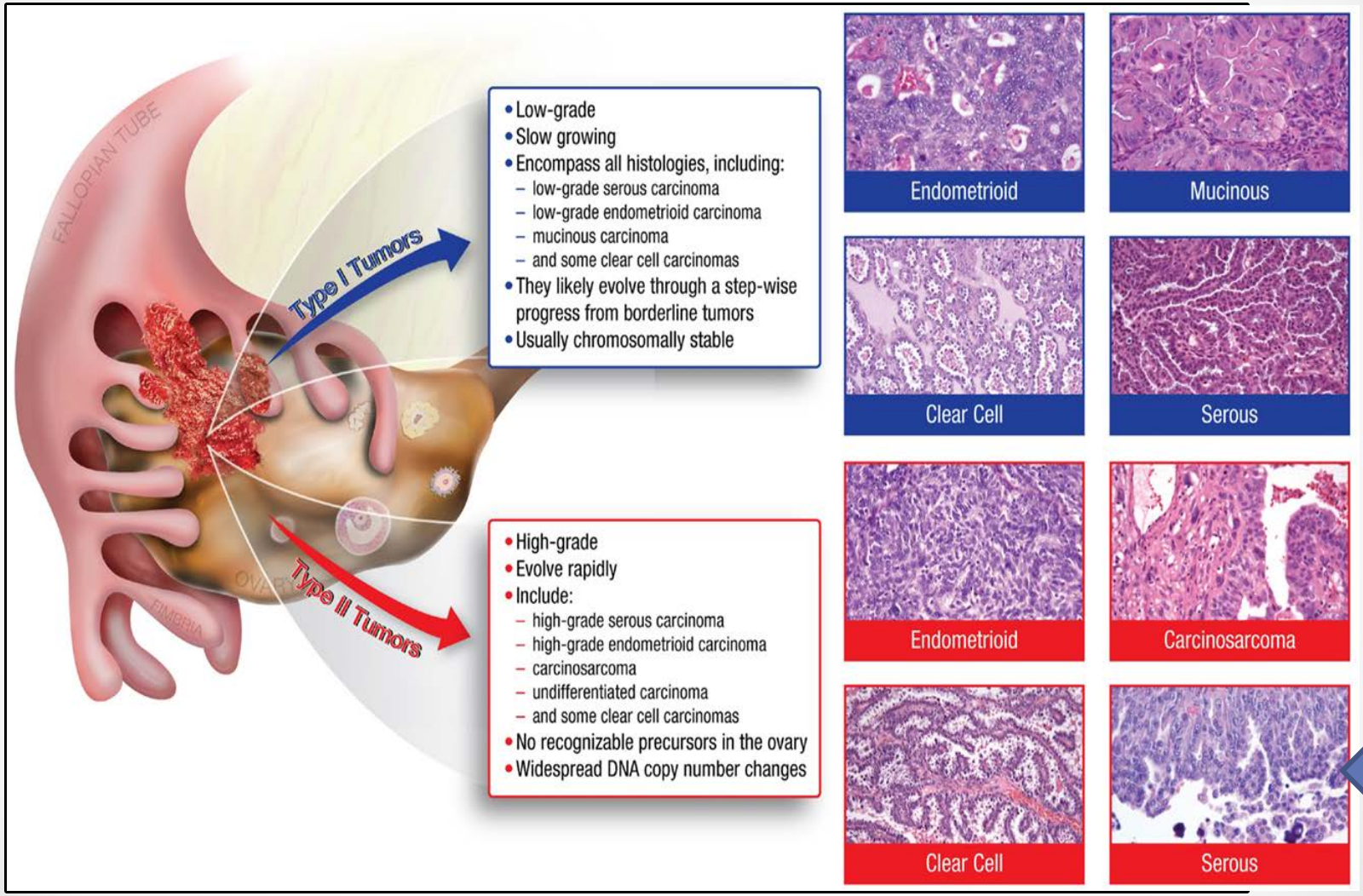
I have no disclosures, no conflicts of interest, and none of my income is from Pharma.

Thanks to Dr. Brad Nelson of Deeley Research for the slides on their immunotherapy program.

High Grade Serous Carcinoma: the Ugly Stepsister of ovarian tumours



Second Case

- **Sarah is a 54 year old woman referred to the Gynecology team at the BCCA for possible stage 3c ovarian cancer with respect to her treatment options.**

Sarah's history was of being previously very healthy, but she had developed a cough in the fall which did not clear with a couple of rounds of antibiotics. Her appetite and feeling of well-being gradually decreased over the next few months, and she began to notice some mild bloating and early satiety, which was intermittant. This progressed by January to nausea, epigastric discomfort, and marked bloating. Sarah herself noticed a palpable RLQ mass. Her bowels and bladder were functioning well. She noted mild shortness of breath and mild reflux symptoms. She had lost about 10 pounds.

At this time her FP re-examined her and had concerns about her abdominal findings, and he arranged for an abdominal US.

The US of the abdomen on February 12 showed a large left sided pelvic mass, ascites, normal intra abdominal organs, and a left pleural effusion. Chest Xray confirmed the pleural effusion. Her family physician referred her to a local gynaecologist, who appropriately referred her to the BCCA.

February 15: initial CA -125 was 1,548 , CEA 0.5, CA 19-9 < 0.5,
alpha fetoprotein < 11, Ca 15-3 was 15.

Second Case

Sarah was a hypnotherapist and an instructor. She is Buddhist. Her family history was negative for any cancers, including 7 siblings. She was on no regular medications, her smoking history amounted to 3-4 cigarettes per day for 5 years in her 20's.

