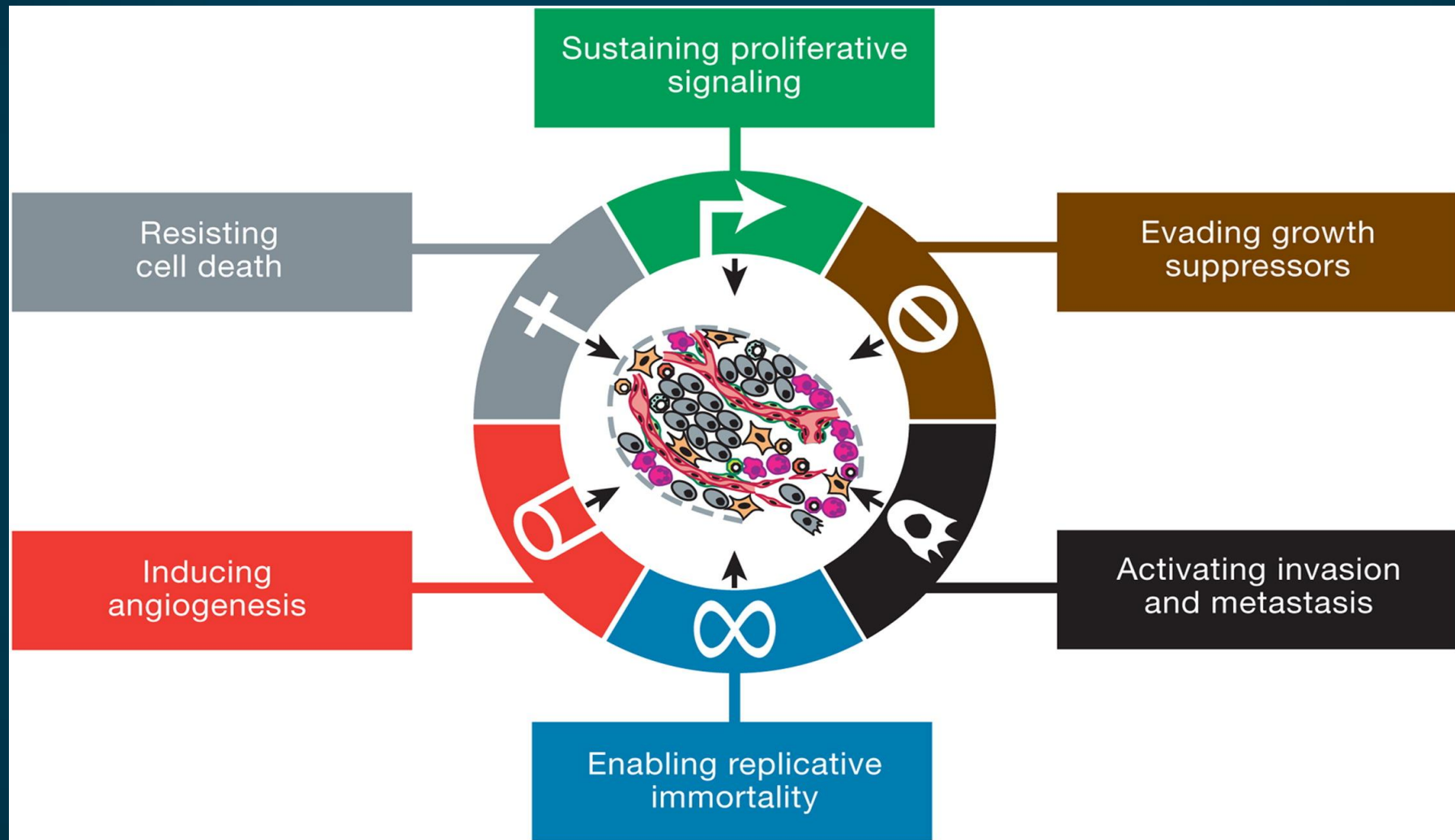


Nýjungar í meðferð krabbameina

Agnes Smáradóttir
Krabbameinslæknir

Hallmark of Cancer, next generation

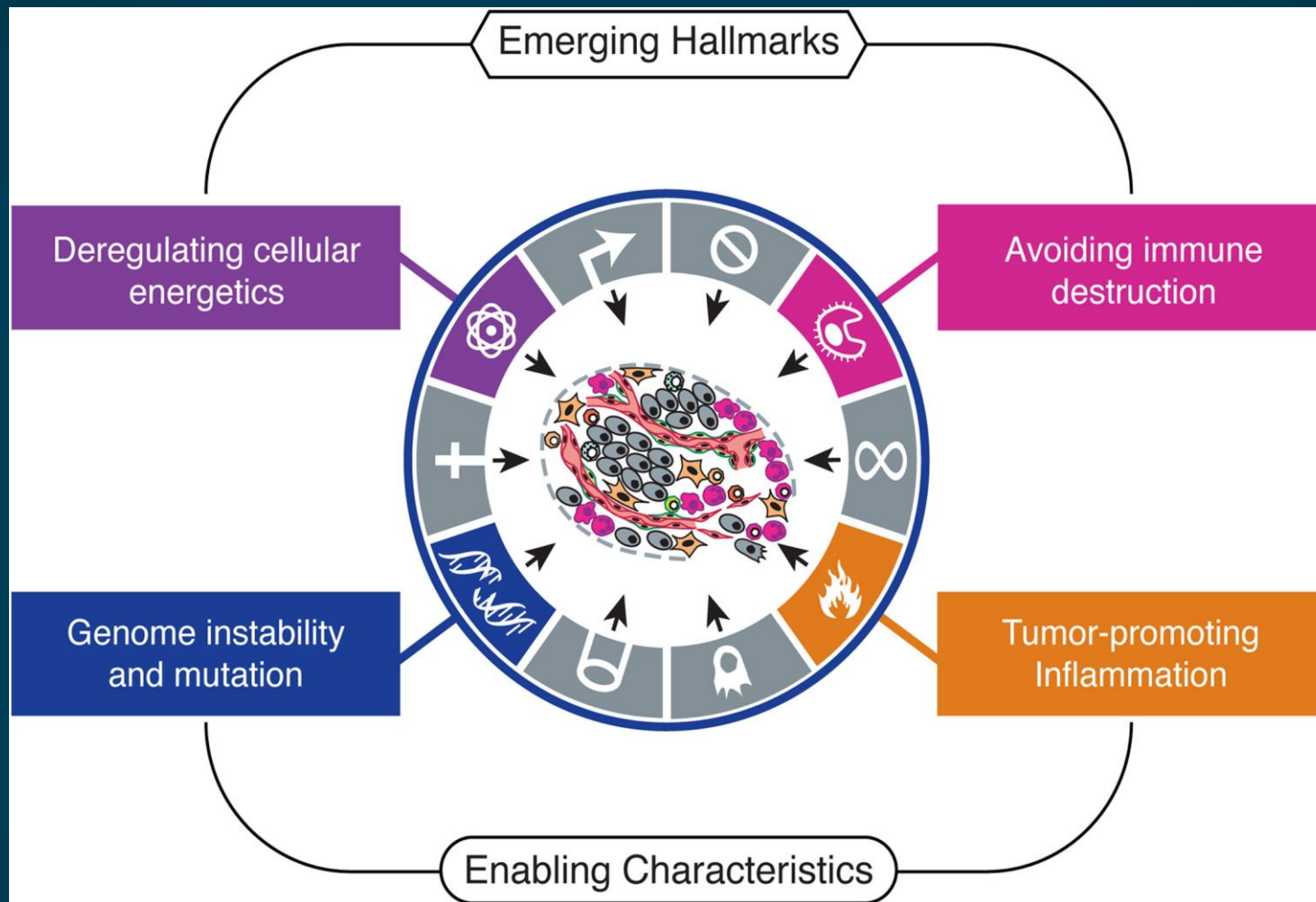
D. Hanahan, RA Weinberg



Cell

Volume 144, Issue 5, Pages 646-674 (March 2011)

