Farmaci Innovativi in Oncologia

Umberto Ricardi

DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

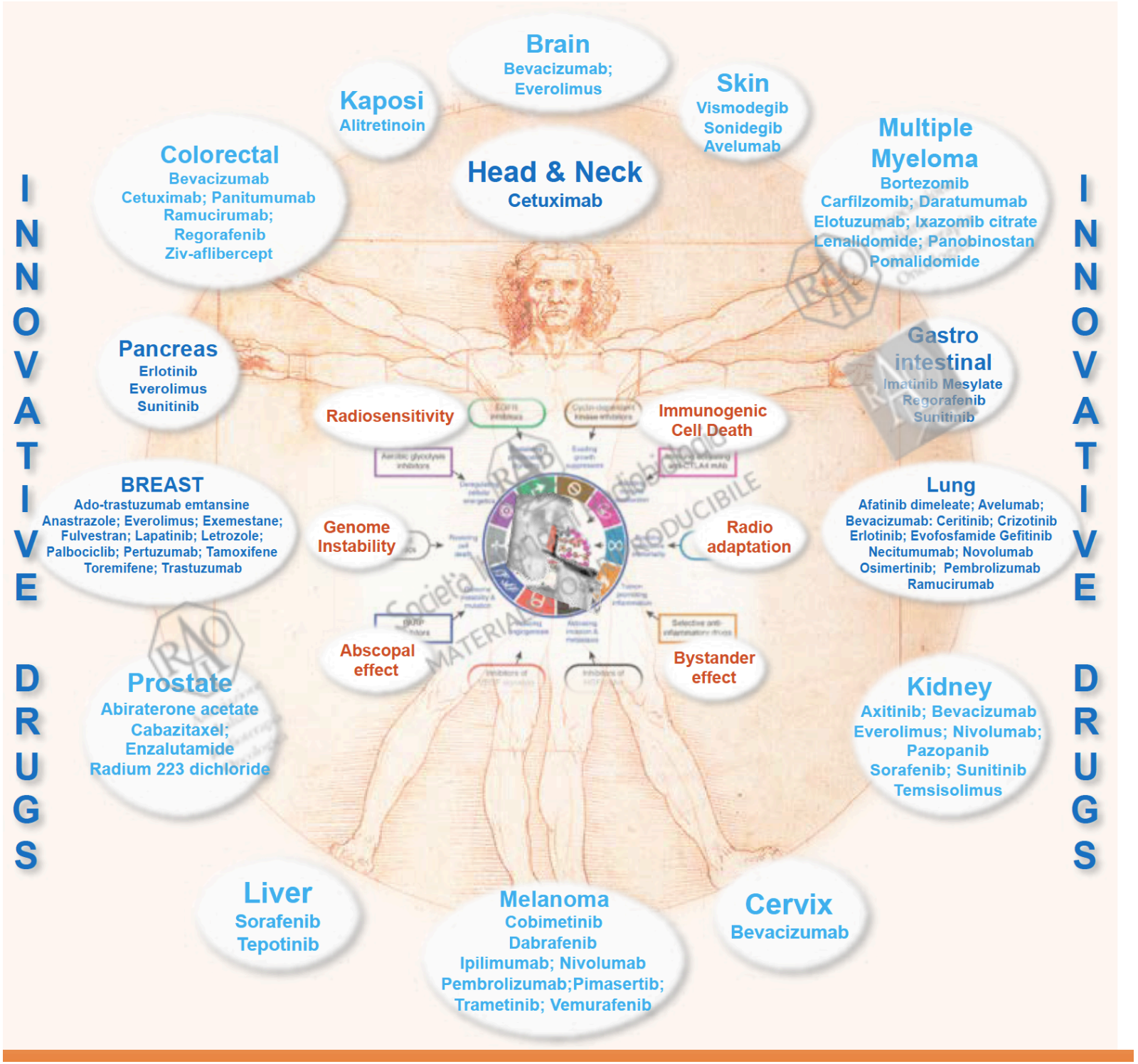
DICHIARAZIONE

Relatore: Umberto Ricardi

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board/Honoraria:

