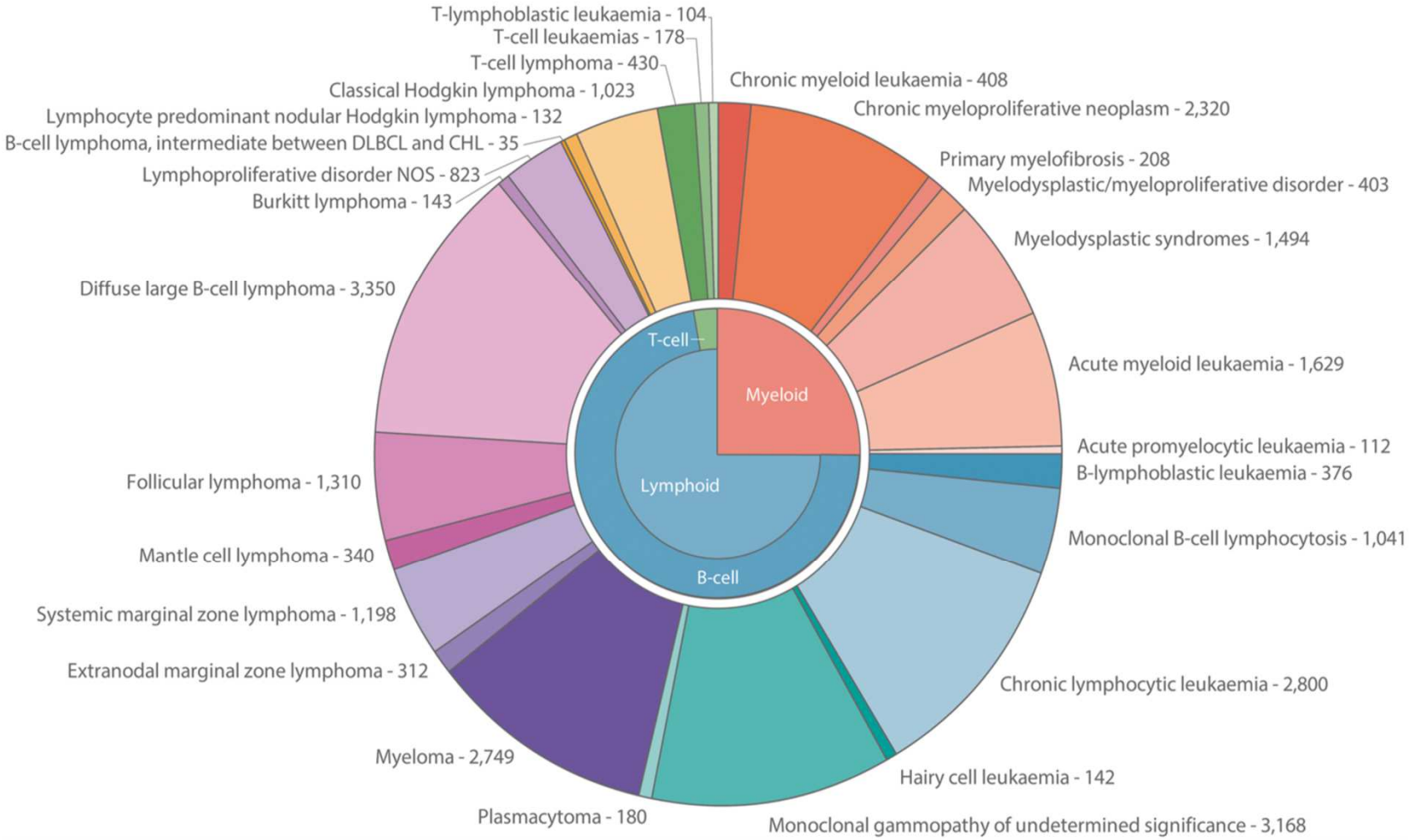
Maliigsete hematoloogiliste haiguste ravi