DOI: 10.1016/j.cell.2011.02.013



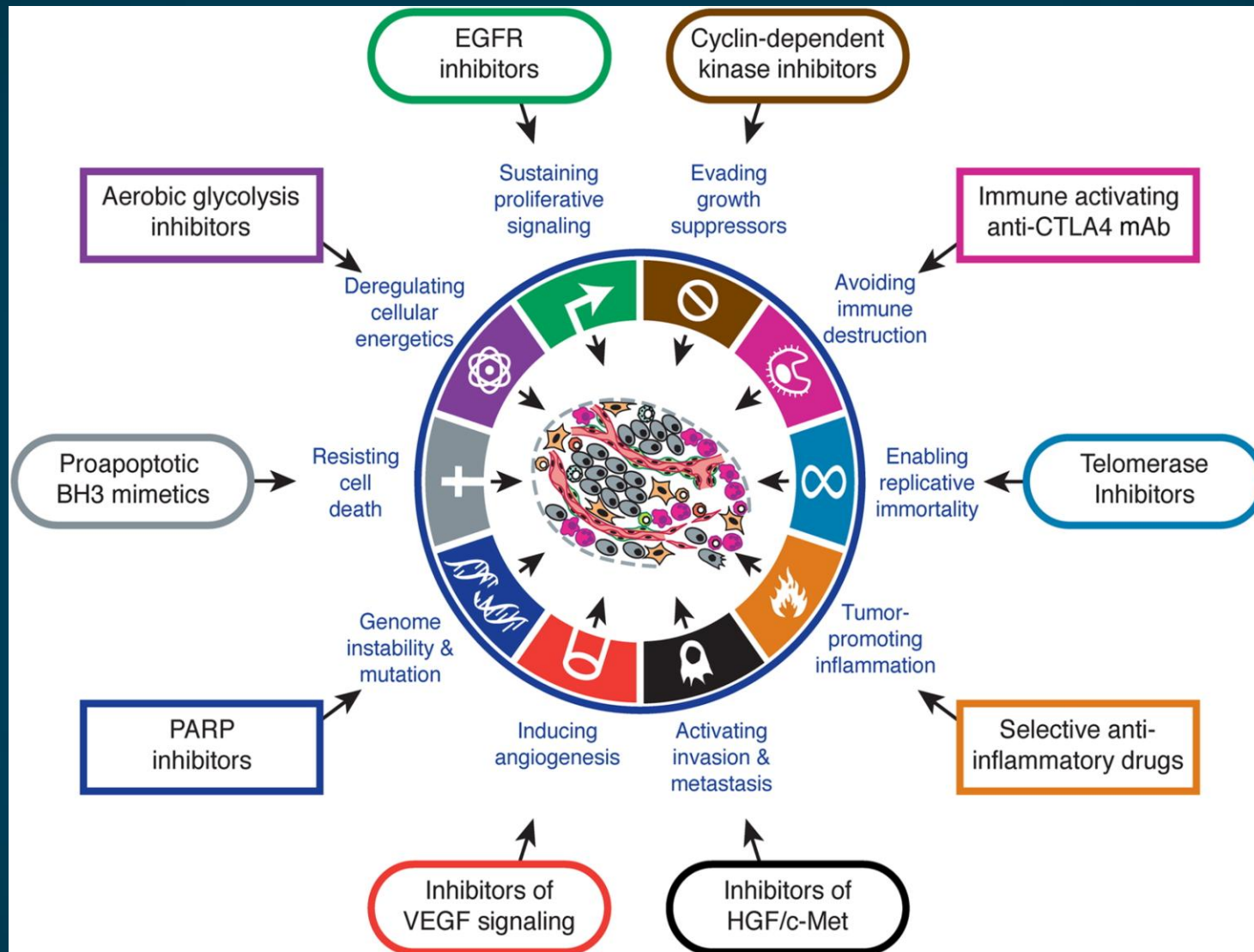
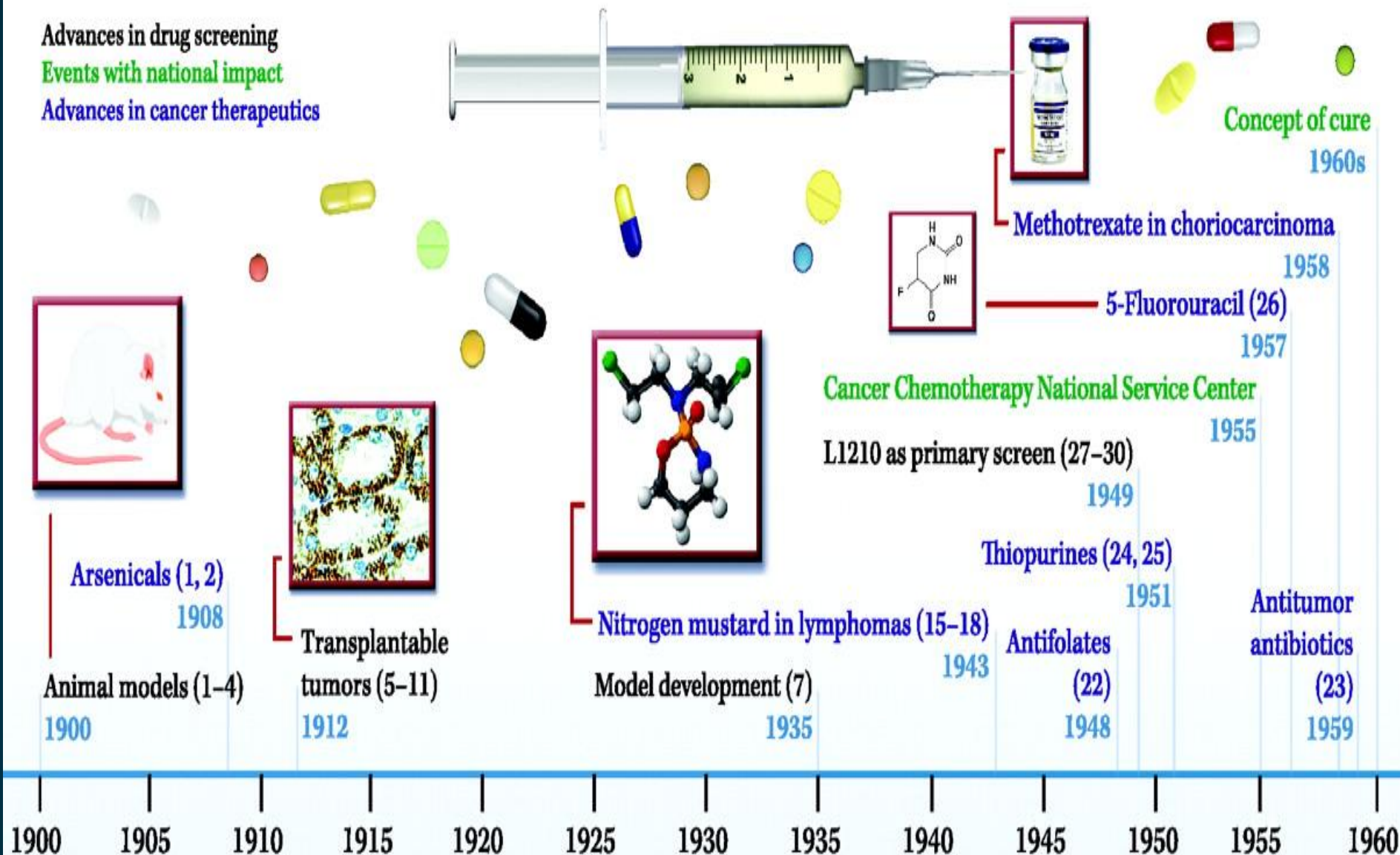
