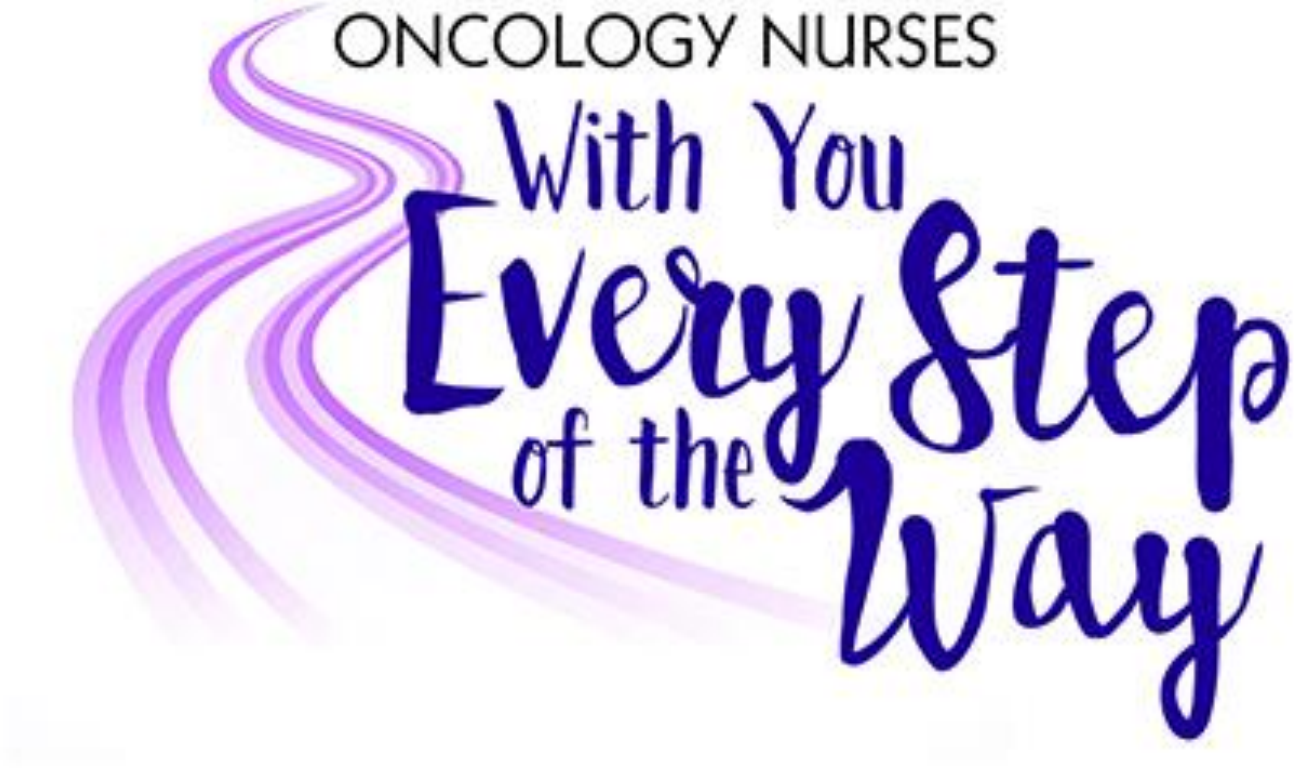
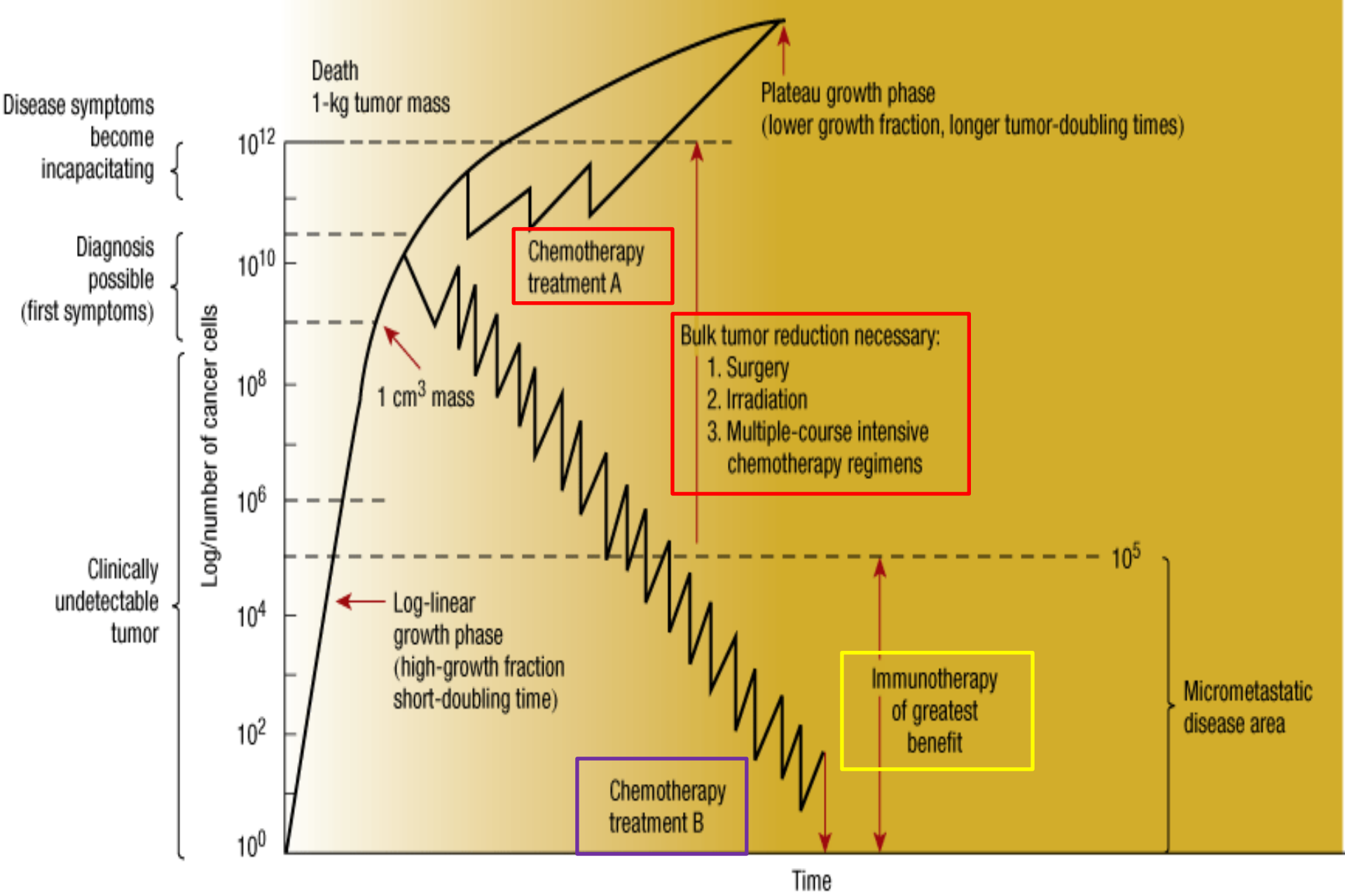
“Cancer treatment modalities”

Phichai Chansriwong, MD
30th July 2016


ONCOLOGY NURSES
With You
Every Step
of the Way

Gompertazin growth curve

- Natural history of Cancer
- Gompertazin growth curve demonstrates the theoretical pattern of tumor growth
  - exponential growth
  - The growth fraction decreases as the tumor mass increases in size



DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A pathophysiologic Approach,* 7th Edition: Http://www.accesspharmacy.com

Modalities of treatment

1-local therapy:

-surgery.

-radiation therapy.

2-systemic treatment:

- chemotherapy.
- Hormonal therapy.
- Targeted therapy
- Radioactive material.
- Immunotherapy

3-supportive care.

Modalities of cancer treatment

The most appropriate type of therapy for each individual patient is determined by

- Type and extent of tumor involvement
- Treatment goals
- Performance status
- Age
- Concomitant disease
- Team
- Consider multi-modalities treatment

Surgery

- Surgery was the first modality used successfully in the treatment of cancer.
- It is the only curative therapy for many common solid tumors

Surgery

- Early Cancer with or with out other modalities
    - Curative Intent
- Advance Cancer (Intention is to Increase the Lifespan, improve on symptoms and Increase the Quality of Life)
    - Local Control of the tumor
    - Regional control
    - Cytoreduction
    - Palliative Symptom control

Principles of surgical resection

- Assessment (Patient, Tumor, Reconstruction plan, Immediate Post op, Adjuvant therapy, Follow up)
- Adequate margin of resection
- Prevention of tumor spillage
- What to do for Lymph Nodes
- Minimal manipulation
- Reconstruction

Metastasectomy

- The primary tumor is controlled or can be controlled
- Metastasis is single or localized (Resectable)
- Evidence that metastasectomy benefits the patient (Colorectal, breast cancer)
- Tumor Biology (Slow tumors)
- Co-morbid factors

Palliative Surgery in Oncology

Goals of Palliative Surgery

- Patient should be better at the completion of the procedure
- Relieve symptoms for patients beyond cure when non-surgical measures are not feasible, not effective, or not expedient.
  - Control of pain, Relief gastrointestinal and biliary obstruction, Stop hemorrhage, Supplement poor nutrition, Airway obstruction, Renal failure, Rectal or urinary incontinence

Radiation therapy:

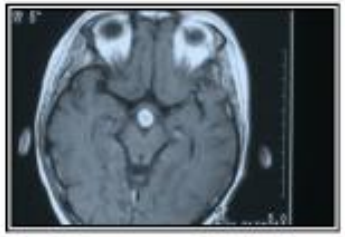
- Radiation therapy: is a local modality used in the treatment of cancer .
- It involves the administration of ionizing radiation in the form of x-ray or gamma rays to the tumor site.
- Method of delivery: External beam(teletherapy).

Internal beam therapy(Brachytherapy).

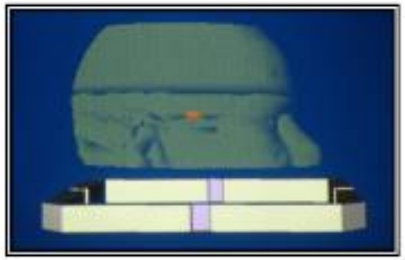
Radiotherapy

- The aim of radiation therapy is to deliver a **precisely** measured dose of irradiation to a defined tumor volume with as **minimal damage** as possible to surrounding healthy tissue, resulting in eradication of the tumor, a **high quality of life**, and prolongation of survival at competitive cost.
- Role: curative efforts, effective palliation or prevention of symptoms of the disease

EVOLUTION IN TREATMENT PLANNING SYSTEMS



2D → 3D



BEAM CONFORMATION

CUSTOMIZED BLOCKS → MULTILEAF COLLIMATOR

MLC

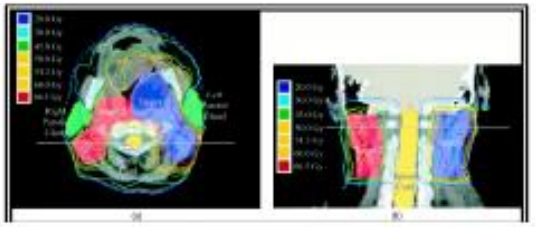
BEAM MODULATION

COMPENSATORS

WEDGES

SPECIAL TECHNIQUES

SRT - 3DCRT - IMRT - IMPT

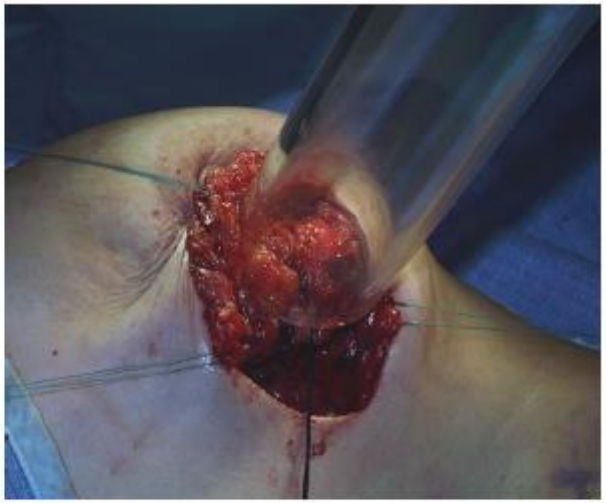


Laura Lozza

RADIOTHERAPY TECHNIQUE

- Conventional RT
- Intraoperative RT (IORT)
- Brachytherapy (BRT)
- Stereotactic Radiotherapy (SRT)
- Conformal RT (3DCRT)
- Intensity Modulated Radiotherapy (IMRT)
- Intensity Modulated Proton Therapy (IMPT)

INTRAOPERATIVE RADIATION THERAPY



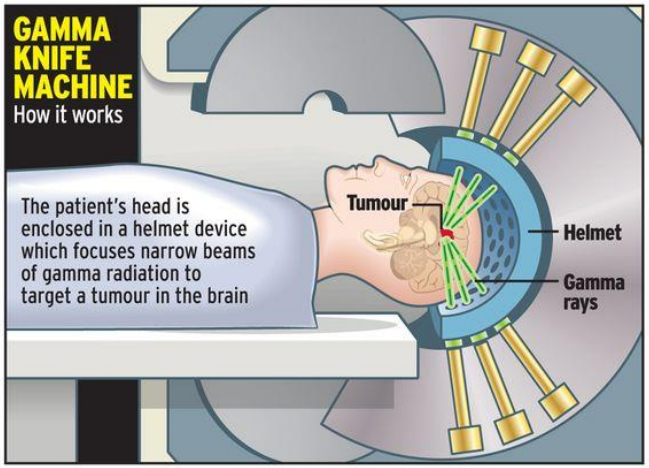
- Intraoperative radiation therapy (IORT) is a specialized treatment technique that uses either electron or orthovoltage irradiation for deep-seated cancers

STEREOTACTIC IRRADIATION

- Radiosurgery is a procedure that delivers three-dimensional (3-D) stereotactic external-beam irradiation (SEBI/SBRT).
- First reported in 1949, an intracranial target
- various techniques, including gamma-units using 60Co photons, protons, helium ions, and neutron beams and modified linear accelerator (linac) units.
- Primary treatment : Lung, prostate
- Metastases treatment: oligometastases

INDICATIONS FOR RADIOSURGERY
Treatment of brain metastases

- lesions ≤4cm
- controlled systemic disease
- Eastern Cooperative Oncology Group (ECOG) rating of less than 3, 4
- less metastasis prior to procedure (maximum 5 fractions)

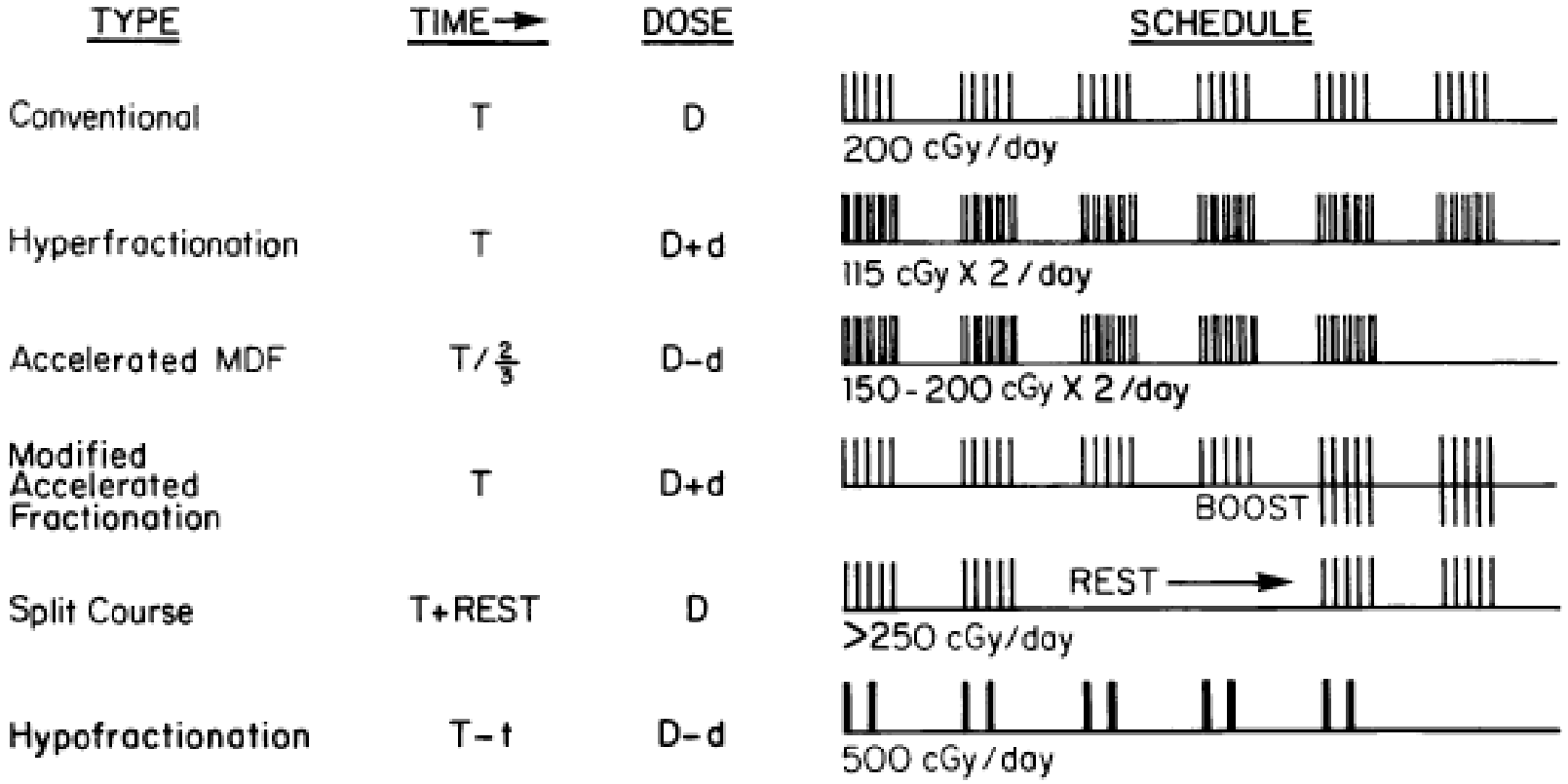


effects of irradiation

- ACUTE (first 6 months)
- SUBACUTE (second 6 months)
- LATE (depending on the time they are observed)
- The gross manifestations depend on the kinetic properties of the cells (slow or rapid renewal) and the dose of irradiation given.

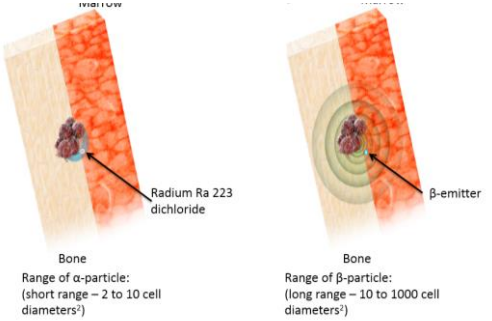
Fractionation of radiotherapy

- The "standard fractionation" for radiation therapy has evolved into five fractions weekly.



Radionuclides

- For decades have been used systemically to treat malignant disorders.
- They are administer by specialists in nuclear medicine or radiation oncologist.
- Radioactive iodine: in the from of ^{131}I is effective therapy for well differentiated thyroid cancer
- Strontium-89. Is used for the treatment of body metastasis.it is an alkaline earth element in the same family as calcium



Chemotherapy

- Term: use of chemicals to treat any disease (chemo- + -therapy)
- Early 20th century, Mustard gas was used as a chemical warfare agent during World War I
- Nitrogen mustards were studied further during World War II at Yale December 1942, several patients with advanced lymphomas were given the drug by vein. Their improvement, although temporary, was remarkable
- The first chemotherapy drug to be developed from this line of research was mustine

Categories of drugs

- Phase specific
  - Cycle-specific, phase specific
  - The longer period the concentration is maintained, the more cells enter the specific lethal phase of cycle killed
  - G1 phase
    - L-asparagenase
  - S phase
    - Antimetabolites
  - M phase
    - Plant alkaloids, Taxanes

Classification

- Antimetabolites
- Covalent DNA-Binding drugs
- Antitumor Antibiotics
- Microtubule-targeting drugs
- Topoisomerase inhibitors
- Hormones
- Biologic Response Modifiers
- Targeting therapy

Chemotherapy

- The last 50 years.

- Empirical drug screening of cytotoxic agents against uncharacterized tumor models

- Target-oriented drug screening of agents with defined mechanisms of action.

