INTRODUCTION TO CLINICAL ONCOLOGY
AGENDA

- CHEMOTHERAPY
- ENDOCRINE THERAPY
- TARGETED THERAPIES
- PERSONALIZATION OF ONCOLOGY
- IMMUNOTHERAPY
Cell Cycle Phases

Premitotic synthesis of structures

Synthesis of DNA precursors, proteins, etc.
Uncontrolled Proliferation

- Result of action of proto-oncogenes or inactivated tumor suppressor genes
  - Change in growth factors, receptors
    - increased growth factors production
  - Change in growth factor pathways
  - Change in cell cycle transducers
    - Cyclins, Cdk’s, Cdk inhibitors
Anticancer Drugs are Antiproliferative

- Affect cell division
  - Active on rapidly dividing cells
- Most effective during S phase of cell cycle
  - Many cause DNA damage
- Damage DNA → initiation of apoptosis
- Side effects greatest in other rapidly-dividing cells
  - Bone marrow toxicity
  - Impaired wound healing
  - Hair follicle damage
  - GI epithelium damage
  - Growth in children
  - Gametes
  - Fetus

- May themselves be carcinogenic
Difficulties in Chemotherapy Effectiveness

- **Solid tumors**
  - Growth rate decreases as neoplasm size increases
    - Outgrows ability to maintain blood supply AND
  - Not all cells proliferate continuously
- **Compartments**
  - Dividing cells (may be ~5% tumor volume)
    - Only population susceptible to most anticancer drugs
  - Resting cells (in G0); can be stimulated → G1
    - Not sensitive to chemotherapy, but activated when therapy ends
  - Cells unable to divide but add to tumor bulk
Drugs Used in Cancer Chemotherapy

- Cytotoxic Agents
  - Alkylating Agents
  - Antimetabolites
  - Cytotoxic antibiotics
  - Plant derivatives
**PURINE SYNTHESIS**

- PENTOSTATIN
  - inhibits adenosine deaminase

- 6-MERCAPTOPURINE
  - 6-TIOPURINE
  - inhibit purine synthesis
  - inhibit nucleotide interconversions

- METHOTREXATE
  - inhibits purine synthesis
  - inhibits DTMP synthesis

- CYTARABINE
  - inhibits DNA polymerase
  - inhibits RNA function

- CRISANTASPASE
  - deaminates asparagine
  - inhibits protein synthesis

**PYRIMIDINE SYNTHESIS**

- 5-FLUOROURACIL
  - inhibits DTMP synthesis

- BLEOMYCINS
  - damage DNA and prevent repair

- ALKYLATING AGENTS
  - MITOMYCIN
  - CISPLATIN
  - cross-link DNA

- CAMPOTHECINS
  - DOXORUBICIN
  - ETOPOSIDE
  - AMSACRINE
  - inhibit topoisomerase II

- DACTINOMYCIN
  - intercalates in DNA
  - inhibits topoisomerase II

- VINCA ALKALOIDS
  - TAXANES
  - inhibit function of microtubules

**RIBONUCLEOTIDES**

**DEOXYRIBONUCLEOTIDES**

**DNA**

**RNA** (transfer, messenger, ribosomal)

**PROTEINS**

- ENZYMES (etc.)
- MICROTUBULES
Bifunctional alkylation agents can cause intrastrand linking and cross-linking.
Antimetabolites

- Mimic structures of normal metabolic mol’s
  - Inhibit enzymes competitively OR
  - Incorporated into macromolecules → inappropriate structures

- Kill cells in S phase

- Three main groups
  - Folate antagonists
  - Pyridine analogs
  - Purine analogs
M Phase Specific

Antimicrotubule Agents
Inhibit function of microtubules
- Epothilones
- Halichondrin B analogue
- Taxanes
- Vinca alkaloids

Topoisomerase II Inhibitors
Block topoisomerase function (unwinding DNA)
- Anthracemedione
- Anthracyclines
- Epipodophyllotoxins

Agents Affecting Multiple Phases of the Cell Cycle

Antitumor Antibiotics
Induce DNA lesions, inhibit topoisomerase, among other effects
- Bleomycin
- Dactinomycin
- Mitomycin

