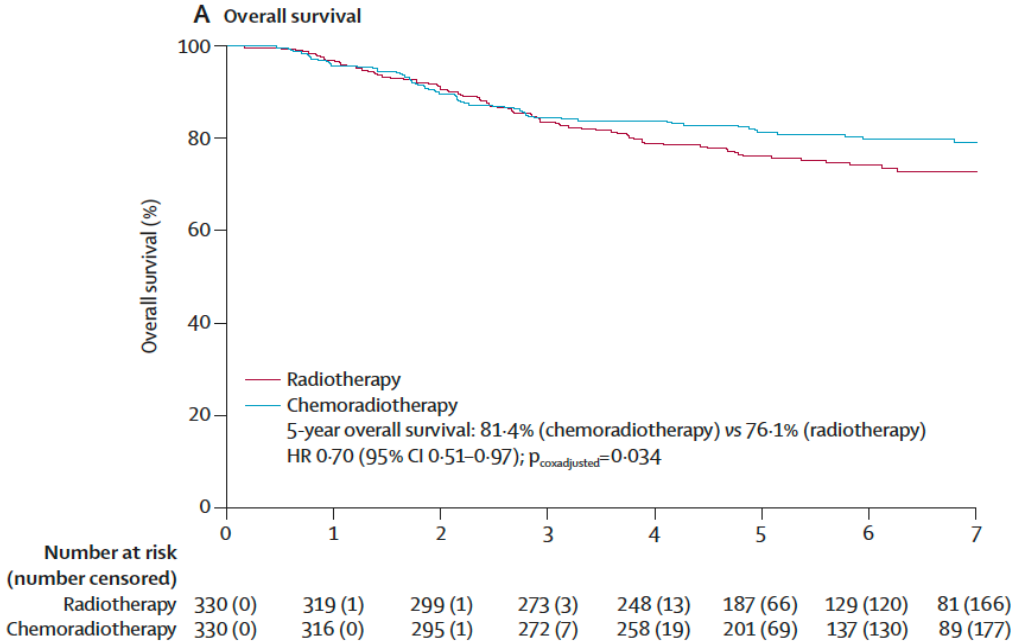
Stage: Is the tumour only in one area, or has it spread?

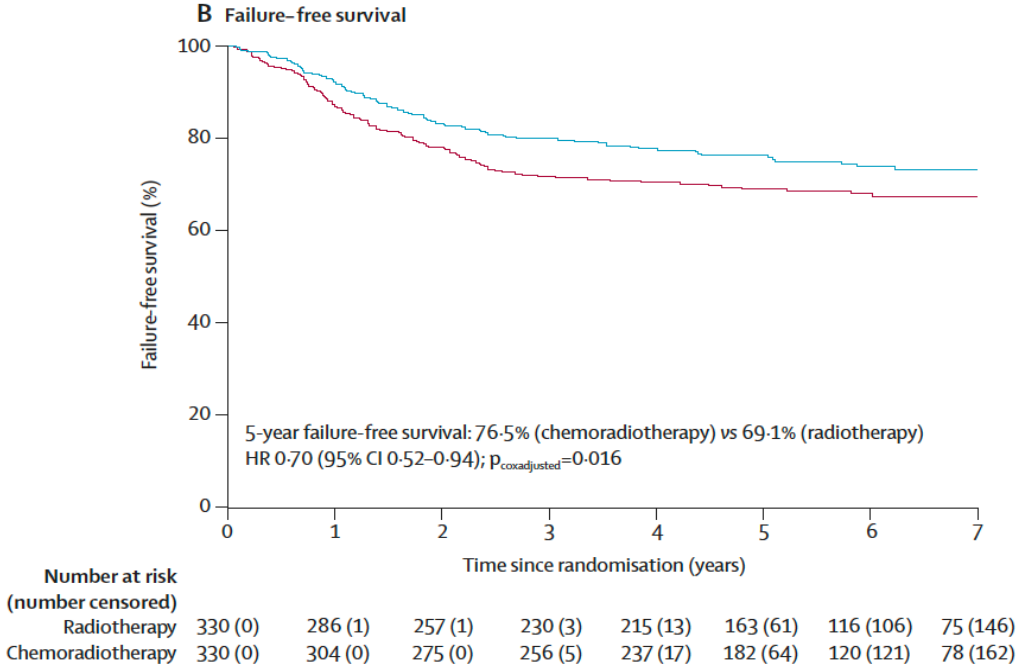


Endometrial cancer: PORTEC-3 trial

Does the addition of chemotherapy to radiation treatment result in prolonged survival?

