cancer incidence forecast – unfavourable situation:

the annual number of cancer cases in the world will increase from 19.3 million in 2020 to 28.4 million in 2025

an **increase of 47% compared to 2020 in five years**

cancer incidence forecast:

the annual number of cancer cases in the world will increase from 19.3 million in 2020 to 28.4 million in 2025

an increase of 47% compared to 2020 in five years

other methods than conventional chemotherapy / radiation are needed that would enable progress in the treatment of many types of cancer

classical chemotherapy is already reaching the limits of its effectiveness

Cancer targeted therapy – biological therapy, precise medicine

changing oncology conventional treatment

- neoplastic cells are **directly targeted**
- influence (side effects) to non-neoplastic tissues reduced

Biological cancer therapy involves treatment with
natural molecules made by the body or made in a laboratory

- help the **immune system** fight the cancer
or
- **attack the cancer directly**

Include treatment with
- monoclonal antibodies
- adoptive cell transfer
- gene therapy
- treatment with cytokines
- cancer vaccines
- oncolytic viruses
- immunoconjugates and the use of targeted therapy

Combining various biological therapies, immunotherapy with oncolytic viruses or cancer vaccines - gaining importance

A new term in seeking the molecules for therapy targeting:

precision oncology, uses the results by ***next generation sequencing (NGS)*** methods to detect new / rare mutations in cancer cells in order to tailor treatment to a specific patient

in the biological therapy of cancer,
molecules that **target** genetic aberrations in
oncogenes / tumor suppressor genes
leading to tumor development are essential

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Classic examples of such molecules are:
imatinib - a BCR-ABL tyrosine kinase inhibitor
- chronic myeloid leukemia
- GISTs

vemurafenib - a BRAF seronine / threonine kinase inhibitor
- melanoma

osimertinib - non-small cell lung cancer
in the presence of the EGFR T790M mutation