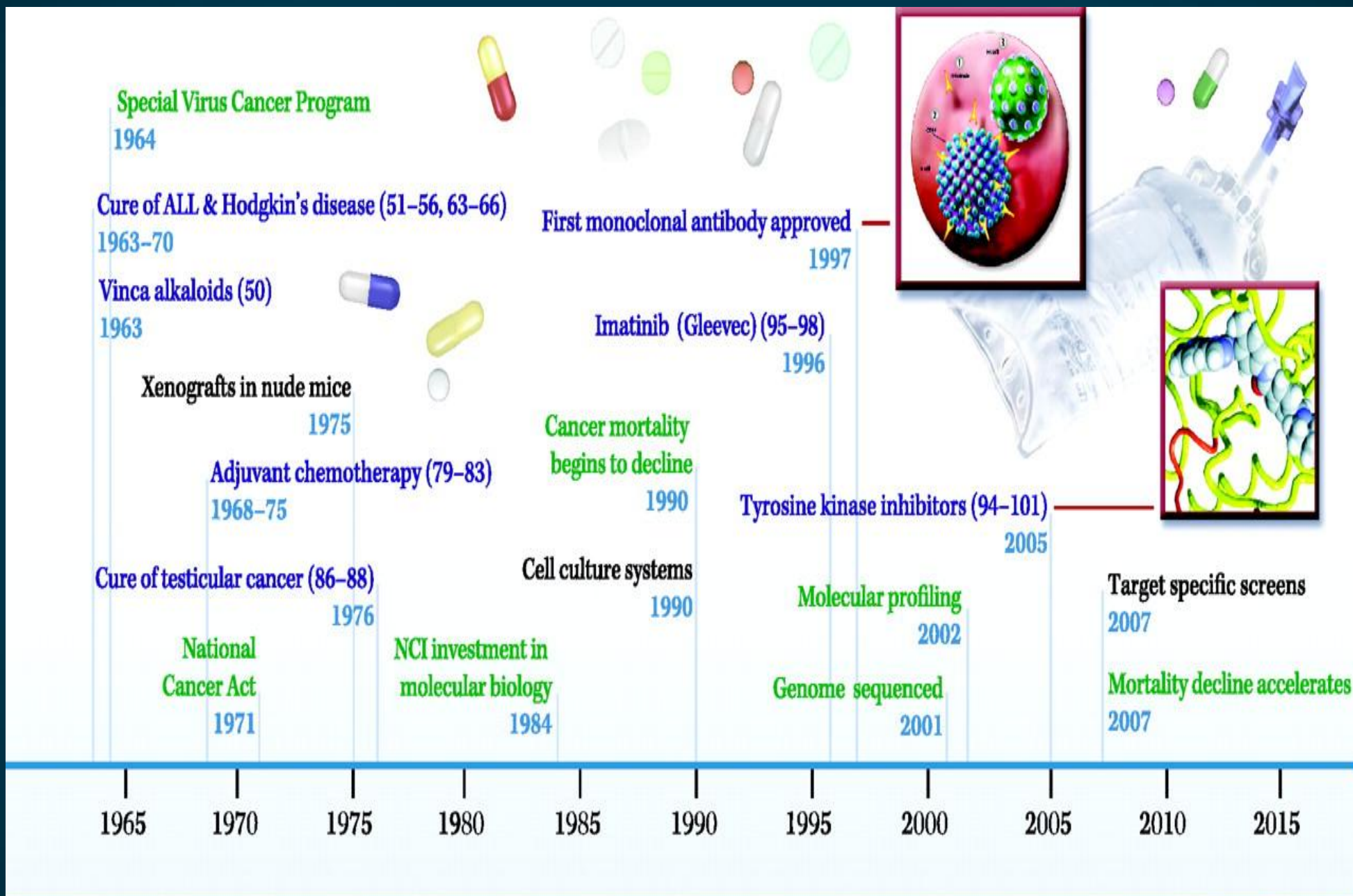
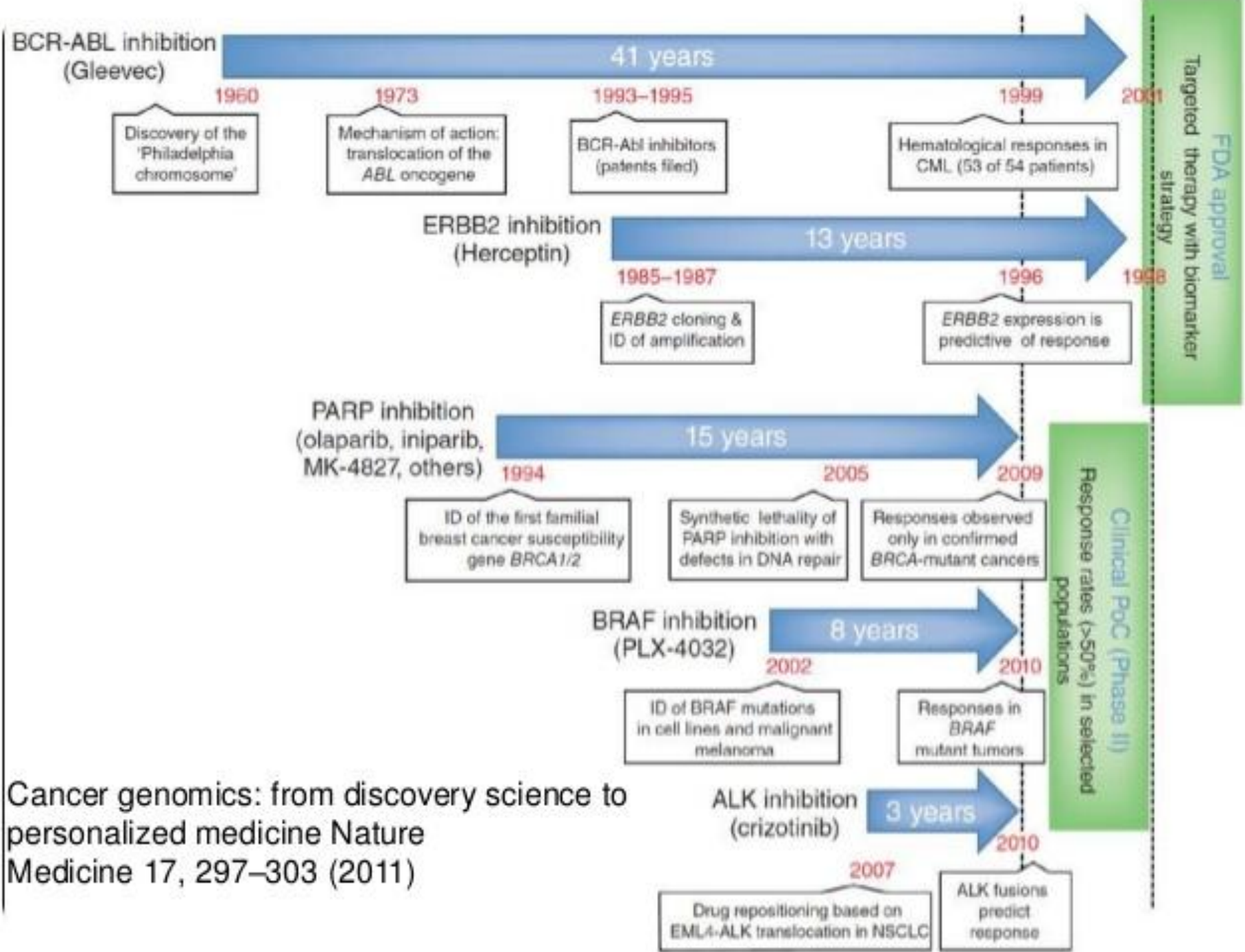