- Phase 3 randomized controlled trial
- 686 patients with high-risk endometrial cancer
- Follow up was 72 months
- Significant improved disease-free and overall survival with chemotherapy





Lynch

Tumour suppressor gene mutated (disables gene repair)

Lynch = 4 separate genetic mutations (MLH1, MSH2, PMS2, MSH6)

Lynch causes cancer of uterus, bowel, ovaries, stomach, bladder, breast, …

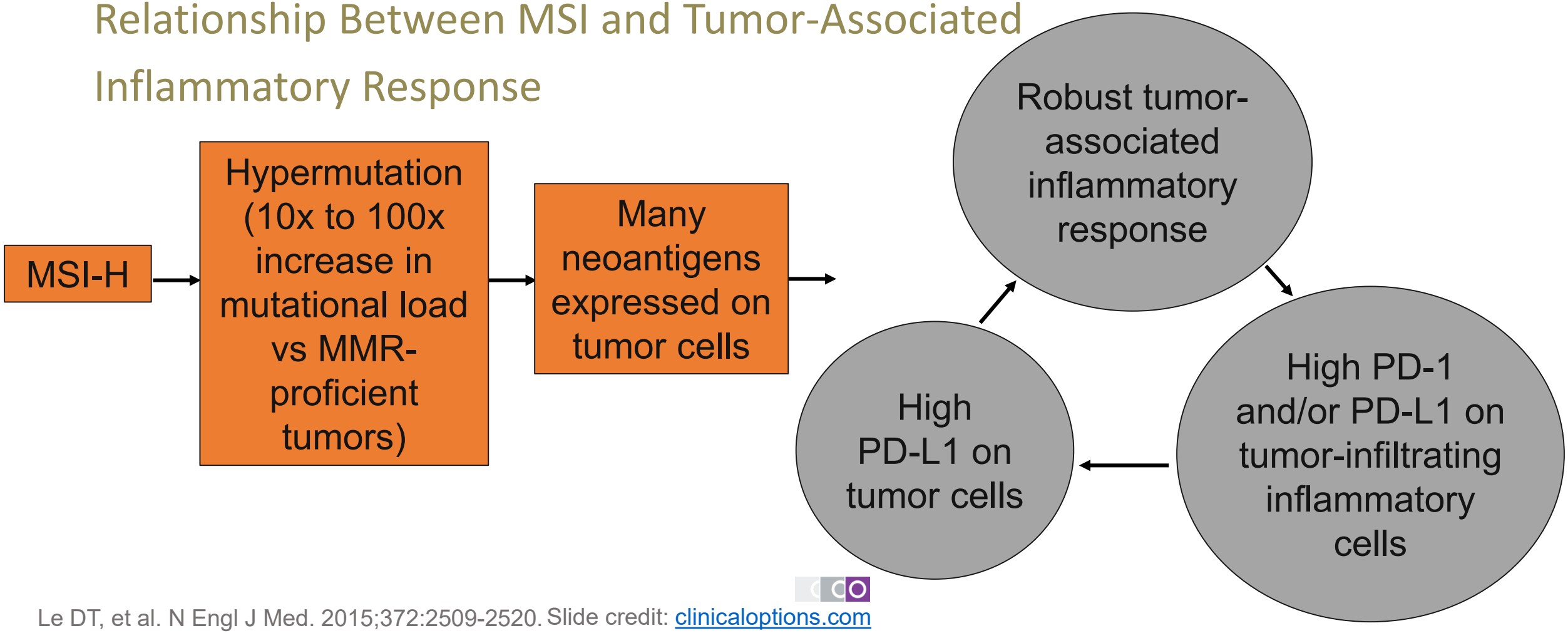
Risk for a Lynch carrier to develop uterine cancer up to 60% (slightly more aggressive)