She was G2P2, breast fed, went through natural menopause at age 51, with no HRT. She had regular pelvic/pap exams, the last pap was 2 years prior to this illness.

February 15: initial tumour markers:

CA -125 was 1,548 , CEA 0.5, CA 19-9 < 0.5,
alpha fetoprotein < 11, Ca 15-3 was 15.

Second Case

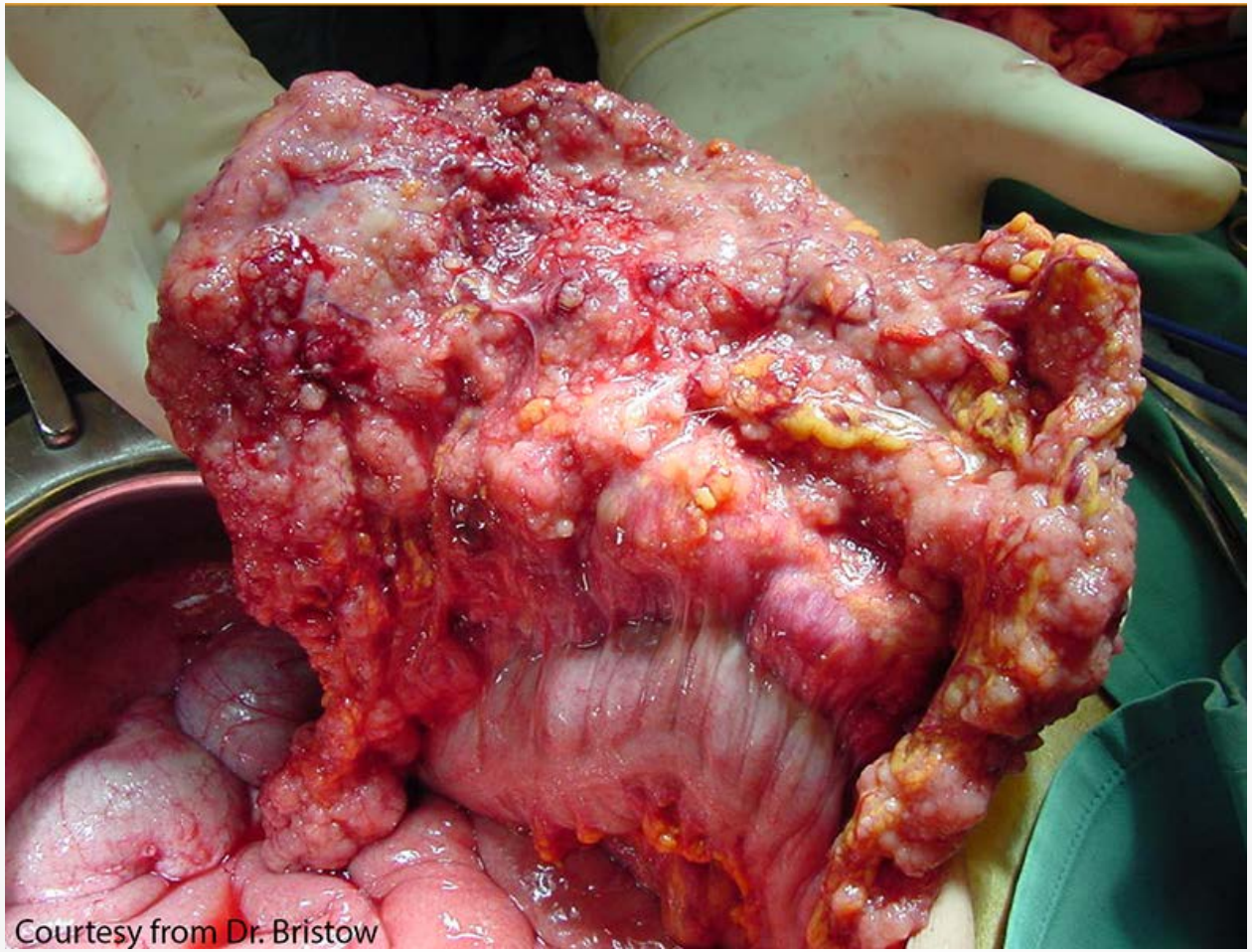
The gyne oncology surgeon performed a lapaparotomy on March 1, which revealed extensive tumor throughout the abdomen. She was suboptimally debulked, undergoing drainage of ascites, partial hysterectomy, BSO, omentectomy, and tumor debulking.

Tumor left in situ included a 5 cm L perirectal mass and a 3 cm mass in the porta hepatis. Blood loss was significant, and recovery was a little slow due to sluggish return of bowel function, but otherwise uncomplicated.

When seen by the medical oncologist 11 days post-op, she was asymptomatic, with no significant pain, and her bowels were moving well.

Post-op Ca 125 had decreased to 600, from 1548, as a result of debulking.

High grade serous carcinoma at debulking surgery, a loaded omentum.



Questions

- What are the current indications for choosing upfront debulking surgery versus interval debulking surgery, performed after 2 or 3 cycles of chemotherapy, in high grade serous cancer of ovarian, tubal or primary peritoneal origin?
- How important is obtaining tissue pathology prior to planning primary debulking surgery versus interval debulking surgery? How can a tissue diagnosis be established quickly to aid the Gyne Oncology team to plan a treatment strategy?
- How would a different pathology result affect treatment planning? For example: low grade serous, borderline serous, or high grade mucinous?
- Is a complete staging workup prior to surgery, including a CT of the chest abdo, and pelvis, as well as baseline tumor markers necessary? Why?