Lilly, Takeda, Astra Zeneca, Merck, MSD, Bayer

- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**


INNOVATIVE DRUGS
INNOVATIVE DRUGS
Brain
Bevacizumab;
Everolimus
Kaposi
Alitretinoin
Skin
Vismodegib
Sonidegib
Avelumab
Colorectal
Bevacizumab
Cetuximab; Panitumumab
Ramucirumab;
Regorafenib
Ziv-aflibercept
Head & Neck
Cetuximab
Multiple Myeloma
Bortezomib
Carfilzomib; Daratumumab
Elotuzumab; Ixazomib citrate
Lenalidomide; Panobinostan
Pomalidomide
Pancreas
Erlotinib
Everolimus
Sunitinib
Gastro intestinal
Imatinib Mesylate
Regorafenib
Sunitinib
Radiosensitivity
Immunogenic Cell Death
BREAST
Ado-trastuzumab emtansine
Anastrazole; Everolimus; Exemestane;
Fulvestran; Lapatinib; Letrozole;
Palbociclib; Pertuzumab; Tamoxifene
Toremifene; Trastuzumab
Genome Instability
Radio adaptation
Lung
Afatinib dimeleate; Avelumab;
Bevacizumab: Ceritinib; Crizotinib
Erlotinib; Evofosfamide Gefitinib
Necitumumab; Novolumab
Osimertinib; Pembrolizumab
Ramucirumab
Abscopal effect
Bystander effect
Prostate
Abiraterone acetate
Cabazitaxel;
Enzalutamide
Radium 223 dichloride
Kidney
Axitinib; Bevacizumab
Everolimus; Nivolumab;
Pazopanib
Sorafenib; Sunitinib
Temsisolimus
Liver
Sorafenib
Tepotinib
Melanoma
Cobimetinib
Dabrafenib
Ipilimumab; Nivolumab
Pembrolizumab;Pimasertib;
Trametinib; Vemurafenib
Cervix
Bevacizumab