Cell Cycle Independent

Alkylation Agents
Crosslink guanine nucleobases in DNA
- Alkyl sulfonates
- Ethylenimines
- Nitrogen mustard
- Nitrosureas
- Platinum analogues
- Triazines

S Phase Specific

Antimetabolites
Inhibit DNA synthesis
- Folate antagonists
- Purine analogues
- Pyrimidine analogues
- Hydroxyurea

Topoisomerase II Inhibitors
Block topoisomerase function (unwinding DNA)
- Anthracemedione
- Anthracyclines
- Epipodophyllotoxins
ENDOCRINE THERAPY

CDK4/6 INHIBITORS

ER, PR, AR
PI3K/AKT
RAS/RAF/MAPK
WNT/βcatenin
NF-κB

PJW
ROUTES OF CHEMOTHERAPY ADMINISTRATION

- INTRAVENOUS
- ORAL
  - ANTIMETABOLITES
  - ALKYLATING AGENTS
  - MITOTIS SPINDLE POISONS
- INTRAPERITONEAL
- INTRATUMORAL (TRANSARTERIAL CHEMOEMBOLIZATION)
HIPEC
HYPERTHERMIC INTRA-PERITONEAL CHEMOTHERAPY
TRANSARTERIAL CHEMOEMBOLIZATION
Case Example 1: Chemoembolization of Hepatocellular Carcinoma

This 60 year-old cirrhotic female has a 3 cm mass in the posterior right segment of the liver diagnosed on pre-procedure CT scan (1a arrow). She was referred for chemoembolization. The arteriogram demonstrates the targeted mass (1b arrow). Follow-up imaging demonstrates complete tumor necrosis (1c arrow). The patient went on to liver transplant 6 months later.
ENDOCRINE THERAPY
Hormones

- Tumors derived from tissues responding to hormones may be hormone-dependent
  - Growth inhibited by hormone antagonists OR other hormones w/ opposing actions OR inhibitors of relevant hormone

- Glucocorticoids
  - Inhibitory on lymphocyte proliferation
  - Used against leukemias, lymphomas
- **ESTROGEN RECEPTOR**
  - breast, ovarian, endometrial cancers
  - drugs
    - ER blockers – tamoxifen, fulvestrant
    - estrogen synthesis blockers – aromatase inhibitors
    - estrogen deprivation – aGnRH agonists/antagonists

- **ANDROGEN RECEPTOR**
  - prostate, breast cancer
  - drugs
    - androgen deprivation – aLHRH agonists/antagonists
    - AR blockers – flutamide, bikalutamide, enzalutamide
    - androgen synthesis blocker – abiraterone

- **PROGESTERONE RECEPTOR**
  - specific drugs in development
  - progestogens
ENDOCRINE THERAPY IN BREAST CANCER
PROLIFERATION
SURVIVAL
METASTASES
CHEMORESISTANCE
HER2, EGFR, IGF1-R

ER

E

ER

PROLIFERATION
SURVIVAL
METASTASES
CHEMORESISTANCE

MAPK

PI3K

AKT

CoA

Src

CoA

AP-1

TFs

CoA

CoA

CoA

CoA

CoA
HER2, EGFR, IGF1-R

RAS → PI3K → MAPK → AKT

SERM, FULW.

IA
MALE ENDOCRINE SYSTEM

HYPOTHAMUS

PITUARY GLAND

GONADOTROPIN RELEASING HORMONES

GONADOLIBERIN
- AGONISTS
- ANTAGONISTS

ANTIANANDROGENS

ANDROSTENDIONE

DHEA

TESTOSTERONE

LH

NEGATIVE FEEDBACK LOOP
HORMONE SENSITIVITY OF PROSTATE CANCER
HORMONE SENSITIVITY OF PROSTATE CANCER
ENDOCRINE THERAPY OF PROSTATE CANCER

ANTIANDROGENS
FLUTAMIDE
BIKALUTAMIDE

castration
surgical
pharmacological
tagNRH
RESISTANCE TO CASTRATION
AUTOCRINE PRODUCTION OF ANDROGENS