Regionaalhaigla

Hematoloogiliste kasvajate jaotus diagnoosigruppide kaupa HMRN näitel



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Mature B-cell neoplasms	*Mature B-cell neoplasms*	*Mature B-cell neoplasms*	*Mature T and NK neoplasms*	*Mature T and NK neoplasms*	*Posttransplant lymphoproliferative disorders (PTLD)*	*Histiocytic and dendritic cell neoplasms*
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Extraosseous plasmacytoma	Primary DLBCL of the central nervous system (CNS)	T-cell prolymphocytic leukemia	Primary cutaneous γδ T-cell lymphoma	Plasmacytic hyperplasia PTLD	Histiocytic sarcoma
Monoclonal B-cell lymphocytosis*	Monoclonal immunoglobulin deposition diseases*	Primary cutaneous DLBCL, leg type	T-cell large granular lymphocytic leukemia	Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma	Infectious mononucleosis PTLD	Langerhans cell histiocytosis
B-cell prolymphocytic leukemia	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	EBV+ DLBCL, NOS*	Chronic lymphoproliferative disorder of NK cells	Primary cutaneous acral CD8+ T-cell lymphoma*	Florid follicular hyperplasia PTLD*	Langerhans cell sarcoma
Splenic marginal zone lymphoma	Nodal marginal zone lymphoma	EBV+ mucocutaneous ulcer*	Aggressive NK-cell leukemia	Primary cutaneous CD4+ small/medium Tcell lymphoproliferative disord	Polymorphic PTLD	Indeterminate dendritic cell tumor
Hairy cell leukemia	Pediatric nodal marginal zone lymphoma	DLBCL associated with chronic inflammation	Systemic EBV+ T-cell lymphoma of childhood*	Peripheral T-cell lymphoma, NOS	Monomorphic PTLD (B- and T-/NK-cell types	Interdigitating dendritic cell sarcoma
Splenic B-cell lymphoma/leukemia, unclassifiable	Follicular lymphoma	Lymphomatoid granulomatosis	Hydroa vacciniforme–like lymphoproliferative disorder*	Angioimmunoblastic T-cell lymphoma		Follicular dendritic cell sarcoma
Splenic diffuse red pulp small B-cell lymphoma	In situ follicular neoplasia*	Primary mediastinal (thymic) large B-cell lymphoma	Adult T-cell leukemia/lymphoma	Follicular T-cell lymphoma*		Fibroblastic reticular cell tumor
Hairy cell leukemia-variant	Duodenal-type follicular lymphoma*	Intravascular large B-cell lymphoma	Extranodal NK-/T-cell lymphoma, nasal type	Nodal peripheral T-cell lymphoma with TFH phenotype*		Disseminated juvenile xanthogranuloma
Lymphoplasmacytic lymphoma	Pediatric-type follicular lymphoma*	ALK+ large B-cell lymphoma	Enteropathy-associated T-cell lymphoma	Anaplastic large-cell lymphoma, ALK+		
Waldenström macroglobulinemia	Large B-cell lymphoma with IRF4 rearrangement*	Plasmablastic lymphoma	Monomorphic epitheliotropic intestinal T-cell lymphoma*	Anaplastic large-cell lymphoma, ALK?*		
Monoclonal gammopathy of undetermined significance (MGUS), IgM*	Primary cutaneous follicle center lymphoma	Primary effusion lymphoma	Indolent T-cell lymphoproliferative disorder of the GI tract*			
μ heavy-chain disease	Mantle cell lymphoma	HHV8+ DLBCL, NOS*	Hepatosplenic T-cell lymphoma			
γ heavy-chain disease	In situ mantle cell neoplasia*	Burkitt lymphoma	Subcutaneous panniculitis-like T-cell lymphoma			
α heavy-chain disease	Diffuse large B-cell lymphoma (DLBCL), NOS	Burkitt-like lymphoma with 11q aberration*	Mycosis fungoides			
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*	Germinal center B-cell type*	High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*	Sézary syndrome			
Plasma cell myeloma	Activated B-cell type*	High-grade B-cell lymphoma, NOS	Lymphomatoid papulosis			
Solitary plasmacytoma of bone	T-cell/histiocyte-rich large B-cell lymphoma		Primary cutaneous anaplastic large cell lymphoma			

PK10: Pahaloomuliste kasvajate esmasjuhud paikme, soo ja vanuserühma järgi	
	Vanuserühmad kokku
Hodgkini tõbi (C81)	33
Mitte-Hodgkini lümfoom (C82-C85/96)	199
Immunoproliferatiivhaigused (C88)	4
Hulgimüeloom (C90)	89
Leukeemia (C91-C95)	210
..Äge lümfoidleukeemia (C91.0)	12
..Krooniline lümfoidleukeemia (C91.1)	106
..Lümfoidleukeemia (muu) (C91.2-C91.9)	4
..Äge müeloidleukeemia (C92.0)	51
..Krooniline müeloidleukeemia (C92.1)	19
..Müeloidleukeemia (muu) (C92.2-C92.9)	8
Leukeemia (muu) (C93-C95)	10

Peamised väljakutsed hematoloogias

- Väga heterogeenne tegevusala, mis diagnooside ning käsitluse osas pidevalt uueneb.
- Suurenev patsientide hulk, mis seab nõudmisi nii polikliinilisele kui statsionaarsele tööle
- Uued ravimid, uued ravimeetodid, uued kõrvaltoimed