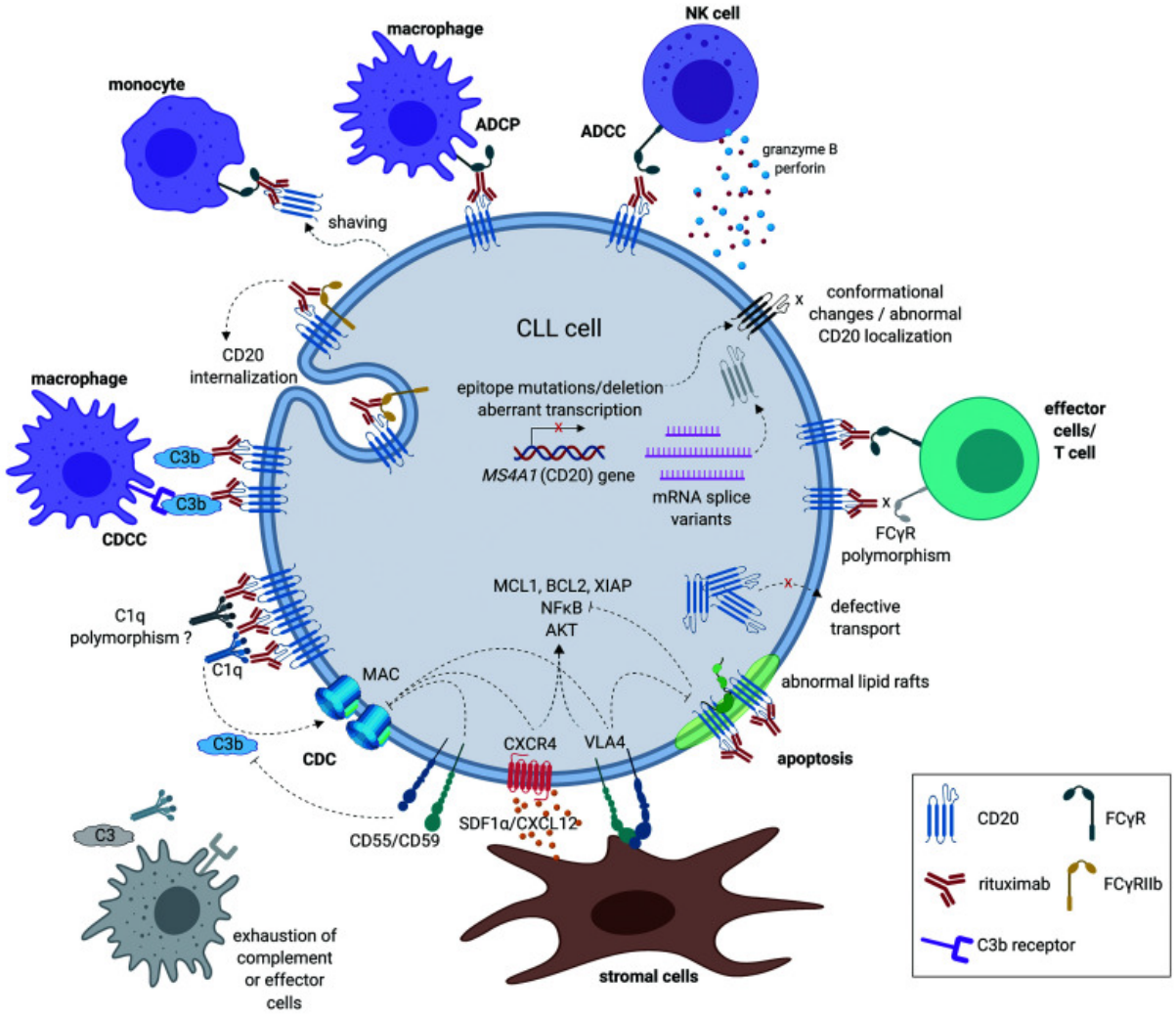
•**Rituximab – anti CD20 treatment**

- approved to be used in alone or with other drugs to treat:

Acute lymphoblastic leukemia or **acute myeloid leukemia**
- advanced and CD20positive

B-cell non-Hodgkin lymphoma (NHL) CD20 positive
- in **adults** with *follicular lymphoma* or *low-grade lymphoma*
- in adults with *diffuse large B-cell NHL* (*DLBCL*)
  with anthracycline combination chemotherapy

- in **children** aged 6m and older with chemotherapy
- *Burkitt lymphoma* that is advanced and has not been treated
- *diffuse large B-cell NHL* (*DLBCL*)


NK cell
macrophage
monocyte
ADCP
ADCC
granzyme B
perforin
shaving
CD20
internalization
CLL cell
conformational
changes / abnormal
CD20 localization
macrophage
epitope mutations/deletion
aberrant transcription
effector
cells/
T cell
C3b
C3b
MS4A1 (CD20) gene
mRNA splice
variants
CDCC
FCγR
polymorphism
MCL1, BCL2, XIAP
NFκB
AKT
defective
transport
C1q
polymorphism ?
C1q
MAC
abnormal lipid rafts
C3b
CDC
CXCR4
VLA4
apoptosis
SDF1α/CXCL12
CD55/CD59
C3
exhaustion of
complement
or effector
cells
stromal cells
CD20
FCγR
rituximab
FCγRIIb
C3b receptor

Targeted therapy approved for lymphoma

acalabrutinib (Calquence)
axicabtagene ciloleucel (Yescarta)
belinostat (Beleodaq)
bexarotene (Targretin)
bortezomib (Velcade)
brentuximab vedotin (Adcetris)
brexucabtagene autoleucel (Tecartus)
copanlisib hydrochloride (Aliqopa)
crizotinib (Xalkori)
denileukin diftitox (Ontak)
duvelisib (Copiktra)
epcoritamab-bysp (Epkinly)
glofitamab-gxbm (Columvi)
ibritumomab tiuxetan (Zevalin)
ibrutinib (Imbruvica)
lisocabtagene maraleucel (Breyanzi)
loncastuximab tesirine-lpyl (Zynlonta)
mogamulizumab-kpkc (Poteligeo)
mosunetuzumab-axgb (Lunsumio)