Figure 1. Key advances in the history of cancer chemotherapy







Cancer genomics: from discovery science to personalized medicine Nature Medicine 17, 297-303 (2011)

Krabbameinslyf

- “Hefðbundin krabbameinslyf
 - Virka fyrst og fremst á frumur sem eru að skipta sér.
 - Hindra skiptingunna með því að trufla tvöföldun erfðaefnis frumunnar eða skemma prótein sem sér um að draga þær í sundur

Aukaverkanir

“hefðbundinna krabbameinslyfja”

Hármissir

Beinmergsbæling

Ógleði/uppköst

Niðurgangur/hægðatregða

Þreyta/slappleiki

Nýrnabilun

Hjartabilun



Einstofna mótefni

- **Herceptin**, blokkerar Her-2 viðtaka á brjóstakrabbmeinsfrumum. (Her-2 einnig í hjartavöðva)
- **Rituximab** einstofna mótefni gegn CD-20 sem er yfirborðsprótein sem eitlakrabbameinsfrumur framleiða of mikið.
- **Cetuximab** einstofna mótefni gegn EGFR viðtaka á yfirborði fruma
- **Avastin** hemur VEGF (vascular endothelial growth factor) sem er mikilvæg í æðanýmyndun æxla

Einstofna mótefni

- Cetuximab (Erbix)
 - Hemill á EGFR á yfirborði krabbameinsfruma
 - Notað í ristilkrabbameini hjá sjúklingum sem eru ekki með stökkbreytingur í KRAS eða NRAS geni

Cetuximab

Aukaverkanir

- Útbrot
- Lungnabólga
- Lágt magnesium
- Bólgur í kringum neglur



Bevacizumab

- Háþrýstingur
- Blæðingar
- Gat á meltingarveg
- Nephrotic syndrome, nýru leka próteinum

Sunitinib (sutent), Sorafenib (nexavar)

- Háþrýstingur
- Hand and foot syndrome
- Hjartabilun
- Vanstarfsemi skjaldkirtli eða nýrnahettu
- Niðurgangur

Science

29 December 2013 | \$14

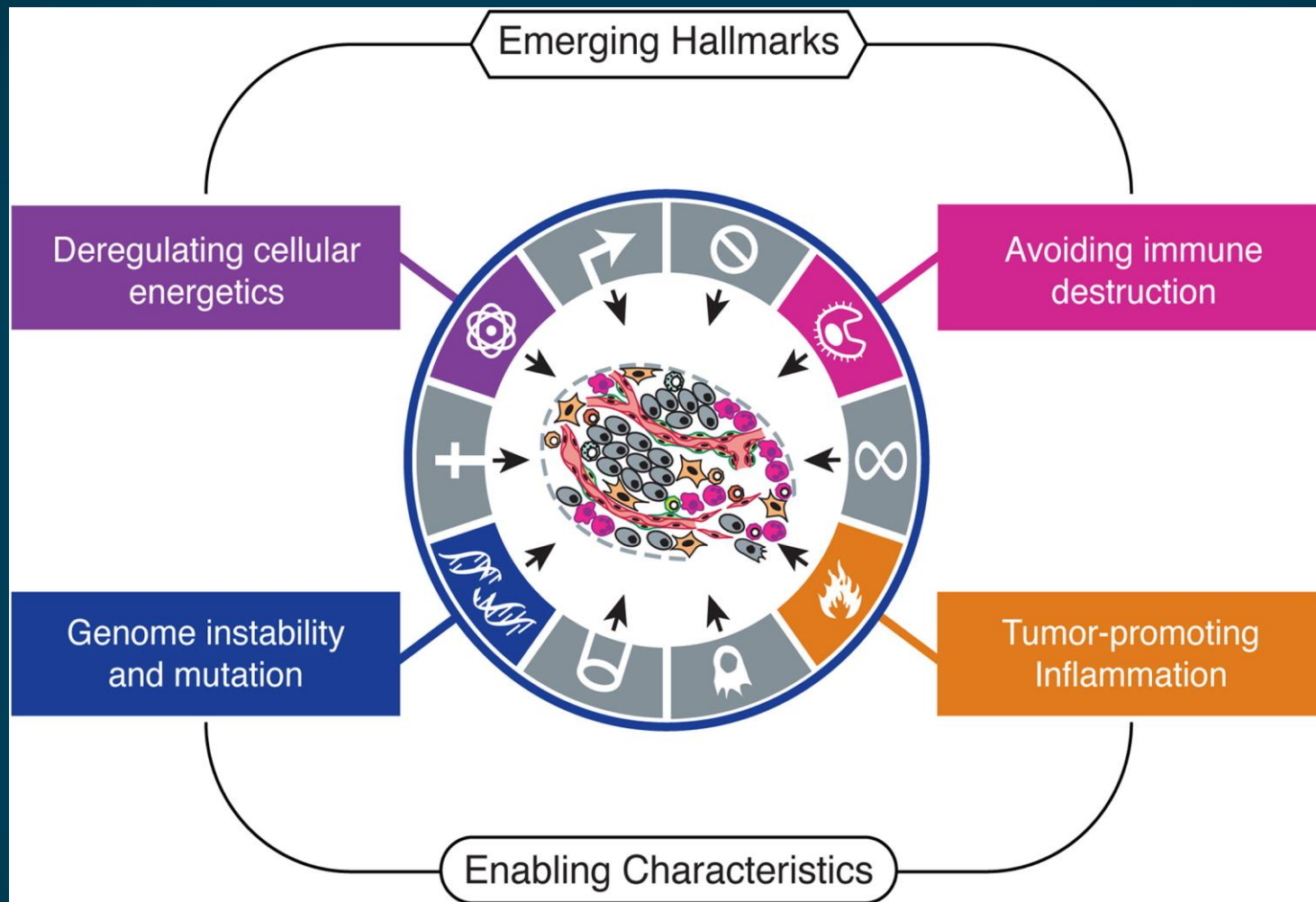
Breakthrough of the Year

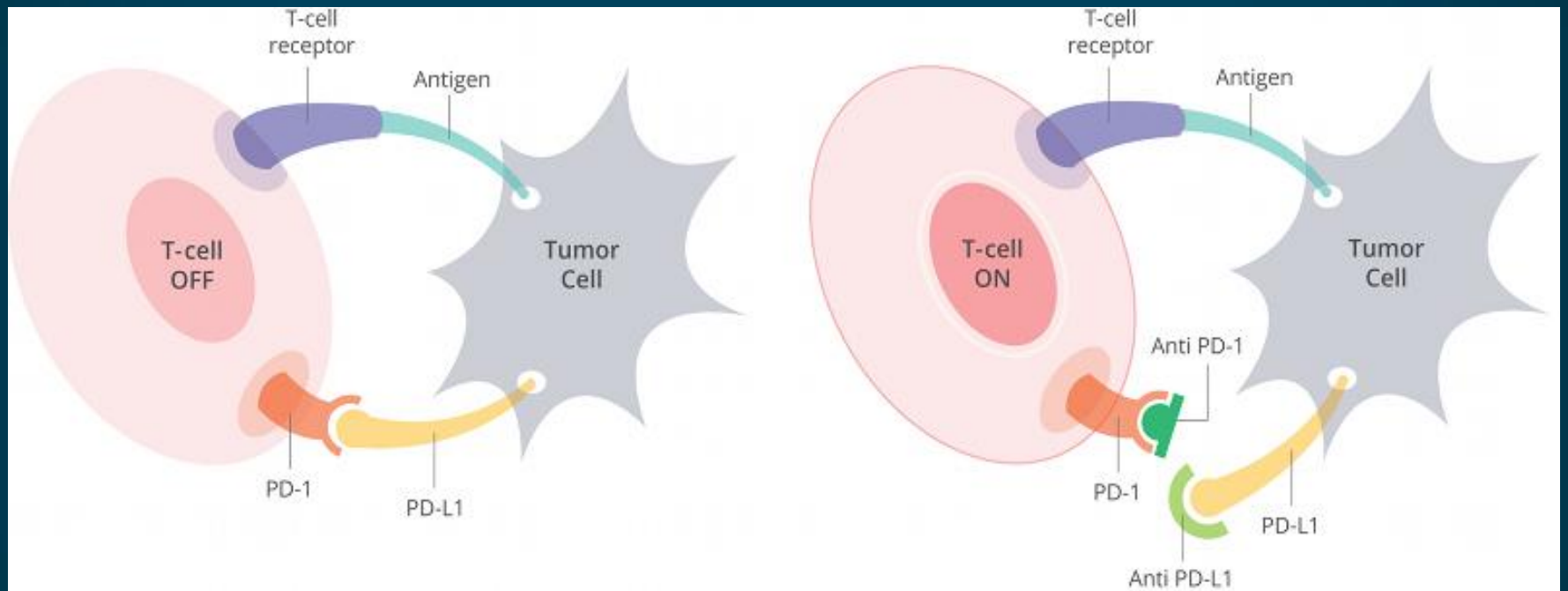
Cancer Immunotherapy

T cells on the attack

AAAS







Algengustu lyfin nú....nóvember 2017

- Nivolumab (Opdivo[®])
- Pembrolizumab (Keytruda[®])
- Atezolizumab (Tecentriq[®])