SURVIVAL
PROLIFERATION
ANGIOGENESIS
METASTASIS
RESISTANCE TO CASTRATION

AR amplification

SURVIVAL
PROLIFERATION
ANGIOGENESIS
METASTASIS
RESISTANCE TO CASTRATION
AR overexpression

Survival
Proliferation
Angiogenesis
Metastasis
RESISTANCE TO CASTRATION
hypersensitivity of AR

SURVIVAL
PROLIFERATION
ANGIOGENESIS
METASTASIS
RESISTANCE TO CASTRATION
co-regulators

SURVIVAL
PROLIFERATION
ANGIOGENESIS
METASTASIS
RESISTANCE TO CASTRATION
activation of AR by other factors

- prolactin
- growth hormone
RESISTANCE TO CASTRATION activation of AR via various signalling pathways

- IGF-1
- KGF
- TGF
- IL-6
- IL-8

SURVIVAL
PROLIFERATION
ANGIOGENESIS
METASTASIS
Antitumor Agents Working through Cell Signalling

<table>
<thead>
<tr>
<th>Proto-oncogene</th>
<th>Proto-oncogene products</th>
<th>Cancer</th>
<th>Anticancer drugs</th>
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<tbody>
<tr>
<td>Genes for growth factors e.g. for IGF</td>
<td>Growth factors e.g. IGF</td>
<td>Prostate, breast colorectal, etc.</td>
<td>Research in progress. WTS</td>
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<tr>
<td>Gene for EGF receptors (e.g. c-erbB)</td>
<td>Her2* (a receptor tyrosine kinase)</td>
<td>Breast</td>
<td>Inhibited by trastuzumab</td>
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<tr>
<td>Gene for PDGF (c-sis)</td>
<td>PDGF (a receptor tyrosine kinase)</td>
<td>Chronic myeloid leukaemia</td>
<td>Inhibited by imatinib (aka Gleevec)</td>
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<tr>
<td>c-ras</td>
<td>Ras proteins</td>
<td>30% of all tumours</td>
<td>Ras inhibitors in clinical trial</td>
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<tr>
<td>abl</td>
<td>Abl tyrosine kinase (cytoplasmic)</td>
<td>Chronic myeloid leukaemia</td>
<td>Inhibited by imatinib (aka Gleevec)</td>
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<td>c-src</td>
<td>Cytoplasmic tyrosine kinase</td>
<td>Breast, pancreas, bone</td>
<td>Research in progress. WTS</td>
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<td>Genes for JAK, Lck</td>
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<td>Leukemias</td>
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<td>c-jun/c-fos</td>
<td>Transcription factors (Jun, Fos, Myc)</td>
<td>Colorectal</td>
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<tr>
<td>c-myc</td>
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<td>Lung, neural tissue</td>
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Mutation of the delayed response nuclear proto-oncogenes can alter expression of the regulators of the cell cycle, e.g. more than 50% of human tumours have mutations of the tumour suppressor gene that codes for p53 protein.
Drugs Targeting Growth Factor Receptors

- Cetuximab, Panitumumab
  - Monoclonal Ab directed against EGFR
- Erbitux – anti-EGFR Ab
- **Trastuzumab**
  - “Humanized” mouse monoclonal Ab
  - Binds HER2
    - Membrane protein structurally similar to EGFR
    - Has integral tyrosine kinase activity
  - Important in breast cancer cells
  - May also induce p21 and p27
  - Cell cycle inhibitors

PERSONALIZED HEALTHCARE IN ONCOLOGY

- WE ARE NOT THERE YET-
Tailoring Treatment?

„If I go to my tailor to buy a new suit, I do not ask for a suit for a group of Caucasian men with white hair–

- I expect to be measured for the suit so that it fits me alone

It’s important to differentiate between treatment that is tailored individually....