Tissue testing (initial): inaccurate

If tissue testing positive: confirmatory testing

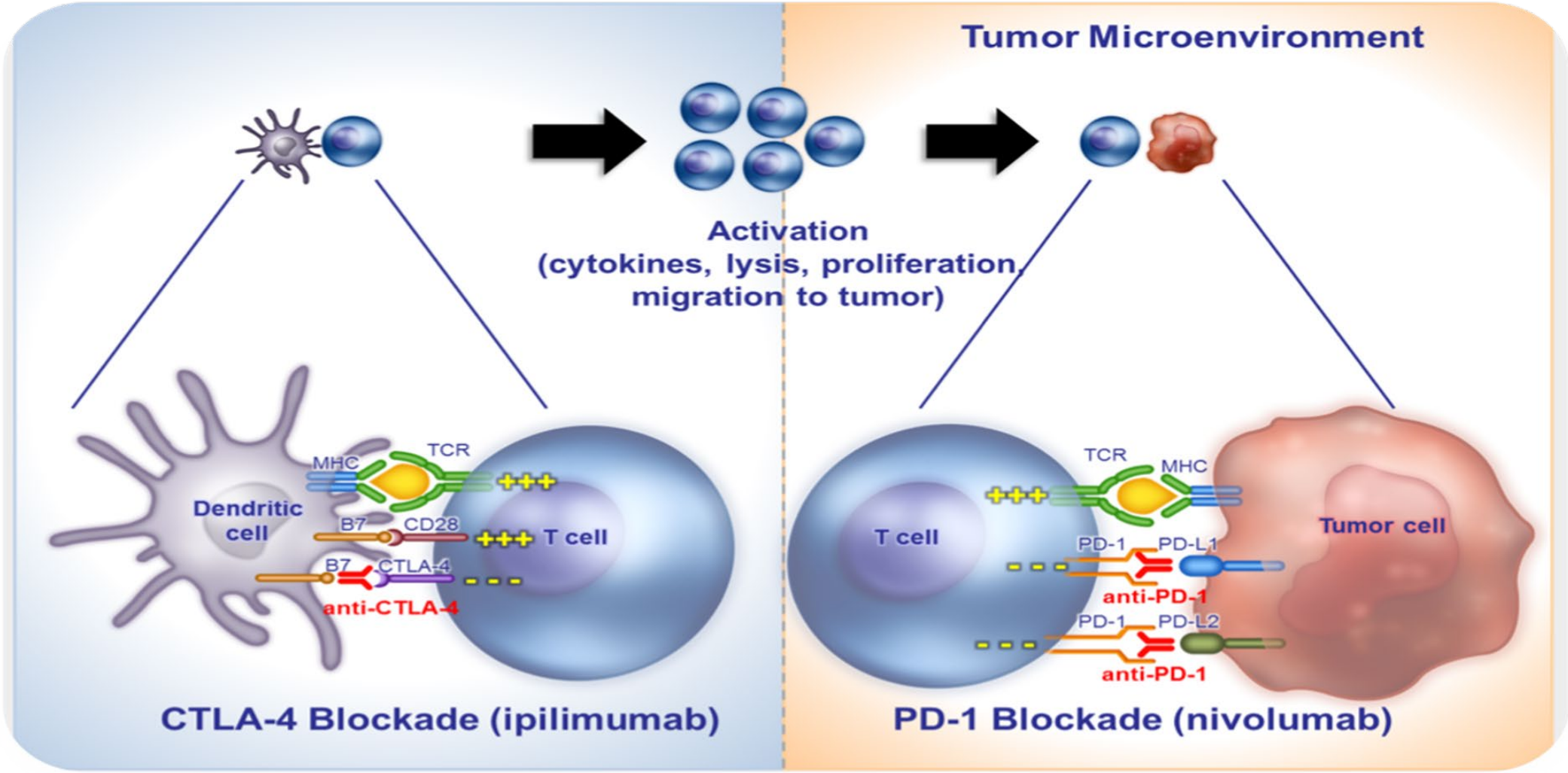
MSI high immunotherapy (microsatellite instability – high)