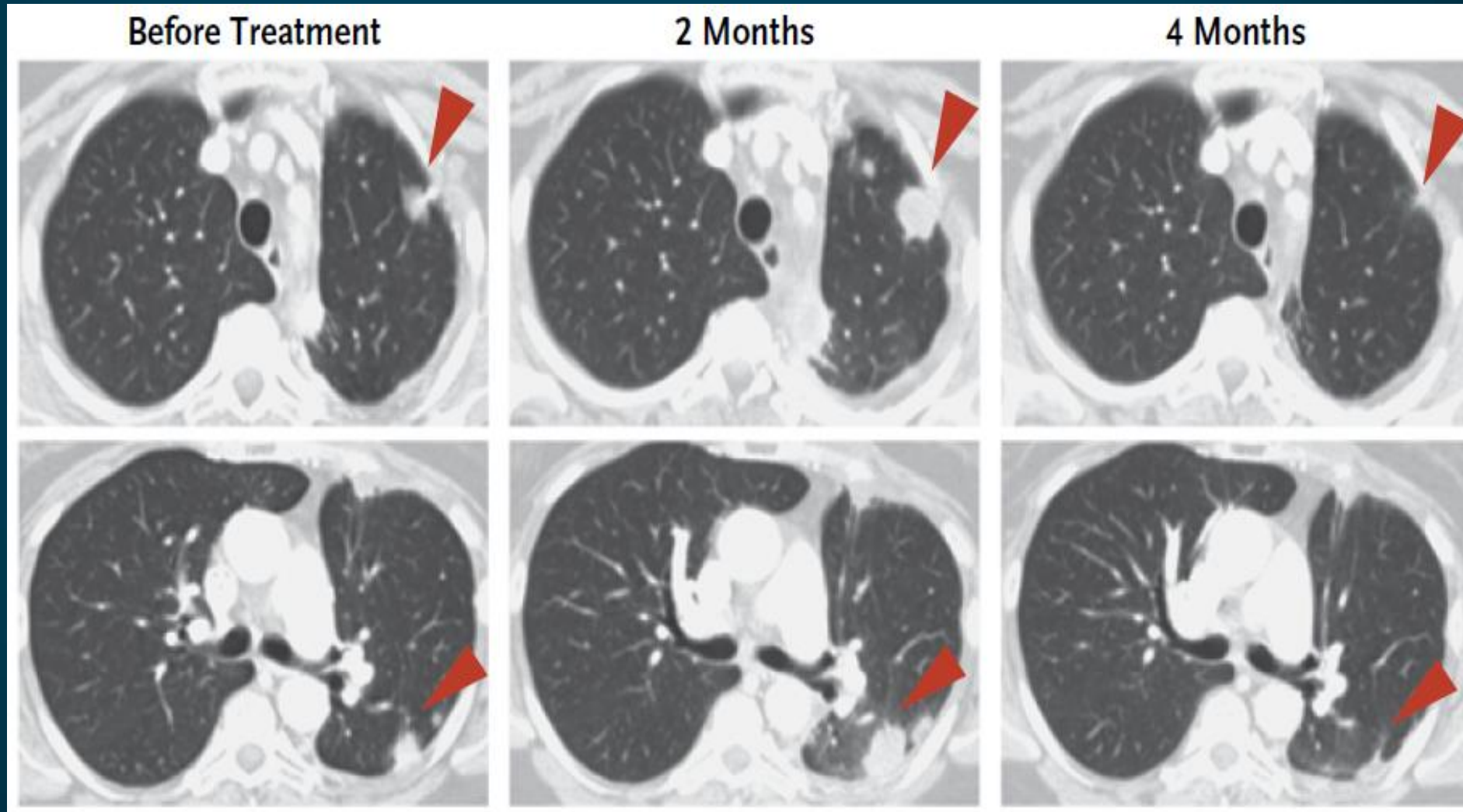
- Einstofna mótefni gegn PD – 1 (pembro og nivo)
- Einstofna mótefni gegn PDL-1 (atezolizumab)

Fjöldi krabbameina tjá PD-L1

- Sortuæxlum
- Nýrnakrabbameinum
- Lungnakrabbameinum
- Þvagblöðrukrabbamein
- Meltingarfærakrabbamein sem bera ákveðin galla í DNA viðgerðapróteinum virðast einnig næm fyrir þessum lyfjum.

EKKI ER ALLT SEM SÝNIST

Sjúklingur með lungnakrabbamein, meðhöndlaður með PD-1 hemli



Overview of irAEs

Endocrine

- Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
- Hypophysitis



Eye

- Uveitis
- Iritis



Pulmonary

- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis



GI

- Colitis
- Enterocolitis
- Necrotizing colitis
- GI perforation



Hepatic

- Hepatitis, autoimmune



Renal

- Nephritis, autoimmune
- Renal failure



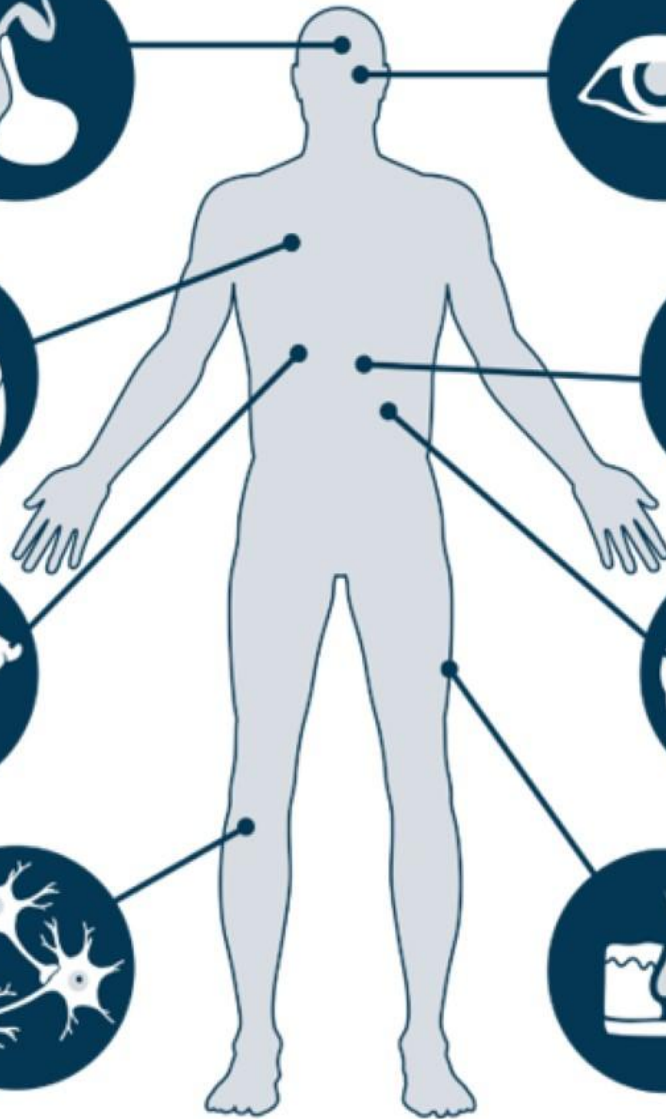
Neurologic

- Autoimmune neuropathy
- Demyelinating polyneuropathy
- Guillain-Barré syndrome
- Myasthenia gravis-like syndrome



Skin

- Dermatitis exfoliative
- Erythema multiforme
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Vitiligo
- Alopecia



Potentially Severe AEs

AE	Notes
Pneumonitis	• Rare (< 10%) but potentially life-threatening • Tends to occur later (after several months) • Managed with steroids • Immunosuppression for severe cases; discontinue immunotherapy
Colitis	• Common onset ~6 to 8 weeks • Steroids for moderate to severe cases; infliximab may be used • Hold immunotherapy until resolution
Hepatitis	• Common onset ~8 to 12 wks • More common with anti-CTLA-4 (still < 10%) • Monitor hepatic function before each immunotherapy dose
Endocrinopathies	• Usually requires permanent hormone replacement • Most severe type: acute adrenal insufficiency
Pancreatitis	• Only check amylase, lipase if clinical symptoms; value of steroids in asymptomatic patients unclear
Neurologic AEs	• Early recognition important; high-dose steroids important • If grade 3/4, permanently discontinue immunotherapy

Keytruda PI 2016; Opdivo PI 2016; Tecentriq PI 2016; Friedman CF, et al. *JAMA Oncol.* 2016; 2:1346-1353.