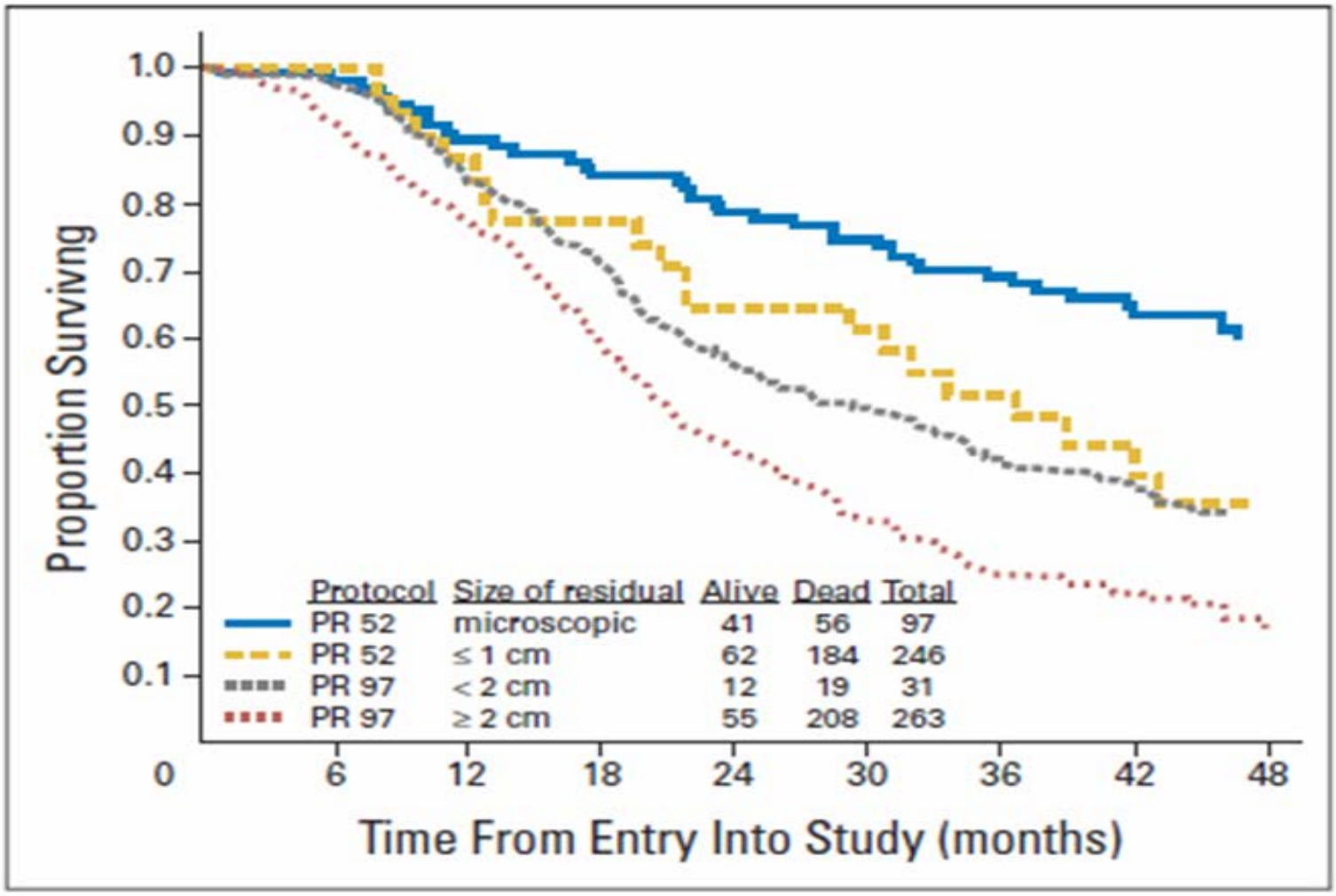


Fig 1. Survival related to maximum residual disease less than 2 cm. Reprinted with permission.[29]

- Role of surg in ov ca. Fader. JCO 10Jul2007
-

Second Case

- At gyne tumour conference, Sarah's pathology was reviewed. The right ovary was 14 x 11 x 6 cm and the left was 10 cm, both diffusely replaced by tumour. Pathology was consistent with a grade 3/3 poorly differentiated papillary serous carcinoma (HGS) with a solid growth pattern. The omentum was extensively involved with the largest mass measuring 20 cm. Tumour was also seen in the cul de sac biopsies and in the lower wall of the uterus. Stage was IIIc (confined to abdomen with extensive peritoneal involvement of the upper abdomen)

- **Question:**

  What chemotherapy agents would likely be prescribed to Sarah? When should the first cycle be given? What is her expected response rate for her tumour type?

Second Case

Sarah was recommended to start chemotherapy with 6 cycles of Carbo/Taxol, each given every 3 weeks. She was scheduled to start as soon as her surgical sites were healed, March 17.

Questions:

Sarah asked about supplements, what advice would you give her?

What side effects would you expect from this treatment?

How would you monitor Sarah for response to treatment?

What about dose dense chemotherapy with weekly taxol and every three weekly carboplatin ? Is there evidence of a superior response rate?

Why wasn't IP chemotherapy considered for Sarah?

Second Case

Sarah completed 6 cycles of Carbo/Taxol under the GOOVCATX protocol. X for high risk due to visible residual tumour left in situ at surgery.