Chemotherapy

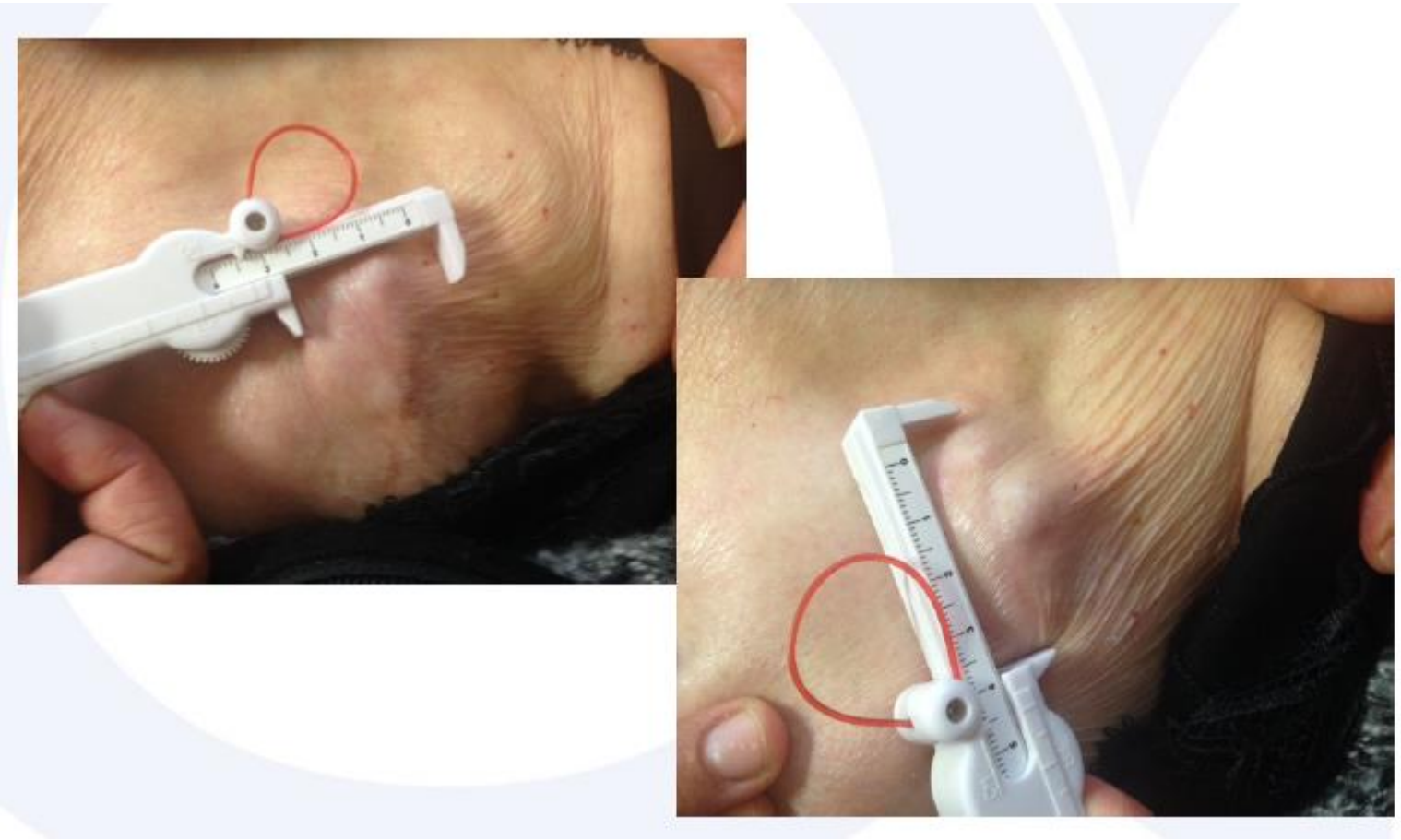
1945
Mechloretamin
1950
Methotrexate
6-mercaptopurin
Busulfan
1955
Clorambucil
Ciclophophamide
1960
Vinblastin, vincristin
Fluorouracile, actinomycinaD
Melphalan
1965
Procarbazin, 6-thioguanin
Cytosin arabinoside
Adriamicyn
1970
Bleomycin, dacarbazine
1975
CCNU, BCNU, cisplatin
1980
Epirubicin
Etoposide, mitoxantrone
1985
Ifosfamide + mesna
Carboplatin
1990
Vinorelbin
Paclitaxel
Docetaxel
1995
Camptotecin
TARGETED THERAPY

The goal of chemotherapy in patients with advanced cancer

- Chemotherapy objective response rates(CR,PR) are leading to an increase in survival And generally to an improvement in the quality of life

How to assess response?

- Calipers & Rulers

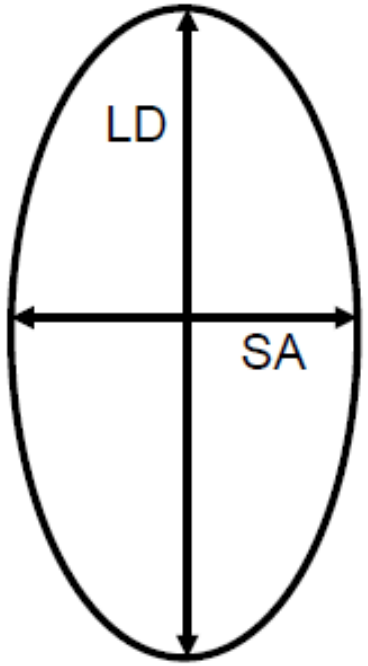


Response Evaluation Criteria in Solid Tumors

- RECIST is a combination of both qualitative and quantitative assessment
- Based on concept of target lesions and non-target lesions
- Target lesions are quantitatively assessed
- Non-target lesions are qualitatively assessed
- Target Lesions: Must be EASILY (and reproducibly) measurable
- • Must be representative of the disease (clearly metastasis)
  - Must be representative of distribution (choose)
  - measurable lesions from all involved organs)

Measurable lesion

- Tumor ≥10mm in longest diameter (LD) on axial image
  - If slice >5 mm, at least 2 times the thickness
    - For MRI, thickness includes gap
- Lymph nodes
  - Always measure short axis (SA)
  - ≥ 15 mm measurable
  - < 10 mm is normal



RECIST - Tumor Response

- Complete response (CR): Disappearance of all target lesions
- Partial response (PR): > 30% decrease in the Sum of longest diameter (SLD) taking as reference the baseline SLD
- Stable decrease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
- Progression (PD): > 20% increase in the SLD taking as reference the nadir compared to baseline measurement or present of new lesions

Tumors in which **cure** by chemotherapy is possible in advanced-stage disease

- Germ cell tumor
- Testicular cancer
- Hodgkin's lymphoma
- Aggressive non-Hodgkin's lymphoma
- ALL,AML

Tumors in which **useful** responses by chemotherapy are possible in advanced-stage disease

- Breast Carcinoma
- Lung Carcinoma
- Colorectal Carcinoma
- Ovarian Carcinoma
- Prostate Carcinoma

Chemotherapy

Cancer chemotherapy may be

- Primary
- Palliative
- Adjuvant
- neoadjuvant

Neoadjuvant and Adjuvant Therapy

- What is **Adjuvant** Therapy?
  - Therapy given after surgery (post-operative therapy)
  - Indication:
    - Decrease the risk of cancer relapse
    - Decrease the risk of cancer mortality
- **Neoadjuvant** Therapy
  - Indication:
    - Inoperable: Locally advanced disease
    - Operable: Breast conservation is not possible, but desired
    - Clinical status: Need time to optimize the patient for surgery
    - Breast cancer/ laryngeal cancer/ rectal cancer/ bladder cancer/ Osteosarcoma

COMBINATION CHEMOTHERAPY :
a strategy to increase response and tolerability and to decrease resistance

1) use drugs with non overlapping toxicities so that each drug can be administered at near maximal dose

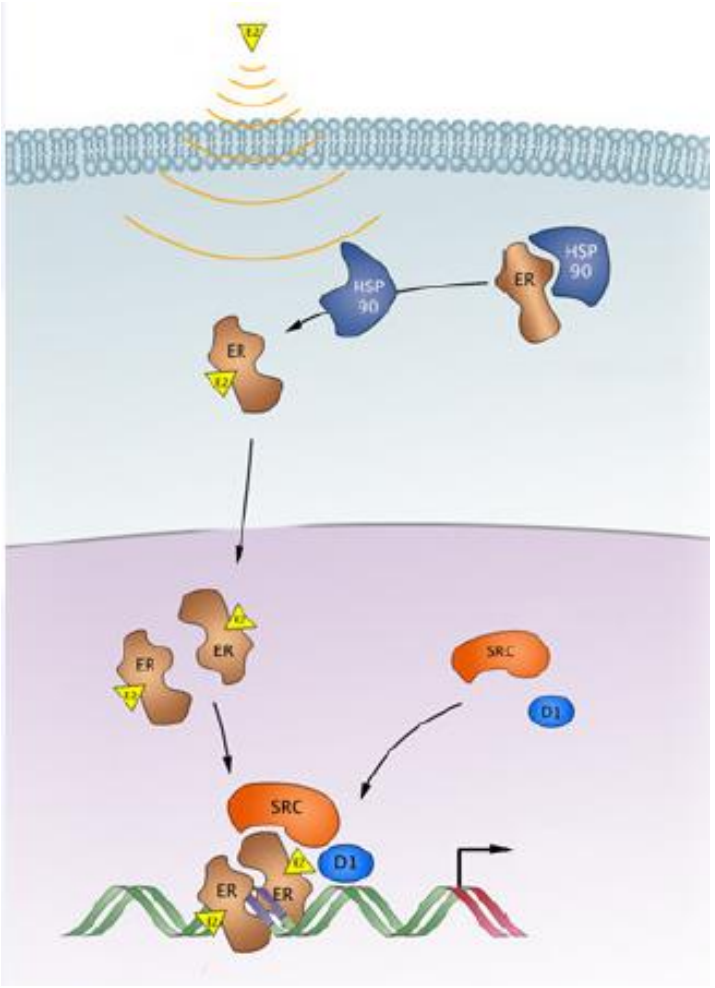
2)combine agents with different mechanisms of action to inhibit the emergence of broad spectrum drug resistance

Major hormonal agents used in cancer

Class of drug	Individual drug	Dose	Route	Frequency
SERMs	Tamoxifen	20 mg	oral	Once daily
AIs	Anastrozole Letrozole Exemestane	1 mg 2.5 mg 25 mg	oral	Once daily
ER dowregulator	Fulvestrant	500 mg	i.m.	Once montly
GnRH agonist	Goserelin Leuprorelin Triptorelin	7.5 mg 3.75 mg 3.75 mg	i.m. i.m. i.m.	Once monthly
GnRH antagonist	Degarelix	240 mg loading dose	s.c.	80 mg monthly maintainance
Antiandrogen	Flutamide Bicalutamide	250 mg 50 mg	oral	TID Once daily
CYP450 17α inhibitors	Abiraterone	1,000 mg	oral	Once daily
AR "super antagonists"	Enzalutamide	160–240 mg	oral	Once daily
Somatostatin analog	Octreotide	Variable	s.c. or i.v.	Up to three times daily
Progestational agents	Megestrol Medroxyprogesterone	Variable	oral oral or i.m.	Once daily Varies

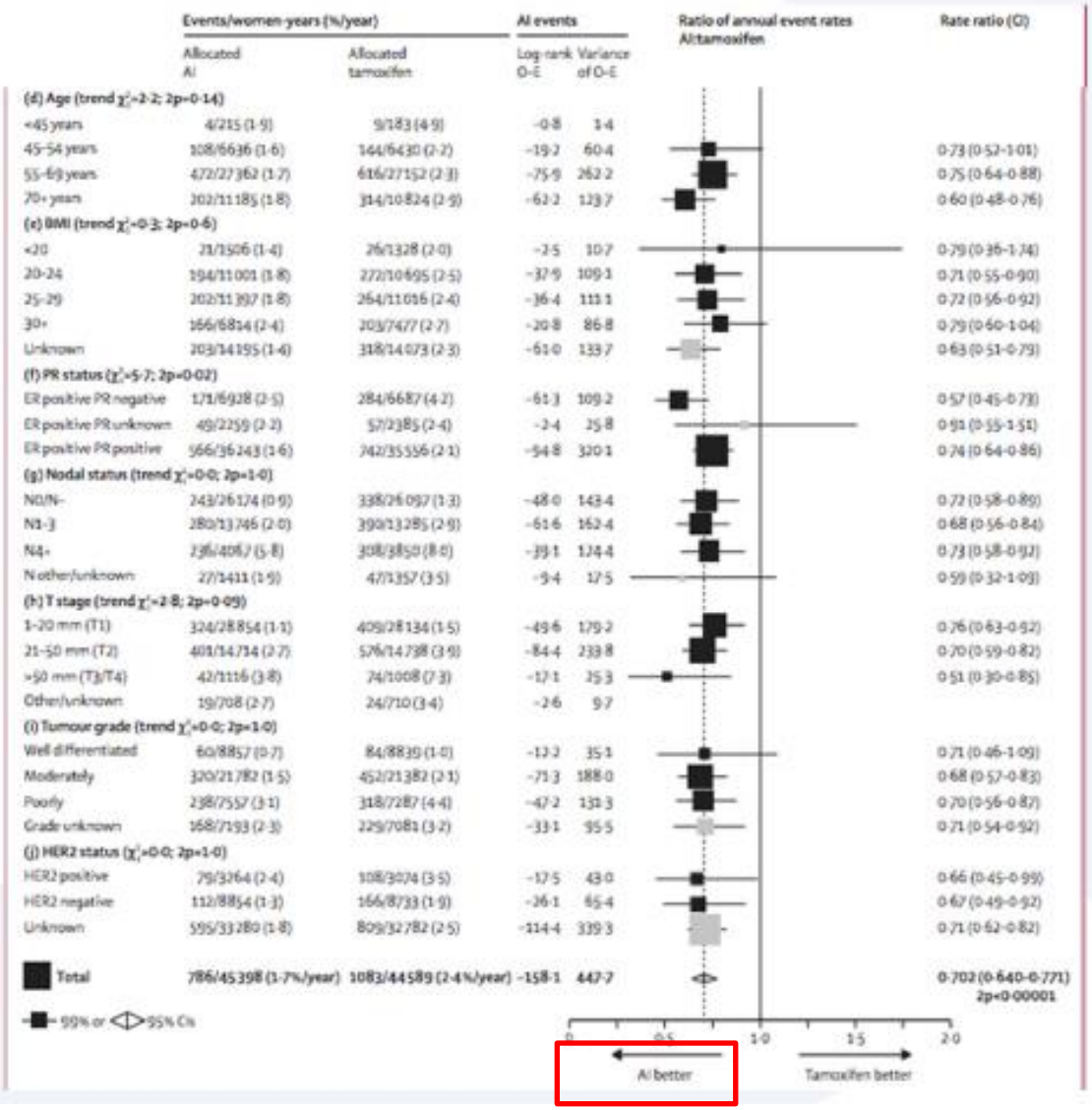
Antonella Brunello

Estrogen & Progesterone receptors



- Several authors demonstrated the relationship of the cytosolic form ER to the efficacy of endocrine therapy.
- The nuclear translocation and subsequent transcription are dependent on several co-repressors and activators.
- The SRC co-activator action is particularly important in this regard.
- Role also of ER-β

AIs vs TAM in Post menopause



EBCTCG Lancet 2015

ATLAS: all subset benefit

'Practice-changing' ATLAS Study Supports 10 vs 5 Years of Tamoxifen Therapy in Women with Breast Cancer

By Charlotte Bath

February 1, 2013

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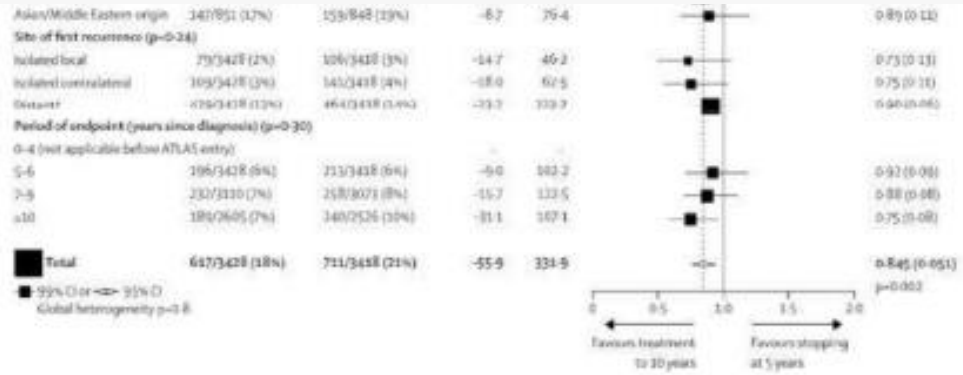

ATLAS, Lancet, 2013

surgery

- Previous TAH
- Menopausal status
- Geography

ASCO 2016: 10 Years of Aromatase Inhibitor Therapy Reduces Breast Cancer Recurrence Without Compromising Quality of Life in Postmenopausal Patients

By The ASCO Post

Posted: 6/5/2016 11:05:15 AM

Last Updated: 6/5/2016 11:05:15 AM

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PREMENOPAUSAL

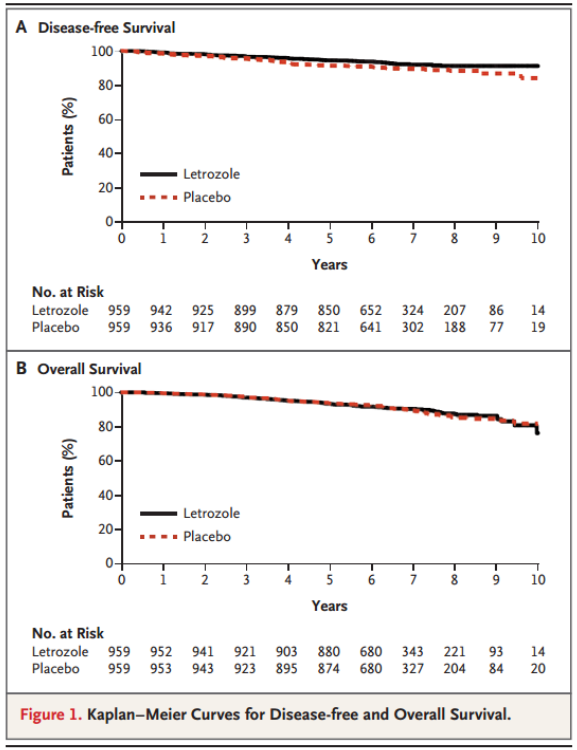


Figure 1. Kaplan–Meier Curves for Disease-free and Overall Survival.

Tam X 5 yr | Tam X 5-10 yr

yr	AI X 5-10 yr or Tam X 5-10 yr
10 yr	or Tam X 5 yr to AI X 5 yr
yr to yr	

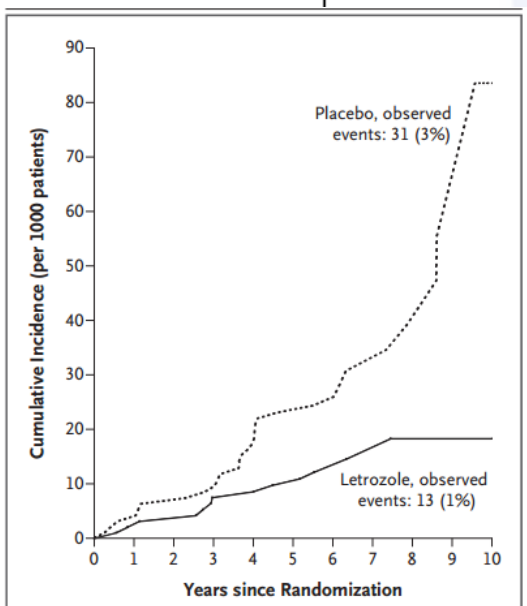


Figure 2. Cumulative Incidence of Contralateral Breast Cancer.

n engl j med 375;3 July 21, 2016

TARGETED THERAPIES

- While oncology of the 80s and 90s has been dominated by cytotoxic drugs, after 2000 there has been a progressive shift towards the so-called TARGETED THERAPIES with the hope to achieve the “CURE” of Cancer

May 28, 2001

WHICH RATIONALE?