Olemasolevad ravimeetodid

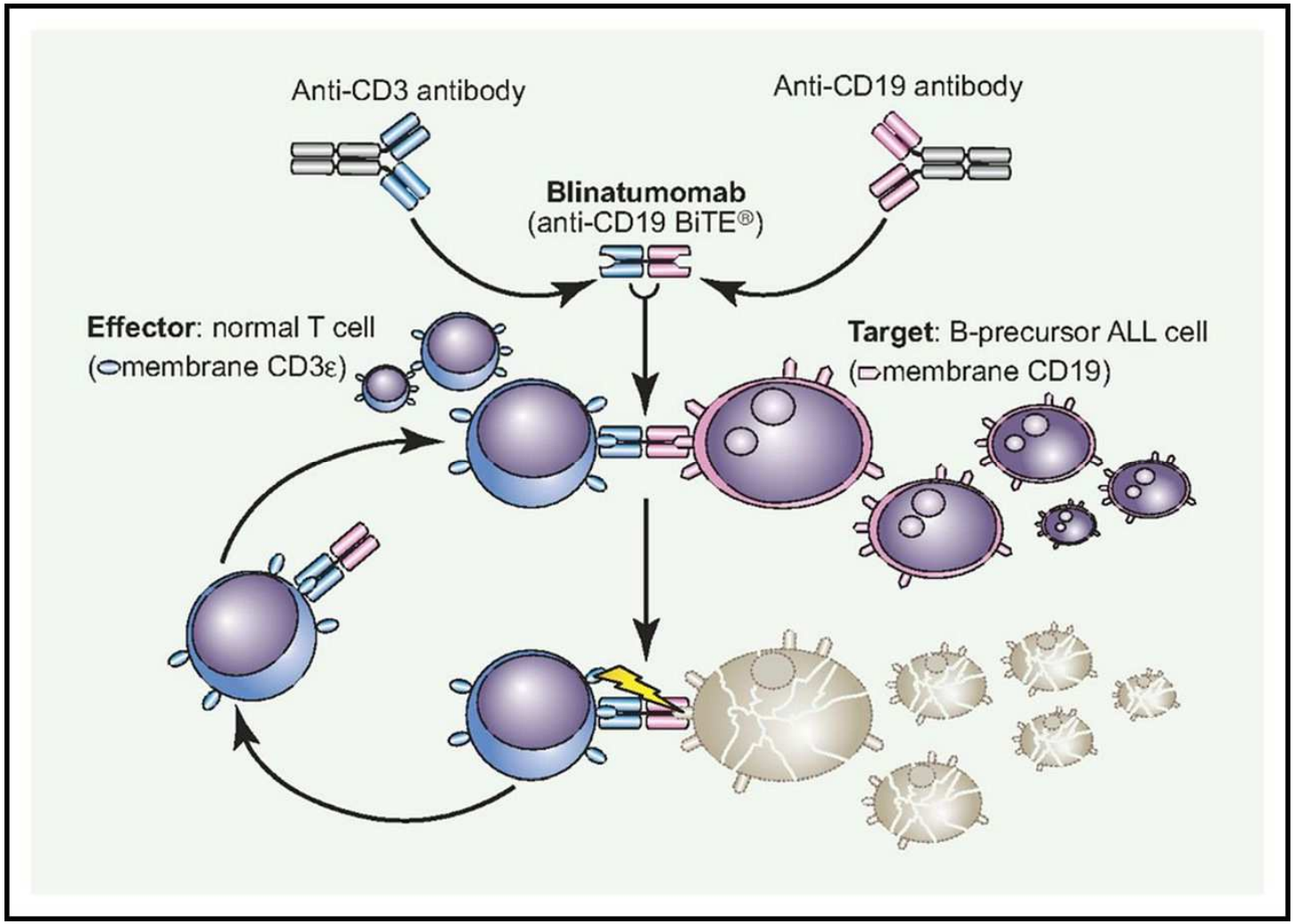
- Klassikaline keemiaravi
- Immuunravi antikehadega (võimalus kombineerida kemoteraapiaga)
- Autoloogne ja allogeenne vereloome tüvirakkude siirdamine
- Sihtmärgistatud ravi suukaudsete preparaatidega (TKId, Ibrutinib, midostauriin jne)

Uued võimalused

- Bispetsiifilised antikehad (BiTe) - Blinatumomab
- Uued monoklonaalsed antikehad - Daratumumab
- Autoloogse siirdamise laienemine (tandem, reumatoloogia, neuroloogia)
- BCL-2 antagonistid (Venetoclax)
- Checkpoint-inhibiitorid (pembrolizumab)

