



Clinical Trials in NETs – lets open some new doors....

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Objective today

- To discuss what are clinical trials
- To review what you want to know about clinical trials
- To share clinical trials at Susan Leslie Clinic for Neuroendocrine Tumours



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Cancer Clinical Trials

The Basics



What Are Cancer Clinical Trials?

- Research studies involving people
- Try to answer scientific questions and find better ways to prevent, diagnose, or treat cancer



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Why Are Cancer Clinical Trials Important?

- Clinical trials translate results of basic scientific research into better ways to prevent, diagnose, or treat cancer
- The more people that take part, the faster we can:
 - Answer critical research questions
 - Find better treatments and ways to prevent cancer



Do Many People Participate in Cancer Clinical Trials?

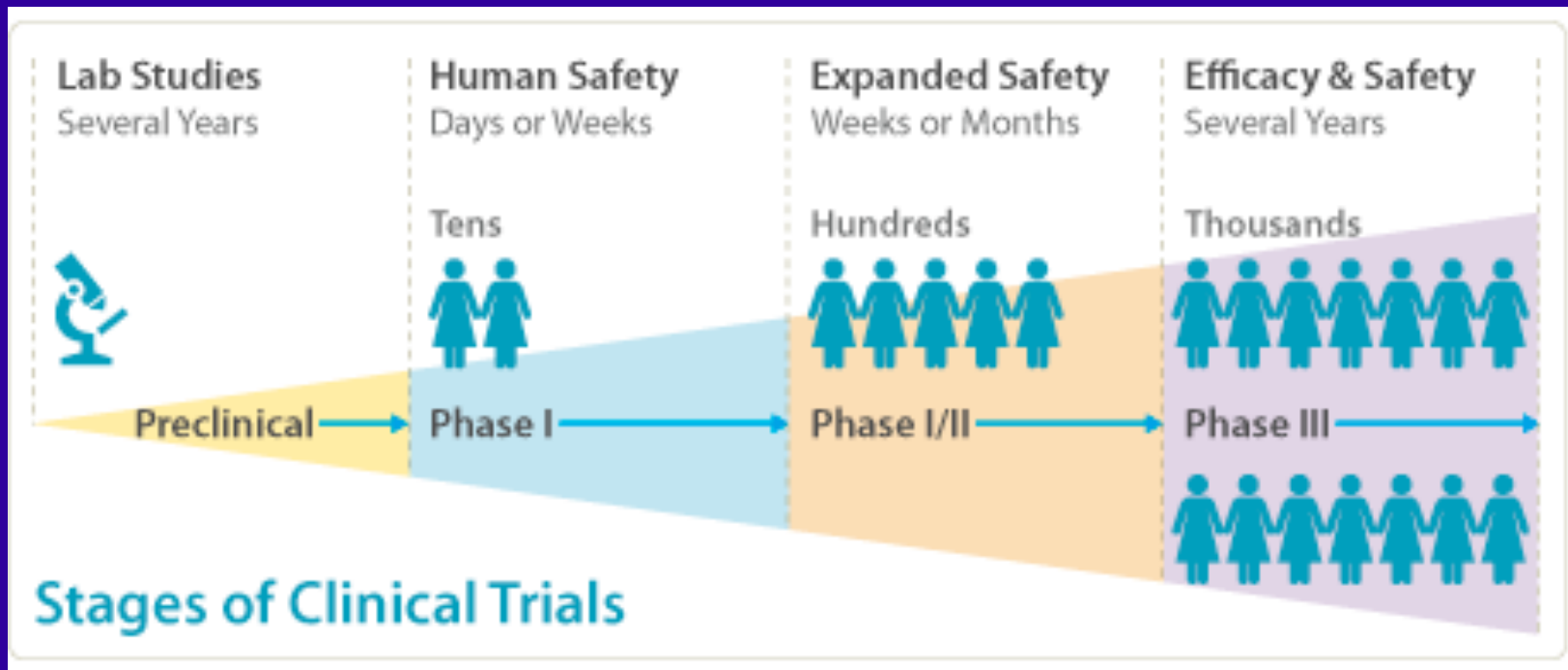
- Only 3 percent of U.S. adults with cancer participate in clinical trials