Aukaverkanir Nivolumab samanborið við Docetaxel

Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.*

Event	Nivolumab (N = 131)		Docetaxel (N = 129)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients with an event (percent)</i>			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

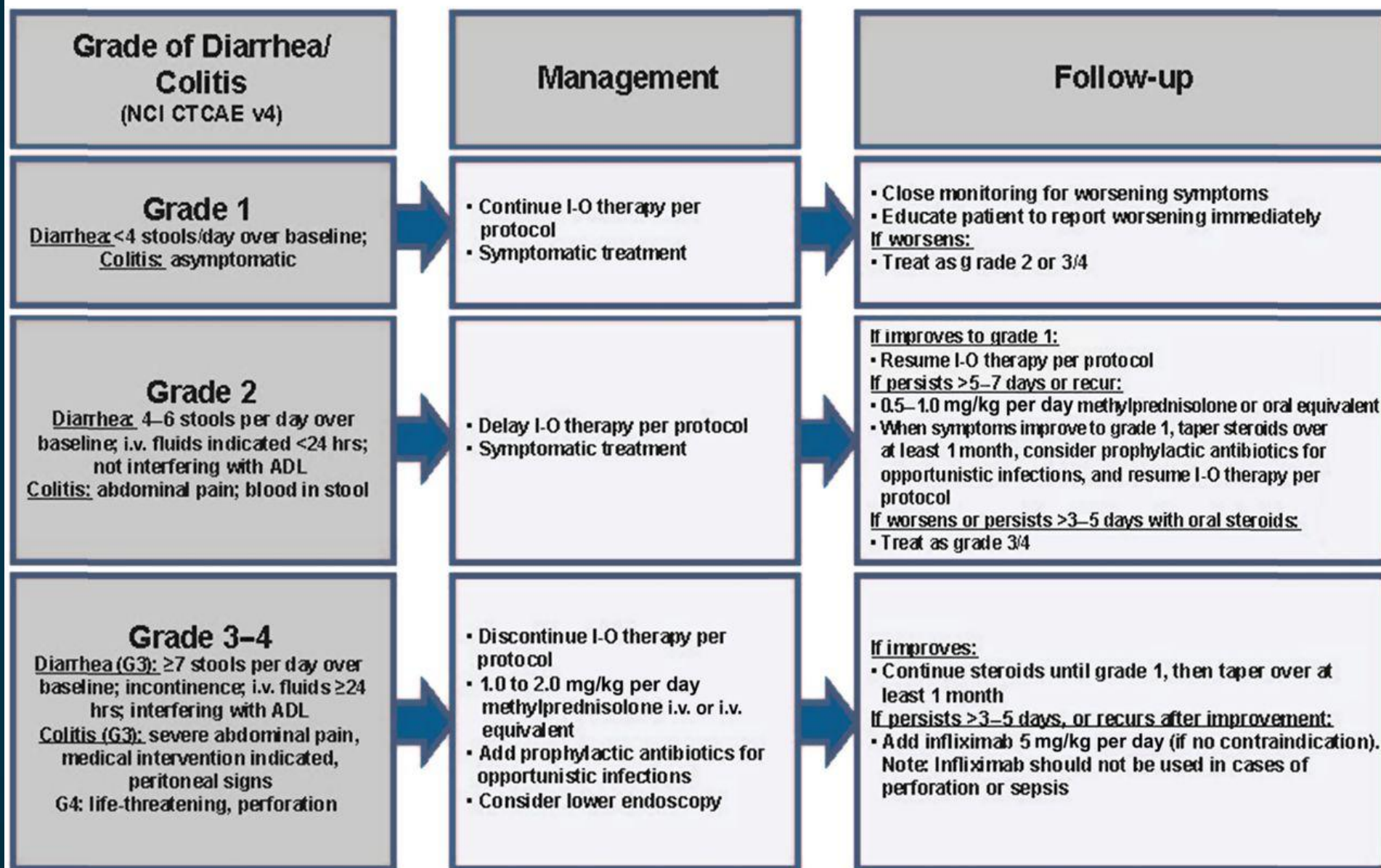
Meðhöndlun aukaverkana

Grade	Management	Continue the drug?
Low	Delay the dose	Resume Nivolumab when AEs resolve to grade ≤ 1 or baseline
Moderate ~ High	Administer Corticosteroids $\pm$ Immunosuppressants (anti-TNF, mycophenolate, etc)	Discontinue Nivolumab permanently (Delay in some situations)

A

GI Adverse Event Management Algorithm

Rule out noninflammatory causes. If noninflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

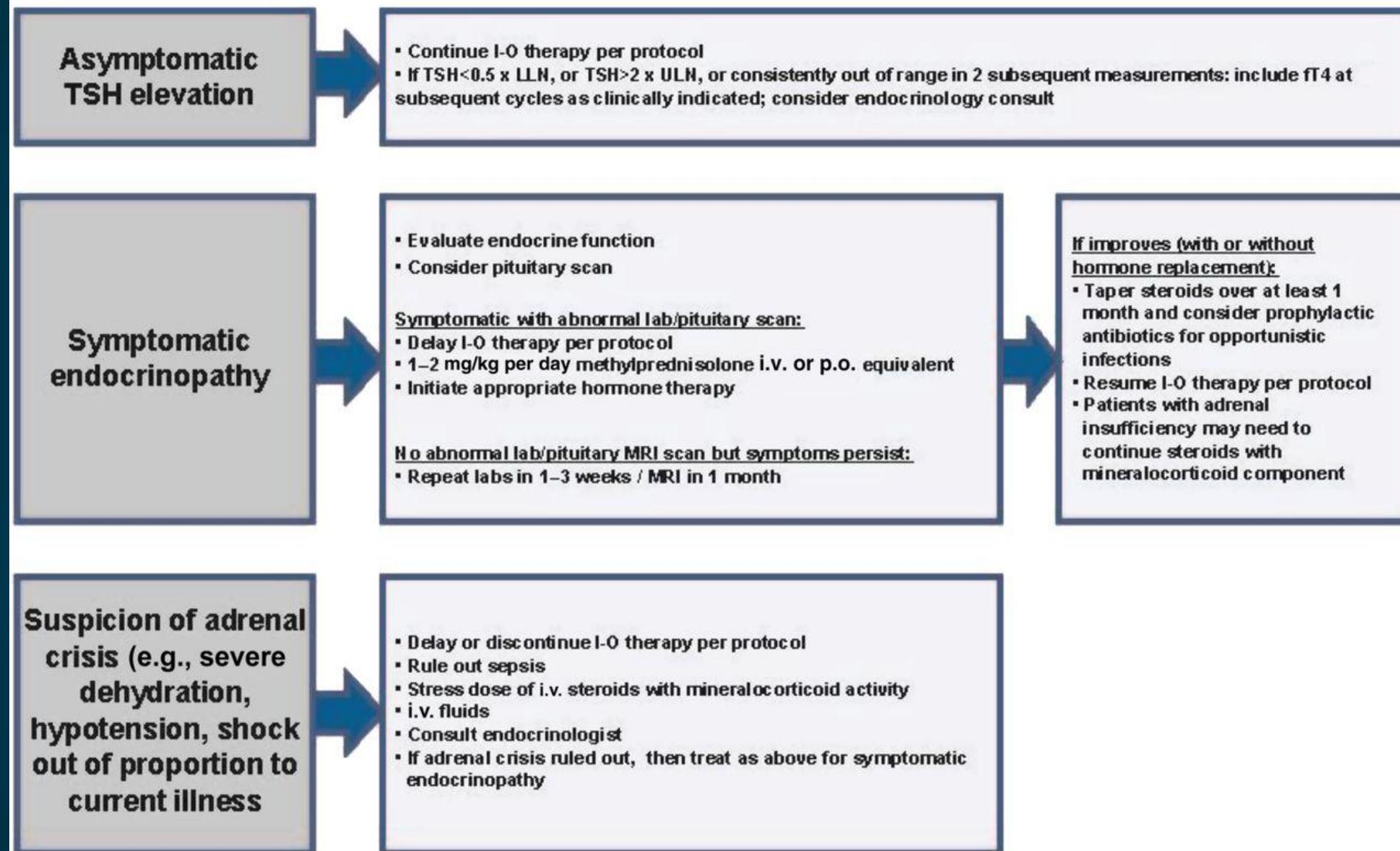


Patients on i.v. steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

B

Endocrine Adverse Event Management Algorithm

Rule out noninflammatory causes. If noninflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.