Relationship Between MSI and Tumor-Associated Inflammatory Response



Le DT, et al. N Engl J Med. 2015;372:2509-2520. Slide credit: clinicaloptions.com

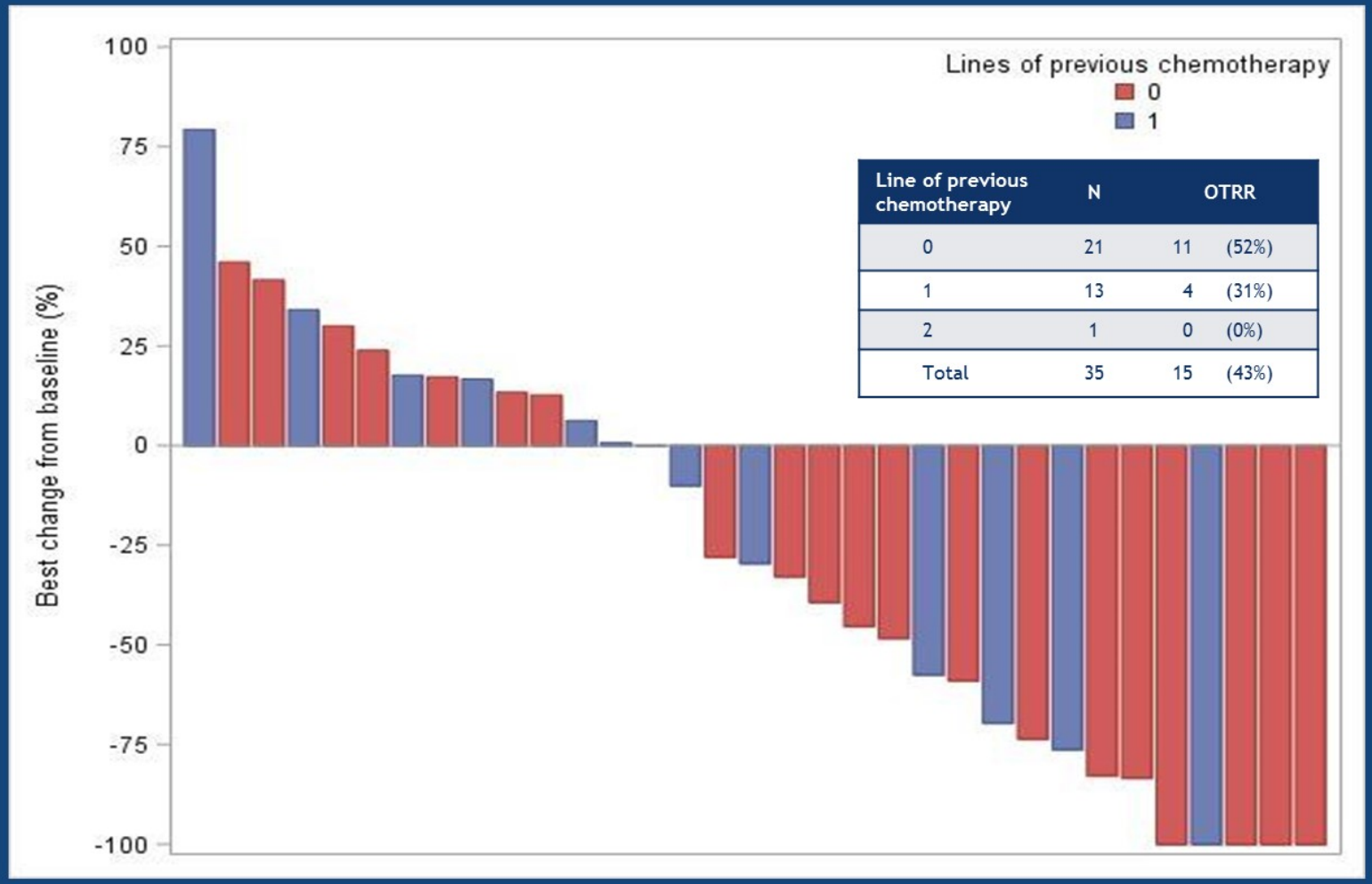
MSI high immunotherapy: Checkpoint Inhibition