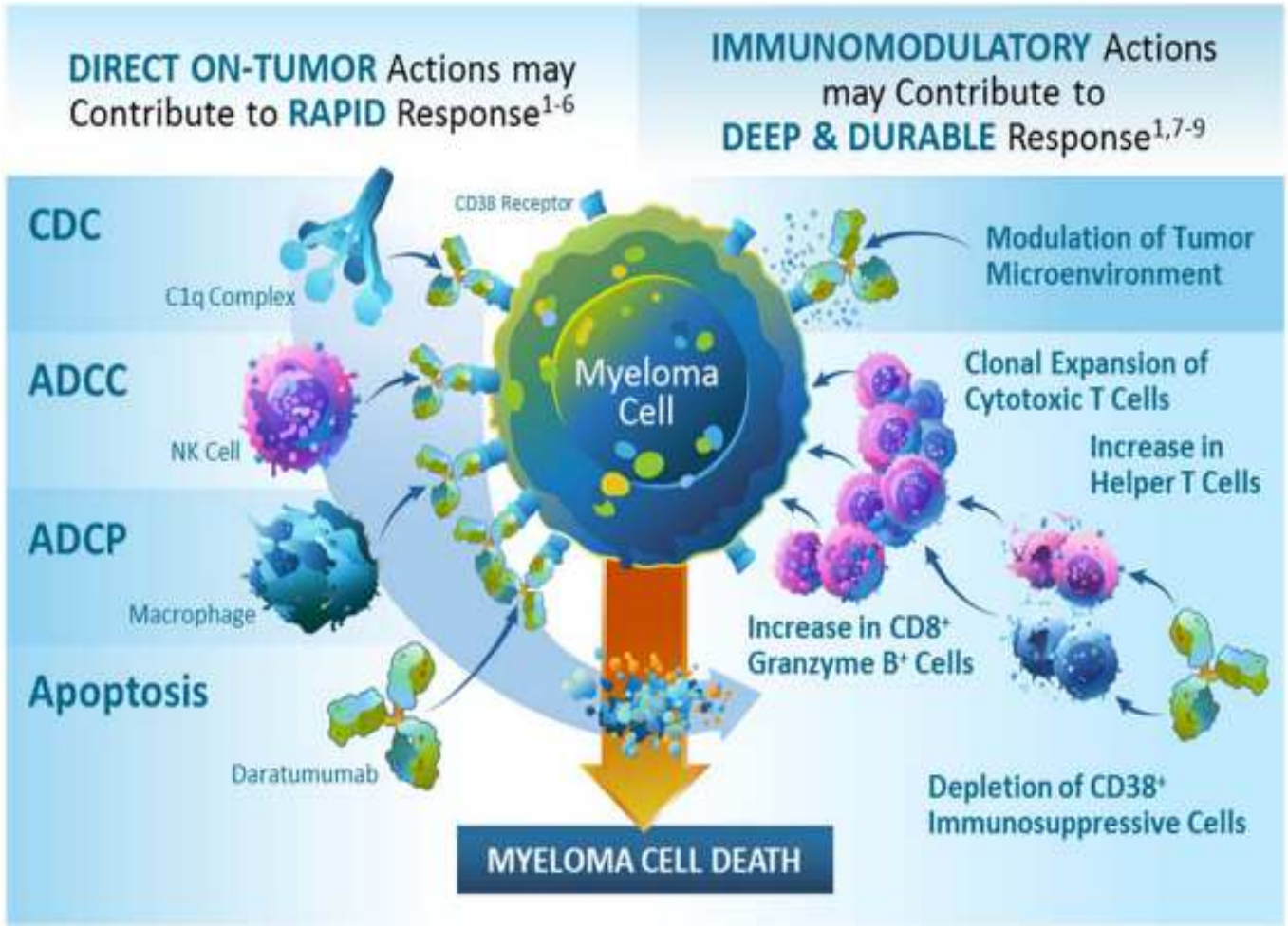
- CAR-T rakuteraapia

Bispetsiifilised antikehad (BiTe) - Blinatumomab



Patrick Brown Blood 2018;131:1497-1498

Daratumumab



Daratumumab

- Vereülekande vajadusel sobitamisprobleemid
- Pre-ja postmedikatsioon
- Suurema riskiga kõrvaltoimeteks olemasoleva kopsuhaiguse (astma, KOK) korral

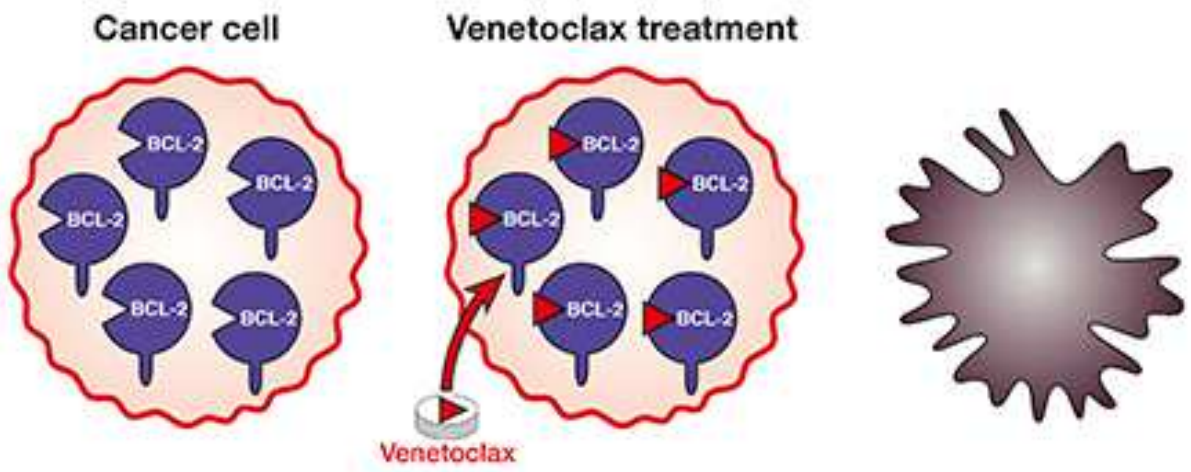
Autoloogne siirdamine - uuendused

- Tandemsiirdamine kõrge riski müeloomipatsientidel
- Süsteemse skleroosi patsiendid
- Sclerosis multiplex
- Crohni tõbi

Summary of major categories and types of autoimmune diseases treated with HSCT in the EBMT registry, as per August 2018

Autologous HSCT for each category of autoimmune disease	Total adult patients (1994–2018)	Total children (≤18 years at the time of transplant, 1994–2018)	Total patients treated in the last 6 years (all ages, 2012–2017)
All diseases	**2387**	**162**	**1090**
Neurological diseases			
Multiple sclerosis	1232	27	679
Other neurological diseases	94	3	51
Rheumatological diseases			
Systemic sclerosis	534	12	222
Systemic lupus erythematosus (SLE or 'lupus')	89	18	9
Other connective tissue diseases	46	5	8
Inflammatory arthritis (including rheumatoid arthritis)	97	67	8
Vasculitis (inflammation of the blood vessels)	39	4	10
Inflammatory bowel diseases			
Crohn's and other	177	15	83
Haematological autoimmune diseases (causing low blood counts)			
Autoimmune cytopenia, haemolytic anaemia, Evans syndrome, neutropenia and other	41	8	8
Type 1 diabetes mellitus	20	0	3
Miscellaneous other autoimmune diseases	18	3	9

Venetoclax


Cancer cell
Venetoclax treatment
BCL-2
Venetoclax
•Addicted to high levels of BCL-2
•Cell becomes long-lived
•Resistant to anti-cancer treatments
•BCL-2 inhibited
•Cancer cell dies, or responds to other anti-cancer treatments
•Cancer cell dies