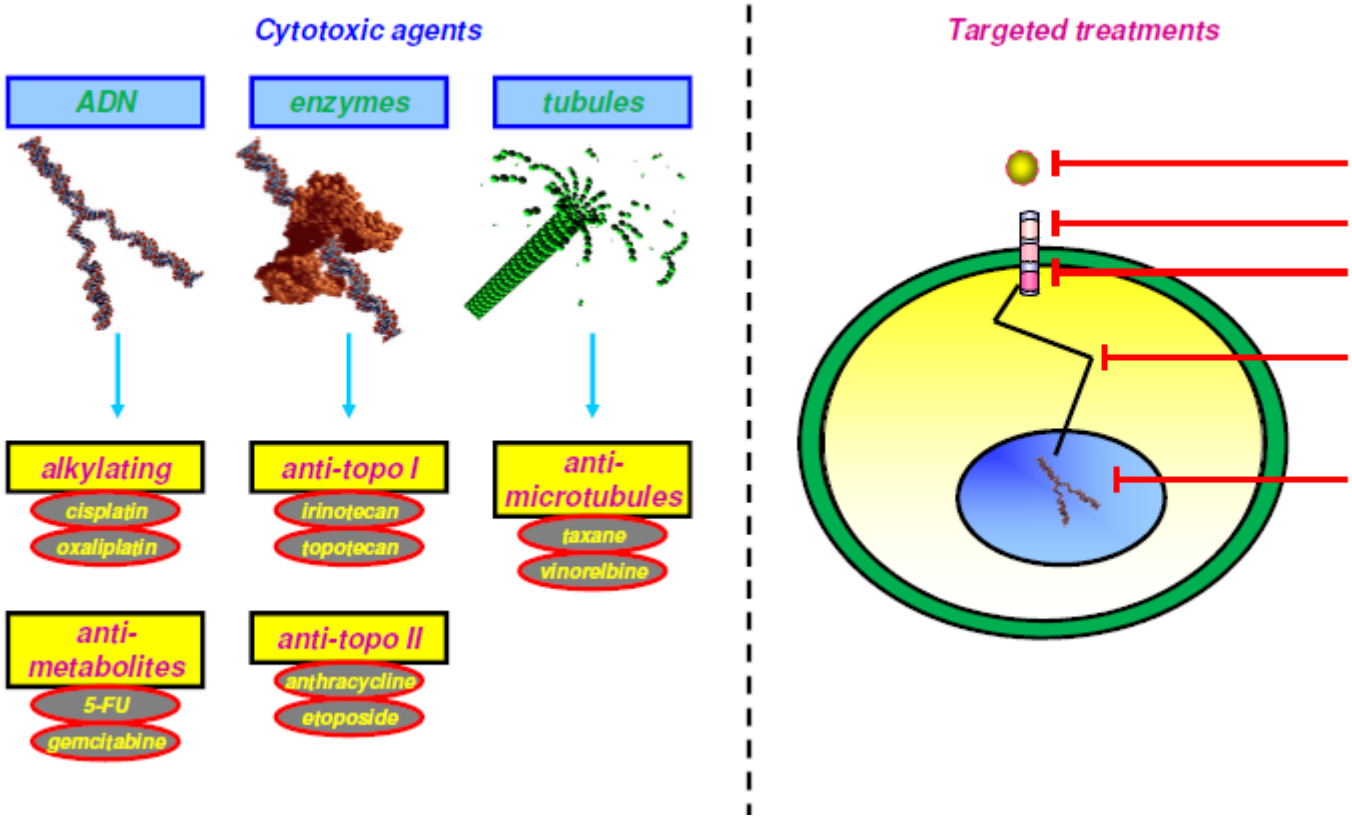
If we find the specific gene alteration responsible for cancer progression (oncogene)

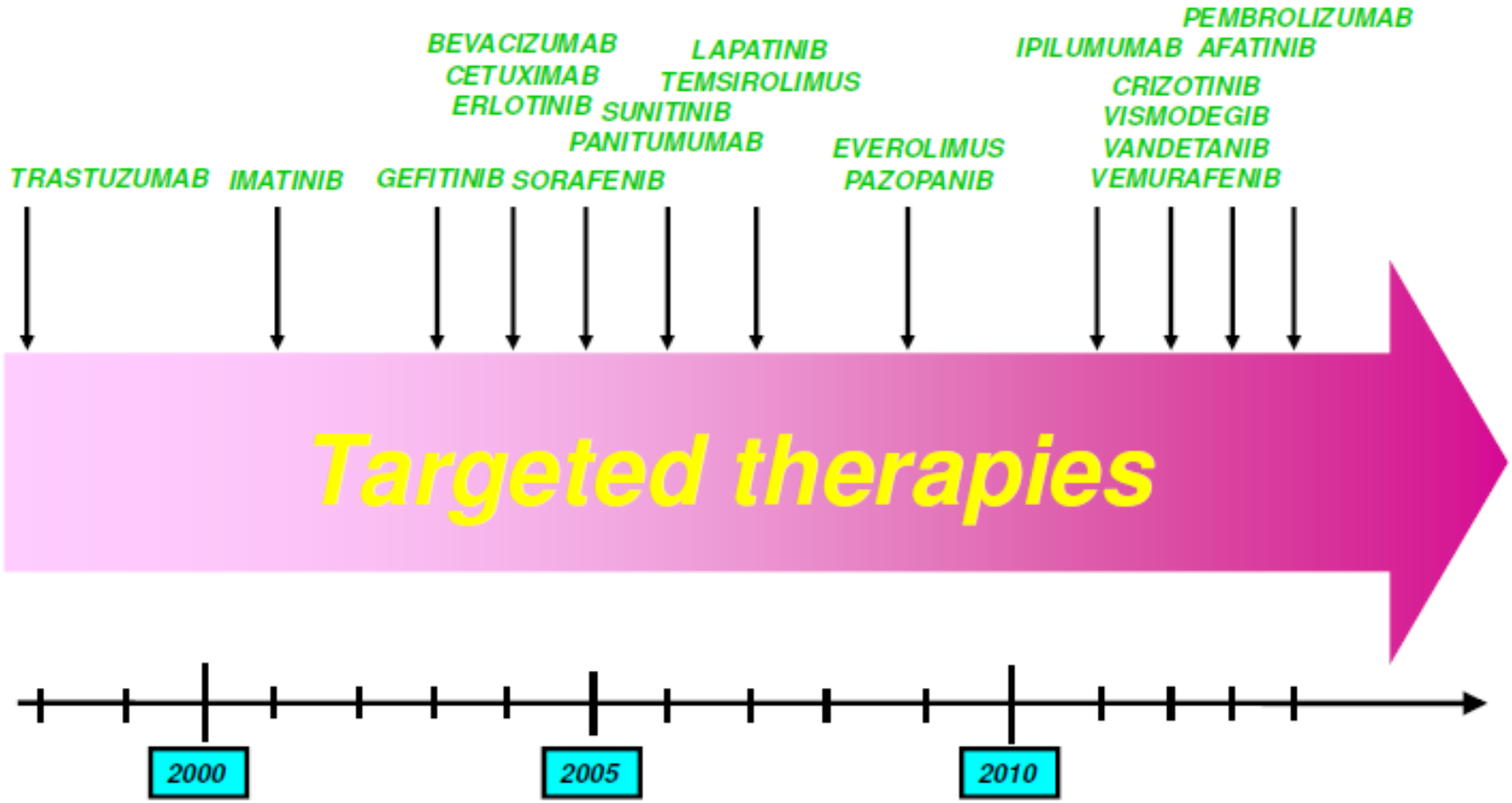
Design a compound that specifically blocks the oncogene without relevant interactions with other proteins

We can stop tumor progression and hopefully cure the cancer without relevant toxicities for the patient

"Standard" vs "innovative" treatments

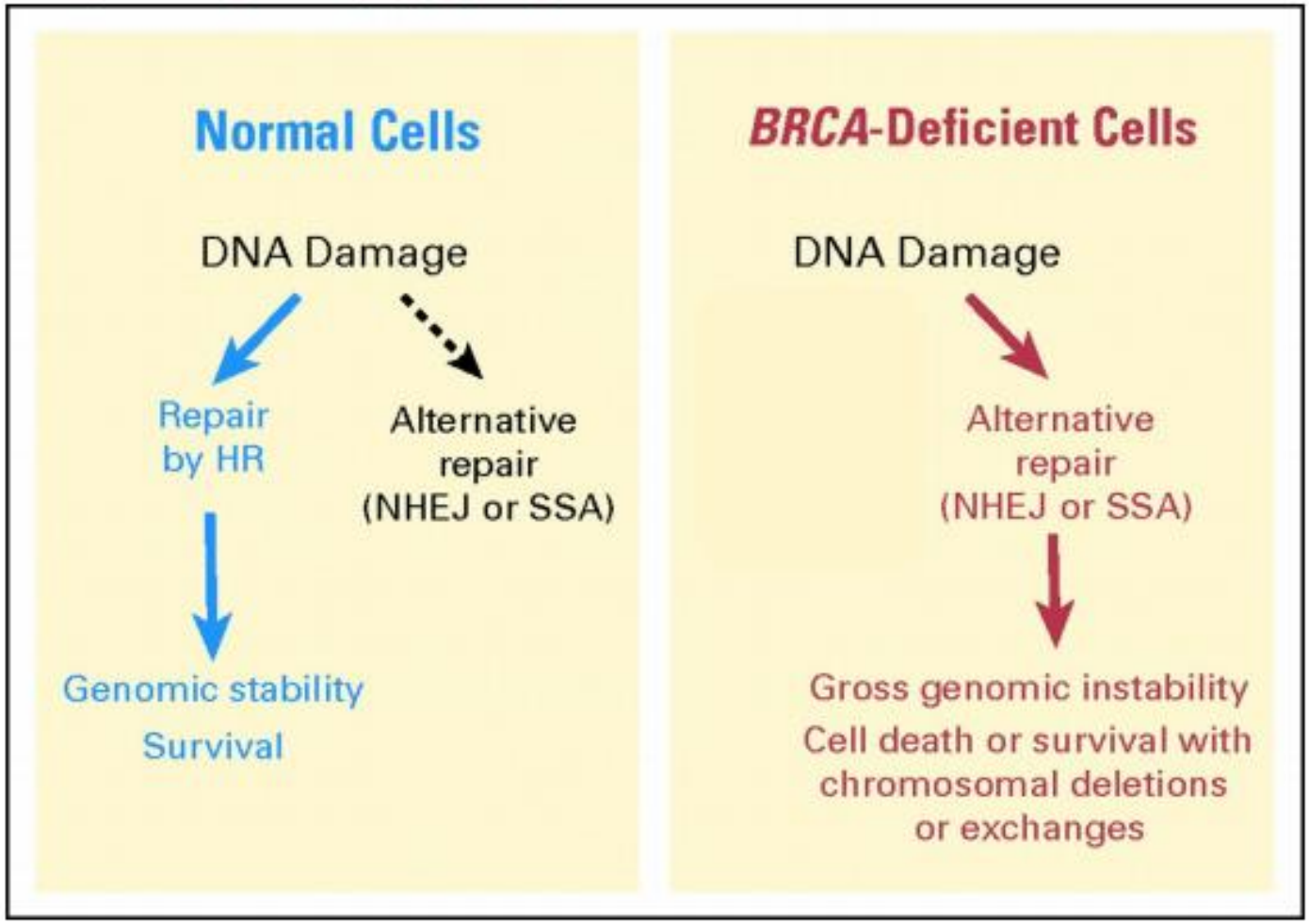
- Cancer = genetic disease – Succession of genome alterations




PEMBROLIZUMAB
BEVACIZUMAB
LAPATINIB
IPILUMUMAB
AFATINIB
CETUXIMAB
TEMSIROLIMUS
CRIZOTINIB
ERLOTINIB
SUNITINIB
VISMODEGIB
PANITUMUMAB
EVEROLIMUS
VANDETANIB
TRASTUZUMAB
IMATINIB
GEFITINIB
SORAFENIB
PAZOPANIB
VEMURAFENIB
Targeted therapies
2000
2005
2010

Targets	Targeted theapy	Tumour type	Biomarker
EGFR	Erlotinib/Gefitinib Cetuximab/Panitumumab Cetuximab	Lung Colon H&N	Mutation EGFR Mutation KRAS -
HER-2	Trastuzumab/TDM-1 Lapatinib/Pertuzumab Trastuzumab	Breast Breast Stomach	Amplification HER2 Amplification HER2 Amplification HER2
mTOR	Temsirolimus/Everolimus Everolimus	Kidney Endocrine tumours	- -
c-Kit	Imatinib	GIST	Over expression c-Kit
SMO	Vismodegib	Basocellular carcinoma	-
VEGF(R)	Bevacizumab Sunitinib Sorafenib	Breast, kidney, colon, lung Kidney, endocrine tumours Kidney, hepatocarcinoma	- - -
HDAC	Vorinostat	Cutaneous lymphoa	-
NF-κB	Bortezomib	Multiple myeloma	-
CTLA4	Ipilumumab	Melanoma	-
RAF	Vemurafenib	Melanoma	Mutation V600E BRAF
ALK	Crizotinib	Lung	Translocation ALK
RET	Vandetanib/Cabozantinib	Thyroid medullary carcinoma	-

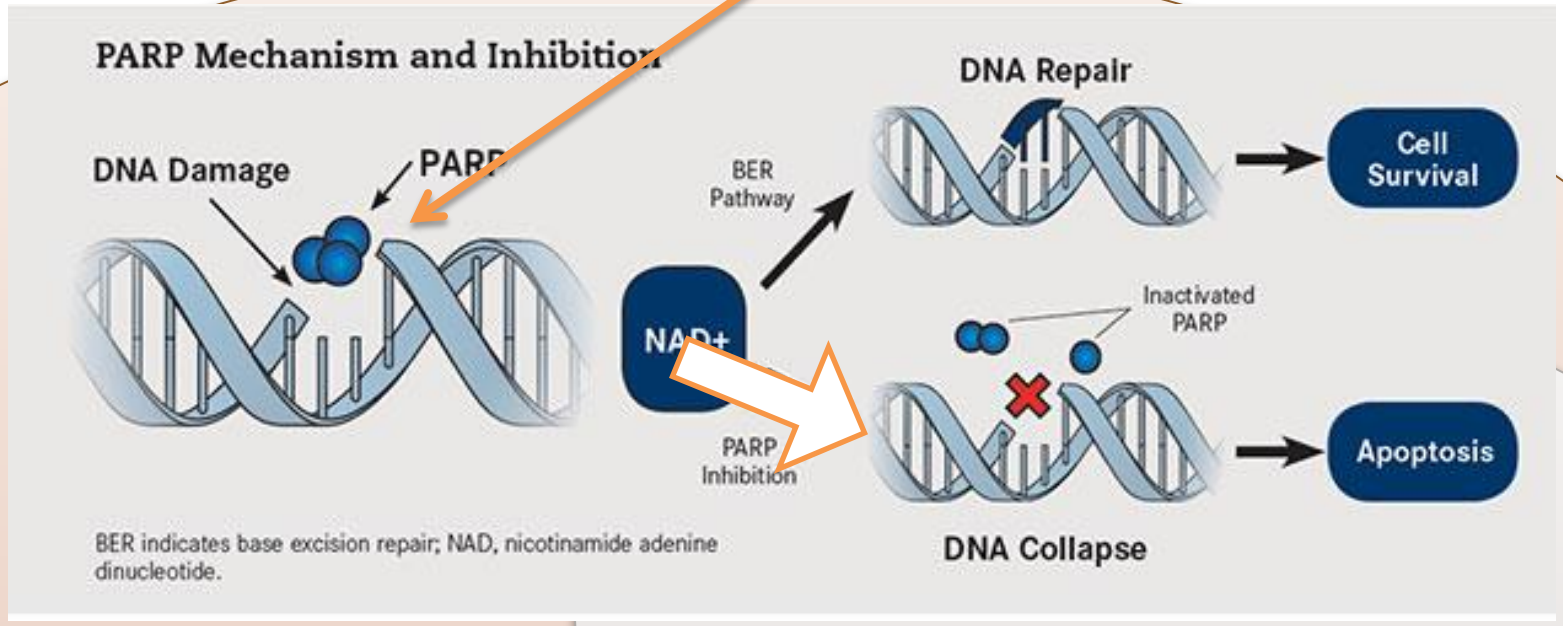
Synthetic lethality: PARP inhibition in patients with BRCA mutations

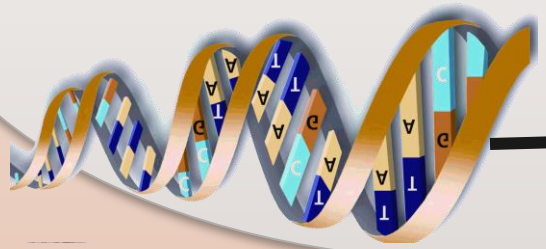


Ashworth A JCO 2008;26:3785-3790

PARP inhibition
poly ADP ribose polymerase

Olaparib, veliparib





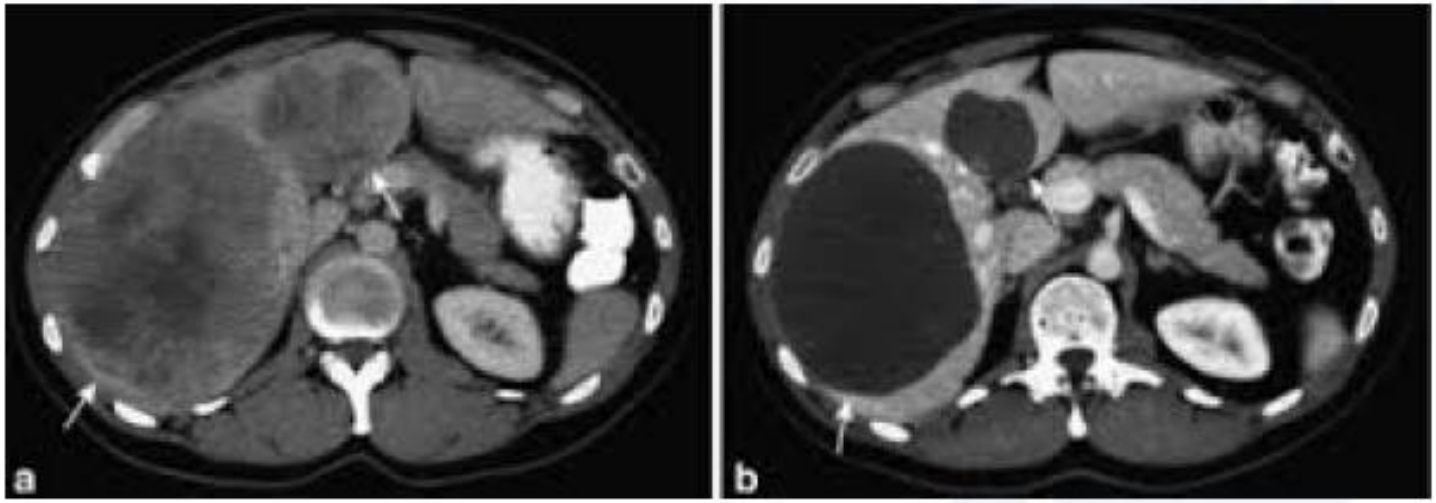
Secretion

Proliferation

Survival

RECIST criteria VS Targeted therapy
Computed Tomography-Based Tumor Density

- So-called “Choi criteria”
- Used in assessing tumor response in GIST, renal cell cancer, or hepatocellular cancer based on density on CT scans
- This variation was prompted by the evident response to treatment with imatinib but with minimal tumor shrinkage
- Still considered exploratory in GIST, and it is too soon to know of benefits in other histology.



BUT HOPES HAVE NOT BEEN COMPLETELY FULLFILLED..

BOOK REVIEW

Cancer Biology & Therapy 14:12, 1189–1190; December 2013; © 2013 Landes Bioscience

Are we losing the war on cancer?

Wafik S El-Deiry

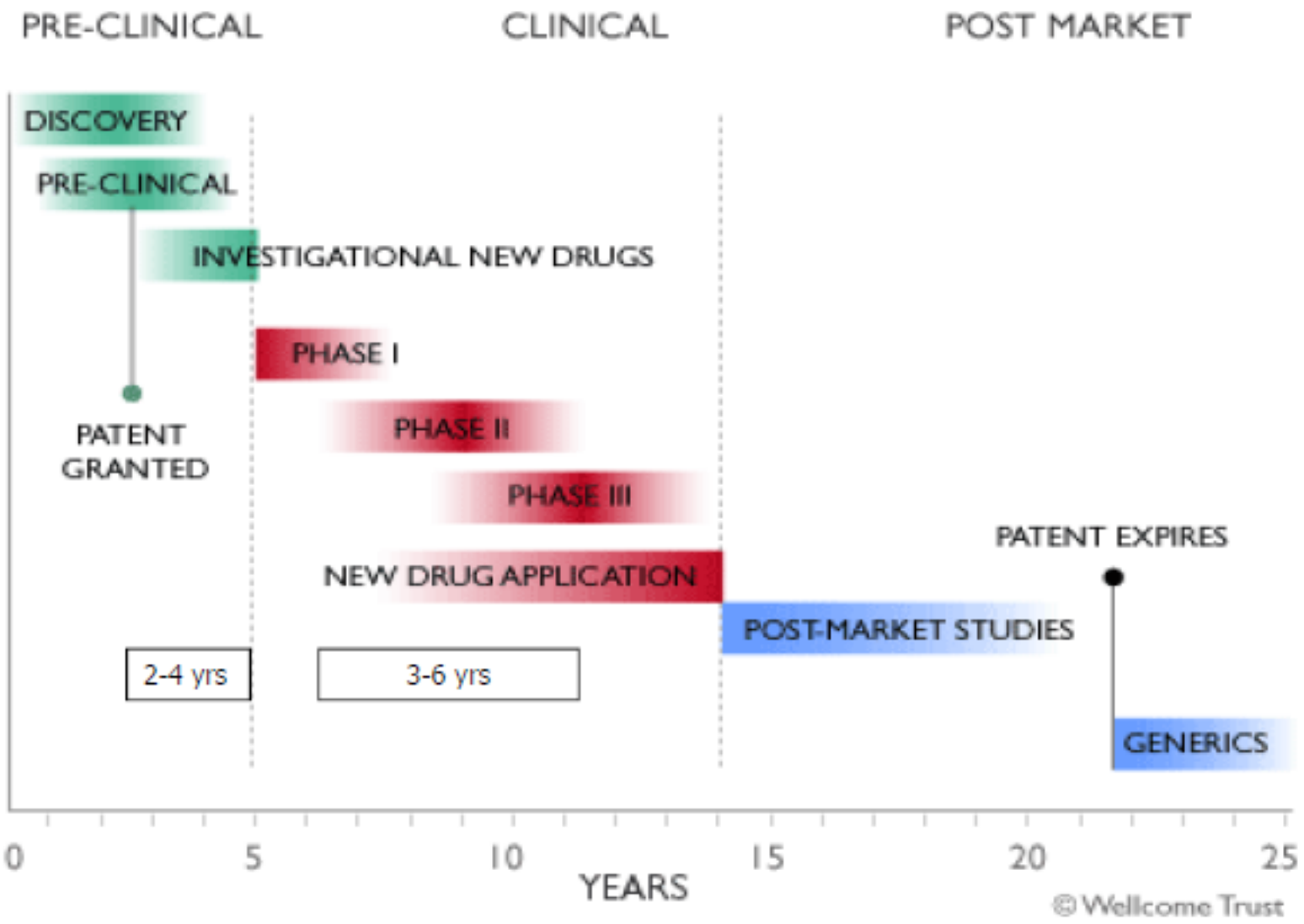
Department of Medicine; Division of Hematology/Oncology; Penn State Hershey Cancer Institute; Hershey, PA USA

Clinicians and scientists in the 21st century in the modern era of cancer care see many great advances moving from the lab to the clinic with demonstrated impact on overall survival of patients with cancer

Without any doubt a lot of progress has been made and continues to be made, and Leaf spends quite a bit of effort in the book studying and speaking to many of those who have made groundbreaking

New targeted therapies may prolong life, but most patients with advanced solid cancer continue to die.