Phase 2 trial of Durvalumab in Advanced Endometrial cancer (PHAEDRA)

Yoland Antill, P-S Kok, E Barnes, K Robledo, M Friedlander, S Baron-Hay, C Shannon, J Coward, P Beale, G Goss, T Meniawy, S Yip, D Smith, A Spurdle, M Parry, J Andrews, M Kelly, MR Stockler and L Mileshkin on behalf of
Australia New Zealand Gynaecological Oncology Group (ANZGOG).

dMMR (n=35)



Line of previous chemotherapy	N	OTRR	
0	21	11	(52%)
1	13	4	(31%)
2	1	0	(0%)
Total	35	15	(43%)

Line of previous chemotherapy excludes

- Adjuvant/ neo-adjuvant chemotherapy received ≥12months prior
- Bevacizumab
- Hormone therapy

Disease Control Rate

	dMMR (n =35)	pMMR (n=35)*
OTRR	15 (43%)	1 (3%)
DCR at 16 weeks	21 (60%)	7 (20%)
Disease Control Rate	23 (66%)	10 (29%)

* = evaluable patients

Take home messages

- As a single agent, anti-PDL1 immunotherapy with durvalumab appears:
  - active in dMMR: RR 43% overall, 52% 1st line, 31% 2nd line
  - minimally active in pMMR: RR 3%
- Few immune-related adverse events
- These results warrant further exploration of immune therapy in the setting of advanced endometrial cancer.

From QCGC Research

2018/2019

We research & develop the best standard of care for women experiencing gynaecological cancer

Training of gyn surgeons in hysterectomy "Project Imagine"

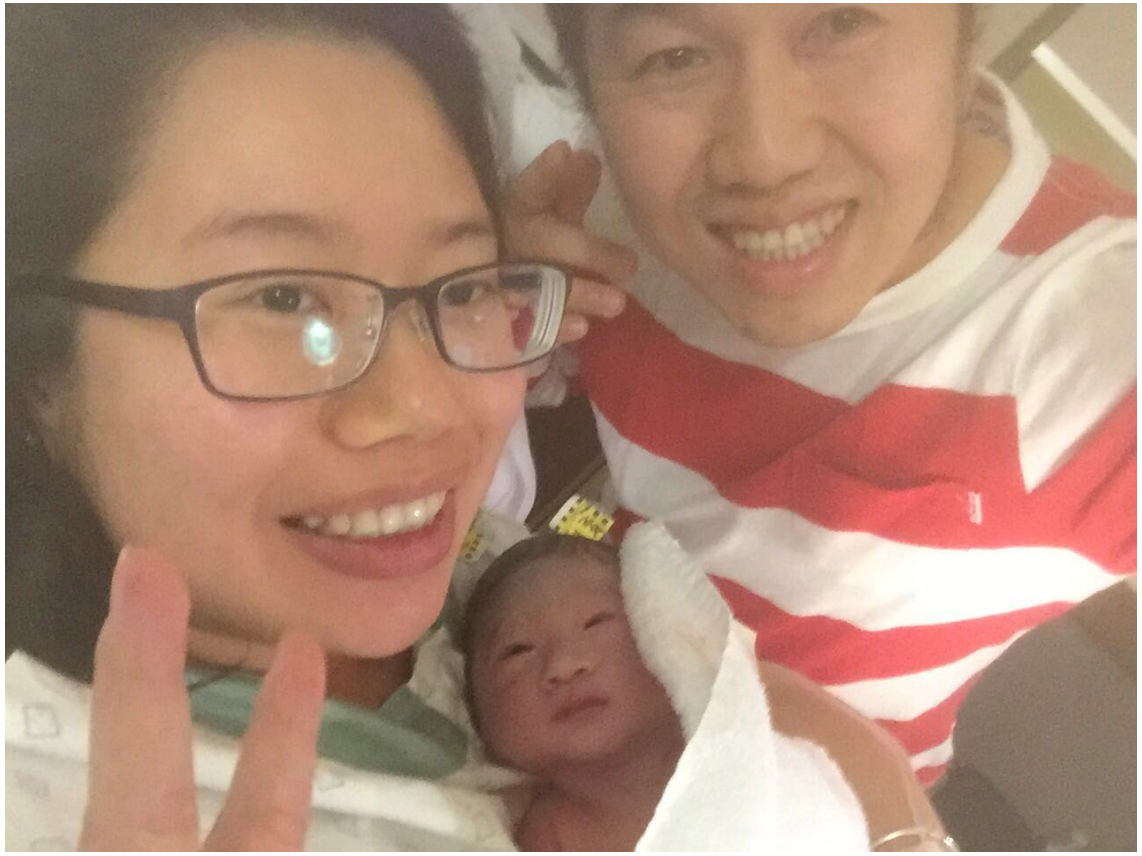
1. Almost 30,000 women per year require a hysterectomy in Australia (due to pain, bleeding, cancer)
2. 40% of women receive an unnecessary incision when having a hysterectomy. Longer recovery, higher complication rates
3. Gynaecologists feel comfortable offering outdated surgery; feel inadequately trained in minimally invasive hysterectomy
4. Women trust that their gynaecologists have their best interest in mind when they recommend a surgical approach
5. We put together a training program to teach minimally invasive hysterectomy to 10 QLD gynaecologists. Program will be completed in June 2020