Targeted therapy approved for lymphoma

nivolumab (Opdivo)
obinutuzumab (Gazyva)
pembrolizumab (Keytruda)
pemigatinib (Pemazyre)
pirtobrutinib (Jaypirca)
polatuzumab vedotin-piiq (Polivy)
pralatrexate (Folotyn)
rituximab (Rituxan)
rituximab and hyaluronidase human (Rituxan Hycela)
romidepsin (Istodax)
selinexor (Xpovio)
siltuximab (Sylvant)
tafasitamab-cxix (Monjuvi)
tazemetostat hydrobromide (Tazverik)
tisagenlecleucel (Kymriah)
venetoclax (Venclexta)
vorinostat (Zolinza)
zanubrutinib (Brukinsa)

Gastrointestinal stromal tumor - GIST

an example of targeted therapy and predictive oncology
in solid tumors

GIST – activated proto-oncogene

c-*kit*, *KIT*, stem cell factor receptor (SCR)

gene at 4q11-21

transmembrane receptor - tyrosine kinase (145kD)

GIST – activated proto-oncogene

c-*kit*, *KIT*, stem cell factor receptor

gen 4q11-21

transmembránový receptor SCF, tyrozín kináza (145kD)

impact on development and survival of

- mast cels
- hemopoietic stem cells and CML (*bcl-abl*)
- melanocytes
- germ cells

interstitial Cajal cells in the GIT

A proportion of genetic changes
N = **239 patients**

primary mutations - *before the treatment start* x
secondary mutations - *following the treatment*

	no of pateints	
KIT	**154**	**65%**
PDGFRA	**39**	**16%**
„wild type“	46	19%

Pimary mutations of genes *KIT* and *PDGFRA*

mut. *KIT* N= 154	**No patients**	**%**
exon 9	10	6,5
exon 11	**142**	**92,2**
exon 13	2	1,3
exon 17	0	0
mut. *PDGFRA* N= 39		
exon 12	5	12,8
exon 14	2	5,1
exon 18	**32**	**82,1**

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primary resistance to biological treatment by **imatinib** IM

Targeted therapy approved for gastrointestinal stromal tumor

avapritinib (Ayvakit)
imatinib mesylate (Gleevec)
regorafenib (Stivarga)
ripretinib (Qinlock)
sunitinib malate (Sutent)

New frontiers in the medical management of gastrointestinal stromal tumours

Alessandro Mazzocca, Andrea Napolitano, Marianna Silletta, Mariella Spalato Ceruso, Daniele Santini, Giuseppe Tonini and Bruno Vincenzi