Elenco dei farmaci innovativi aggiornato al 23 giugno 2016

Agenzia Italiana del Farmaco

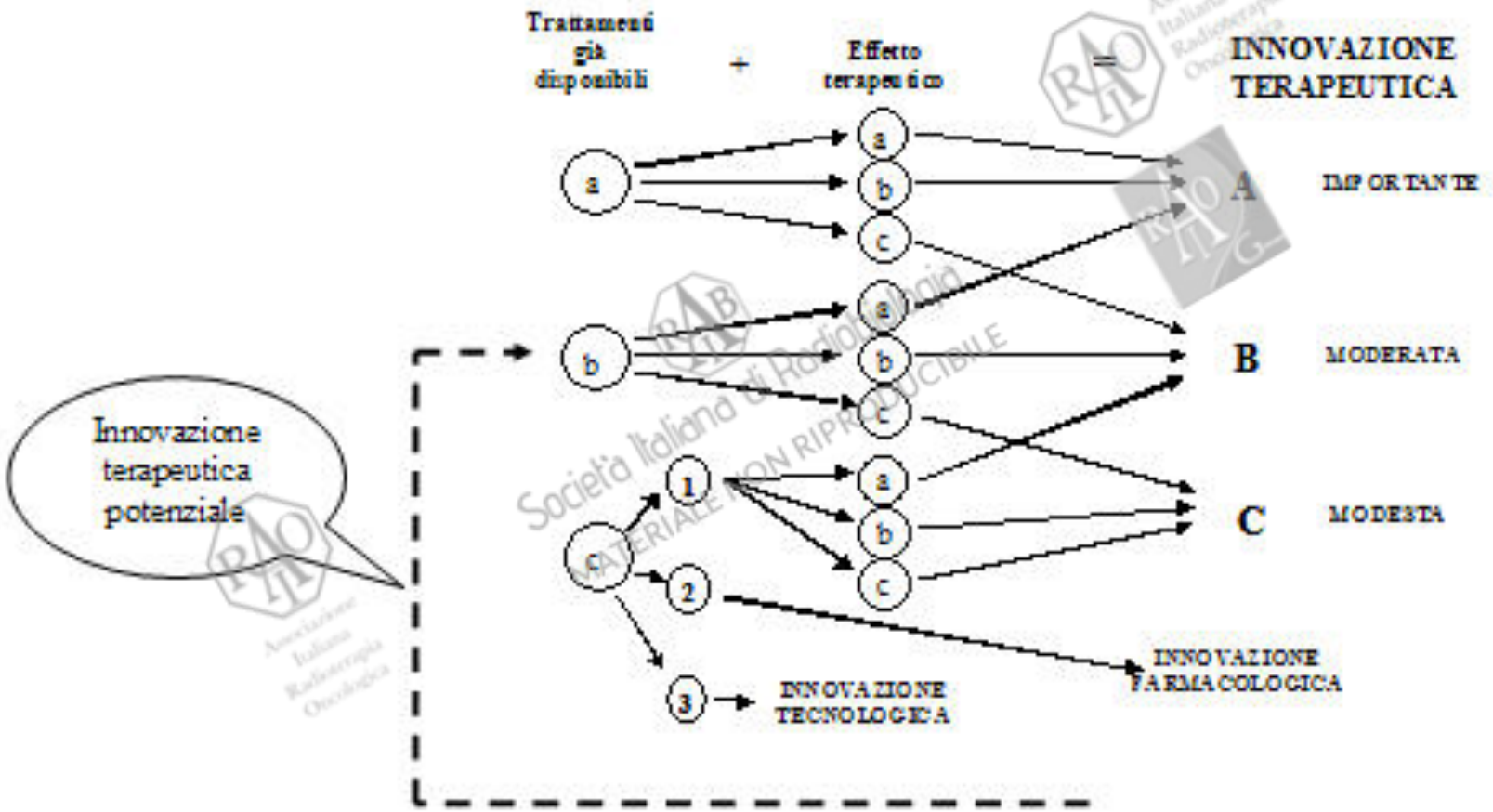
AIFA

Strategie e Politiche del Farmaco

Ufficio "attività di HTA nel settore farmaceutico"

Lista dei farmaci innovativi ai sensi dell'art.1 comma 1 e 2 dell'accordo Stato Regioni del 18 novembre 2010 (Rep.Atti n.197/csr).
Principi Attivi con parere sull'innovatività da parte della Commissione Tecnico Scientifica dell'Aifa in corso di validità - 36 mesi dalla data di pubblicazione in G.U. (data di efficacia del provvedimento).

Terminology and definition



Modello di innovazione terapeutica

AIFA Agenzia Italiana del Farmaco

Elenco aggiornato farmaci innovativi

Ai sensi dell'art.1 comma 1 dell'accordo sottoscritto in data 18 novembre 2010 (Rep.Atti n.197/csr), l'Agenzia Italiana del Farmaco pubblica l'elenco aggiornato dei medicinali che, a giudizio della Commissione Tecnico Scientifica, possiedono il requisito della innovatività terapeutica "importante" ovvero innovatività terapeutica "potenziale".

Di seguito sono elencati i successivi aggiornamenti in ordine cronologico di pubblicazione.

- Elenco aggiornato farmaci innovativi (23/06/2016)
- Elenco aggiornato farmaci innovativi (23/12/2015)
- Elenco aggiornato farmaci innovativi (24/05/2015)
- Elenco aggiornato farmaci innovativi (24/07/2014)
- Elenco aggiornato farmaci innovativi (31/10/2013)
- Elenco aggiornato farmaci innovativi (27/03/2013)
- Elenco aggiornato farmaci innovativi (27/12/2011)
- Elenco aggiornato farmaci innovativi (23/12/2010)