Endometrial Cancer – Learning points

- Laparoscopic surgery is better then open surgery (pain, recovery). Survival of laparoscopic and open surgery is equal
- Anxiety is the 2nd most common comorbidity
- What patients die from?
  - Large Australian National study, 1359 women;
  - After 7 years, 179 women died (123 of cancer, 56 of non-cancer causes)
  - Obesity, diabetes, co-morbidities were the biggest killers
  - Aspirin did not change prognosis
- Prognosis of women with Lynch (genetic) is worse than non-Lynch.

QCGC Research Pipeline

- Continue ongoing trials in ovarian, endometrial, cervical cancer
- Complete feMMe trial: 159 of 165 patients enrolled
- FeMMe trial is the first international trial on intrauterine progestin (Mirena) to treat endometrial cancer. Fertility spared



International consortium on feMMe

- Study molecular markers to understand who will respond to intrauterine progestin treatment or who won't
- Learn about biological mechanisms involved
- Future molecular treatments
- Study group founded in September 2018
- Contracts in place with 7 international groups

ENDO-3

- After LACE, feMMe this will be the 3rd largest flagship trial
- Questions “Lymph Node Dissection”, a paradigm that exists for the last 33 years
- Lymph node dissection is recommended for all patients with endometrial cancer;
  - Its survival benefit is uncertain
  - Side effects are possible (e.g. lymphoedema)
- A study team has been assembled
- Protocol is written
- Ethics application has been submitted, awaiting approval
- Hope to start the trial in May/June 2020
- Will confirm or refute the paradigm of Lymph Node Dissection in Endometrial Cancer

A big thank you

- To our Patients
- QCGC Research Staff: Trudi C, Vanessa B, Vanessa T, Kerry M, Yang P, Emma C, Danielle M and Lisa H
- Cherish Board Members: Anna Tichborne, Anna Katter, Leticia Dorman, Haidee Van Ruth, Nikki Frame, Kathleen Banks, Bev Austen, David Paterson, Gerard Champion
- Donors and Supporters of QCGC Research and Cherish Women's Cancer Foundation
- QLD Gynaecological Oncologists: Drs' Nicklin, Garrett, Land, Tang, Perrin, Chetty, Jagasia, Nascimento, Green, Singh

Larapinta 2020

6-day trek in the red centre of Australia in June/July 2020;
Trekkers raise $3500 each for gynaecological cancer research.