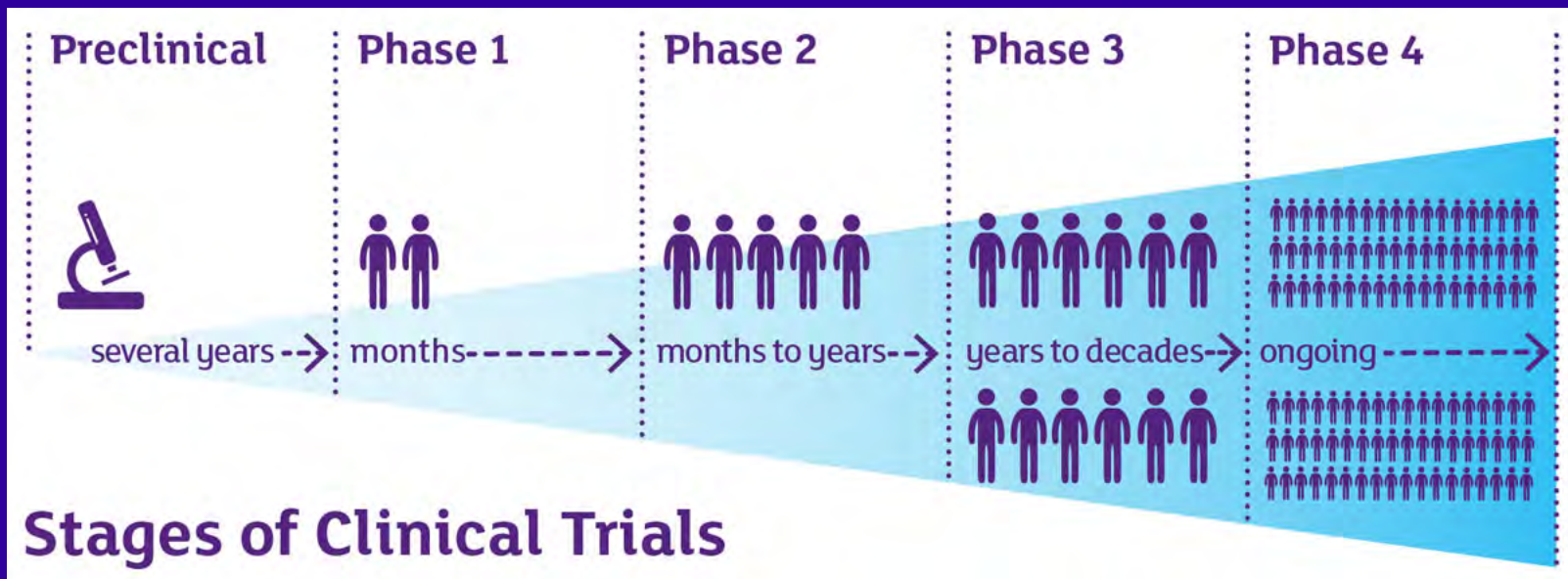
Types of Cancer Clinical Trials

- Treatment trials
- Prevention trials
- Early-detection trials/screening trials
- Diagnostic trials
- Quality-of-life studies/supportive care studies

Stages of clinical trials?



How long do trials take?



Clinical Trial Phases

Phase 1 trials

- How does the agent affect the human body?
- What dosage is safe?

Clinical Trial Phases

Phase 2 trials

- Does the agent or intervention have an effect on the cancer?