....and treatment that is tailored to a group (e.g. women with breast cancer whose cells express HER2)"

prof. Ian Tannock
PMH University of Toronto
BIOMARKERS

BIOMARKER = BIOLOGICAL MARKER THAT CAN BE DEFINED ON GENOMIC OR MOLECULAR LEVEL

- BIOLOGICAL PROGNOSTIC FACTORS
- BIOLOGICAL PREDICTIVE FACTORS
- BIOLOGICAL SIGNS OF TREATMENT EFFICACY (RESPONSE)
- BIOLOGICAL MARKERS DEMONSTRATING RESISTANCE TO TREATMENT
NOVEL antiangiogenic THERAPIES—
are there any biomarkers?
Distant Metastases
BEVACIZUMAB INHIBITION OF ANGIOGENESIS

HYPOXIA ($\downarrow O_2$)

CANCER CELL

EGF

PDGF

VEGF

GLUT-1

HIF-1α

HIF-2α

HIF-1β

VEGFR/PDGFR INHIBITORS

SUNITINIB, SORAFENIB, EVEROLIMUS
BEVACIZUMAB

VEGF – KEY FACTOR IN TUMOR-INDUCED ANGIOGENESIS

VEGF – IMMUNOSUPRESIVE FACTOR

VEGF – PROGNOSTIC FACTOR

BUT

VEGF – PREDICTIVE FACTOR FOR BEVACIZUMAB EFFICACY???
VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, PIGF, sVEGFR??
ANTIANGIOGENIC THERAPIES USED FOR TREATMENT OF RENAL CANCER

TYROSINE KINASE INHIBITORS

• SORAFENIB – VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, RAF
• SUNITYNIB – VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β

SERINE-THREONINE KINASE (mTOR) INHIBITORS

• TEMSIROLIMUS
• EVEROLIMUS

VEGF NEUTRALIZATION

• BEVACIZUMAB

BUT

THERE IS NO SINGLE PREDICTIVE FACTOR
HER2 AND TARGETED THERAPIES IN BREAST CANCER
HER2 (ErbB2)
MEMBER OF EPIDERMAL GROWTH FACTOR RECEPTOR FAMILY

- OVEREXPRESSION OF HER2 – prognostic biomarker in breast cancer

- OVEREXPRESSION OF HER2 – negative predictive biomarker for response to hormonal treatment in breast cancer

- OVEREXPRESSION OF HER2 – predictive biomarker for therapies targeting this receptor (trastuzumab and lapatinib)
HER2 PROGNOSTIC BIOMARKER IN BREAST CANCER PATIENTS

Overall survival probability

HER2 standard level

HER2 overexpression
HER2 – PREDICTIVE BIOMAKER OF TRASTUZUMAB (Herceptin) EFFICACY

B-31 i N9831 – combined analysis

Overall survival probability

<table>
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<tr>
<th>Years</th>
<th>AC→P</th>
<th>n</th>
<th>Deaths</th>
<th>AC→PH</th>
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</table>

HR = 0.67; \( p = 0.015 \)
THE REAL EFFICACY OF TRASTUZUMAB

- IN METASTATIC BREAST CANCER (MBC), RESISTANCE TO TRASTUZUMAB MONOTHERAPY – 66-88%

- THE MAJORITY OF MBC PATIENTS PRIMARILY RESPONDING TO TRASTUZUMAB WILL DEVELOP RESISTANCE WITHIN 1 YEAR

- IN ADJUVANT TREATMENT – DISSEMINATION OF DISEASE WILL OCCUR IN ~15% OF PATIENTS

Nahta R. Breast Cancer Res, 2006
AT THE CELL MEMBRANE
HER2 AND RESPONSE TO TRASTUZUMAB
TRASTUZUMAB IN HER2-OVEREXPRESSING BREAST CANCER

- HER2
- HER2
- HER2
- EGFR

trastuzumab

TK

RAS

PI3K

RAF

AKT

MEK

mTOR

ERK

PROLIFERATION, INVASION, METASTASING, ANGIOGENESIS
Trastuzumab

MONOCYTE

FcγR

TYROSINE KINASE
EFFICACY OF TRASTUZUMAB MAY DEPEND ON FcγR GENE POLYMORPHISM
Loss of extracellular domain of HER2 receptor
Overexpression of MUC4
INSIDE THE CANCER CELL

HER2 AND RESISTANCE TO SYSTEMIC TREATMENT
EVALUATION OF RESPONSE TO TREATMENT

TARGETED THERAPIES – RESPONSE TO TREATMENT
TRASTUZUMAB – CYTOSTATIC BUT ALSO CYTOTOXIC DRUG – EVALUATION OF RESPONSE TO TREATMENT IS OBJECTIVE AND QUITE SIMPLE

BUT

IN THE CASE OF NOVEL ANTIANGIOGENIC TARGETED THERAPIES– BEVACIZUMAB, SORAFENIB, SUNITYNIB,

The same size of tumor following 4 months of treatment – no response?