Ther Adv Med Oncol

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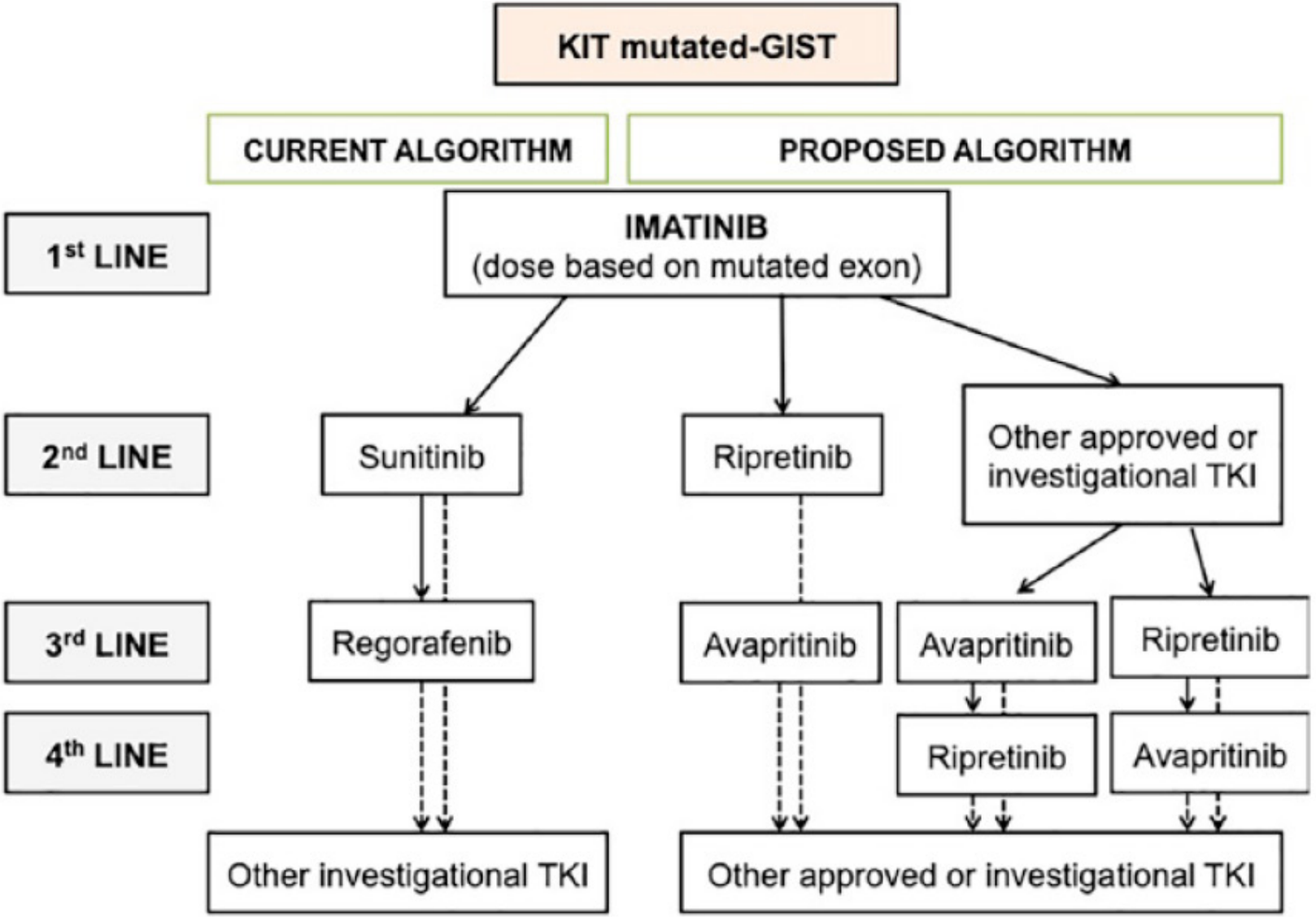

Imatinib mesylate is approved to treat a spectrum of diseases:

Chronic myelogenous leukemia that is Ph chromosome positive

Acute lymphoblastic leukemia in adults and children that is
Ph chromosome positive

Gastrointestinal stromal tumor (GIST) that is *KIT* positive
and cannot be removed by surgery and/or has metastasized
il is also used after surgery to completely remove the tumor

Chronic eosinophilic leukemia or **hypereosinophilic syndrome**

Dermatofibrosarcoma protuberans in adults with relapse, metastases

Myelodysplastic/myeloproliferative neoplasms

Systemic mastocytosis with a mutation in the *c-KIT* gene.

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Systemic mastocytosis with a mutation in the *c-KIT* gene.

other universal therapeutic targets are also sought

such as the neurotrophic receptor tyrosine kinase (NTRK) gene fusion

- many types of neoplasms in adults and children
  (eg. childhood mesoblastic nephroma)

Immune checkpoints and their inhibitors

type of immune checpoints

CTLA-4 Cytotoxic T-Lymphocyte-associated Antigen 4

PD-1 Programmed Death 1

PD-L1 Programmed Death-Ligand 1

Immune checkpoints and their inhibitors

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CTLA-4 Cytotoxic T-Lymphocyte-associated Antigen 4
at early stage of immune response in lymph nodes

PD-1 Programmed Death 1
the effector phase

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Ipilimumab

PD-1 Programmed Death 1
the effector phase, tumor microenvironment

Nivolumab, Pembrolizumab

PD-L1 Programmed Death-Ligand 1
the effector phase, tumor microenvironment

..