Drug Development time line




LOOK
WHAT'S
NEW!


TRUMP CAN WIN. REALLY
Newsweek
19.07.2016-05.08.2016
CHASING CANCER CLUSTERS
DEATH BY STIGMA
SPECIAL HEALTH ISSUE
CURING CANCER
THE TRANS TRAGEDY
THE WAR OVER PATIENT DATA
DISCRIMINATION ON THE RESERVATION


OUTLOOK
Haemophilia
nature
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
Antitumour immunity enhanced by inhibiting PD-L1/PD-1 and identifying mutant neo-antigens
PAGES 496, 558, 563, 568, 572 & 577
IMMUNE-CHECKPOINT BLOCKADE IN CANCER
PEER REVIEW
ACCEPT YOUR OWN PAPER
How some scientists are duping the system
PAGE 480
MICROSCOPY
THE CASE FOR AIMING HIGHER
Atomic resolution is there for the taking
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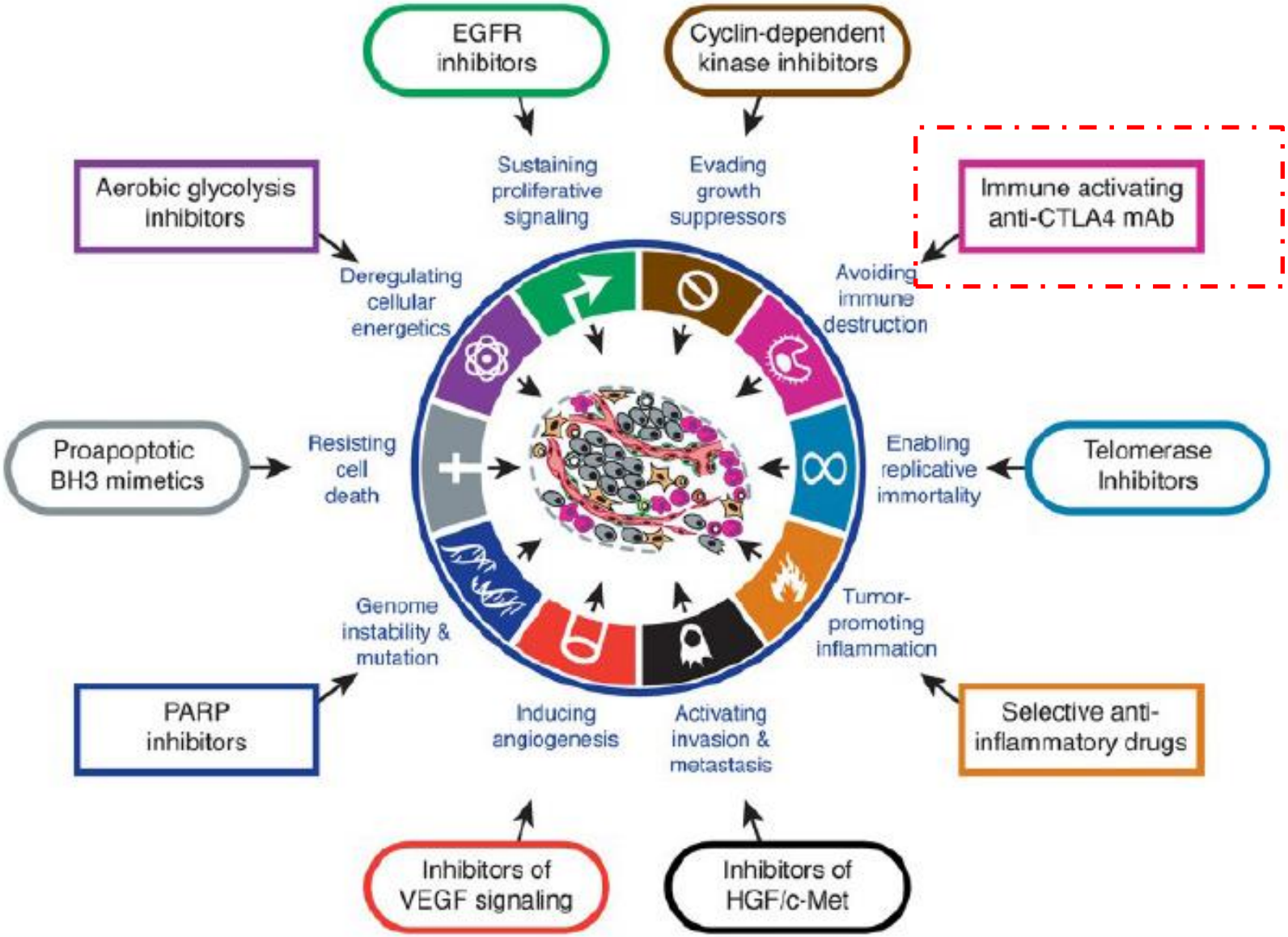
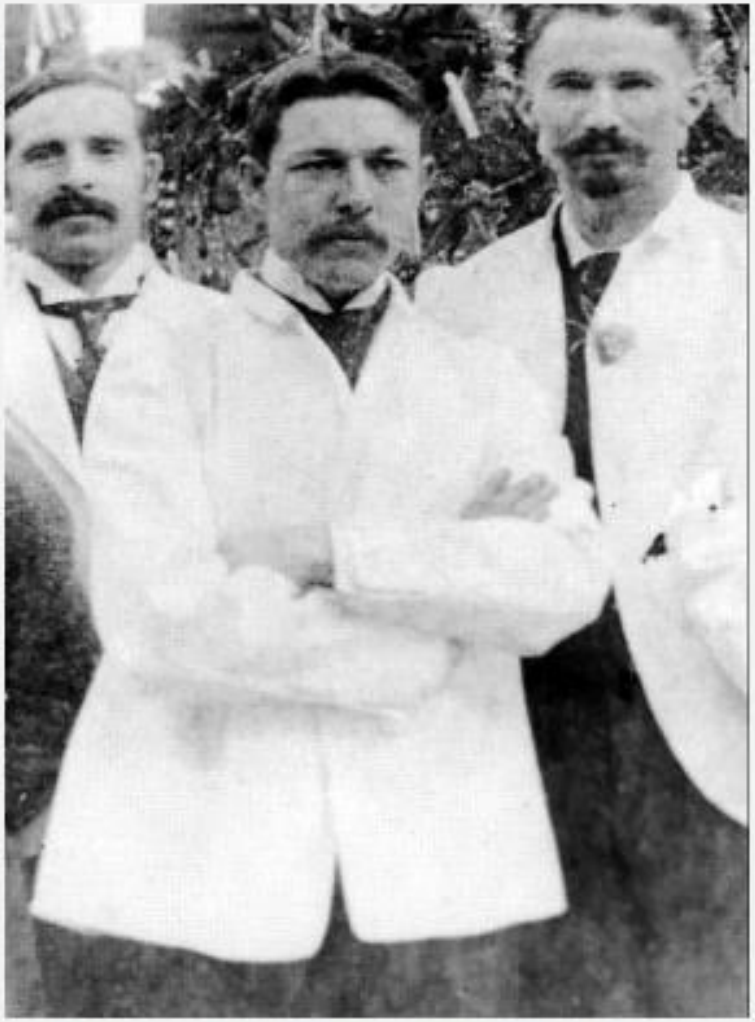


Hanahan D, Weinberg RA. Cell 2011, 144, 646

Cancer immunotherapy



William Coley, the "father of immunotherapy."
(Wikimedia Commons)

1890s
First cancer vaccine developed (Coley)

1953
Coley's work f
published

Renaissance Phase
1997-

2004
Avastin &
Cetuximab
Approved

2006
Panitumumab
Approved

2011
-Peg IFN approved
(adjuvant)
-Ipilimumab/Anti
CTLA-4 approved for
advanced
melanoma

2000s

2011

2010
First cellular
immunotherapy
approved
for prostate
cancer
(Provenge)

Kirkwood JM et al. CA Cancer J Clin 2012, 62, 309-35

cancer immunotherapy

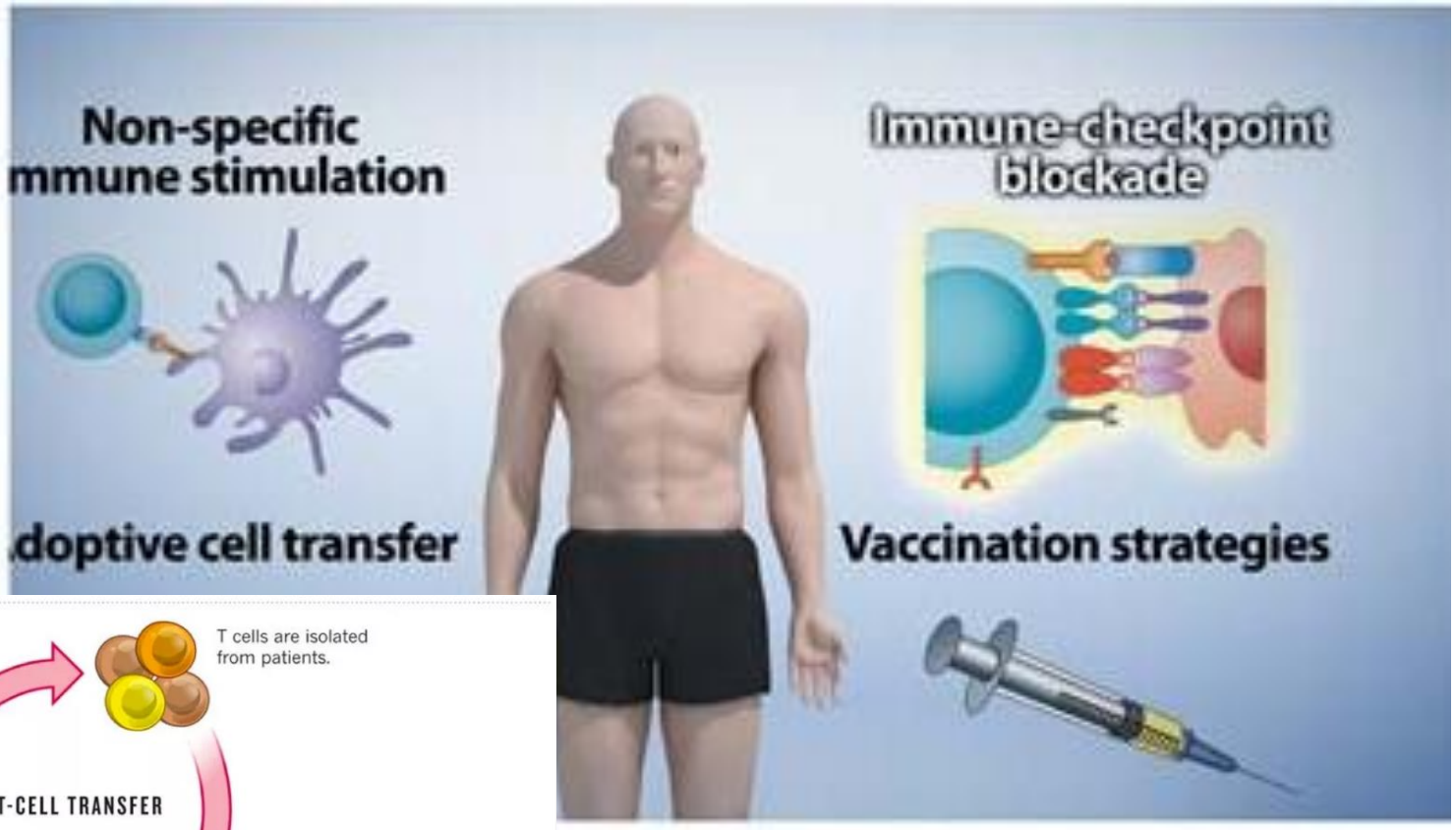
- This can be done in a couple of ways:

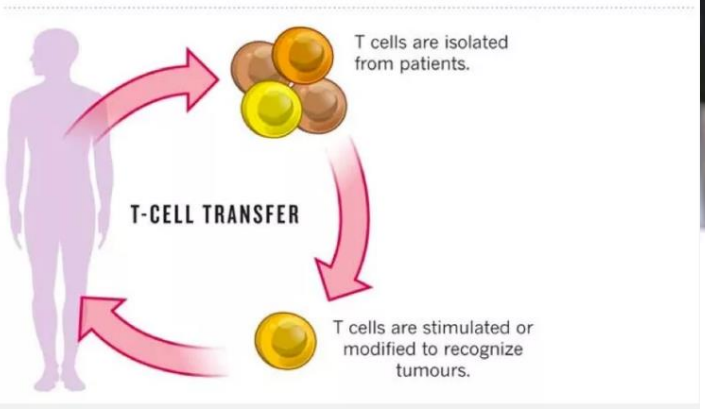
- Stimulating your own immune system to work harder or smarter to attack cancer cells
- Giving you immune system components, such as man-made immune system proteins

- Some types of immunotherapy are also sometimes called biologic therapy or biotherapy.

Mechanism of immunotherapy

IFN
IL-2





BCG
Prsotvac

Biological therapy

Biological response modifiers (BRMs):

They change the way the body's defenses interact

with cancer cells.

- boost the body's ability to fight the disease.
- direct the immune system's disease fighting powers to disease cells.
- strengthen a weakened immune system.

Biological therapy

1-Interferons (IFN)

- A type of BRM that naturally occurs in the body.
- They have been shown to **improve the way a cancer patient's immune system acts against cancer cells**.
  - INFs may work directly on cancer cells to **slow their growth**,
  - they may cause cancer cells to change into cells with more normal behavior.
- Some INFs may also stimulate natural killer cells, T cells, and macrophages.

Biological therapy

2-Interleukins (IL): (Aldesleukin)

– Proteins (cytokines) that occur naturally in the body

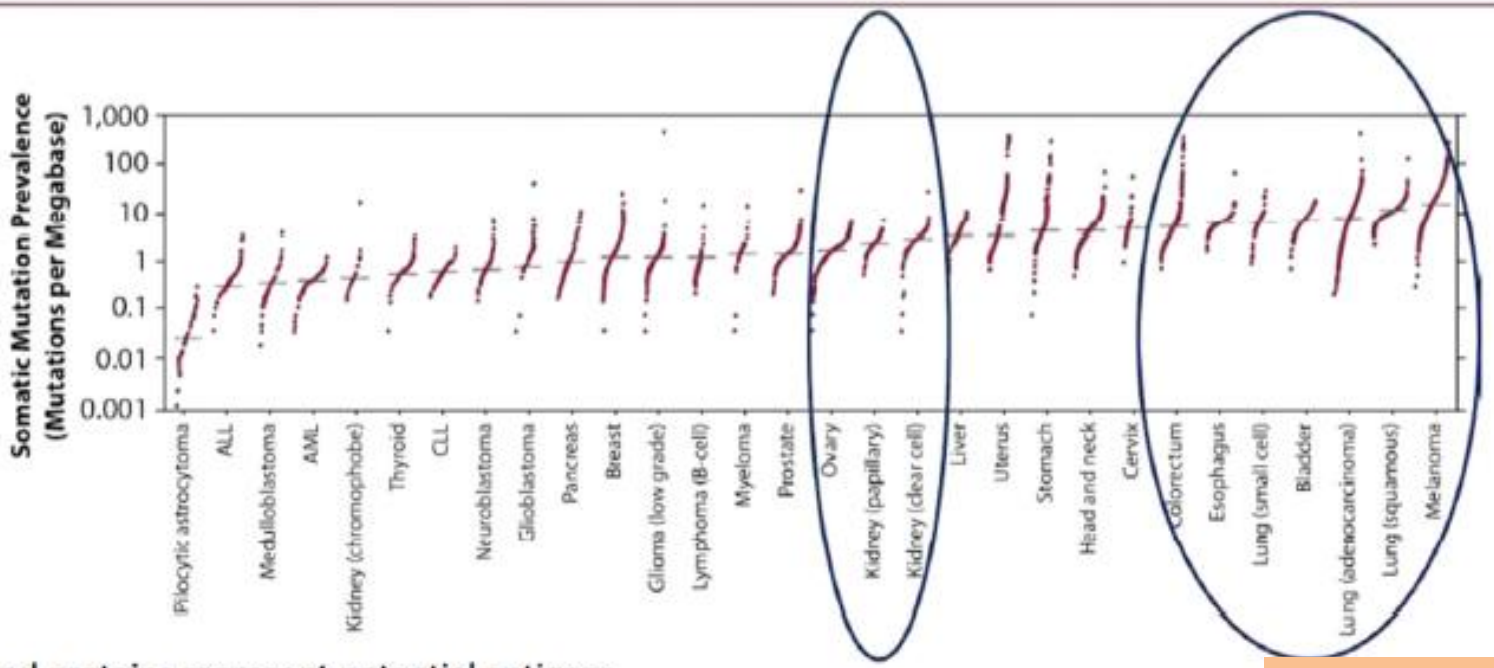
– stimulate the growth and activity of immune cells, such as lymphocytes, which work to destroy cancer cells

Conditions for immunotherapy to work

1. functional immune system
2. minimal mass
3. immunogenicity

PREVALENCE OF DNA MUTATIONS IN CANCER

Most Cancers Have Mutations[1]



- Mutated proteins represent potential antigens
  - Targets for immune recognition and destruction
- Tumors with more mutations appear more likely to respond to PD-1 blockade

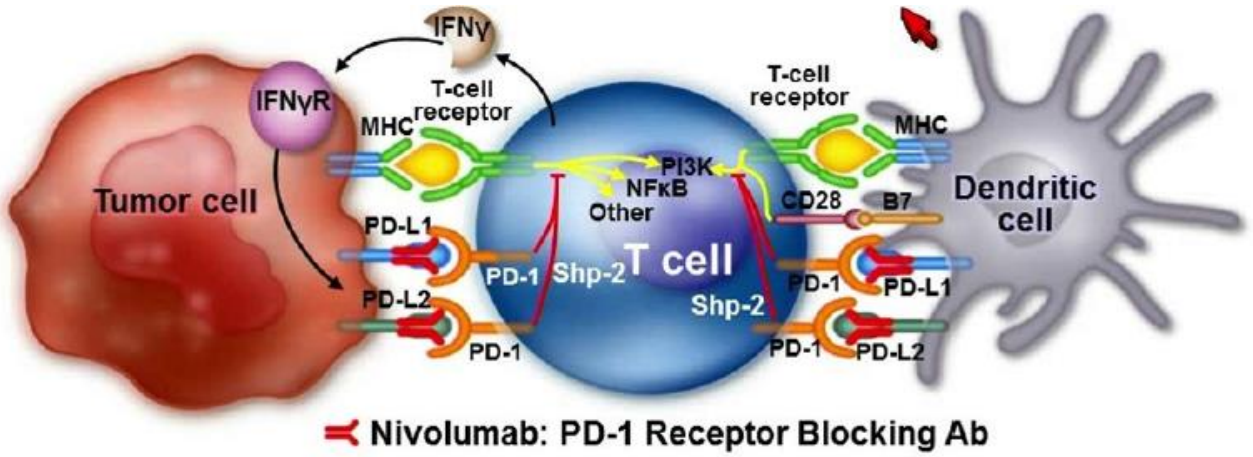
1. Lawrence MS et al. *Nature*. 2013;499:214-218.

RCC
Ovary

- Melanoma
- Lung
- Bladder
- Esophagus
- Colon

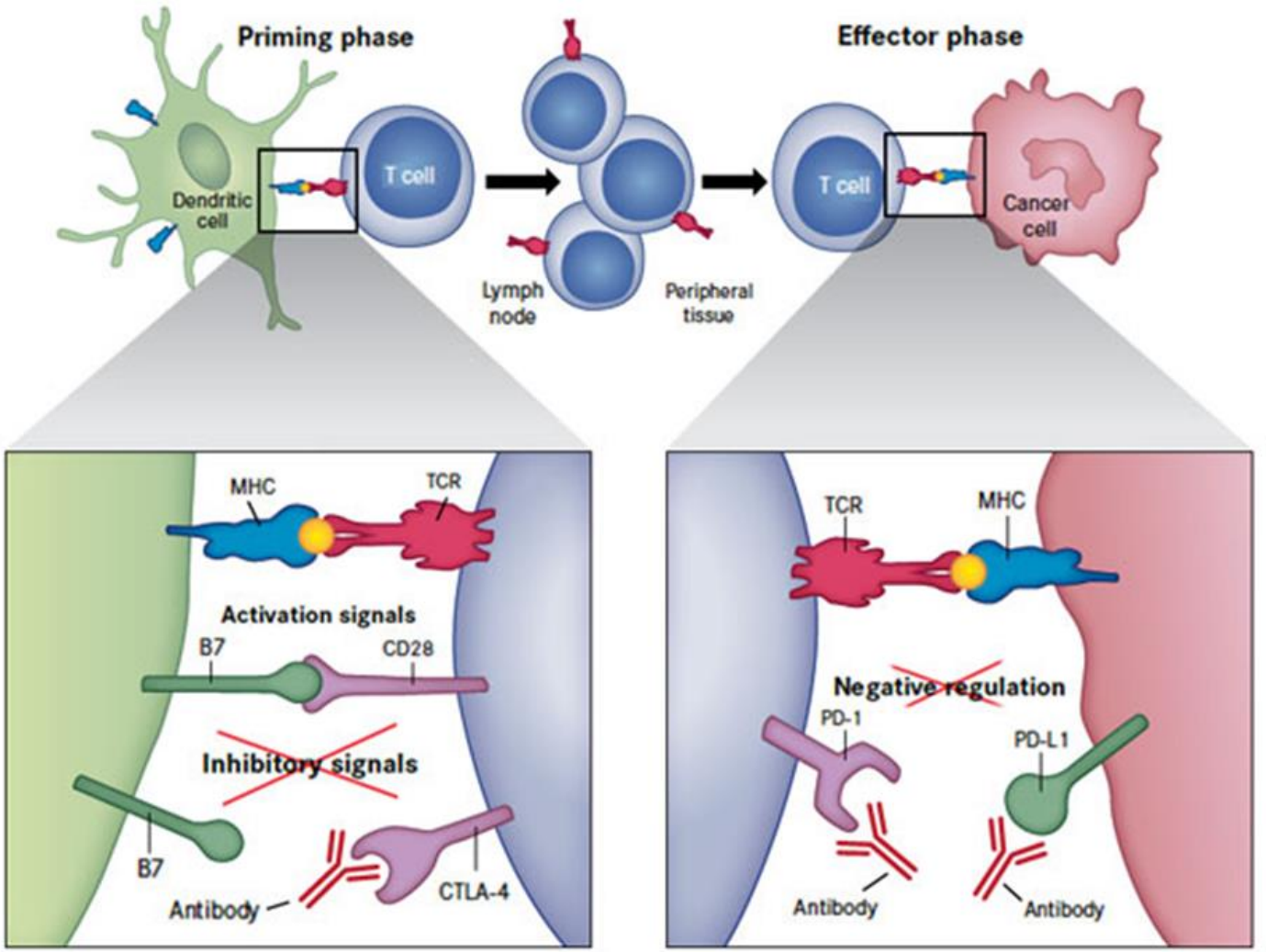
The PD1- PDL-1 system

- PD-1: protein on the surface of T-lymphocytes
- PD-L1: tumor cells, macrophages, dendritic cells, etc..