Patients on i.v. steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

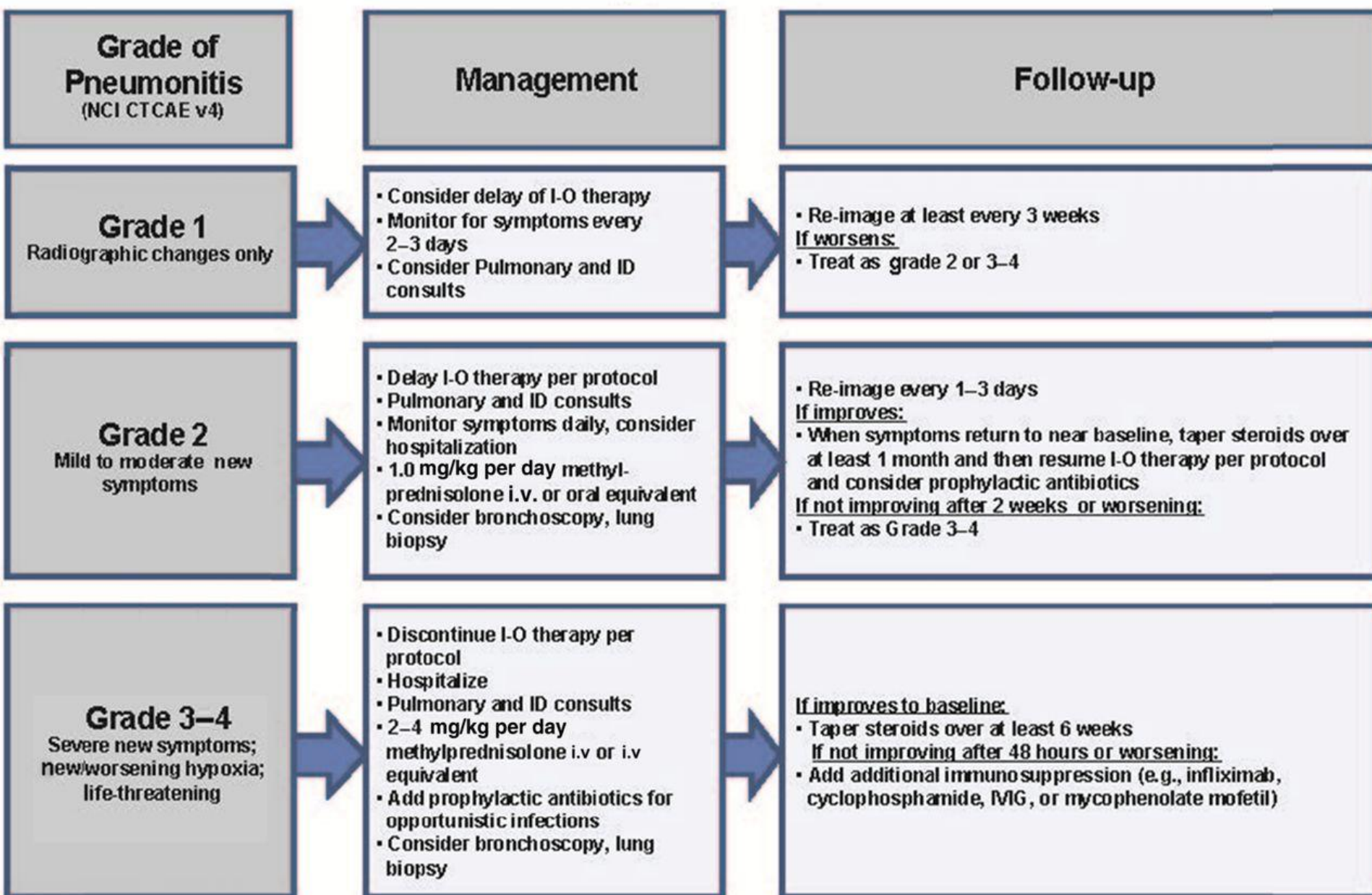
Jeffrey S. Weber et al. The Oncologist 2016;21:1230-1240

D

Pulmonary Adverse Event Management Algorithm

Rule out noninflammatory causes. If noninflammatory cause, treat accordingly and continue I-O therapy.

Evaluate with imaging and pulmonary consultation.