Venetoclax

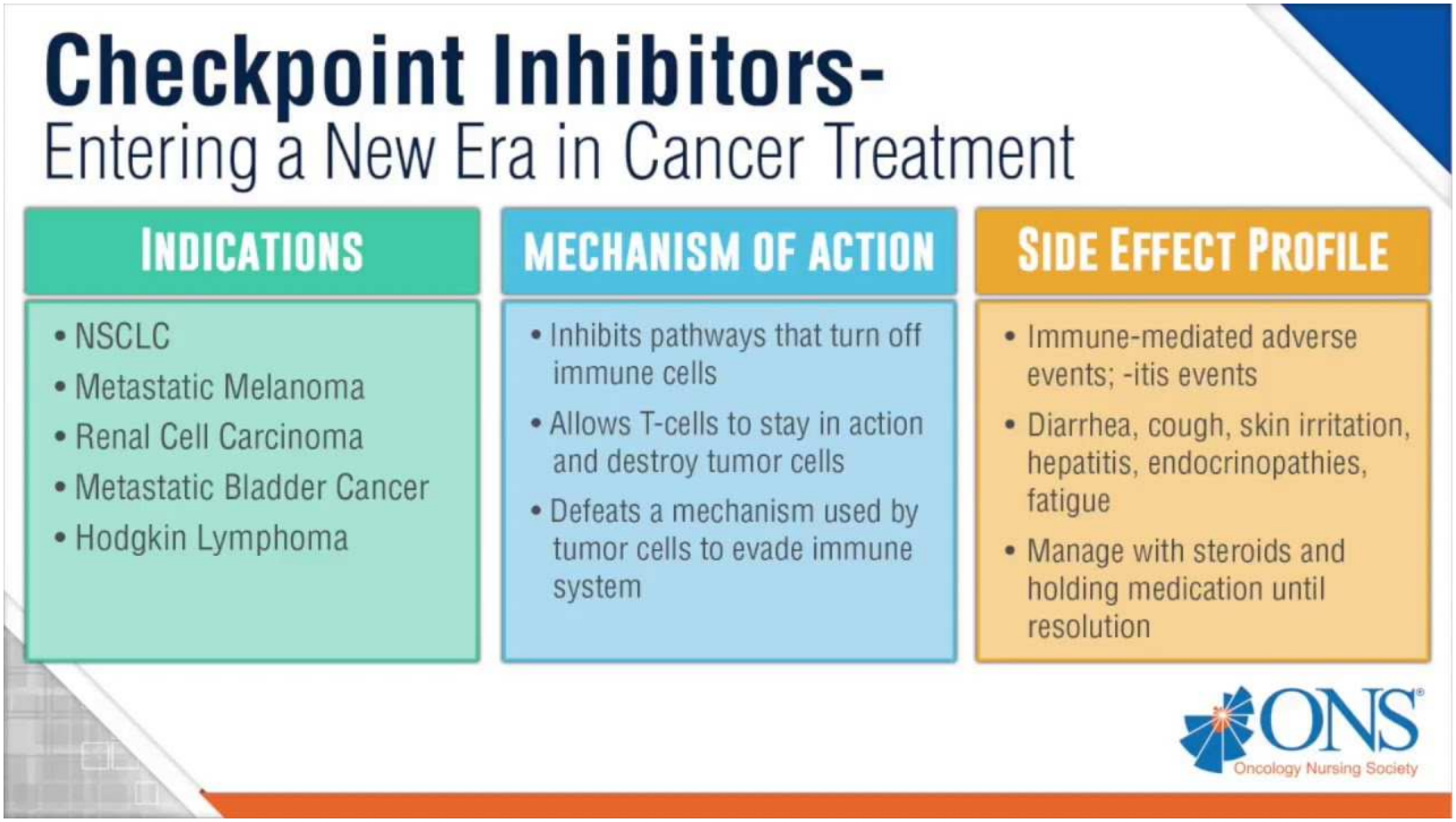
Table 2 Ongoing clinical trials investigating venetoclax in combination with other agents for the treatment of hematological malignancies

Intervention	Disease	Study phase(s)	Estimated* or actual** enrollment	Register number in clinical trials.gov
V + ibrutinib + obinutuzumab	MCL	I/II	48*	NCT02558816
V + ibrutinib	MCL	II	24*	NCT02471391
V + ibrutinib	R/R MCL	I	28*	NCT02419560
V + low-dose cytarabine	Treatment-naïve AML	I/II	94**	NCT02287233
V + rituximab	Relapsed CLL and SLL	I	49**	NCT01682616
V + bortezomib + dexamethasone	R/R MM	I	66**	NCT01794507
V + bendamustine + obinutuzumab	CLL	II	66**	NCT02401503
V + dexamethasone	R/R MM t(11;14)-positive MM	II	166*	NCT01794520
V + bendamustine/rituximab	R/R NI IL	I	60**	NCT01594229
V + decitabine or azacitidine	AML	I	260*	NCT02203773
V + obinutuzumab	Untreated or R/R CLL	I	82**	NCT01685892
V + rituximab or obinutuzumab and standard doses of CHOP	NHL	I/II	267**	NCT02055820
V + rituximab vs bendamustine + rituximab	Relapsed/resistant CLL	III	389**	NCT02005471
V+ bendamustine +rituximab vs BR alone	R/R FL	II	164**	NCT02187861
V + bortezomib and dexamethasone	R/R MM	III	291**	NCT02755597
V + bendamustine + rituximab or bendamustine and obinutuzumab	R/R or untreated CLL	I	84**	NCT01671904
V + obinutuzumab + ibrutinib	R/R or untreated CLL	I/II	63**	NCT02427451
V + obinutuzumab + vs obinutuzumab + chlorambucil	CLL with coexisting medical conditions	III	445**	NCT02242942