Atezolizumab, Durvalumab, Avelumab

Immune checkpoints and their inhibitors

immunogenic tumor - melanoma

a breakthrough in treatment x *dacarbazine* (classical ChTh)

the annual overall survival rate increased

ipilimumab anti-CTLA-4 therapy twofold ↑

nivolumab or ***pembrolizumab*** anti-PD-1 threefold ↑

combining the two therapies fourfold ↑

non-immunogenic neoplasms

also positive therapeutic effects

- lung
- kidney, urinary tract
- GIT – colorectal, stomach, liver carcinomas
- head and neck
- Hodgkin's lymphoma
- breast, cervix

The Progress of Targeted Therapy

Current methods in research on anti-cancer drugs such as NGS and advanced computational methods allow for search for small molecule targeted drugs

- inhibitors of ***protein kinases*** or
- inhibitors of the ***mTOR pathway***

The Progress of Targeted Therapy

Current methods in research on anti-cancer drugs such as NGS and advanced computational methods allow for search for small molecule targeted drugs

- inhibitors of ***protein kinases*** or
- inhibitors of the ***mTOR pathway***

protein kinases and mTOR pathways modify the activity of other proteins involved in various cell functions through phosphorylation

impairment of their functions is observed in various neoplasms

mTOR

the mammalian Target Of Rapamycin signaling pathway

integrates signals from

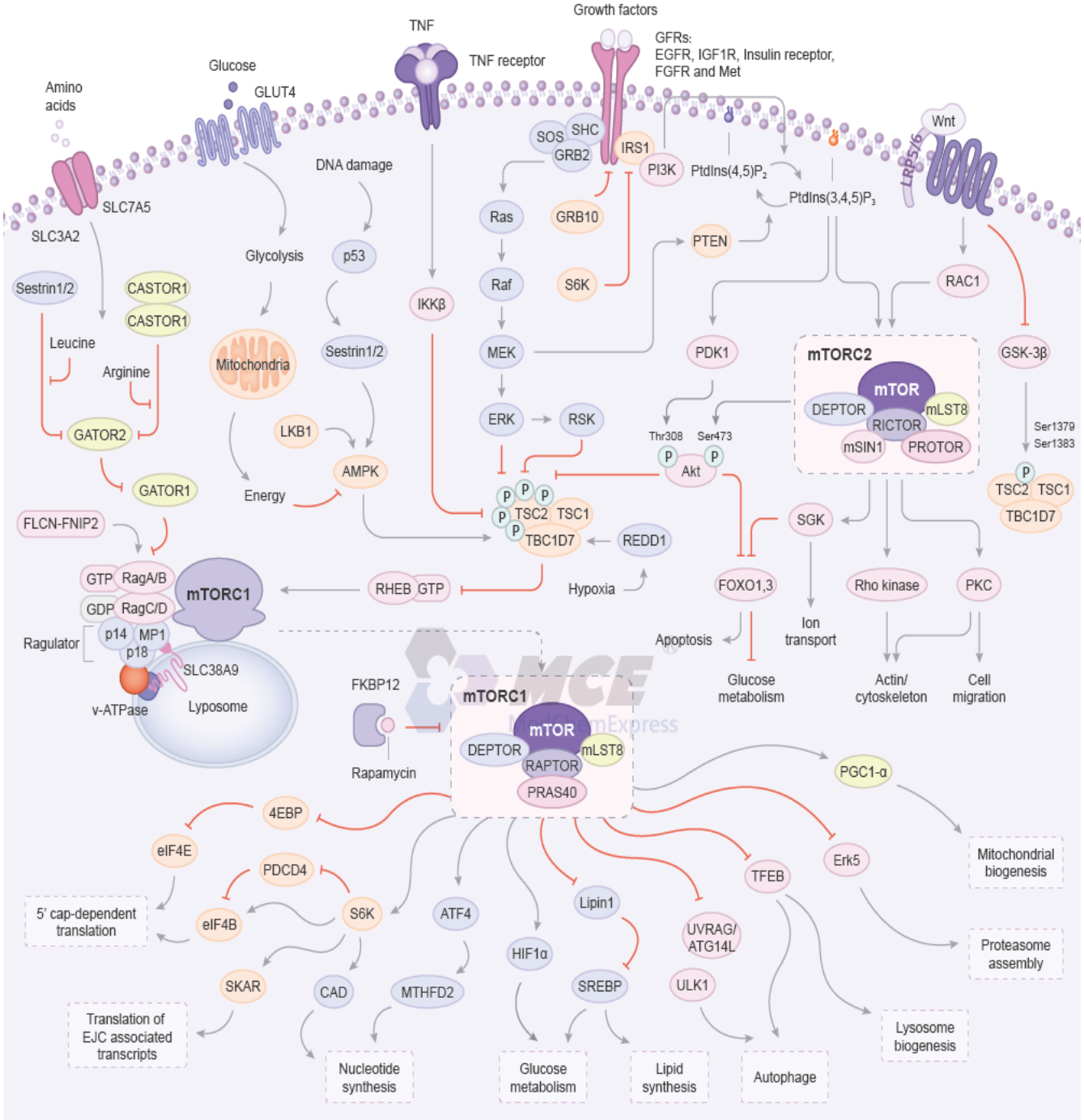
- intracellular
- extracellular

space

serves as a

-central regulator of cell

metabolism
growth
proliferation