She achieved a full response, measured by normal Ca125 after the 6th cycle, of 7.4, and post treatment CT of the CAP showing no evidence of residual tumour.

Questions:

Sarah is delighted by her post treatment CT results and normal tumour markers. She tells you she feels cured. How do you counsel her? Is she cured? How should she be monitored going forwards? If she lives fairly remotely from a regional cancer center, do you feel comfortable following her along? What would that involve?

Second Case

Sarah does very well. It is several years before she has her first relapse. Her recurrence was mainly in the upper abdomen in the spleen, extending to the pancreas on CT imaging. She is not particularly symptomatic, just some occasional LUQ pressure discomfort and a minor early satiety, not impacting her weight or energy levels. Her Ca-125 is now 91. All other labs are normal.

Questions:

- Would you recommend second line chemotherapy?
- What agents would you select?
- What is the likelihood that her recurrence is still platinum sensitive? What is her response rate likely to be?
- How would this be different if she had recurred less than 1 year prior to completing first line platinum based chemo? 6 months?
- How important might it be to confirm the tumour is recurrent HGS by a tissue diagnosis?

Second Case

Sarah tells you she "is done" after 5 cycles of second line carbo/taxol, and refuses any further chemotherapy at that time. She feels entirely well, except for some minor chemotherapy related side effects.

A post treatment CT Scan shows a very good reduction in the size of the upper abdominal tumour, no new sites of tumour. Ca-125 is 22.4.

Questions:

- Would you try to counsel Sarah to accept additional chemotherapy cycles, in order to cyto-reduce her HGS carcinoma further? As her tumour marker has consistantly dropped with each cycle given, and assuming ongoing response is therefore likely, how many more cycles would you offer Sarah? Does it make much difference to her DFS or her OS?

Second Case

Sarah thanks you for your advice, but insists that she is done with chemotherapy for now.

BRCA testing results shows no mutations. If Sarah had a BRCA mutation, she would be offered a PARP inhibitor treatment in order to try to prolong her remission.

Question:

What are the indications for Olaparib (PARP inhibitor) therapy? What is the expected benefit from current evidence? How is it taken? What are the common side effects?

Second Case

It seems that Sarah understood her body well. She refused further cycles at that time, and remained asymptomatic for 18 months. She then had symptoms of LUQ discomfort and CT evidence of tumour growth in the same splenic/pancreatic region, with no other sites of tumour. Ca 125 is 43 , up from her baseline of 22.4.

Questions:

Would you offer Sarah 3rd line chemotherapy?

What agents would you choose from? One agent or doublet?

Is she still platinum sensitive? What response rates do you expect?

Sarah accepts and completes 6 cycles of carboplatin and liposomal doxorubicin. With the last cycle, she had a moderate infusion reaction to the carboplatin. This was promptly and successfully treated, but it frightened her significantly. Her post treatment Ca125 is 19.5, and her CT shows the tumour mass is still present, by reduced by about 50%, with no new lesions. Sarah is asymptomatic.

Second Case

Sarah goes back on to surveillance.

Her medical oncologist considers using an aromatase inhibitor, but decides to save it for later. Sarah herself has been following an alkaline diet and using "Phoenix Tears" in order to delay tumour progression.

Questions:

What is the BCCA position of the use of cannabis preparations in cancer patients and survivors?

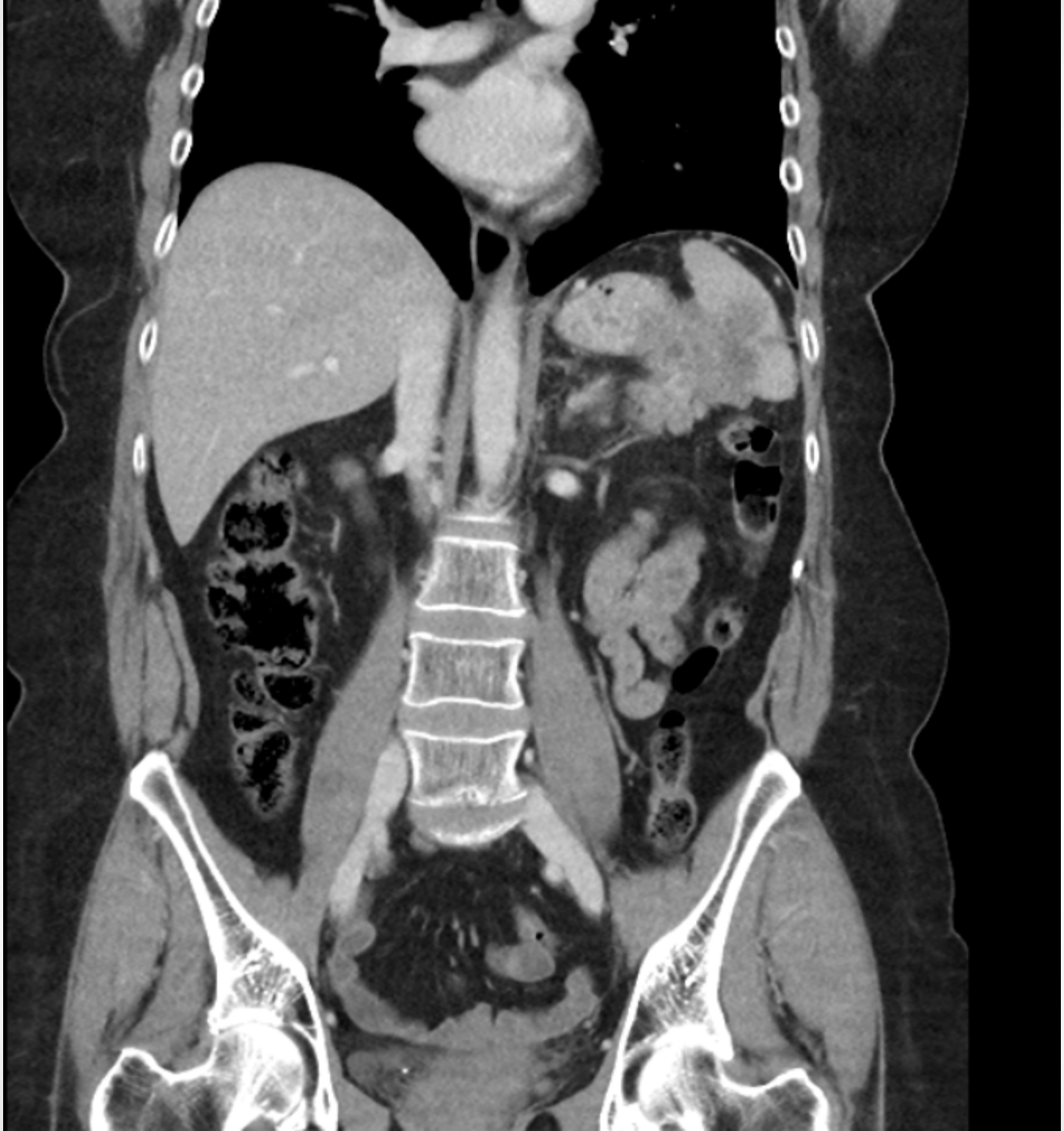
What about all those other naturopathic measures? Patients are looking for alternative therapies. Metformin?