ALMOST 95% OF TUMOR – NECROSIS - BIOMARKERS OF RESPONSE ARE EXTREMELY HELPFUL-
TOXICITY AND PATIENTS’ SELECTION

TARGETED THERAPIES
ADVERSE EVENTS ASSOCIATED WITH TARGETED THERAPIES

- MYELOSUPPRESSION
- HEART FAILURE
- HYPERTENSION
- HYPOTHYROIDISM
- IMMUNOSUPPRESSION
- DERMATOLOGIC DISORDERS
- AUTOIMMUNOLOGICAL DISORDERS
- ANAPHYLAXIS, ALLERGIC REACTIONS
- ELECTROLYTE IMBALANCE
- HEMORRHAGE
- THROMBOEMBOLIC EVENTS
- NEUROPATHY
- IMPOTENCE
- INTESTINAL PERFORATION
- MUSCLE CRAMPS
- PERIPHERAL OEDEMA
A CRUCIAL POINT IN CLINICAL ONCOLOGY

EARLY DETERMINATION OF RESISTANCE TO TREATMENT WHEN A PARTICULAR DRUG IS STILL ADMINISTERED

CIRCULATING TUMOR CELLS
GENOMIC AND PROTEOMIC ANALYSIS OF CIRCULATING TUMOR CELLS
- INTELLIGENCE SERVICE IN ONCOLOGY -
TARGETED THERAPIES – STRIKE ON A WELL-KNOWN ENEMY
FROM A HISTORICAL POINT OF VIEW
TARGETED THERAPIES

Precise weapon

The U.S. Navy's Tomahawk cruise missile is the weapon of choice for precision strike missions against high value or heavily defended targets. First used in Operation Desert Storm, the Tomahawk has gone through numerous improvements in range and accuracy. Upgrades include the addition of Global Positioning System (GPS) guidance ability which reduces mission planning time and provides the option for missions guided by GPS only.

**Tomahawk Land Attack Missile**

- **Launch**
  - Can be launched from Seawolf or Los Angeles-class submarines, or cruisers and destroyer surface ships.

- **Flight**
  - A booster rocket propels the missile to about 1,200 feet, where the wings fold out and the turbopump engine takes control.

- **Cruise**
  - Can hug terrain at an altitude as low as 50 feet, using stored elevation maps, on-board radar and GPS.

- **Strike**
  - On-board camera compares the actual target to a stored image, and makes any final route changes. Can carry payloads ranging from a single warhead to combined bombs and boobytraps capable of striking up to three targets.

**Specifications**

- **Length:** 18 feet, 3 inches
- **Wingspan:** 8 feet, 9 inches
- **Weight:** 2,650 pounds
- **Range:** 700-1000 miles
- **Speed:** 550 mph
- **Warhead:** 1,000 pound conventional warhead; submunition dispenser with 166 combined effect bomblets; 297 pound nuclear device
- **Cost per missile**: $600,000

**In arsenal of:** United States, United Kingdom

*Figures are approximate

SOURCES: Program Executive Office Strike Weapons and Unmanned Aviation; Jane's Information Group; GlobalSecurity.org
TO KNOW WHERE, WHEN AND HOW WE CAN TARGET THE ENEMY (CANCER CELLS)

IN ORDER TO BE PREPARED ON A COUNTERSTRIKE

WE NEED A LOT OF INTEL DATA!!!!
WE NEED
A PERFECT INTELLIGENCE SERVICE
IMMUNOTHERAPY
BEGINNING OF IMMUNOTHERAPY

1893 – Wilam B Coley, New York – case report on spontaneous regression advanced sarcoma in a patient following a high fever from erisipelas infection

1895 – First ‘trials’ on immunotherapy – subcutaneous injection of streptococcus pyogenes to patients with advanced tumors to provoke immune response

MECHANISM OF ACTION – RAPID INFLAMMATORY REACTION – ”CYTOKINE STORM” LEADING TO REACTIVATION OF SUPPRESSED IMMUNE RESPONSES.