survival


TNF
Growth factors
TNF receptor
GFRs:
EGFR, IGF1R, Insulin receptor,
FGFR and Met
Glucose
GLUT4
Amino acids
SLC7A5
SLC3A2
DNA damage
SOS
SHC
GRB2
IRS1
PI3K
PtdIns(4,5)P2
PtdIns(3,4,5)P3
Wnt
LRP5/6
Ras
GRB10
Raf
S6K
PTEN
RAC1
Glycolysis
p53
IKKβ
MEK
PDK1
GSK-3β
Sestrin1/2
CASTOR1
CASTOR1
Leucine
Arginine
Mitochondria
Sestrin1/2
mTORC2
mTOR
DEPTOR
mLST8
RICTOR
mSIN1
PROTOR
GATOR2
LKB1
AMPK
ERK
RSK
Thr308
Ser473
Akt
Ser1379
Ser1383
TSC2
TSC1
TBC1D7
GATOR1
Energy
FLCN-FNIP2
REDD1
SGK
GTP
RagA/B
GDP
RagC/D
mTORC1
RHEB
GTP
Hypoxia
FOXO1,3
Rho kinase
PKC
Ragulator
p14
MP1
p18
SLC38A9
v-ATPase
Lyposome
Apoptosis
Ion transport
Glucose metabolism
Actin/ cytoskeleton
Cell migration
FKBP12
Rapamycin
mTORC1
mTOR
DEPTOR
mLST8
RAPTOR
PRAS40
PGC1-α
4EBP
eIF4E
PDCD4
eIF4B
S6K
ATF4
Lipin1
TFEB
Erk5
Mitochondrial biogenesis
5' cap-dependent translation
UVRAG/ ATG14L
Proteasome assembly
HIF1α
SREBP
ULK1
SKAR
CAD
MTHFD2
Translation of EJC associated transcripts
Lysosome biogenesis
Nucleotide synthesis
Glucose metabolism
Lipid synthesis
Autophage

mTOR
targeted by

everolimus (Afinitor)
sirolims (Rapamune)
temsirolimus (Torisel)

in
breast carcinoma
neuroendocrine carcinoma
pancreatic carsinoma
renal cell carcinoma
subependymal giant cell astrocytoma

and other diseases

to be continued at any appropriate time in the summer semester especially in a context of neoplastic diseases of

lungs
GIT (stomach, large bowel, liver, pancreas)
kidneys
mammary gland
male and female reproductive systém