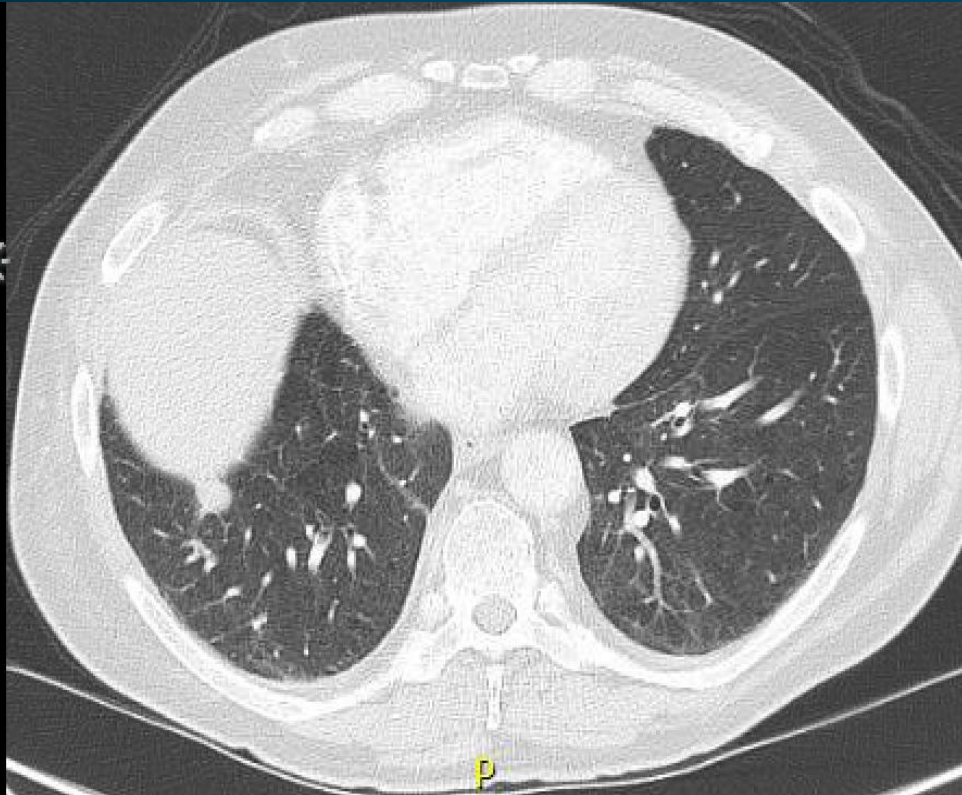


Patients on i.v. steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

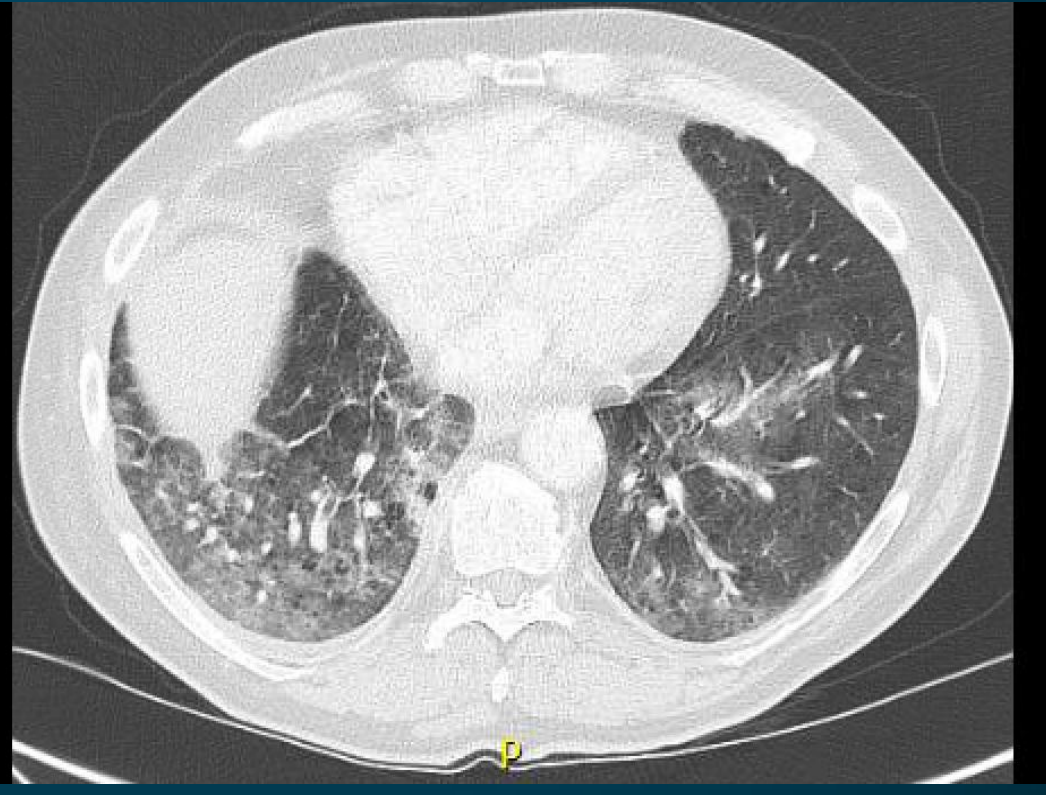
Pneumonitis

67 ára kk hér á Íslandi með lungnakrabba

CT lungu í apríl fyrir meðferð



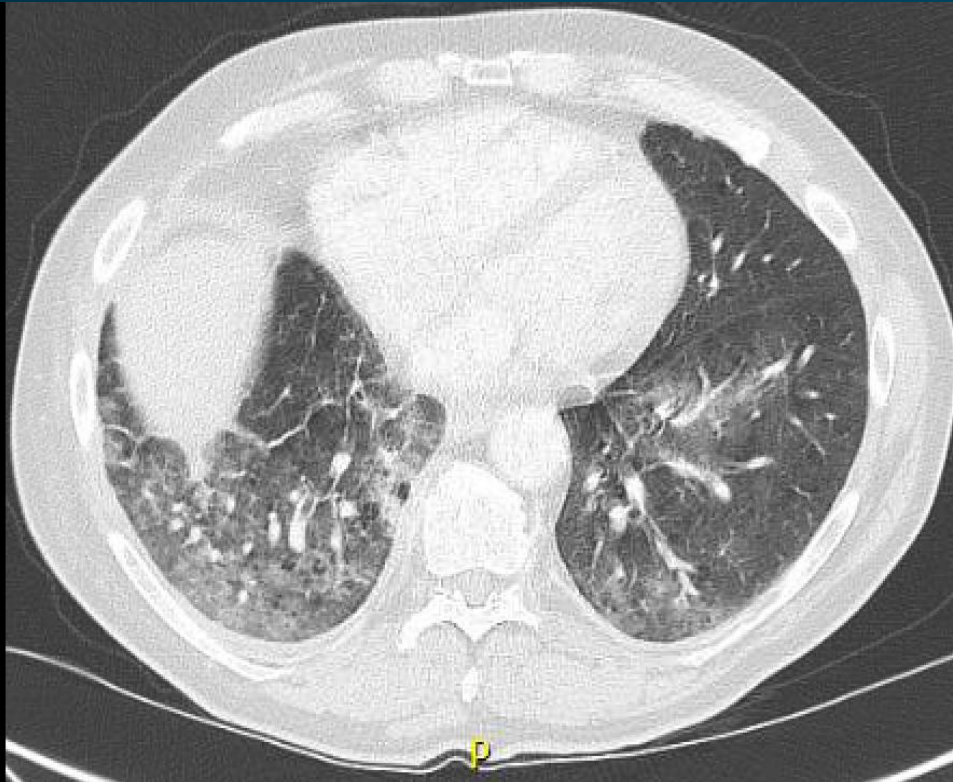
CT lungu í júlí eftir 4 skammta
- Nú vaxandi mæði og hósti -



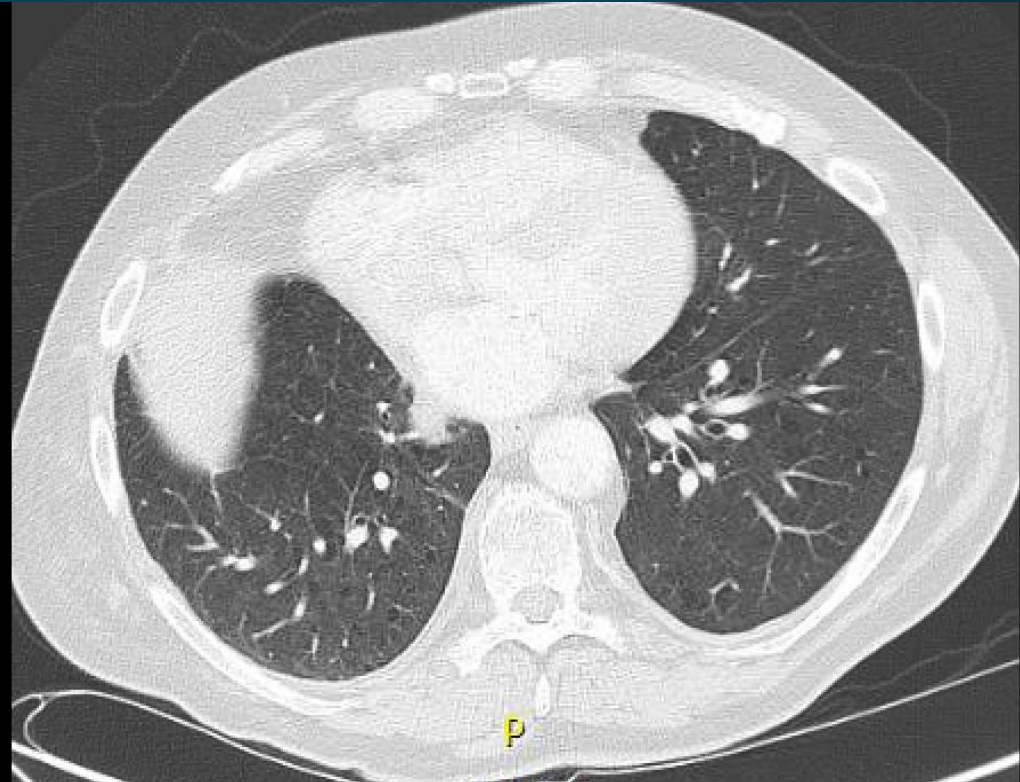
Pneumonitis

- Meðhöndlun með 1 mg/kg Prednisone -

CT lungu í júlí fyrir
sterameðferð (Nivo stoppað)



CT lungu í ágúst (eftir 1 mánuð
á sterum)



Samantekt

- Síðan 2014, búið að samþykkja lyf við sortuæxlum, lungnakrabbameinum, nýrnakrabbameinum og Hodgkins, blöðrukrabbameini, HNE krabba
 - Mörg fleiri lyf og við mörgum fleiri ábendingum væntanleg
- Mikilvægt að vera vakandi fyrir mögulegum aukaverkunum lyfjanna sem geta verið ófyrirsjáanlegar
 - Ónæmisbælandi lyf, s.s. sterar sem meðferð þegar á þarf að halda