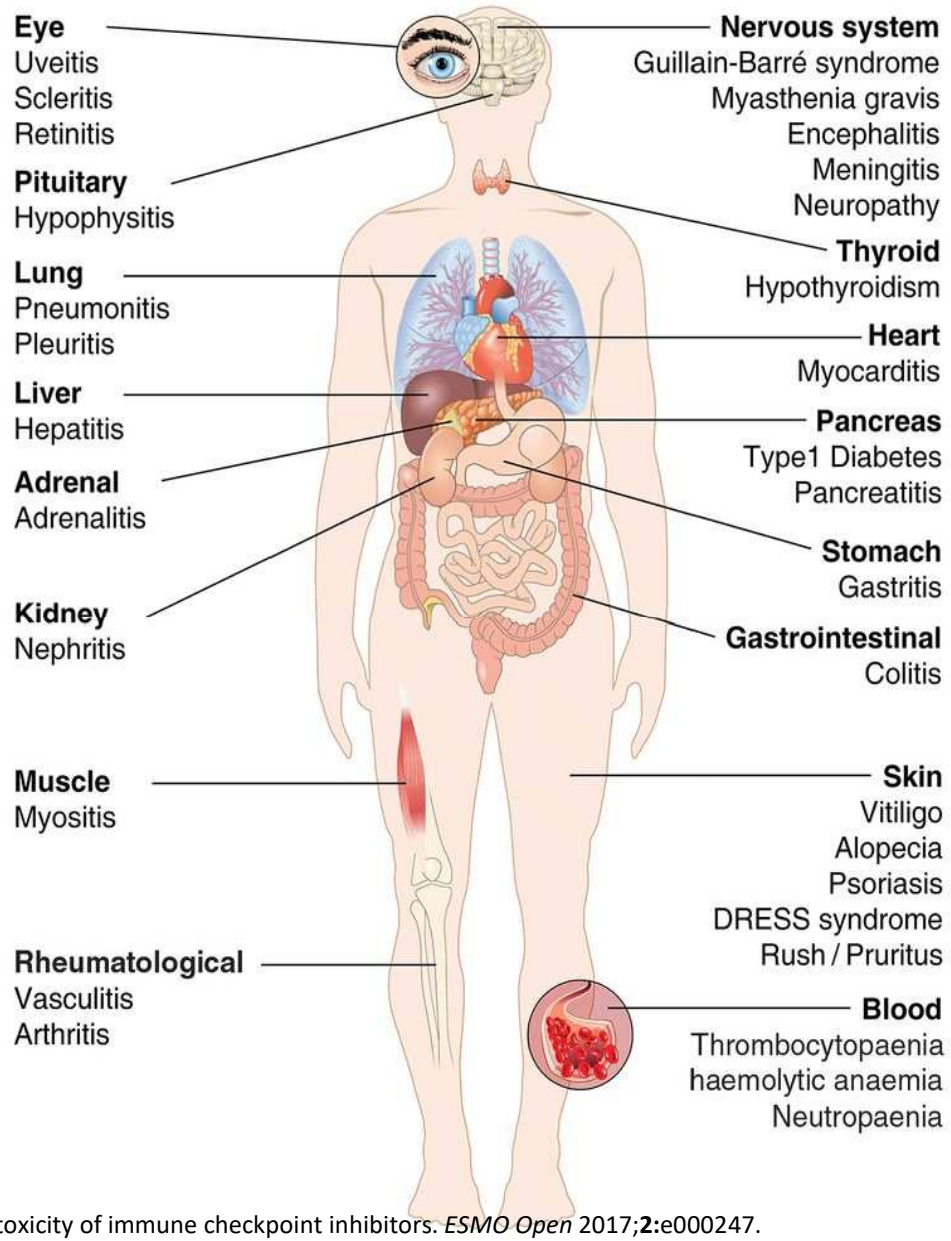
Venetoclax

V + azacitidine vs placebo + azacitidine	Treatment-naïve AML	III	400*	NCT02993523
V + obinutuzumab	R/R DLBCL	II	21*	NCT02987400
V + carfilzomib + dexamethasone	R/R MM	II	40*	NCT02899052
V + ibrutinib	R/R FL	I/II	41*	NCT02956382
V + ibrutinib	CLL; SLL	II	160*	NCT02756897
V + obinutuzumab	Untreated FL	I	25*	NCT02877550
V + lenalidomide + obinutuzumab	R/R NHL	I	60*	NCT02992522
V + decitabine	R/R AML	II	160*	NCT03404193
V + standard chemotherapy	ALL	I	22*	NCT03319901
V with or without chemotherapy	Pediatric and young adult R/R malignancies (ALL, AML, NHL, and other non-hematological tumors)	I	135*	NCT03236857
V + ibrutinib	CLL/SLL with progressive disease on ibrutinib	I	24*	NCT03422393
V + obinutuzumab and bendamustine	FL	II	56*	NCT03113422
V + dose-adjusted EPOCH-R	Richter's syndrome	II	20*	NCT03054896
V+ navitoclax + chemotherapy	R/R ALL	I	42*	NCT03181126
V + ibrutinib	High-risk CLL; SLL	II	45*	NCT03128879
V + obinutuzumab, after different debulking regimens	Untreated CLL		100*	NCT03406156
V + ublituximab + umbralisib (TGR-1202)	R/R CLL; SLL	I/II	30*	NCT03379051
V + TAK-659	R/R NHL	I	53*	NCT03357627
V + R-ICE	R/R DLBCL	I	18*	NCT03064867
V + chemotherapy (FLAG-IDA)	AML	I/II	56*	NCT03214562

