
# καρκίνος του πνεύμονα

## ακτινοθεραπεία στην εποχή της ανοσοθεραπείας

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# conflict of interest

- I have no potential conflict of interest to report

# general facts

- ✓ RT: safe use of controlled doses of ionizing radiation to treat cancer
- ✓ as frontline therapy to approximately 60% of all patients with newly diagnosed cancer, usually in combinations with chemotherapy

Jaffray DA. *Nat Rev Clin Oncol* 2012

# general facts

- ✓ understanding radiobiology: optimization of dosage and fractionation
- ✓ cutting edge technology:
  - intensity modulated radiation therapy (IMRT)
  - image guided radiation therapy (IGRT)
  - stereotactic radiotherapy
  - medical imaging (π.χ. PET/CT)

➡ precise delivery of higher doses of RT per fraction (hypofractionation) with minimal damage to healthy tissues

Jaffray DA. *Nat Rev Clin Oncol* 2012

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*Whole Body Irradiation—Radiobiology or Medicine?*

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are more radiosensitive than other c
This last principle has important exc
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repair of radiation damage takes place in bone marrow or lymph nodes, then it cannot be true that the primitive and undifferentiated cells are more radiosensitive than those more mature cells which are killed (see footnote on page 238).

The idea that the nucleus is the most sensitive part of the cell was a deduction from the belief that the nucleus controls cell growth and division, from the visible changes the nucleus undergoes when the cell is irradiated, and from the evidence that chromosome and genic damage are produced by radiation. Trowell (1952) has pointed out that it is not legitimate to conclude from the fact that structural changes occur in the nucleus before the cytoplasm that the nucleus is, in fact, damaged primarily and not as a consequence of cytoplasmic damage. Experimental evidence is not available for mammals, and for other forms of life is conflicting (Vintemberger, 1928, 1929; Duryee, 1949; Harriss, Lamerton, Ord and Danielli, 1952).

One result of belief in primary nuclear damage is the idea that radiation-induced cancer is due to a

## abscopal* effect

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that the
only be
ed it, to
mean the effect on an object of irradiation of its environment, and that some other word, for which I have suggested abscopal, should be chosen for the different sense of action "at a distance from the irradiated volume but within the same organism".

This is not merely a theoretical discussion but directly relevant to all work done on the effects of whole body irradiation. One clear-cut example will illustrate this. Three days after 600–1000 r, rats show a depression to one-quarter of normal of the synthetic ability of the thyroid gland (Mole and Batt, 1953). This is not due to whole body irradiation, however, nor to direct irradiation of the thyroid or the pituitary gland. The depression of thyroid function appears only when a sufficiently large volume of the abdomen is irradiated (unpublished observations), and is therefore an abscopal effect of radiation.

The effects of whole body irradiation are sometimes summed up as due to the cellular damage radiation does. From one point of view this is a truism: apart from a certain amount of intercellular

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* Ab- is a prefix with the meaning "position away from" (*O.E.D.*) and scopos (Latin) is a mark or target for shooting at. The derived adjective therefore conveys the exact meaning required.

biological characteristic of creatures like mammals is that it is literally impossible to produce an effect in them limited to a small volume. The interdependence of all the cells in the organism's body means that damage to one cell must inevitably alter the body as a whole, *i.e.* all the other cells of the body. This is almost a biological platitude but it has such far-reaching consequences that it needs stressing. For example, it is meaningless to ask the question about the mammal: Is there an indirect effect of radiation? in the sense in which this question is normally asked. It would be a sensible, if not very important question if it meant: Does irradiation of the mammal's environment have an effect? But normally what the questioner means to ask is: Has irradiation of a mammal an effect at a distance from the volume irradiated? and to this there can only be one answer. What is important is to ask: How much of this

hazardous without particular proof. This is really self-evident, yet the rate of loss of cells from the peripheral blood after whole body irradiation has been used as a measure of their natural life span. For red cells there is clear proof that the cellular hypothesis is untrue. Hæmorrhage and erythrophagocytosis produce a loss of red cells which is not explained by death of red cell precursors, and quantitatively even more important may be the finding of widespread capillary leakage of red cells (Furth, 1952). And if the hypothesis is untrue for red cells why assume that it is true for white cells or platelets? Every time someone is taken off work with irradiation because of a low white count, the assumption is made that the

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# abscopal effect
## immune dependent mechanisms

evident that this effect is mediated by immune mechanisms

- tumor specific
- does not occur in immunodeficient individuals
- could be potentiated by interventions that mobilized antigen presenting cells (APCs)