Is there evidence aromatase inhibitors delaying progression of HGS ovarian/ft cancer? Is it worthwhile to ask for estrogen receptor staining to be performed on the most recent pathology specimen?

Second Case

6 months after completing third line chemotherapy, Sarah has progressive upper abdominal symptoms. CT shows significant growth of the splenic mass and a new satellite lesion close to the main tumour. All disease is confined to the LUQ.

Ca125 is 43.3, rest of her labs unremarkable. She has an excellent performance status, and no comorbidities.



Second Case

Sarah asks, because her tumour is apparently still localized to her upper abdomen, if she can have a surgeon take it out.

Radiation oncology is consulted as to whether radiation would be helpful to debulk her tumour. Note: this is considered a palliative maneuver.

Because the lesion involves the pancreatic tail, they decline.

A pancreatic/biliary oncology surgeon performed a laparoscopic resection of the spleen, pancreatic tail, and part of the greater curvature of the stomach. Surgery and recovery were without complication. H. pylori gastritis is an incidental finding, and treated by her FP post-op.

Pathology confirms HGS carcinoma of ovarian origin. Estrogen receptors were requested, and were weakly positive.

NOTE: a secondary (optimal) debulking surgery is not standard of care, but sometimes may be a reasonable thing to consider.

She went through all the post splenectomy immunizations.

Second Case

Sarah's current status (24 months almost to the day) after her second surgery is stable. She is symptom free, has good energy, no pain, normal bowel and bladder function. She takes a multivitamin, Phoenix tears, "anone" (an anti-inflammatory herbal prep) protein powder and tumeric. She practices meditation and maintains a positive attitude. She was briefly on letrozole, but did not tolerate it well, (myalgia, arthralgia, chest pains) and went off it after one month.

Recent physical examination was normal. October 22, 2017 labs show normal CBC, Ca, Cr, Lytes, bili and liver enzymes, albumin.

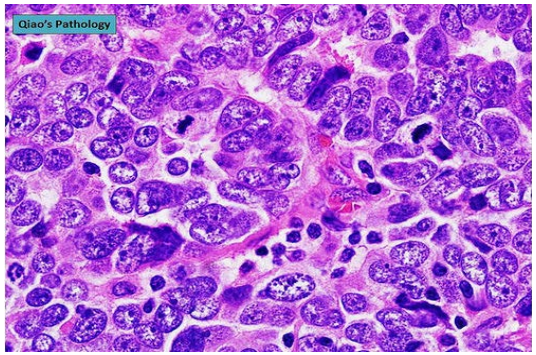
Ca 125 is 89.6, Ca 19-9 5.1, Ca 15-3 is 10.4

Sarah tells me that she does not want any further imaging, or chemotherapy, but will have bloodwork and tumour markers. She is now 67 years old. I think she might possibly change her mind if her symptoms are significant enough to warrant palliation with further chemotherapy, or she may opt for end of life care.

Second Case

- How would you counsel Sarah in the future, if/when she has recurrent symptomatic HGS ovarian cancer? What chemotherapy may you offer her? Why? What are expected response rates to fourth line chemo?

- What is on the horizon that might become a useful new tool?
- ? Immunotherapy – avelumab: Javelin study
- Tumour infiltrating lymphocyte therapy: Deeley Research
- Targeted therapies



Second Case

- Sarah was originally diagnosed in 2004. She has survived 13 years. She went 8 years after her first line chemotherapy to her first relapse. Her last chemotherapy was completed in January 2015.

- Her long first clinical remission is unusual, but not unknown. I suspect that there are factors in her own immune system that has contributed to her long remission periods.