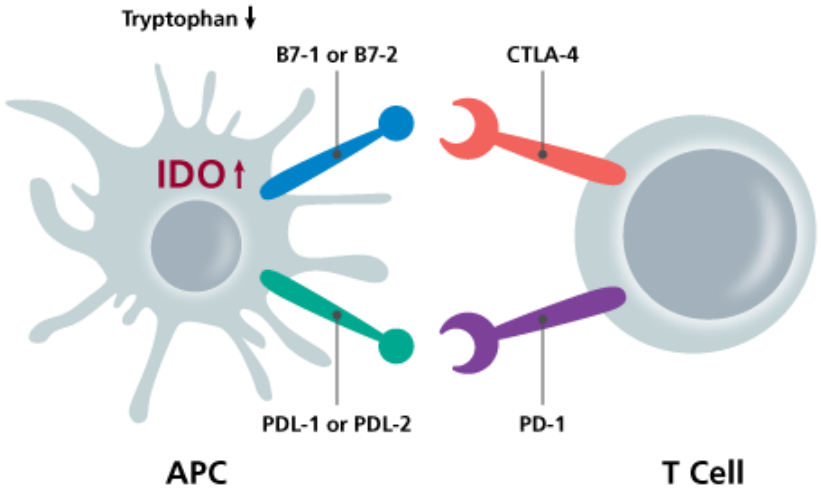


Physiologic role (modulated by gamma-Interferon): taper down immune response after resolution of infections in order to prevent auto-immunity.

PD1, PDL-1, CTLA-4



Key Immune Checkpoints



IDO is one of several immune response checkpoints that may be involved in tumor immune escape. Increased IDO expression by antigen presenting cells leads to tryptophan depletion, resulting in antigen-specific T-cell anergy, and regulatory T-cell recruitment.

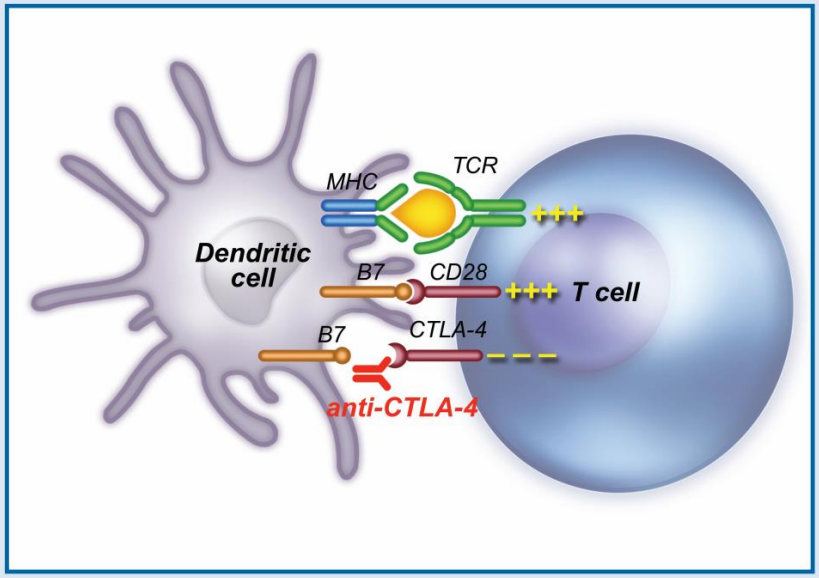


Figure 1. Ipi Blocks Negative Signaling of CTLA-4

IPILIMUMAB IN MELANOMA

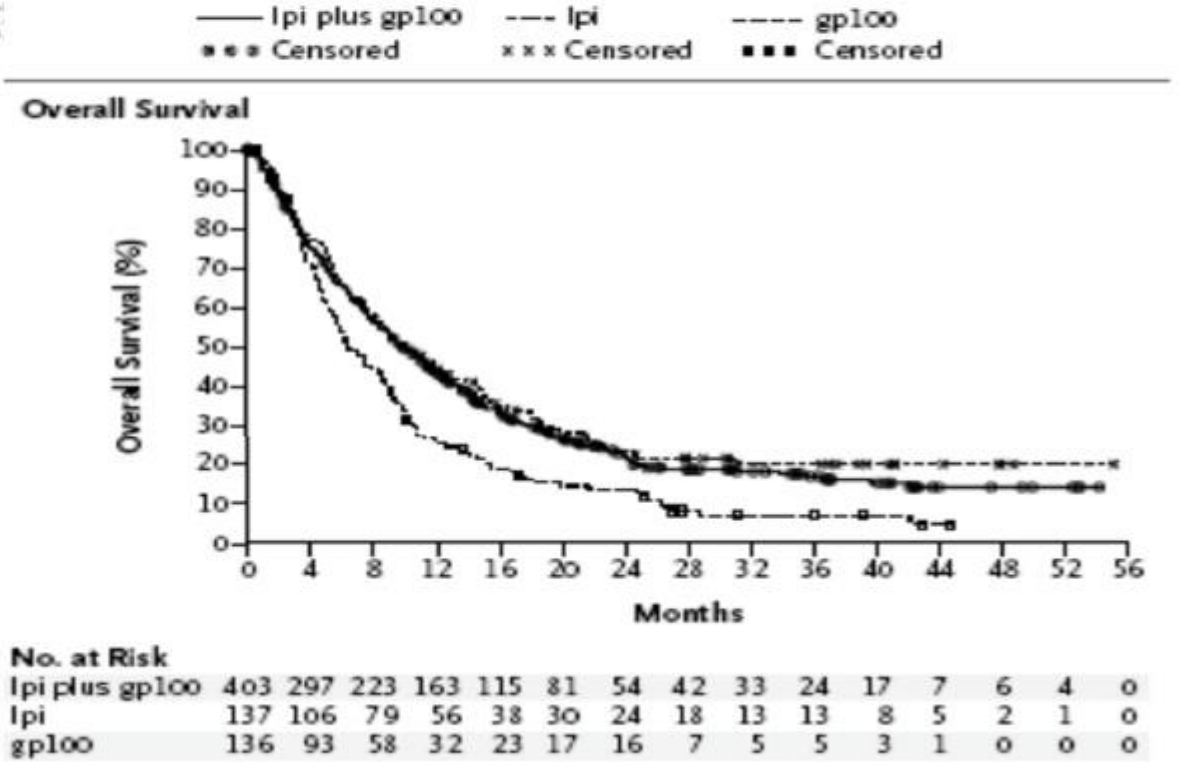
The NEW ENGLAND JOURNAL of MEDICINE

AUGUST 19, 2010

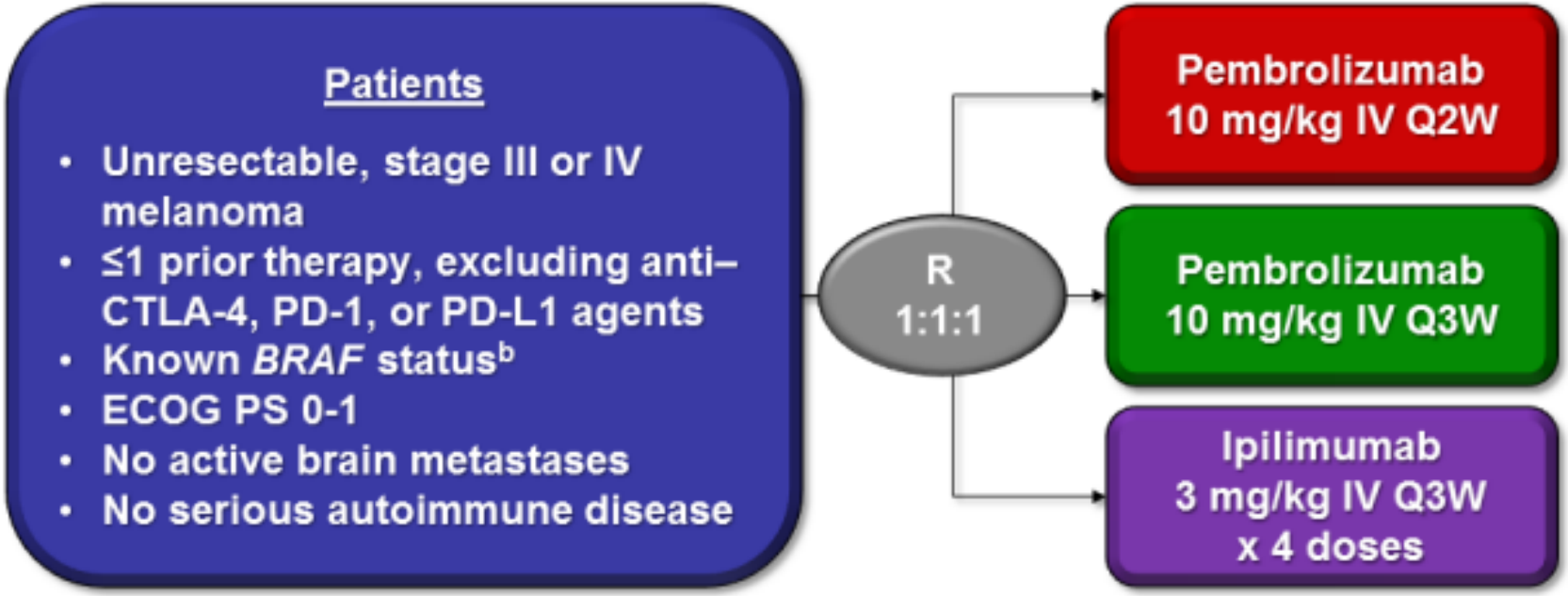
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, Christian H. Ottensmeier, M.D., Ph.D., Celeste Lei Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph. Michael J. Yellin, M.D., Geoffrey M. Nichol, M.S., Ch.B.

10.0 vs 10.1 vs 6.4 months



KEYNOTE-006 (NCT01866319): International,[a] Randomized, Phase III Study



Stratification factors:
- ECOG PS (0 vs 1)
- Line of therapy (first vs second)
- PD-L1 status (positive[c] vs negative)

- Primary end points: PFS and OS
- Secondary end points: ORR, duration of response, safety

[a]Patients enrolled from 83 sites in 16 countries.
[b]Prior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.
[c]Defined as membranous PD-L1 expression in ≥1% of tumor cells as assessed by IHC using the 22C3 antibody.

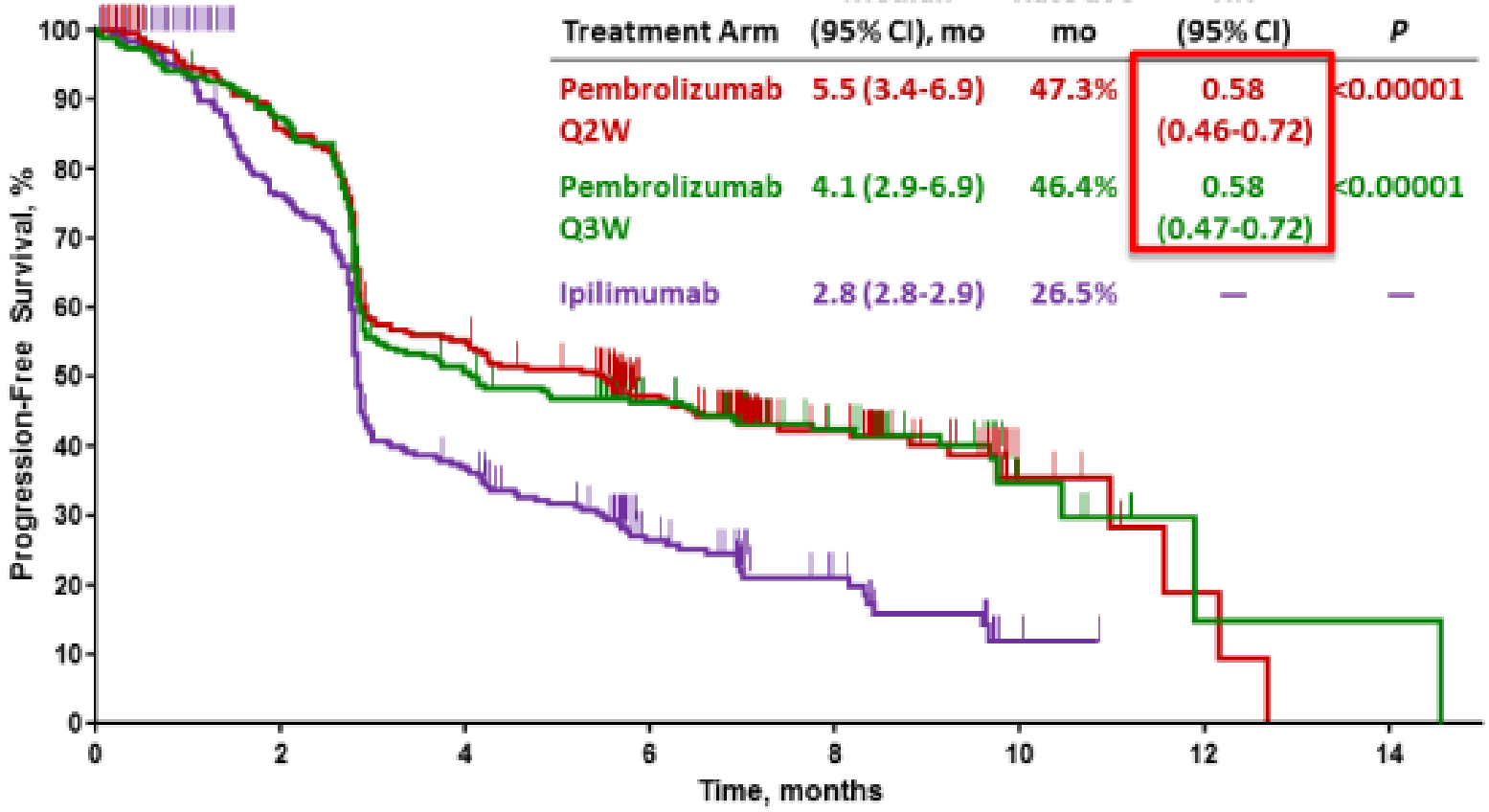
Tumor Response at the First Interim Analysis (RECIST v1.1, Central Review)

	Pembrolizumab Q2W n = 279	Pembrolizumab Q3W n = 277	Ipilimumab n = 278
ORR (95% CI)	33.7% (28.2-39.6)	32.9% (27.4-38.7)	11.9% (8.3-16.3)
Best overall response			
Complete response (CR)	5.0%	6.1%	1.4%
Partial response	28.7%	26.7%	10.4%
Stable disease	13.3%	14.1%	16.5%
NonCR/nonPD[a]	4.7%	5.1%	3.6%
Progressive disease (PD)	38.0%	41.2%	48.9%
Not evaluable[b]	7.2%	5.4%	18.3%
No assessment[c]	3.2%	1.4%	0.7%
Ongoing responses	89.4%	96.7%	87.9%
Median duration of response (range), days	251 (42+ to 251)	NR (42+ to 246+)	NR (33+ to 239+)

Δ 21%
x 2,78

*Patients without measurable disease per central review at baseline who did not experience complete response or disease progression.
[b]Target lesion not captured by postbaseline scans or for whom a target lesion was surgically removed.
[c]No postbaseline scan performed or were not able to be evaluated.
Analysis cut-off date: September 3, 2014.

PFS at the First Interim Analysis (IA1)



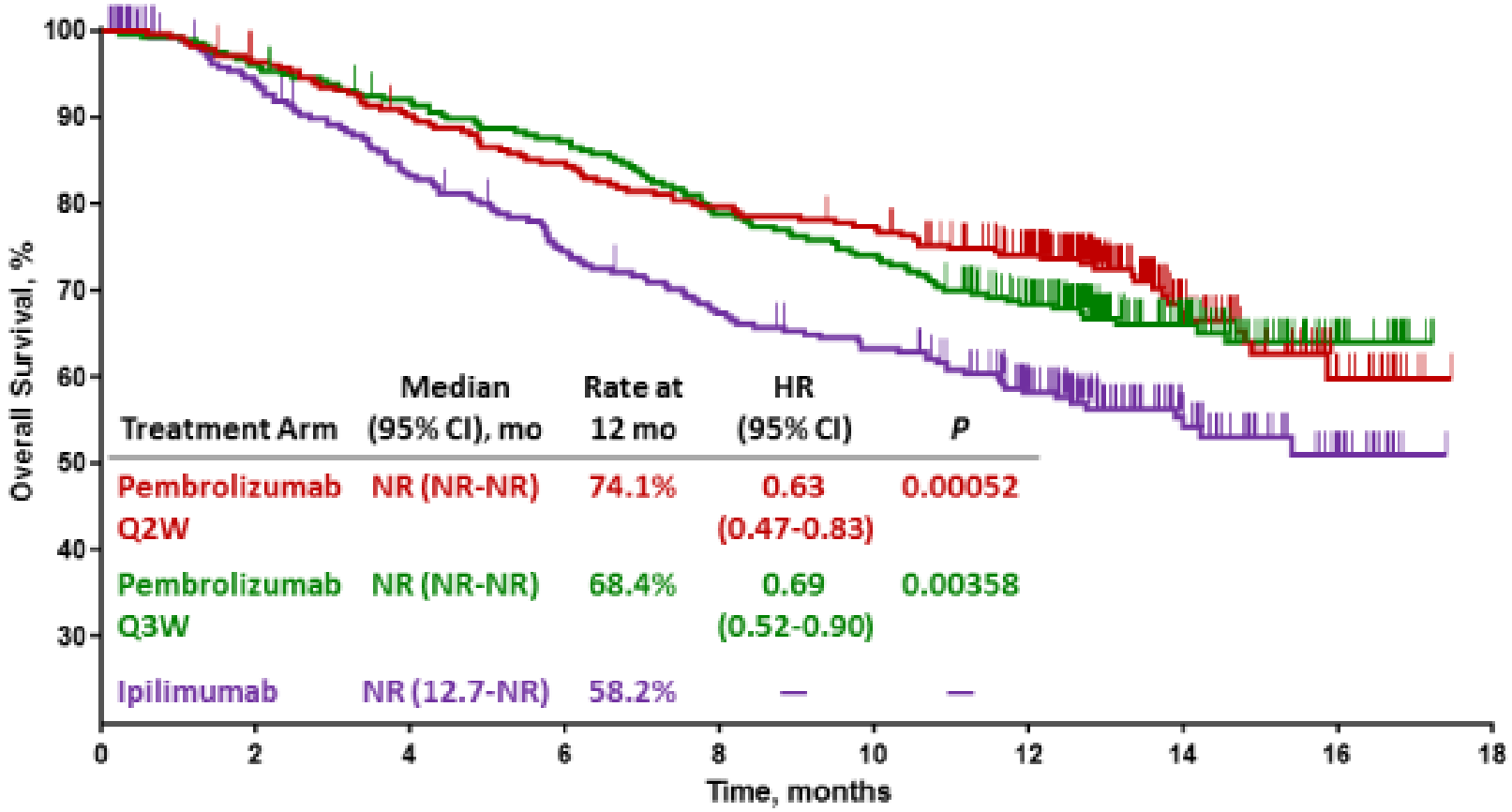
Treatment Arm	Median (95% CI), mo	Rate at 6 mo	HR (95% CI)	*P*
Pembrolizumab Q2W	5.5 (3.4-6.9)	47.3%	0.58 (0.46-0.72)	<0.00001
Pembrolizumab Q3W	4.1 (2.9-6.9)	46.4%	0.58 (0.47-0.72)	<0.00001
Ipilimumab	2.8 (2.8-2.9)	26.5%	—	—

No. at risk

279	231	147	98	49	7	2	0
277	235	133	95	53	7	1	1
278	186	88	42	18	2	0	0

Analysis cut-off date: September 3, 2014.