Clinical Trial Phases

Phase 3 trials

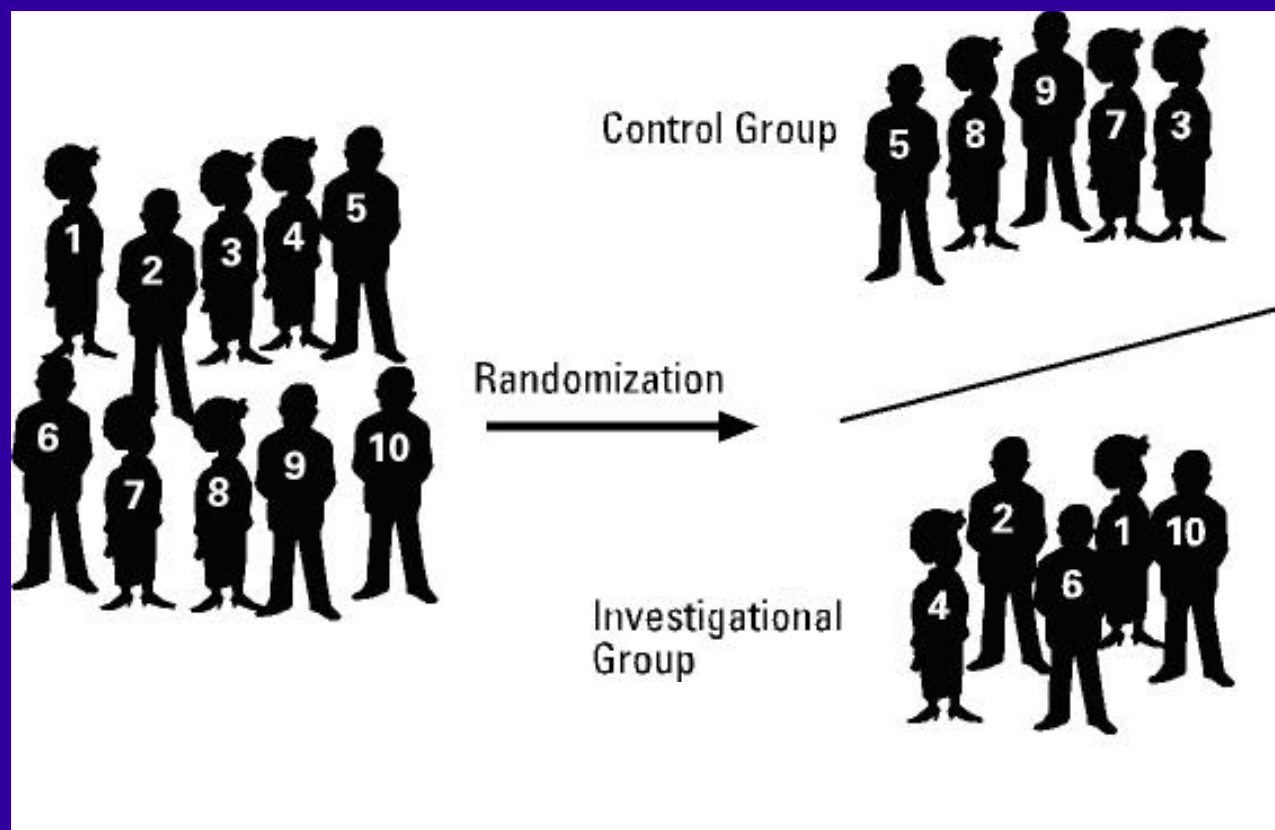
- Is the new agent or intervention (or new use of a treatment) better than the standard?
- Participants have an equal chance to be assigned to one of two or more groups

Randomized Trials

Participants have an equal chance to be assigned to one of two or more groups:

- One gets the most widely accepted treatment (standard treatment)
- The other gets the new treatment being tested, which researchers hope and have reason to believe will be better than standard treatment

Randomization



Why Is Randomization Important?