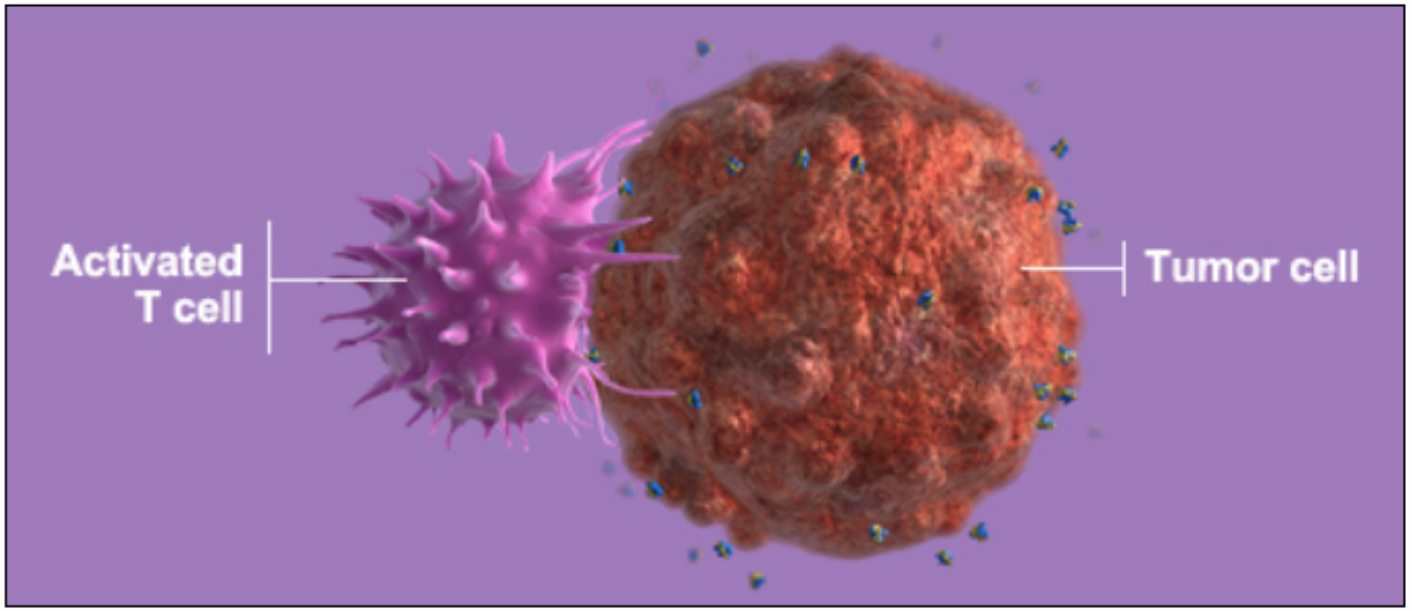
- What can we do to prevent more women developing this disease?

- What novel treatments are in development?

BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority

BC CANCER FOUNDATION
partners in discovery

Immunotherapy Program



Directors: Brad Nelson PhD, Deeley Research Centre, Victoria
Robert Holt PhD, Genome Sciences Centre, Vancouver

IROC*2017*: The Immune Response to Ovarian and other gynecological Cancers

Overview

- Started as collaborative project in 2006
  - DRC, TTR, clinicians, surgeons, OvCaRe
- Extensive ovarian cancer tissue bank
  - Poor 5yr survival
  - High recurrences
  - Older Caucasian women, mean age in 60s
- Paved path toward immunotherapy clinical trials at DRC

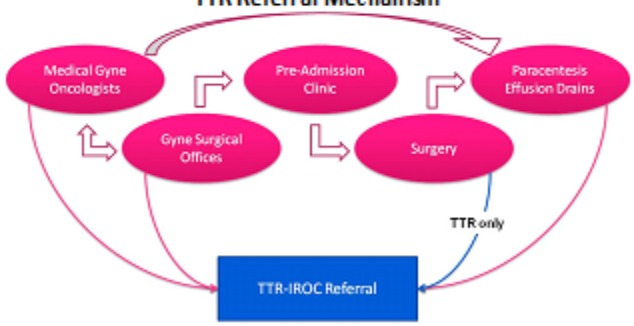
IROC Progress report

- 150+ participants
- 20+ publications
- One-million+ $ in grant funding
- Immunotherapy clinical trials
- Knowledge gained, and relayed through numerous KT activities

Highlight of changes

- Phase II: (date TBD)
  - Endometrial, cervical and other gyne cancers
- Medical Oncology referral process
- Effusion referrals for IROC