OS at the Second Interim Analysis (IA2)



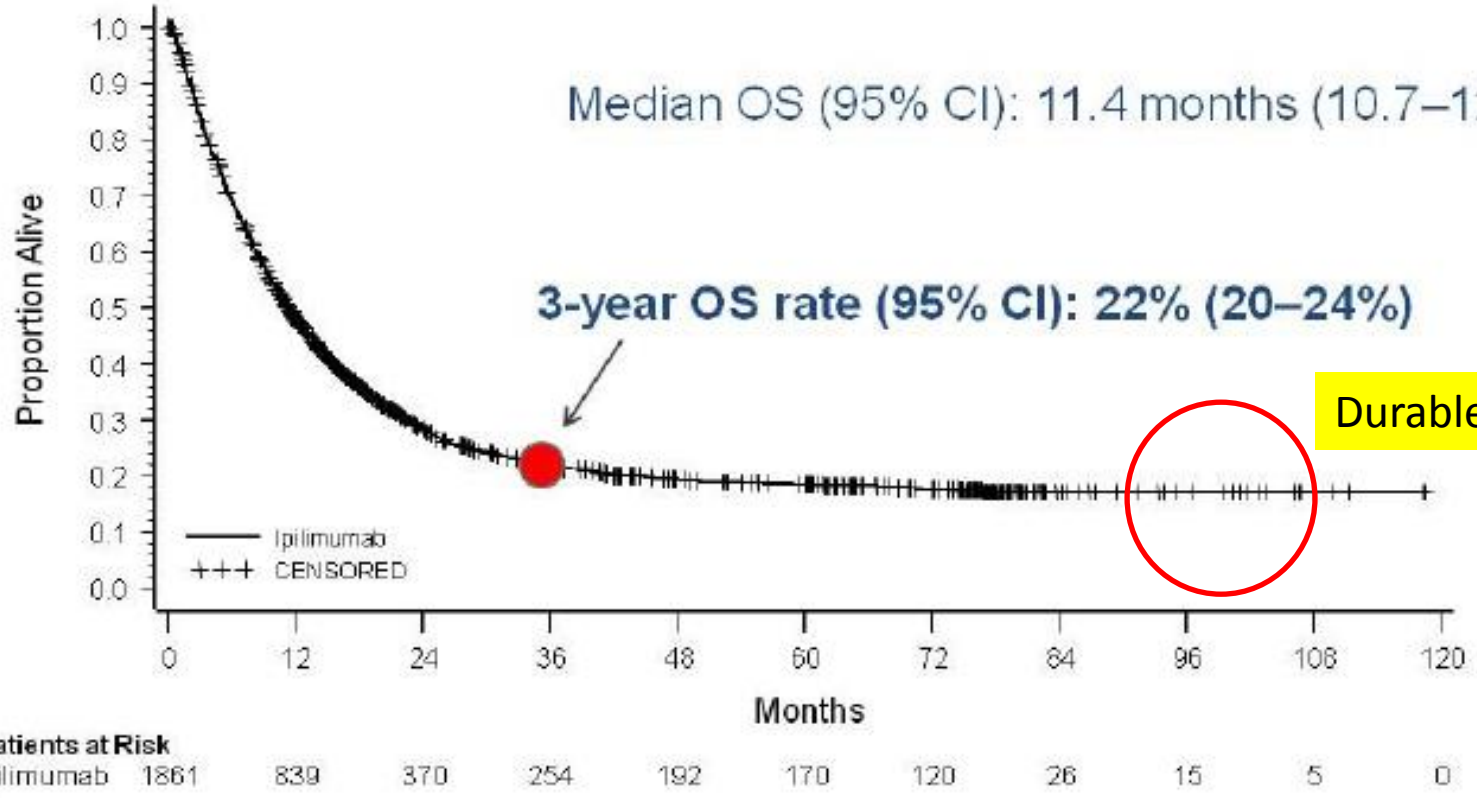
Treatment Arm	Median (95% CI), mo	Rate at 12 mo	HR (95% CI)	*P*
Pembrolizumab Q2W	NR (NR-NR)	74.1%	0.63 (0.47-0.83)	0.00052
Pembrolizumab Q3W	NR (NR-NR)	68.4%	0.69 (0.52-0.90)	0.00358
Ipilimumab	NR (12.7-NR)	58.2%	—	—

No. at risk

279	266	248	233	219	212	177	67	19	0
277	266	251	238	215	202	158	71	18	0
278	242	212	188	169	157	117	51	17	0

Analysis cut-off date: March 3, 2015.

Primary Analysis of Pooled OS Data on Ipilimumab in 1861 Patients



Schadendorf et al, ESMO 2013

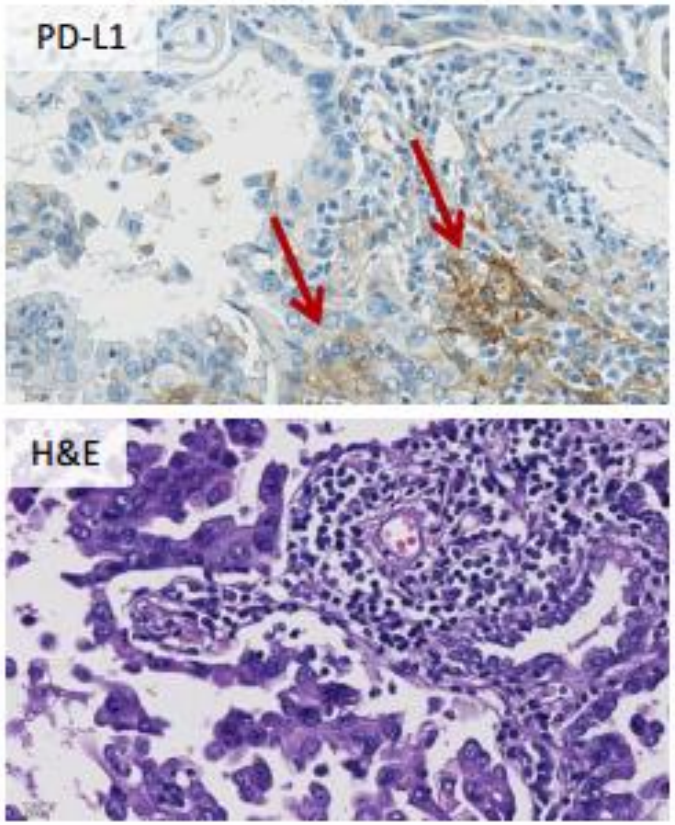
PD-1/PD-L1 inhibitors

	Agent	Type of mAb	Company	Phase
Anti PD-1	Nivolumab	Fully Human IgG4	BMS	Phase III
	Pembrolizumab	Humanized IgG4	MSD	Phase III
Anti PD-L1	Atezolizumab	Engineered Human IgG1	Roche	Phase III
	Durvalumab	Engineered Human IgG1	Medimmune/AZ	Phase III

PD-L1 is Broadly Expressed in NSCLC

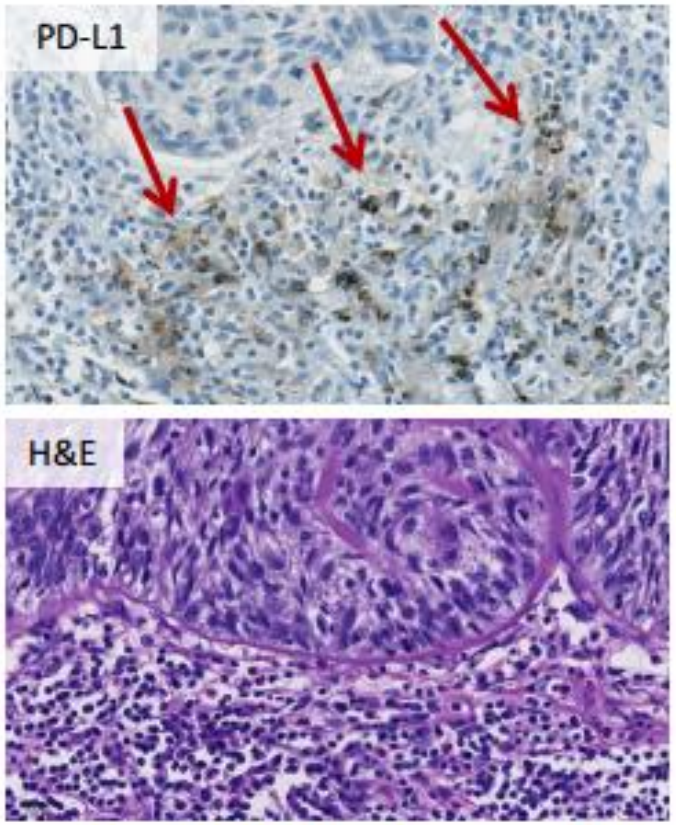
Adenocarcinoma

Prevalence of PD-L1 ≈ 45%



Squamous cell carcinoma

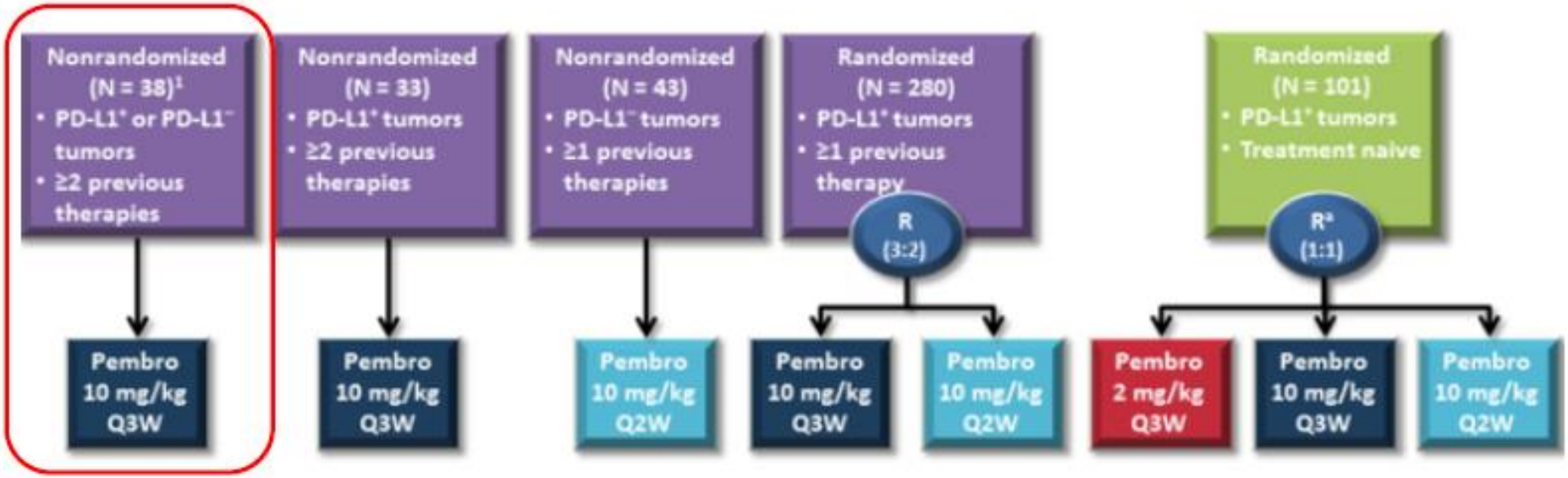
Prevalence of PD-L1 ≈ 50%



Koeppen H. and Kowanetz M., Genentech
Proprietary Genentech/Roche PD-L1 IHC

High sensitivity and specificity in FFPE samples

Keynote - 001 NSCLC



N= 495

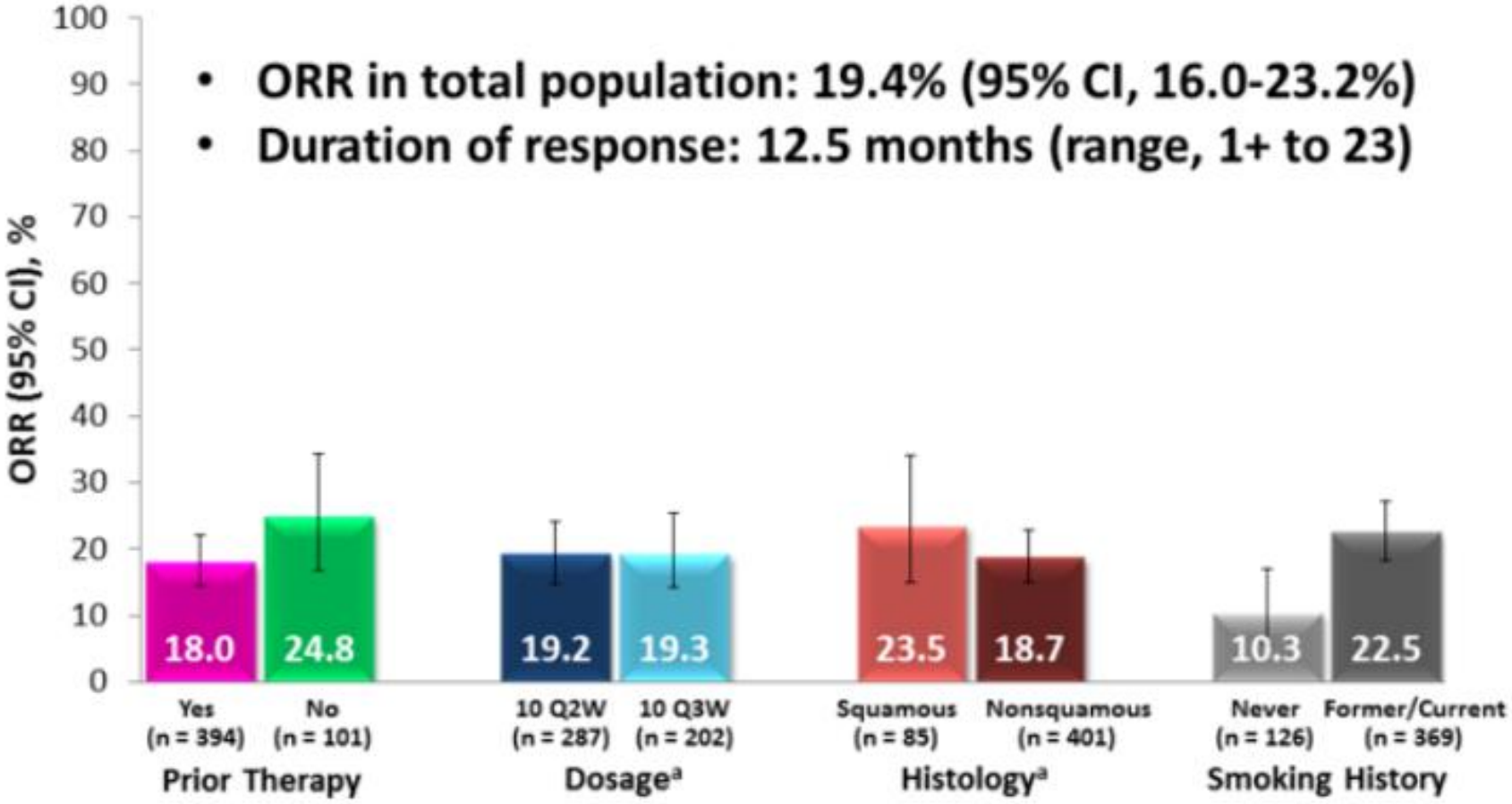
65% of patients received ≥ 2 lines of treatment

Garon et al, NEJM 2015

The Christie
Research Division

Objective Response Rate

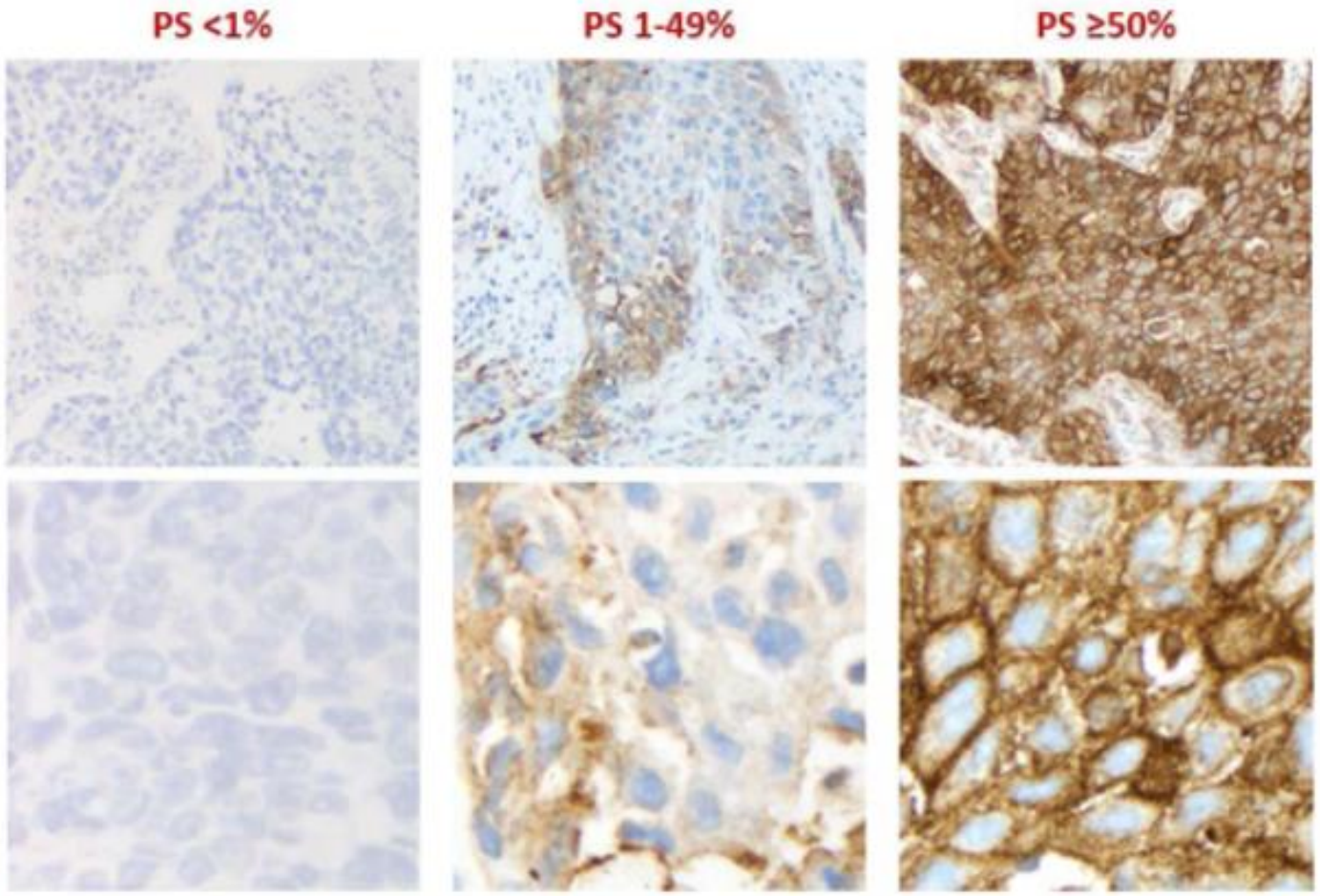
- ORR in total population: 19.4% (95% CI, 16.0-23.2%)
- Duration of response: 12.5 months (range, 1+ to 23)