Demaria S, *Int J Radiat Oncol Biol Phys* 2004

# abscopal effect

- renal cell carcinoma
- malignant melanoma
- hepatocellular carcinoma
- lung cancer
- other tumor types & hematologic malignancies

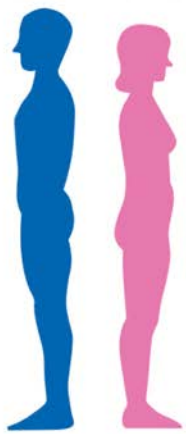
# lung cancer

**Estimated New Cases**

| Males | | | Females | | |
|---|---|---|---|---|---|
| Prostate | 174,650 | 20% | Breast | 268,600 | 30% |
| Lung & bronchus | 116,440 | 13% | Lung & bronchus | 111,710 | 13% |
| Colon & rectum | 78,500 | 9% | Colon & rectum | 67,100 | 8% |
| Urinary bladder | 61,700 | 7% | Uterine corpus | 61,880 | 7% |
| Melanoma of the skin | 57,220 | 7% | Melanoma of the skin | 39,260 | 4% |
| Kidney & renal pelvis | 44,120 | 5% | Thyroid | 37,810 | 4% |
| Non-Hodgkin lymphoma | 41,090 | 5% | Non-Hodgkin lymphoma | 33,110 | 4% |
| Oral cavity & pharynx | 38,140 | 4% | Kidney & renal pelvis | 29,700 | 3% |
| Leukemia | 35,920 | 4% | Pancreas | 26,830 | 3% |
| Pancreas | 29,940 | 3% | Leukemia | 25,860 | 3% |
| **All Sites** | **870,970** | **100%** | **All Sites** | **891,480** | **100%** |

**Estimated Deaths**

| Males | | | Females | | |
|---|---|---|---|---|---|
| Lung & bronchus | 76,650 | 24% | Lung & bronchus | 66,020 | 23% |
| Prostate | 31,620 | 10% | Breast | 41,760 | 15% |
| Colon & rectum | 27,640 | 9% | Colon & rectum | 23,380 | 8% |
| Pancreas | 23,800 | 7% | Pancreas | 21,950 | 8% |
| Liver & intrahepatic bile duct | 21,600 | 7% | Ovary | 13,980 | 5% |
| Leukemia | 13,150 | 4% | Uterine corpus | 12,160 | 4% |
| Esophagus | 13,020 | 4% | Liver & intrahepatic bile duct | 10,180 | 4% |
| Urinary bladder | 12,870 | 4% | Leukemia | 9,690 | 3% |
| Non-Hodgkin lymphoma | 11,510 | 4% | Non-Hodgkin lymphoma | 8,460 | 3% |
| Brain & other nervous system | 9,910 | 3% | Brain & other nervous system | 7,850 | 3% |
| **All Sites** | **321,670** | **100%** | **All Sites** | **285,210** | **100%** |