TTR Referral Mechanism



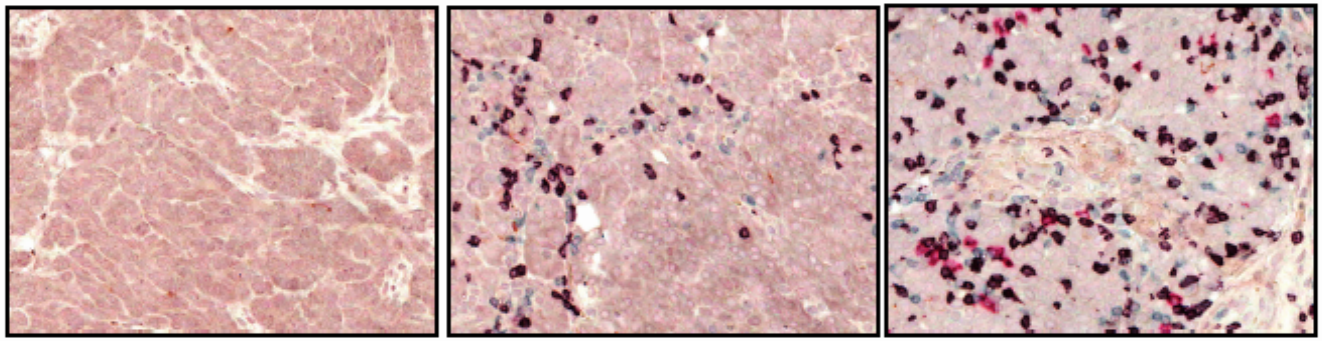
Contact

TTR Project Coordinator: (250) 519-5713 (for non-urgent matters)
PI of the TTR: Dr. Peter Watson: (250) 519-5700
PI of the IROC project: Dr. Brad Nelson: (250) 519-5700

The immune system can recognize cancer, leading to increased patient survival

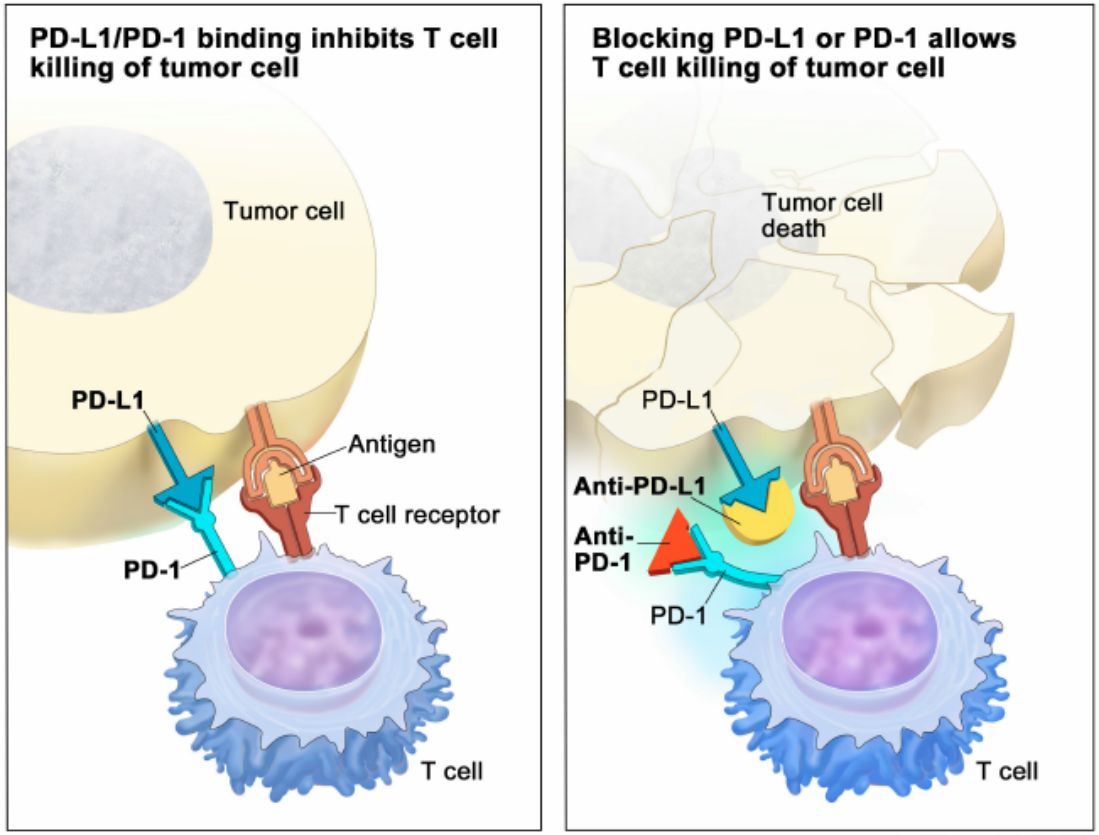
Example: tumour samples from 3 ovarian cancer patients

CD8 killer T cells
CD4 helper T cells
CD20 B cells



Weak immune response	Moderate immune response	Strong immune response
	↓	↓
	~2 fold higher survival	~3 fold higher survival

“Checkpoint blockade” releases the brakes on anti-tumor immunity



Checkpoint blockade: Recent clinical successes

anti-CTLA-4 (eg, Ipilimumab)

- Metastatic melanoma – FDA approval

anti-PD-1 (eg, Nivolumab, Pembrolizumab, others):

- Metastatic melanoma – 38% Objective Responses (Hamid, NEJM 2013), 53% Objective Responses with Ipilimumab (Wolchok, NEJM 2013) and FDA approval
- Non-small cell lung cancer – 18% Objective Responses and FDA approval
- Kidney cancer – 27% Objective Responses (Topalian, NEJM 2012); 52% ORR nivolumab + sunitinib (Amin, JCO abstract, 2014), FDA approval
- Bladder cancer – 52% Objective Responses (Powles, Nature 2014), FDA approval
- Hodgkin's Lymphoma – 87% Objective Responses (Ansell, NEJM 2015), FDA approval
- Colorectal cancer (MSI) – 40% Objective Responses (Le, NEJM 2015), FDA Breakthrough Status 2015
- Replacing frontline chemotherapy for melanoma and lung cancer (so far)