Garon et al, NEJM 2015

The Christie
Research Division

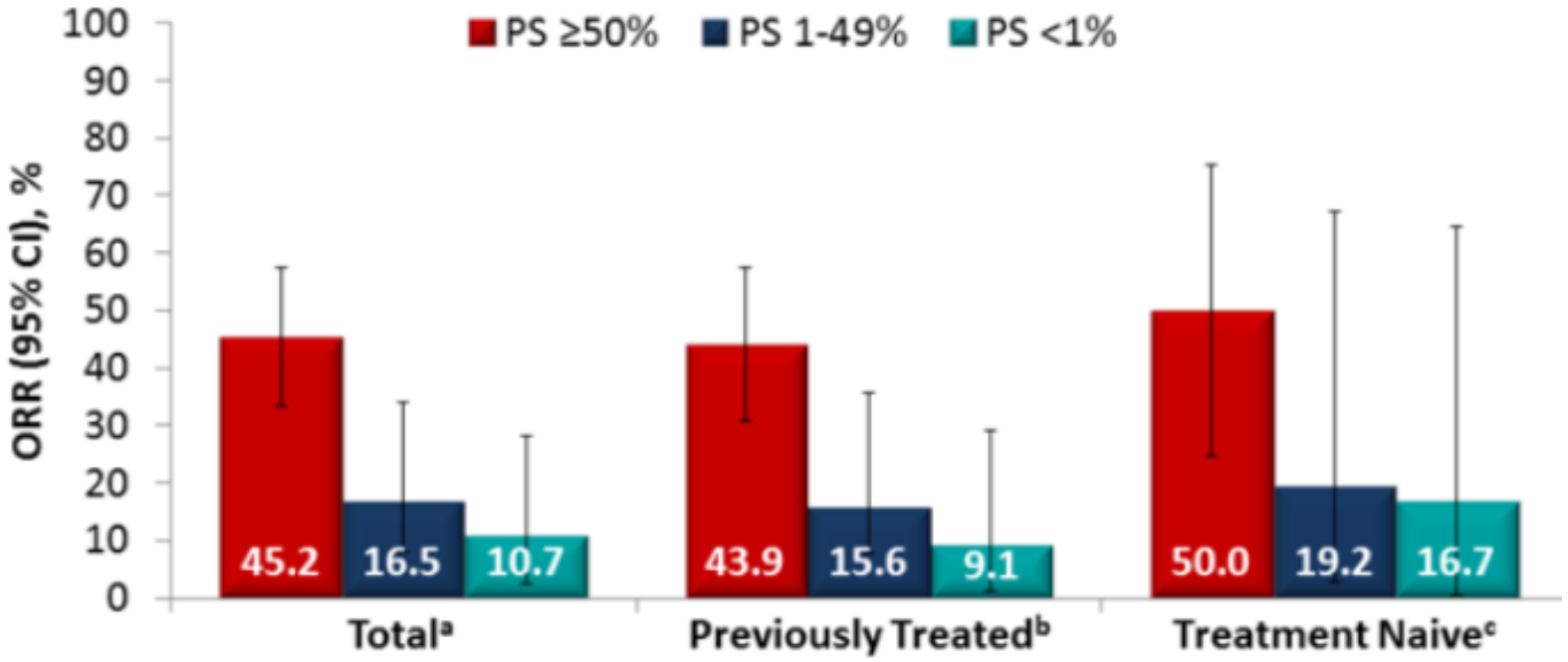
Examples of PD-L1 IHC staining



Garon et al, NEJM 2015

The Christie
Research Division

ORR by PD-L1 proportion score
Pts with measurable disease

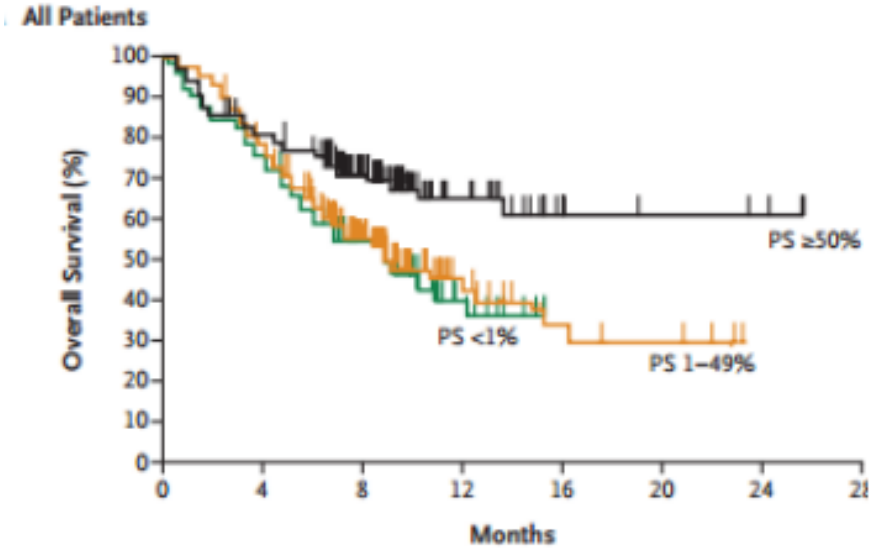


When measurable disease is NOT required, the ORR (95% CI) in the PS ≥50% subgroups are: **42.3%, 41.0%, and 47.1%** in the total, previously treated, and treatment-naive populations[d]

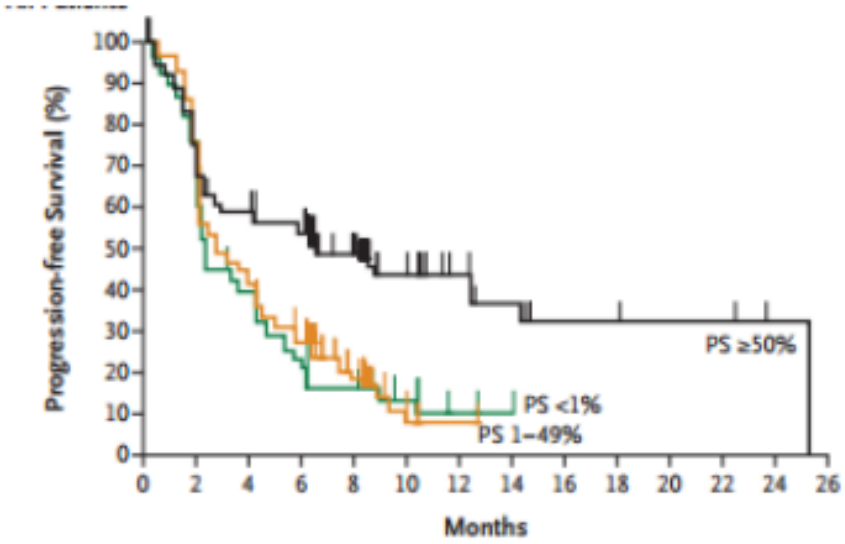
Garon et al, NEJM 2015

KEYNOTE-001 Phase 1 Study with Pembrolizumab in NSCLC: Efficacy

Overall Survival



Progression Free Survival

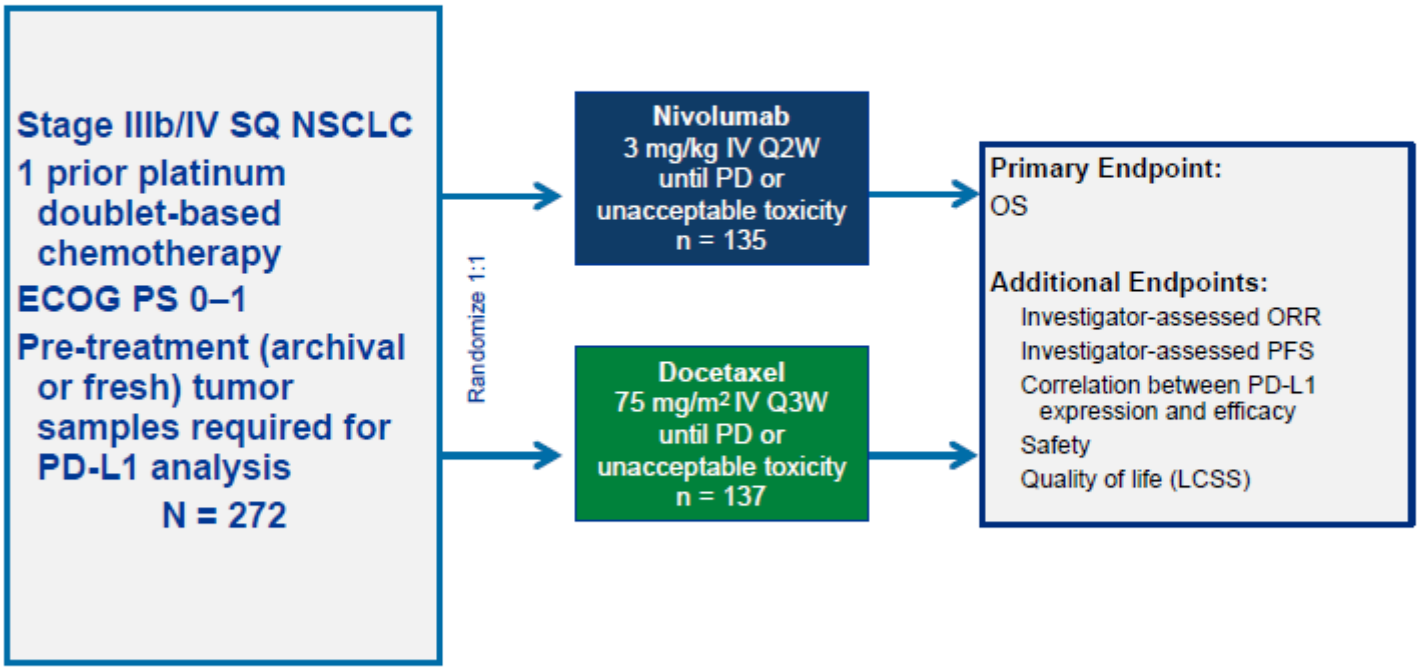


PD-L1 expression in at least 50% of tumor cells correlated with improved efficacy of pembrolizumab.

Garon E, et al. N Engl J Med 2015 Apr 19. [Epub ahead of print].

Nivolumab
(Anti PD-1 antibody)

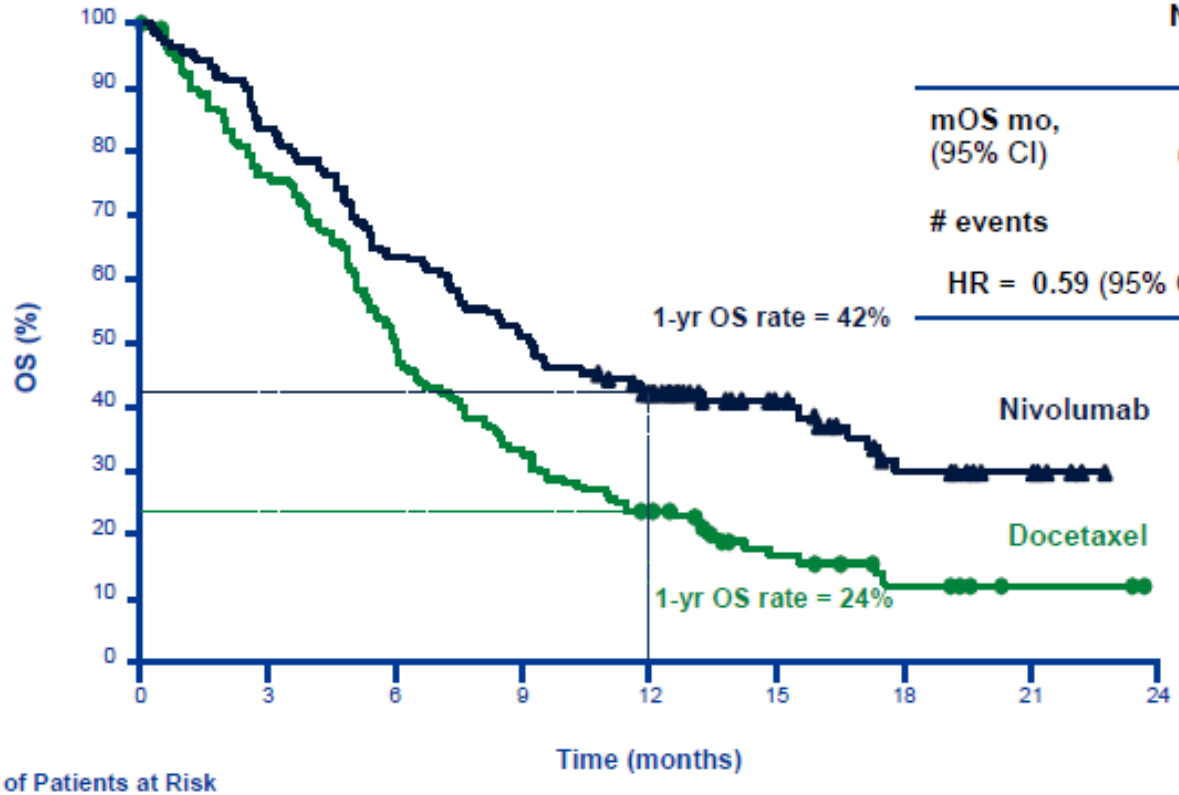
CheckMate 017 - Squamous



83% of patients had quantifiable PD-L1 expression

Brahmer, et al, NEJM July 2015

Overall Survival



	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
# events	86	113

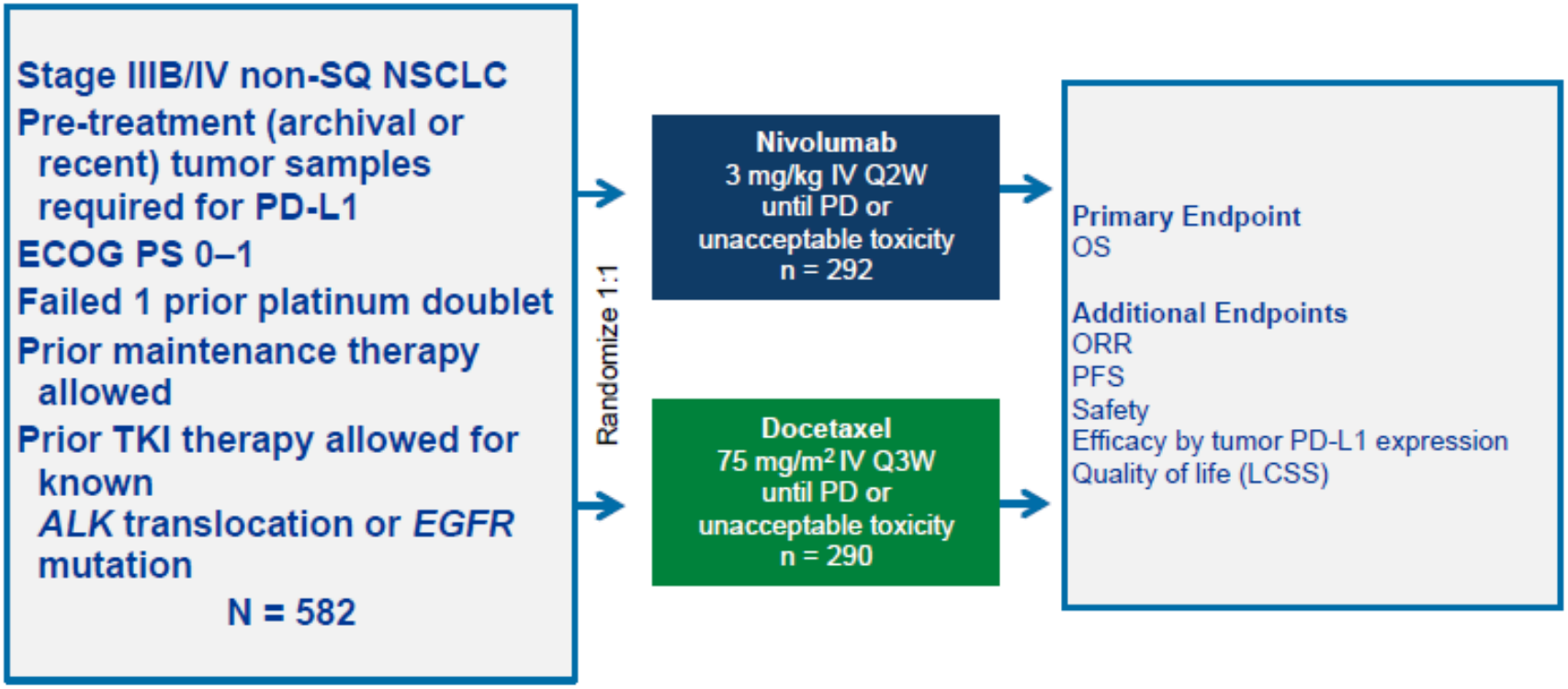
HR = 0.59 (95% CI: 0.44, 0.79), *P* = 0.00025

Number of Patients at Risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Brahmer, et al, NEJM July 2015

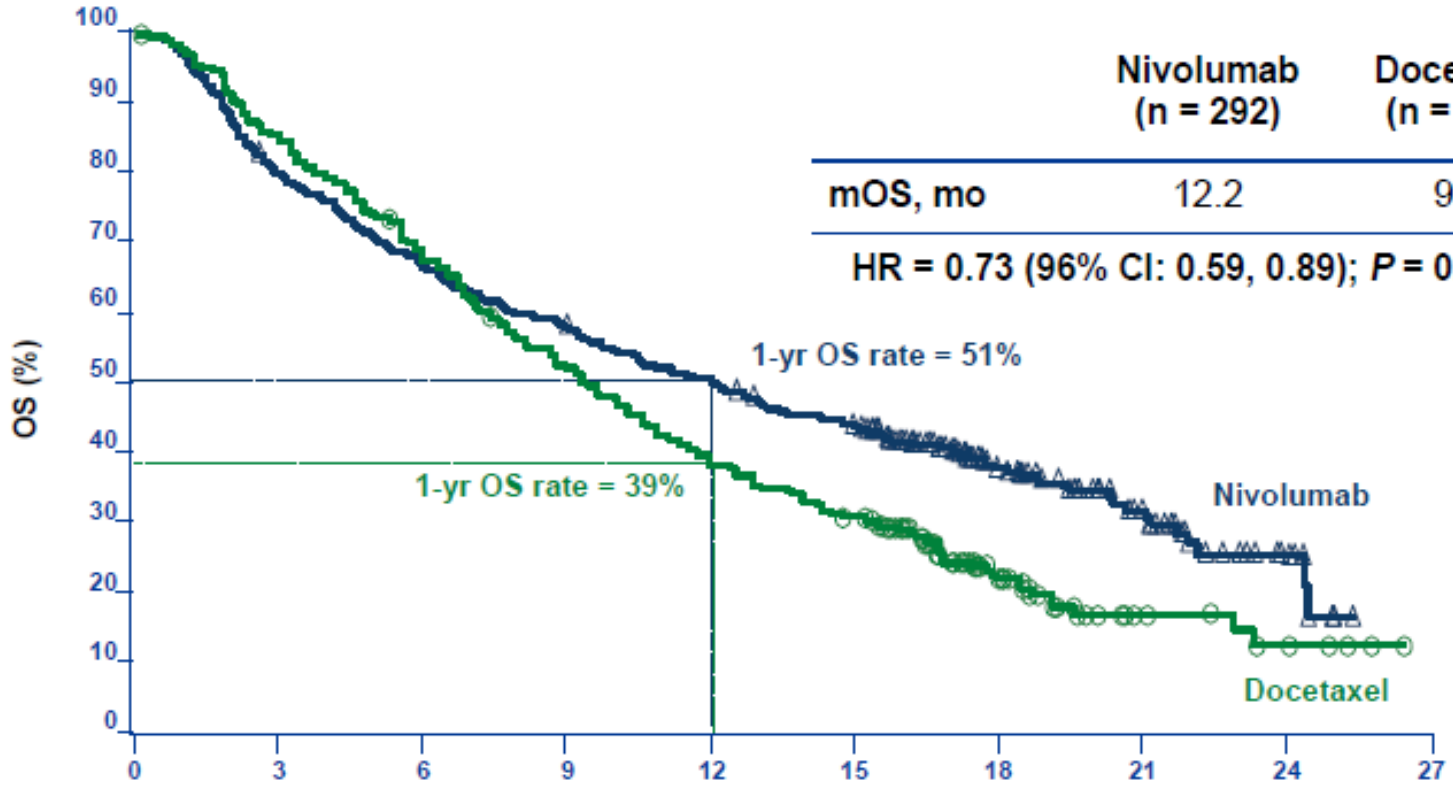
CheckMate 057 – Non Squamous



PD-L1 expression measured using the Dako/BMS automated IHC assay

Paz Ares, ASCO 2015

Overall Survival



	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015

Number of Patients at Risk										
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Paz Ares, ASCO 2015

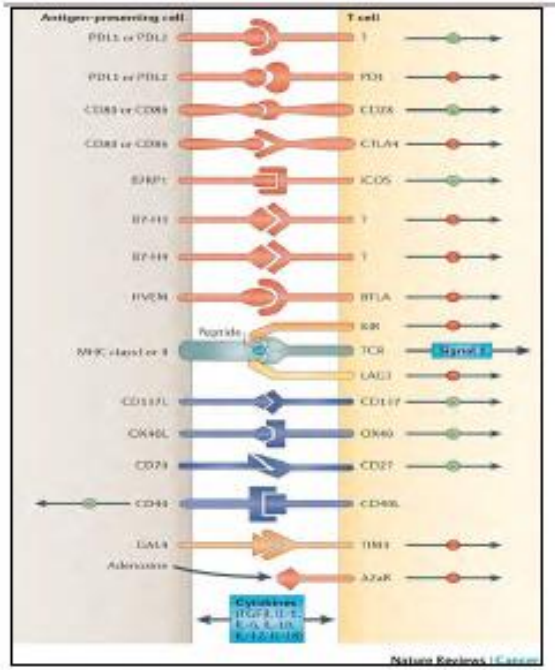
FAST TRACK APPROVAL BY FDA

ANTI-PD1 ANTIBODIES	Approval Status
NIVOLUMAB	Melanoma Lung cancer Renal cell carcinoma
PEMBROLIZUMAB	Melanoma Lung cancer
ANTI PD-L1 ANTIBODIES	
ATEZOLIZUMAB	Bladder cancer

THE PICTU

Immune Checkpoints

Antitumor Immune R



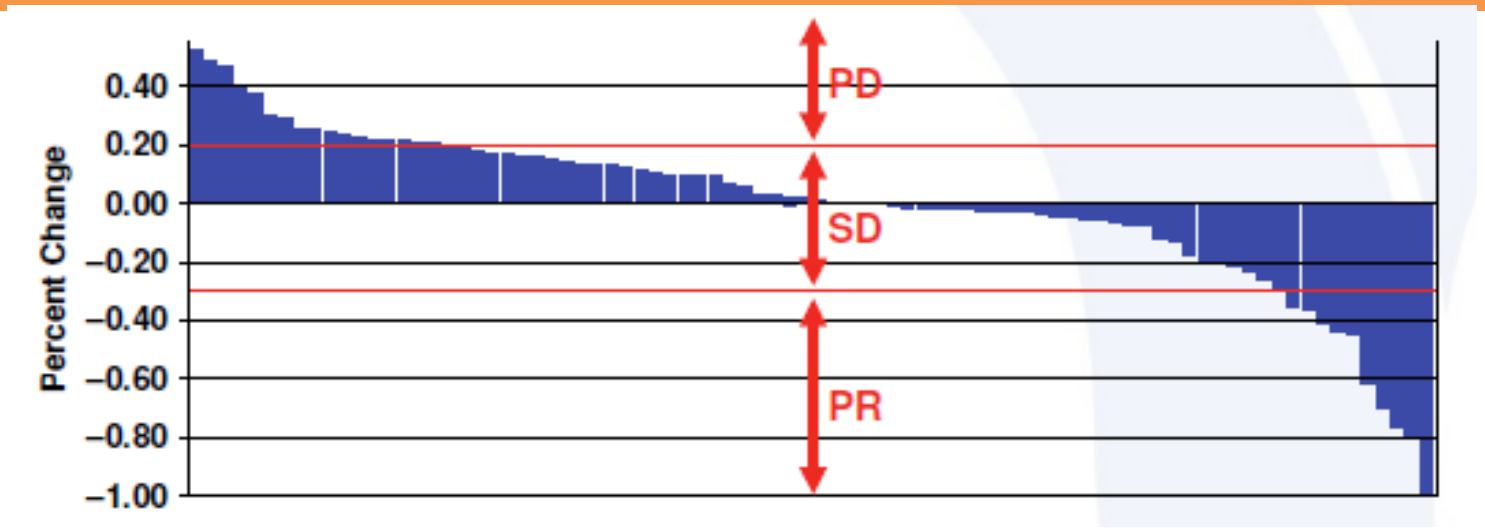
1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-26

Table 1. Immunological Targets in Clinical Development.			
Target	**Agent**	**Cancer Types**	**Current Development**
Inhibitory pathways	***Checkpoint blockade***		
CTLA-4	Ipilimumab	Melanoma	FDA approved
		Multiple tumors	Phase I-III
	Tremelimumab	Multiple tumors	Phase I-III
PD-1	Nivolumab	Melanoma, lung	FDA approved
		Multiple tumors	Phase I-III
	Pembrolizumab	Melanoma	FDA approved
		Multiple tumors	Phase I-III
	Pidilizumab	Multiple tumors	Phase I-II
	AMP-224	Multiple tumors	Phase I
PD-L1	Atezolizumab (MPDL3280A)	Multiple tumors	Phase I-III
	MED14736	Multiple tumors	Phase III
	Avelumab	Multiple tumors	Phase I
	MDX1105; BMS-936559	Multiple tumors	Phase I
LAG-3	IMP321	Multiple tumors	Phase I
	BMS-986016	Multiple tumors	Phase I
TIM-3			Preclinical
BTLA/HVEM/CD160			Preclinical
B7-H3	MGA271	Melanoma, prostate	Phase I
B7-H4			Preclinical
TIGIT			Preclinical
Co-stimulatory pathways	***Immune agonists***		
ICOS			Preclinical
CD40	CP-870893	Pancreatic Ca, Melanoma	Phase I
	Dacetuzumab (SGN-40)	Lymphoma, MM	Phase I-II
	Lucatumumab	Lymphoma, MM	Phase I
4-1BB (CD137)	Urelumab (BMS-663513)	Multiple tumors	Phase I-II
	PF-05082566	Lymphoma	Phase I
OX40	MEDI6469	Multiple tumors	Phase I
	MOXR0916	Multiple tumors	Phase I
CD27	Varlilumab (CDX-1127)	Multiple tumors	Phase I
GITR	TRX518	Multiple tumors	Phase I
	MK-4166	Multiple tumors	Phase I

MM, multiple myeloma.