Checkpoint-inhibiitorid

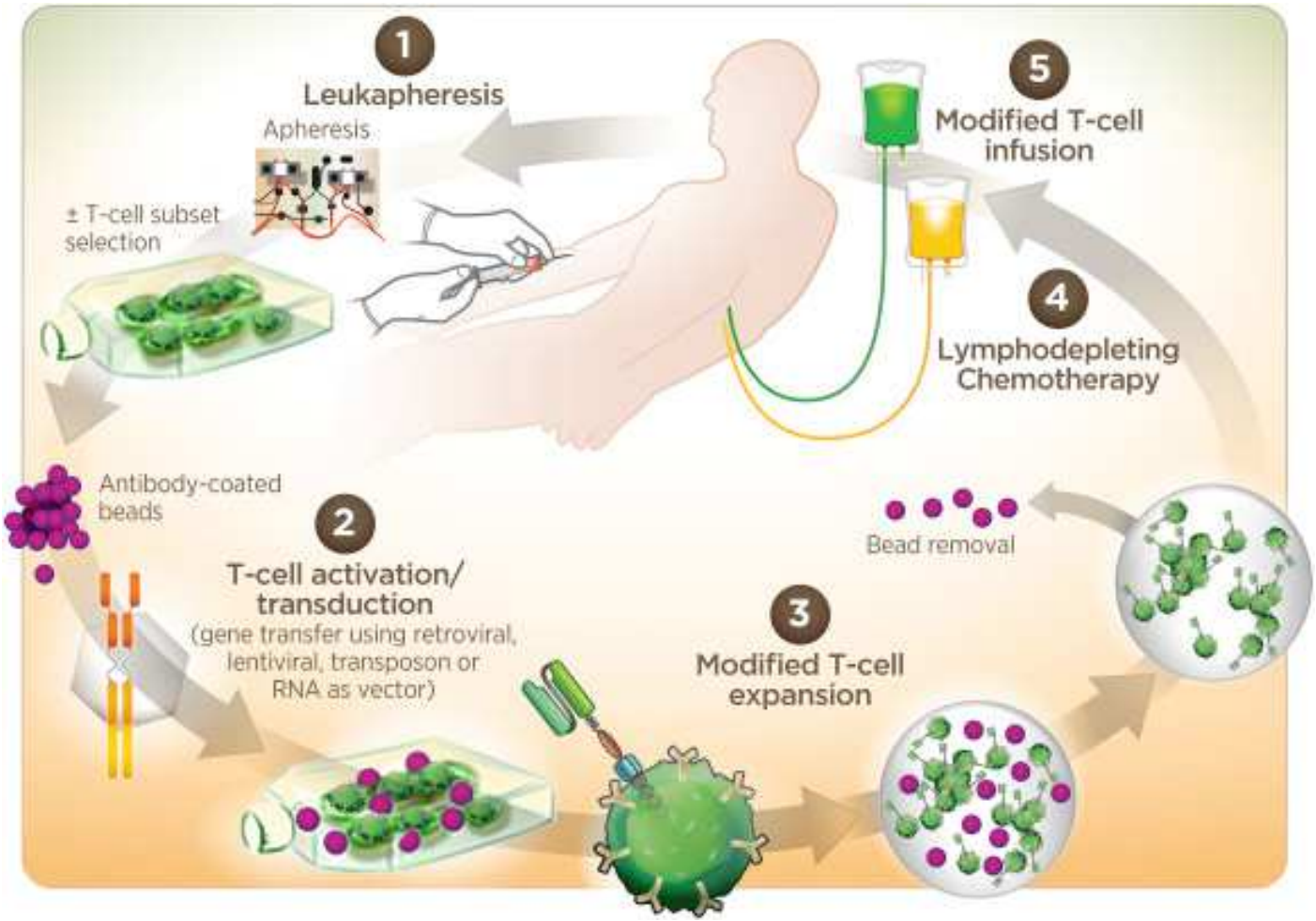


-itis



Varricchi G, Galdiero MR, Marone G*, et al.* Cardiotoxicity of immune checkpoint inhibitors. *ESMO Open* 2017;**2:**e000247.