COLEY’S TOXIN INDUCED PRODUCTION OF TNFα

PFIZER CONTINUES DEVELOPMENT OF COLEY TOXIN
IMMUNE HOMEOSTASIS MECHANISMS
THE KEY TO CANCER-INDUCED IMMUNOSUPPRESSION
CHECKPOINTS

COSTIMULATORY RECEPTORS
MHC I
CD28
IL-12R
IL-2R

IMMUNOSUPPRESSIVE MOLECULES
CTLA4
PD-1

STOP

ANTI-CTLA4
IPILIMUMAB

ANTI-PD1
NIVOLUMAB
PEMBROLIZUMAB

ANTI-PDL1
ATEZOLIZUMAB
CHECKPOINT INHIBITORS
THE BREAK THROUGH IN
CLINICAL ONCOLOGY
Breakthrough of the Year 2013

1. Cancer Immunotherapy
2. CRISPR
3. CLARITY
4. Human Stem Cells from Cloning
5. Mini-Organs
6. Cosmic Particle Accelerators
7. Perovskites Solar Cells
8. Why We Sleep
9. Our Microbes, Our Health
10. In Vaccine Design, Looks Do Matter
IPILIMUMAB (ANTI-CTLA4) OVERALL SURVIVAL

Hodi SF NEJM 2010

IPI – mediana follow-up (27 mies.)

23%
ADVANCED MELANOMA
OVERALL SURVIVAL
IPILIMUMAB vs HISTORICAL CONTROL

Korn EL i wsp. JCO 2008
Schadendorf D i wsp. ESMO 2013
Patients at Risk
Ipilimumab  4846  1786  612  392  200  170  120  26  15  5  0

3-year OS, % (95% CI): 21 (20–22)

Median OS, months. (95% CI): 9.5 (9.0–10.0)
ANTI-PD1/ANTI-PD-L1 CHECKPOINT INHIBITORS
PD-1 – PD-L1 – MECHANISM OF IMMUNOSUPPRESSION
anti-PD1 – MECHANISM OF ACTION

activated specific T cell

CANCER CELL

PD-1

PD-L1

MHC I

TCR
ANTI-PD-L1 – MECHANISM OF ACTION

CANCER CELL

activated specific T cell

PD-

PD-L1

TCR

MHC I
CHECK-POINT INHIBITORS APPROVED 2014-2016

- ANTI-PD1
  - MELANOMA
  - SQUAMOUS NON-SMALL CELL LUNG CANCER
  - NON-SQUAMOUS NON-SMALL CELL LUNG CANCER
  - RENAL CELL CANCER
  - HODGKIN LYMPHOMA

- ANTI-PDL1
  - BLADDER CANCER

EXPECTED APPROVAL – COLRECTAL CANCER, HEAD&NECK CANCER, BLADDER CANCER, BREAST CANCER,
ONCOLOGYC VIRUSES
E.G. „WILD” ADENOVIRUS INFECTS A TARGET CELL PRODUCT OF THE E1 VIRAL GENE PREVENTS TP53-MEDIATED APOPTOSIS OF INFECTED CELL
ADENOVIRAL REPLICATION IN THE INFECTED CELL
LYSIS OF THE INFECTED CELL AND RELEASE OF VIRAL PARTICLES AND TUMOR ANTIGENS
REPLICATED VIRUSES INFECT ADJACENT CELLS
T-VEC – NOVEL IMMUNOTHERAPY BASED ON ONCOLYTIC HSV – APPROVED IN MELANOMA

Selective viral replication in tumor tissue

Tumor cells rupture for an oncolytic effect

Systemic tumor-specific immune response

Death of distant cancer cells

Local Effect: Tumor Cell Lysis

Systemic Effect: Tumor-Specific Immune Response
T-VEC

Screening

Cycle 3

Cycle 8