- So all groups are as alike as possible
- Provides the best way to prove the effectiveness of a new agent or intervention

Cancer Treatment Trials

- What new treatments can help people who have cancer?
- What is the most effective treatment for people who have cancer?



Cancer Treatment Trials

Placebos are almost never used:

- Placebos are used only when no standard treatment exists
- Patients are told of this possibility before deciding to take part

Clinical Trial Protocol

- A recipe or blueprint
- Strict scientific guidelines:
 - Purpose of study
 - How many people will participate
 - Who is eligible to participate
 - How the study will be carried out
 - What information will be gathered about participants
 - Endpoints

Benefits of Participation

Possible benefits:

- Patients will receive, at a minimum, the best standard treatment
- If the new treatment or intervention is proven to work, patients may be among the first to benefit
- Patients have a chance to help others and improve cancer care

Risks of Participation

Possible risks:

- New treatments or interventions under study are not always better than, or even as good as, standard care
- Even if a new treatment has benefits, it may not work for every patient
- Health insurance and managed care providers do not always cover clinical trials

Patient Protection

- There have, unfortunately, been past abuses in patient protection
- Federal regulations ensure that people are told about the benefits, risks, and purpose of research before they agree to participate



How Are Patients' Rights Protected?

- Informed consent
- Scientific review
- Institutional review boards (IRBs)
- Data safety and monitoring boards

How Are Patients' Rights Protected?

Informed consent:

- Purpose
- Procedures
- Risks and potential benefits
- Individual rights



How Are Patients' Rights Protected?

- Scientific review
- Institutional review boards (IRBs) are required by Federal law for trials that are:
 - Federally funded
 - Subject to FDA regulation



CLINICAL TRIALS AT SUNNYBROOK



NET trials at Sunnybrook

- SPINET – SSA in Lung carcinoid
- OZM-057 – Everolimus + SBRT to liver
- OZM-067 – PRRT
- NET 001 – PDL1 in poorly diff NET
- NET 002 – PDL1 in well diff G2/3 NET
- PDR-001 – Novel Immunotherapy in NETs (full)

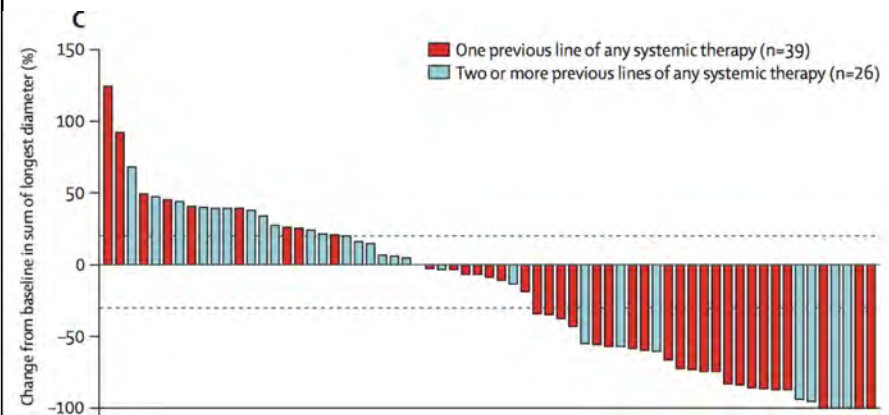
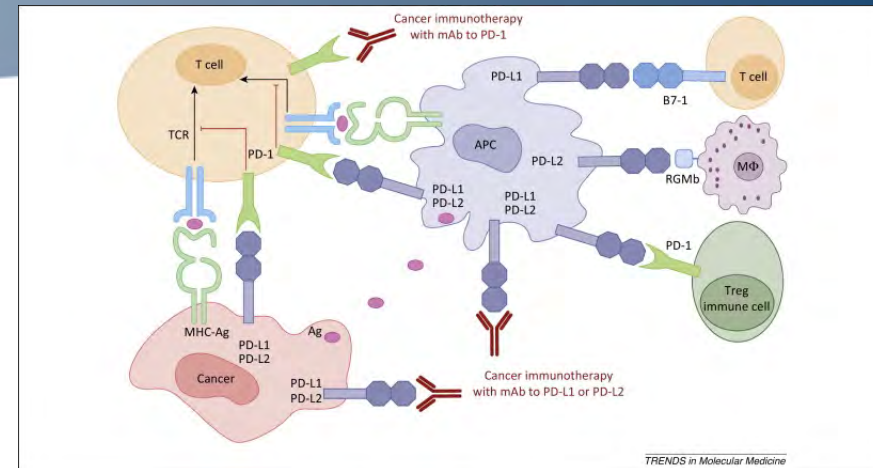