CAR-T ravi

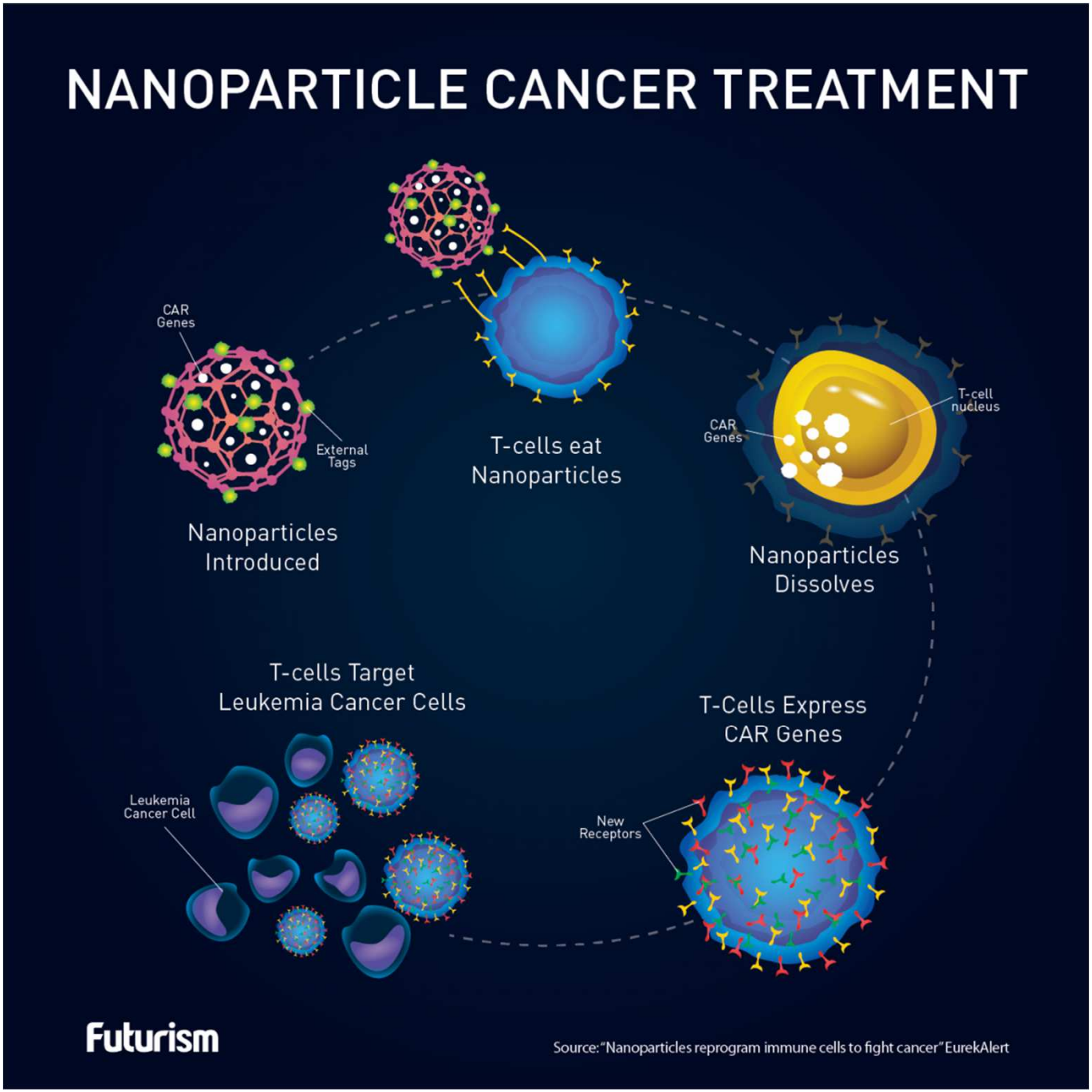

1
Leukapheresis
Apheresis
± T-cell subset selection
5
Modified T-cell infusion
4
Lymphodepleting Chemotherapy
Antibody-coated beads
2
T-cell activation/ transduction
(gene transfer using retroviral, lentiviral, transposon or RNA as vector)
Bead removal
3
Modified T-cell expansion

CAR-T ravi

- Tsütokiinide vabanemise sündroom (CRS, cytokine release syndrome) – palaviku, tahhükardia ning hüpotensiooniga kulgev seisund, kergest kuni üliraske kliinilise väljenduseni.
- Kerge CRS, grade 1 on märgatav ligi 90% CAR-T ravi saavatel patsientidel. 15-40% kulgeb CRS raskelt, grade 3-4, kes vajavad vasopressoreid ja/või juhitavat hingamist.
- Tocilizumab, IL-6 antikeha on valikravimiks raske CRS korral. Kortikosteroidi võivad viia CAR-T rakkude hävimiseni (lümfolüütiline toime), seega näidustatud CRS korral ainult teise liini ravina.
- KNS toksilisus – segasusseisund, treemor, ataksia, afaasia esineb 30-40% patsientidest iseseisva kõrvatoimena või koos CRSiga. Fataalne ajuturse on selle kõrvaltoime raskeim vorm. Patofüsioloogia teadmata.

CAR-T ravi

- CAR-T ravi hind – senini teadmata, USA andmete põhjal tehtavad hinnangud jäävad 400 000 EUR lähedale.
- Põhiprobleemiks on ajafaktor ning logistika, ideaalis võtab rakkude kogumine, töötlemine, paljundamine ning transport aega vähemalt 2 nädalat, reaalselt kuluv aeg 6-10 nädalat või kauem.
- Paljulubav tulevik, käesoleval hetkel on kuumimaks aruteluteemaks selles osas “off-the-shelf product”.


NANOPARTICLE CANCER TREATMENT
CAR Genes
External Tags
Nanoparticles Introduced
T-cells eat Nanoparticles
T-cell nucleus
CAR Genes
Nanoparticles Dissolves
T-Cells Express CAR Genes
New Receptors
T-cells Target Leukemia Cancer Cells
Leukemia Cancer Cell
Futurism
Source: "Nanoparticles reprogram immune cells to fight cancer" EurekAlert

Tänan!