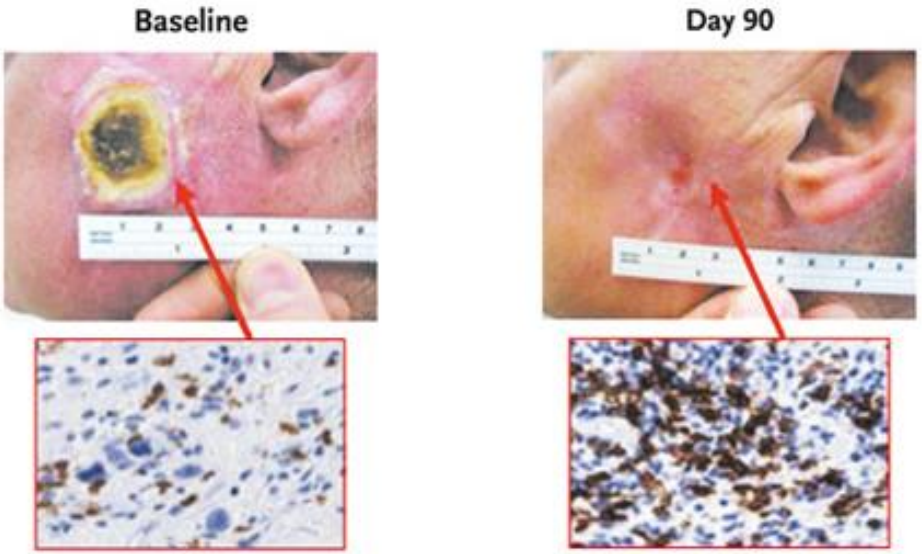
Table 1. Immunological Targets in Clinical Development.

RECIST Criteria: Clinical benefit

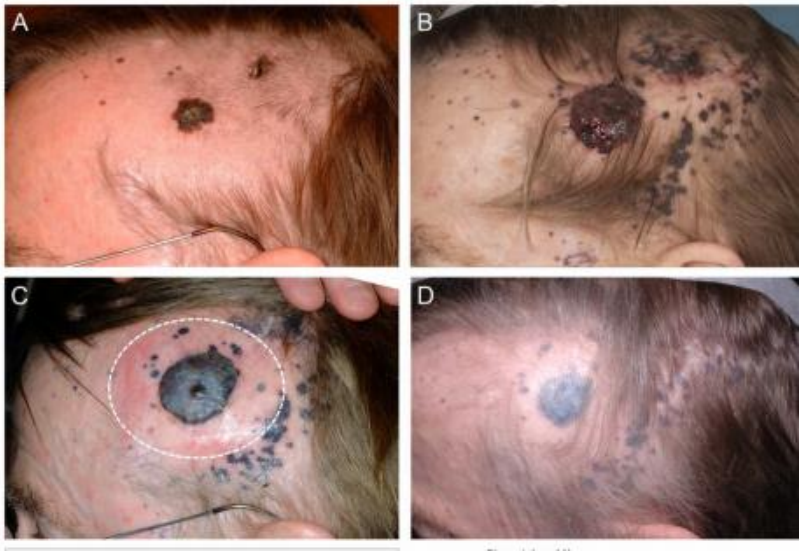


- Waterfall plots have become increasingly popular because they depict the benefit or lack thereof in all patients as a continuum of response, rather than a dichotomized response rate

DeVita VT, Cancer, 10° Ed. , Huang H, et al. Clin Cancer Res 2010



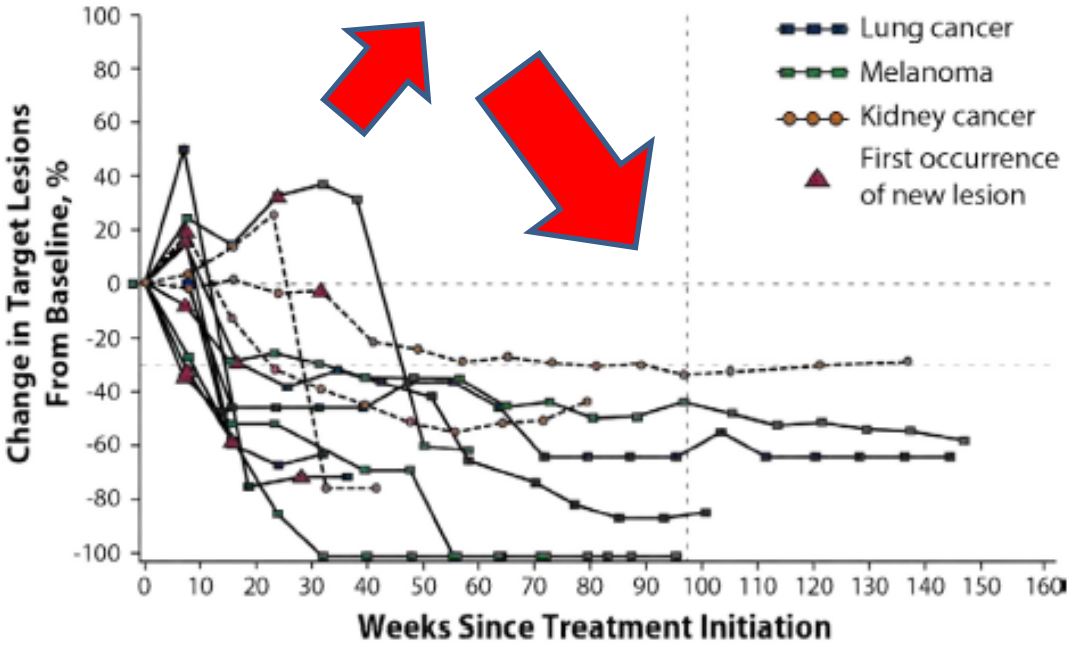
- Post treatment with pembrolizumab



The abscopal effect associated with a systemic anti-melanoma immune response

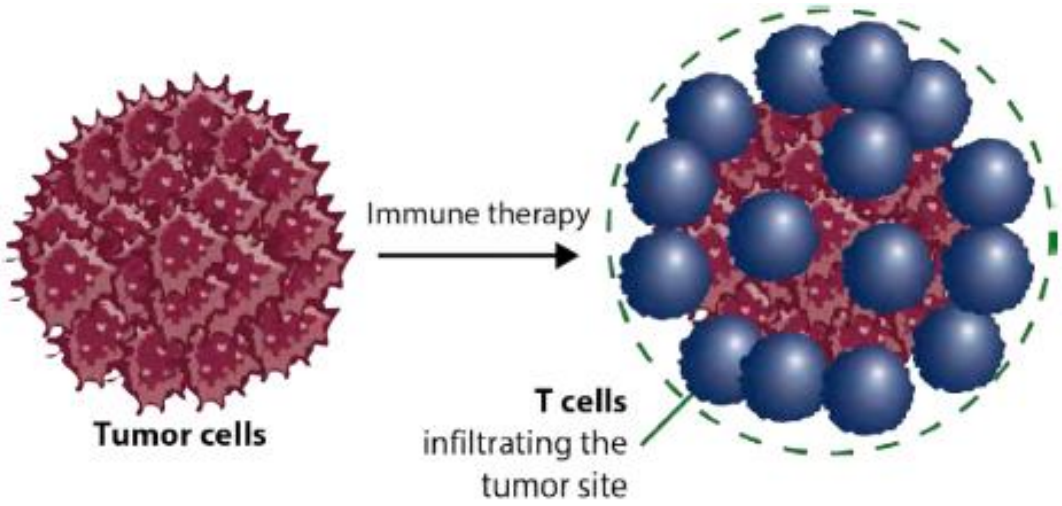
ATYPICAL RESPONSES

Unconventional "Immune-Related" Responses in 13 Patients With NSCLC, Melanoma, and RCC



- 13 of 270 patients (5%) with NSCLC/ melanoma/RCC had unconventional responses
- Response durability and persistence off drug were similar to conventional RECIST responses

PSEUDO-PROGRESSION
Tumor Flare With Immunotherapy



- In patients on immunotherapy, tumor flare or the appearance of new lesions may precede antitumor effects[1]
- This phenomenon may be characterized as a RECIST-defined progression and may result in premature discontinuation of therapy

1. Wolchok JD et al. *Clin Cancer Red*. 2009;15:7412-7420.

Immuno-oncology: time to rethink response assessment

- Following immunotherapy, tumor lesions may increase in size due to the increased infiltration of T cells, even meeting criteria for RECIST-defined PD;
- Previously undetectable lesions may appear.
- Around 2009 the Immune-Related Response Criteria were developed and are used in some immunotherapy clinical trials: Departing from conventional RECIST, which defines any new lesion as PD, the immune response criteria allow the appearance of new lesions, adding them to the total tumor burden.
- An increase in total tumor burden of >25% relative to baseline or nadir is required to define PD.

Immuno-oncology: time to rethink response assessment

- Immunotherapy → tumor "flare" or "pseudoprogression"
  - Lymphocyte invasion and proliferation
  - Apparent growth of existing tumors
  - "New" lesions as microscopic tumor rests become visible

- Immune-related response criteria (irRC)
  - 2009 version based on WHO criteria
  - Elements/concepts added to RECIST
  - Specific to this protocol
    - Note: there are many other systems called "modified RECIST"

Immuno-oncology: time to rethink response assessment

- New lesions ≠ PD
- Measure if measurable, add to target lesions
- Non-target growth ≠ PD
- ONLY total quantified disease PD can drive PD
- … and don’t stop treatment for PD
- If clinical benefit, continue treatment

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE

Metastatic or unresectable disease →

FIRST-LINE THERAPY[1]

- Immunotherapy
  - Anti PD-1 monotherapy
    - Pembrolizumab[2]
    - Nivolumab (category 1)[2]
  - Nivolumab/ipilimumab[2,3]
- Targeted therapy if *BRAF* mutated; preferred if clinically needed for early response
  - Combination therapy (preferred)
    - Dabrafenib/trametinib[2] (category 1)
    - Vemurafenib/cobimetinib[2,4] (category 1)
  - Single-agent therapy
    - Vemurafenib (category 1)[2]
    - Dabrafenib (category 1)[2]
- Clinical trial

→ **Disease progression or Maximum clinical benefit from *BRAF* targeted therapy**

PERFORMANCE STATUS (PS)

PS 0–2 →

SECOND LINE OR SUBSEQUENT THERAPY[5]

- Anti PD-1 monotherapy
  - Pembrolizumab[2]
  - Nivolumab[2]
- Nivolumab/ipilimumab[2,3]
- Ipilimumab (category 1)[2,6]
- Targeted therapy if *BRAF* mutated
  - Combination therapy (preferred)
    - Dabrafenib/trametinib[2]
    - Vemurafenib/cobimetinib[2,4]
  - Single-agent therapy
    - Vemurafenib[2]
    - Dabrafenib[2]
- High-dose IL-2[7]
- Biochemotherapy[8] (category 2B)
- Cytotoxic agents[8]
- Imatinib for tumors with activating mutations of *C-KIT*
- Clinical trial

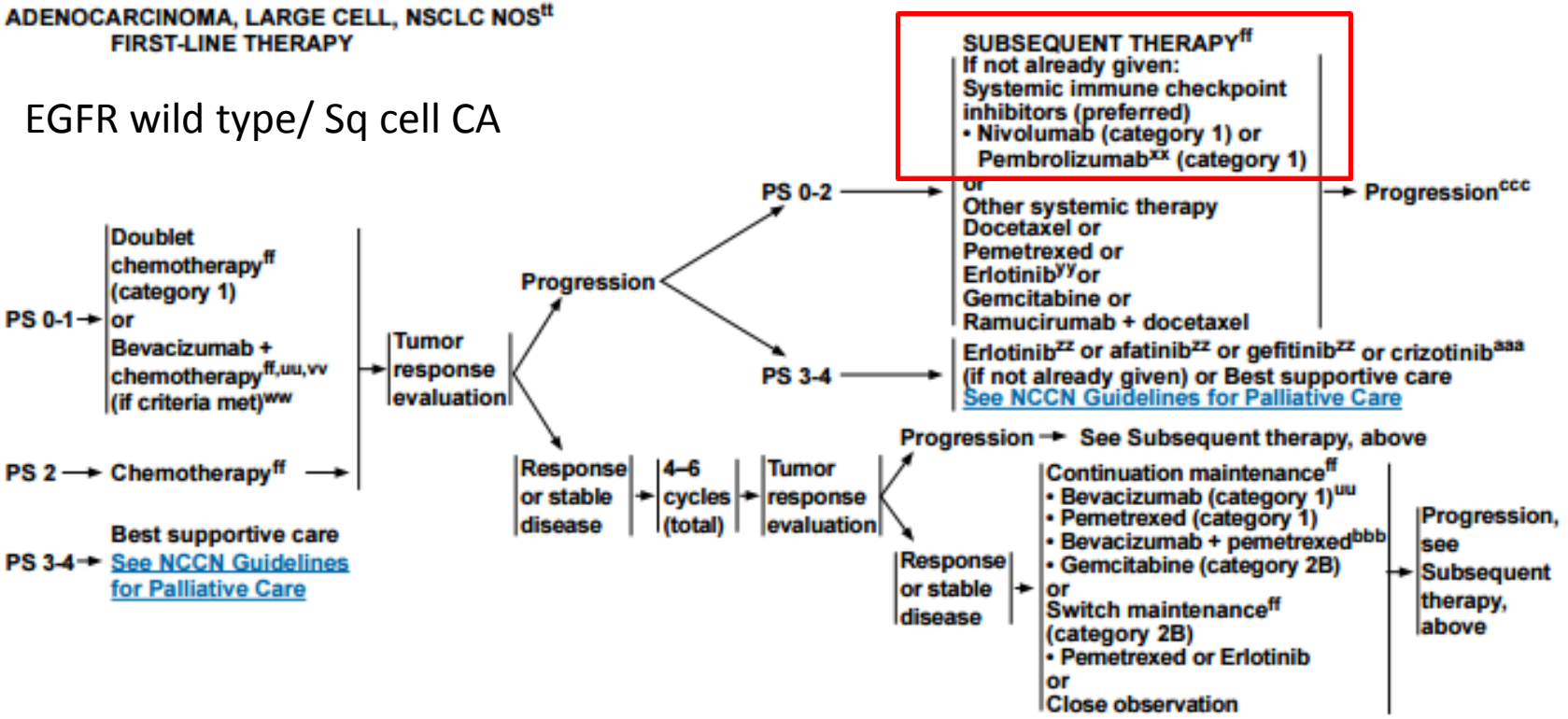
PS 3–4 → **Consider best supportive care** (See NCCN Guidelines for Palliative Care)

[1]The choice of a treatment is based on evaluation of the individual patient.
[2]See Management of Toxicities of Immunotherapy and Targeted Therapy (ME-F)
[3]Nivolumab/ipilimumab combination therapy is associated with improved relapse-free survival compared with single-agent nivolumab or ipilimumab, at the expense of significantly increased toxicity. Compared to single-agent therapy, the impact of nivolumab/ipilimumab combination therapy on overall survival is not known. The phase III trial of nivolumab/ipilimumab versus either nivolumab or ipilimumab monotherapy was conducted in previously untreated patients with unresectable stage III or IV melanoma.
[4]In previously untreated patients with unresectable Stage IIIC or Stage IV disease, the combination of vemurafenib/cobimetinib was associated with improved PFS and response rate when compared to vemurafenib alone. The impact on overall survival compared to single-agent vemurafenib is unknown.
[5]Consider second-line agents if not used first line and not of the same class.
[6]Re-induction with ipilimumab may be considered for select patients who experienced no significant systemic toxicity during prior ipilimumab therapy and who relapse after initial clinical response or progress after stable disease >3 months.
[7]High-dose IL-2 should not be used for patients with inadequate organ reserve, poor performance status, or untreated or active brain metastases. For patients with small brain metastases and without significant peritumoral edema, IL-2 therapy may be considered (category 2B). Therapy should be restricted to an institution with medical staff experienced in the administration and management of these regimens.
[8]For a list of cytotoxic regimens and biochemotherapy regimens, see (ME-E 2 of 6).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

ADENOCARCINOMA, LARGE CELL, NSCLC NOS[tt]
FIRST-LINE THERAPY

EGFR wild type/ Sq cell CA



[ff] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[tt] Consider additional mutational testing if only EGFR and ALK were performed. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
[uu] Bevacizumab should be given until progression.
[vv] Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.
[ww] Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.
[xx] Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression, as determined by an FDA-approved test for PD-L1 with use of pembrolizumab.
[yy] Recommend proteomic testing for patients with NSCLC and wild-type EGFR or with unknown EGFR status. A patient with a "poor" classification should not be offered erlotinib in the second-line setting. Gregorc V, Novello S, Lazzari C, et al. Lancet Oncol 2014; 15:713-21.
[zz] May be considered for PS 3 and 4 patients with sensitizing EGFR mutations.
[aaa] May be considered for PS 3 and 4 patients if positive for the ALK rearrangement.
[bbb] If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.
[ccc] If not already given, options for PS 0-2 include erlotinib, nivolumab, pembrolizumab, docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include erlotinib or best supportive care. Options for further progression are best supportive care or clinical trial.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Anti-Tumor Immune Response
Inhibition by Tumors

1. Insufficient number of T cells generated within the lymphoid compartment.
Clinical Trials

1. Anti-CTLA.4
2. Vaccines
3. Radiation
4. ACT with TILs
5. ACT with CAR or TCR transgenic T cells

2. Insufficient number of T cells extravasate into the tumor.
Clinical Trial

- Pembrolizumab plus vorinostat
- Phase I
- Expansion arms in immunotherapy-naïve and immunotherapy-experienced patients

1. Insufficient number of T cells are generated within the lymphoid compartment.
2. Insufficient number of T cells extravasate into the tumor.
3. T cells are inhibited in the tumor microenvironment.

Presented By Scott Antonia at 2016 ASCO Annual Meeting

3. T cells are inhibited in the tumor microenvironment

Relevant Targets for NSCLC

- **Surface membrane proteins- checkpoints**
  - PD1, CTLA4, LAG3, TIM3, BTLA, Adenosine A2AR
- **Soluble factors and metabolic alterations**
  - IL10, TGFβ, Adenosine, IDO, Arginase
- **Inhibitory cells**
  - Cancer Associated Fibroblasts, Regulatory Myeloid Derived Suppressor Cells, Tumor Associated Macrophages

3. T cells are inhibited in the tumor microenvironment

Clinical Trials

- PBF-509: Adenosine A2AR (T cell checkpoint) antagonist
- Nintedanib: Inhibition of CAFs
- RTA408: Reduction of peroxynitrite derived from myeloid cells to reduce nitrosylation of amino acids on TCR, MHC, etc in TME

Take home points

- Management of cancer is rapid evolving
- Incredibly exciting and effective new drugs!
- New treatment , need to move to a tailored therapy
- Biomarker for immunotherapy – not really there yet
- The most appropriate treatment is the right drug, at the right time, for the right person, at the right place and by the right team
- In the near future, Cancer will be managed as a chronic illness, nursing will be the major part in caring for chronic disease patients.