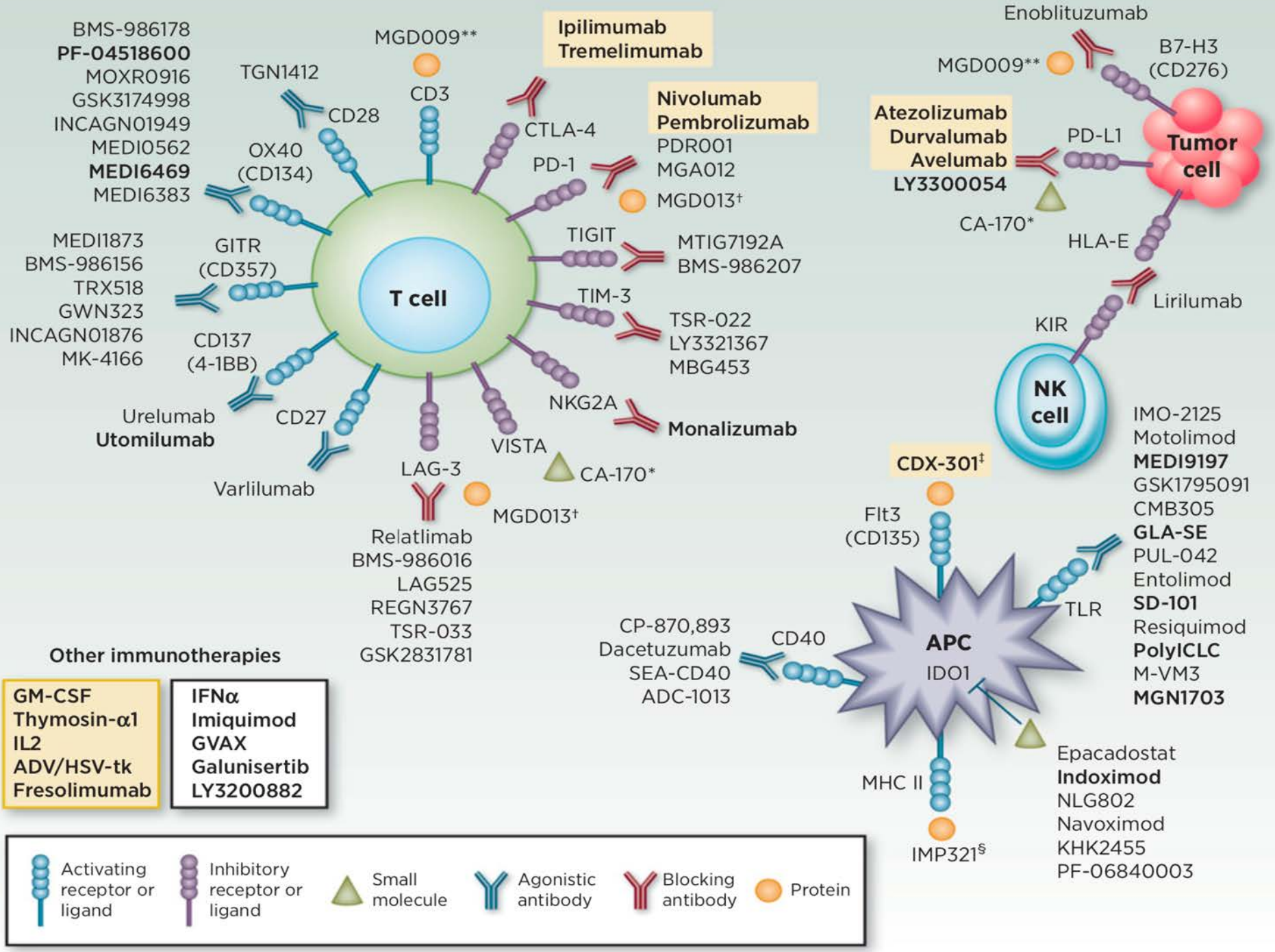


Cancer Statistics 2019

# FDA approved ICIs

✓ NSCLC
- Pembrolizumab
- Nivolumab
- Atezolizumab
- Durvalumab

✓ SCLC
- Nivolumab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MOXR0916
GSK3174998
INCAGN01949
MEDI0562
MEDI6469
MEDI6383
MGD009**
TGN1412
CD28
CD3
Ipilimumab
Tremelimumab
CTLA-4
Nivolumab
Pembrolizumab
PDR001
MGA012
MGD013†
PD-1
OX40
(CD134)
MEDI1873
BMS-986156
TRX518
GWN323
INCAGN01876
MK-4166
GITR
(CD357)
T cell
TIGIT
MTIG7192A
BMS-986207
TIM-3
TSR-022
LY3321367
MBG453
CD137
(4-1BB)
Urelumab
Utomilumab
CD27
Varlilumab
NKG2A
Monalizumab
VISTA
CA-170*
LAG-3
MGD013†
Relatlimab
BMS-986016
LAG525
REGN3767
TSR-033
GSK2831781
Enoblituzumab
MGD009**
B7-H3
(CD276)
Atezolizumab
Durvalumab
Avelumab
LY3300054
PD-L1
Tumor
cell
CA-170*
HLA-E
Lirilumab
KIR
NK
cell
IMO-2125
Motolimod
MEDI9197
GSK1795091
CMB305
GLA-SE
PUL-042
Entolimod
SD-101
Resiquimod
PolyICLC
M-VM3
MGN1703
CDX-301‡
Flt3
(CD135)
TLR
CP-870,893
Dacetuzumab
SEA-CD40
ADC-1013
CD40
APC
IDO1
Epacadostat
Indoximod
NLG802
Navoximod
KHK2455
PF-06840003
MHC II
IMP321§
Other immunotherapies
GM-CSF
Thymosin-α1
IL2
ADV/HSV-tk
Fresolimumab
IFNα
Imiquimod
GVAX
Galunisertib
LY3200882
Activating receptor or ligand
Inhibitory receptor or ligand
Small molecule
Agonistic antibody
Blocking antibody
Protein