Checkpoint blockade: current challenges

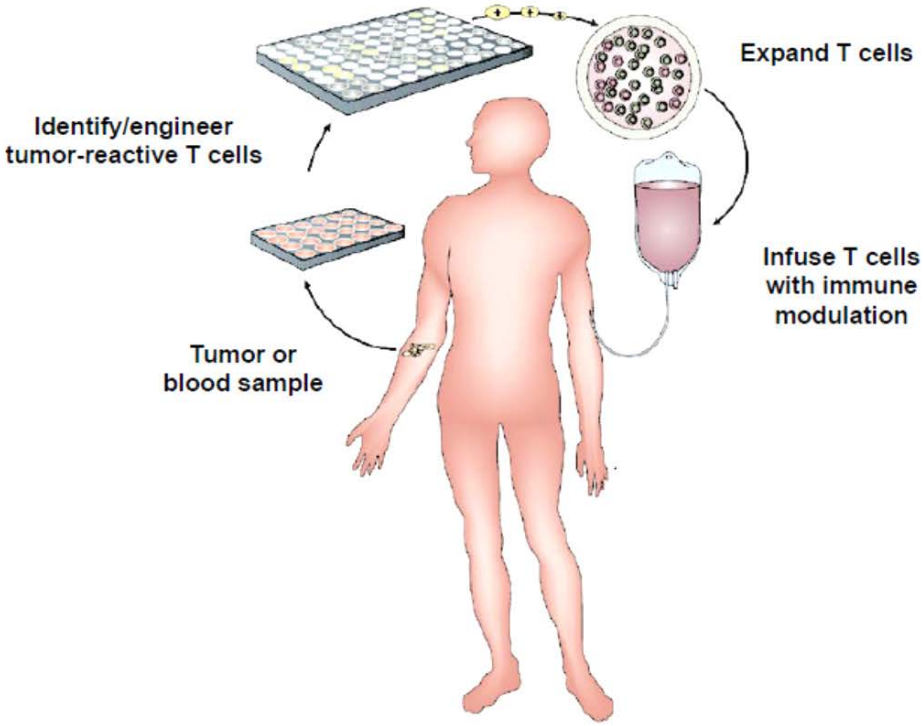
Cost

- approx. $100k/treatment cycle
- combinations may be required for some cancers (e.g. Ipi + Nivo for melanoma)
- long-term use may be required for some cancers

Efficacy

- many cancers (e.g. ovarian, breast) have low response rates (10-20% range)
- responses are often transient (e.g. lung)

Adoptive T cell therapy



BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority

BC CANCER FOUNDATION
partners in discovery

Immunotherapy Program

New provincial program with the expertise and infrastructure to conduct ***innovative clinical trials*** targeting a spectrum of cancers.

Leverages three BCCA strengths:

- Immunology (Deeley Research Centre, Victoria)
- Genomics (Genome Sciences Centre, Vancouver)
- Tumor groups (gyne, lymphoma, leukemia, breast, others)

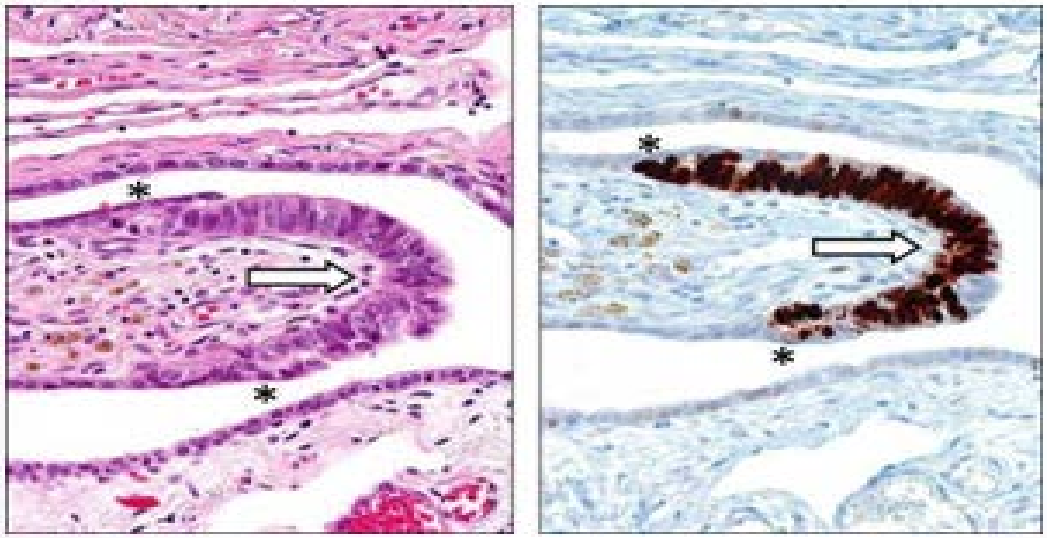
BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority

BC CANCER FOUNDATION
partners in discovery

Initial Clinical Trials

- **Gyne (2018):** *Tumor-infiltrating lymphocyte (TIL) therapy for ovarian, endometrial and cervical cancer*
- **Leukemia/lymphoma (2019):** *CD19 CAR T cells*
  - BioCanRx collaboration with Ottawa Hospital Research Institute (Atkins, Kekre, Bell) and Copenhagen (Muller, Svane)
- **Lymphoma (2019):** *Targeting personal driver mutations with T cells*

STIC : the precursor to HGS carcinoma



Serous tubal intraepithelial carcinoma, p53 stain positive, usually found in the distal fimbriated end of the fallopian tube in aproximately 6 to 10% of BRCA positive women undergoing BSO risk reducing surgery.

The role of the fallopian tube in ovarian cancer