and other neoplasms

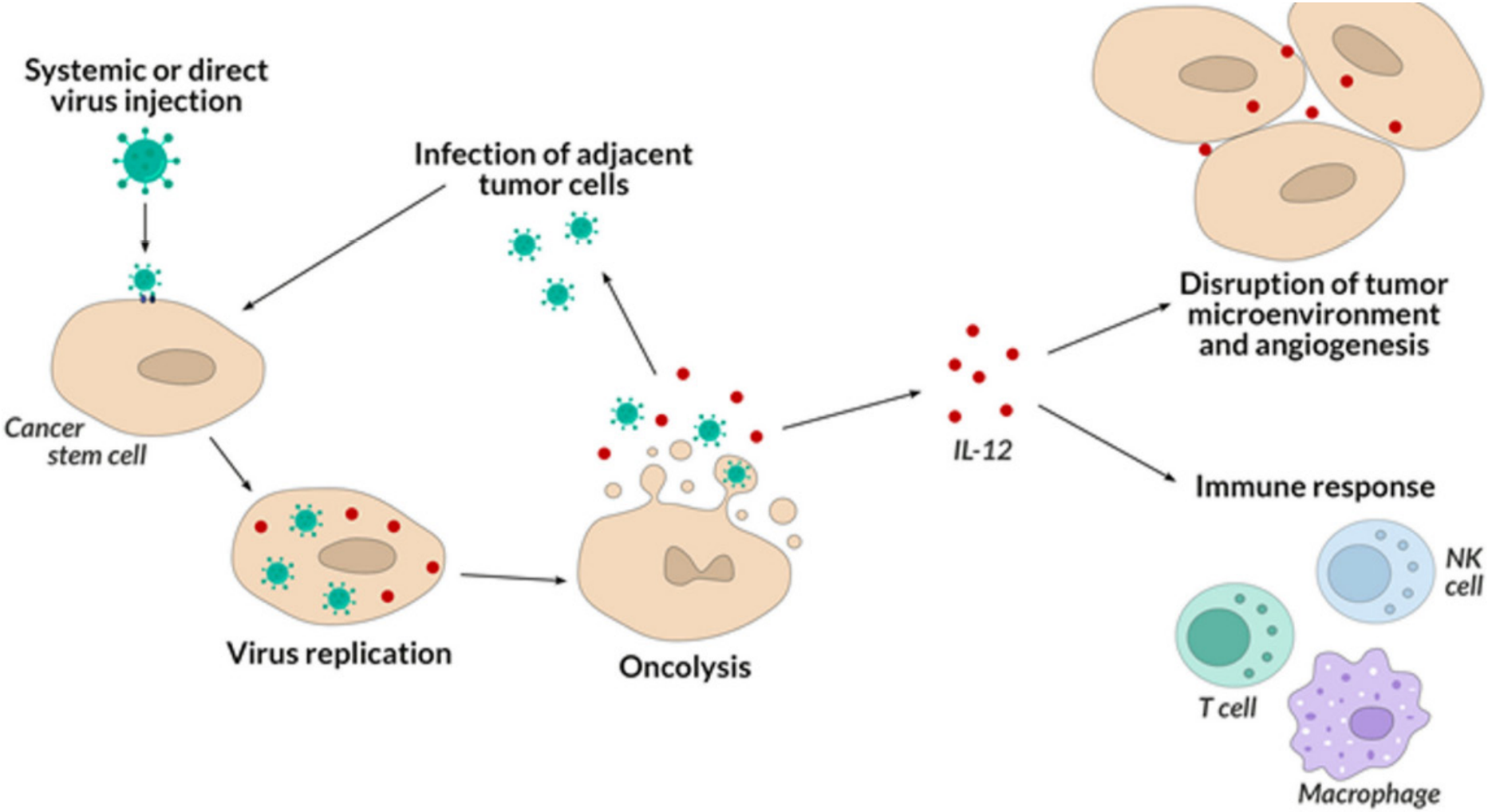
Table 1. Immune checkpoints and their inhibitors. CTLA-4—Cytotoxic T-Lymphocyte-associated Antigen 4, PD-1—Programmed Death 1, PD-L1—Programmed Death-Ligand 1.

Type of Immune Checkpoint	Stage of the Immune Response	Place of Action	Presence on Cells	Inhibitors of Immune Checkpoint
CTLA-4	Early activation phase	Lymph nodes	Activated T and B cells	Ipilimumab
PD-1	The effector phase	Periferal tissue, cancer imcroenvironment	T and B cells, natural killer cells, myeloid-derived suppressor cells	Nivolumab, Pembrolizumab,
PD-L1	The effector phase	Periferal tissue, cancer imcroenvironment	Antigen presenting cells, T and B cells, natural killer cells, myeloid-derived suppressor cells, hematopoietic cells, cancer cells	Atezolizumab, Durvalumab, Avelumab

4. Targeted Immunotherapy Based on Genetically Modified T Cells

5. Oncolytic Viruses

6. Cancer Vaccines


Systemic or direct virus injection
Infection of adjacent tumor cells
Disruption of tumor microenvironment and angiogenesis
Cancer stem cell
IL-12
Immune response
NK cell
T cell
Macrophage
Virus replication
Oncolysis