IMMUNOTHERAPY IN NETS

Immunotherapy in NETs

Overview

- Immunotherapy used in other tumour types
- Now first-line treatment for appropriate melanoma² and NSCLC
- Difference between NETs and other tumours
 - Significant clinical heterogeneity
 - Lower molecular mutation burden overall³
- Recent trial of avelumab in chemo-refractory met. Merkel Cell ca: 31.8% response rate⁴.
- One NET trial thus far showed low RRs
 - KEYNOTE-028⁵: 41 patients (25 carcinoid, 16 pNET)
 - Carcinoid included lung, gut, and “other”
 - Response rate 12% carcinoid, 6% pNET
 - Results not available by grade



1. Ohaegbulam et al. Cell review 2006;17:1733-1742.
2. Robert et al. NEJM 2015; 372:320-330.
3. Annals of Oncology 2016. 27(6): 136-148
4. Lancet Oncol 2016. 17(10): S1470
5. Ann Oncol [Internet]. 2017 Sep 1;28(suppl_5).



Current Immunotherapy/NET trials

- **NET-001 (NCT03278405)**
 - A Pilot Study of Avelumab in Unresectable/Metastatic, Progressive, Poorly Differentiated Grade 3 Neuroendocrine Carcinomas
- **NET-002 (NCT03278379)**
 - A Phase II Study of Avelumab in Unresectable/Metastatic, Progressive Grade 2-3 Neuroendocrine Tumors





Radiation Therapy for NETS

- Traditional external beam radiation therapy (EBRT) for NETs is historically associated with moderate responses¹.
- Increasing interest in use of stereotactic ablative radiotherapy (SABR) as a modality for local control of primary or metastatic disease
- Further, increasing interest in role of radiotherapy to potentiate responses from immunotherapy (abscopal effect)
 - PACIFIC study reported on improved PFS of addition immunotherapy after primary chemoradiation²
 - Specific to NETS a case of significant response of high-grade neuroendocrine ca has been reported following combination of anti-PD-1 and SABR³

1. Clin Oncol. 2018. epub.
2. NEJM. 2017. 377(20): 1919-1929
3. Oncologist. 2017. 22: 631-637



Immunotherapy and RT

- Scientific rationale for RT increasing immunogenicity
 - T cells: Increase in inflammatory cytokines and neoantigen expression¹
 - Increase in intracellular peptide pool, mTOR activation, and MHC class I antigen presentation^{2,3}
- Preclinical models of PD1/PDL1 and radiotherapy
 - Cytotoxic T cell activation
 - Reduction in MDSC (myeloid-derived stem cells)
 - Induces abscopal response
 - Induction of macrophages⁴

1. Formenti et al JNCI 2013; 105(4):256-265. 2. Reits et al J Exp Med 2006; 203(5):1259-1271. 3. Albert et al Nature 1998; 392(6671):86-9. 4. Klug et al Cancer Cell 2013; 24(5):589-602.



NET trials at Sunnybrook

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Other Initiatives

- Shared care model
- Understanding patient preferences /decision making
- Understanding patient symptoms
- PRRT and new clinical trials
- Radiation and immunotherapy





QUESTIONS?