Dati aggiornati al: 23/06/2016

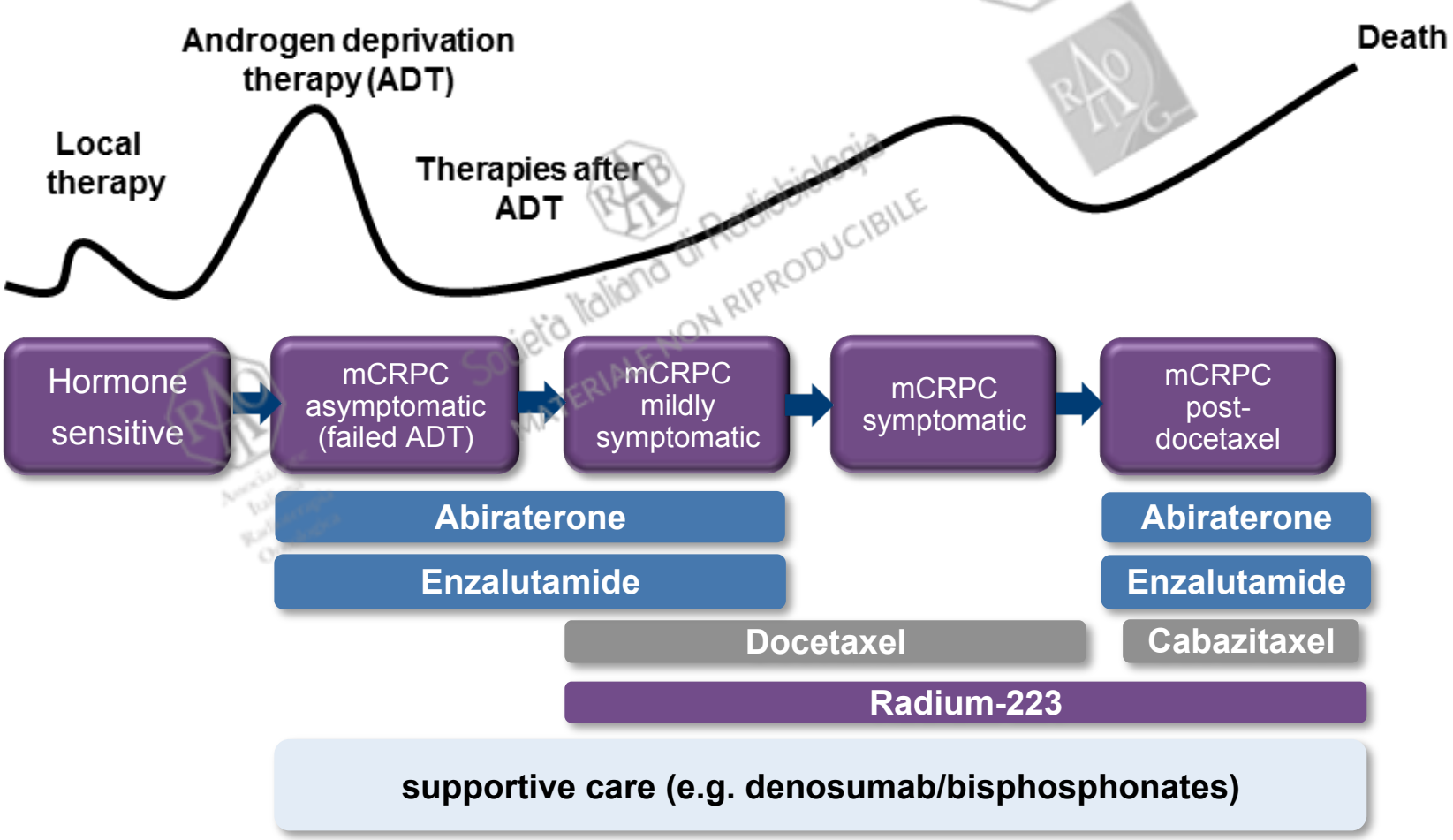
Elenco in base all'Art.1 comma 1

Atc4 livello	Farmaco	Principio attivo	Classe	Innovatività	Data parere CTS	Data G.U. (data efficacia)	Data scadenza requisito
L01XC	ADCETRIS	Brentuximab vedotin	H	Potenziale	02/12/2013	08/07/2014	07/07/2017
L01XC	PERJETA	Pertuzumab	H	Importante	02/12/2013	08/07/2014	07/07/2017
L04AX	REVLIMID	Lenalidomide	H	Potenziale	13/02/2014	30/09/2014	29/09/2017
J05AX	TIVICAY	Dolutegravir	H	Potenziale	10/03/2014	02/11/2014	01/11/2017
J04AK	SIRTURO	Bedaquilina	H	Potenziale	11/03/2014	01/10/2014	30/09/2017
L01XC	KADCYLA	Trastuzumab emtansine	H	Potenziale	07/04/2014	11/10/2014	10/10/2017
L01CD	ABRAXANE	Nab paclitaxel	H	Importante	07/04/2014	21/02/2015	20/02/2018
V10XX	XOFIGO	Radio ra 223 dicloruro	H	Potenziale	13/05/2014	11/06/2015	10/06/2018

Elenco dei farmaci innovativi aggiornato al 23 giugno 2016

Atc4 livello	Farmaco	Principio attivo	Classe	Innovatività	Data parere CTS	Data G.U. (data efficacia)	Data scadenza requisito
J05AX	SOVALDI	Sofosbuvir	A	Importante	15/05/2014	20/12/2014	19/12/2017
L01XE	XALKORI	Crizotinib	H	Potenziale	09/06/2014	11/04/2015	10/04/2018
J05AE	OLYSIO	Simeprevir	A	Potenziale	10/11/2014	24/02/2015	23/02/2018
J05AX	VIEKIRAX	Ombitasvir, paritaprevir, ritonavir	A	Importante	21/01/2015	24/05/2015	23/05/2018
J05AX	EXVIERA	Dasabuvir	A	Importante	21/01/2015	24/05/2015	23/05/2018
J05AX	DAKLINZA	Daclatasvir	A	SI	16/02/2015	05/05/2015	04/05/2018
R07AX	KALYDECO	Ivacaftor	A	SI	16/02/2015	05/05/2015	04/05/2018
J05AX	HARVONI	Ledipasvir + sofosbuvir	A	SI	24/03/2015	14/05/2015	13/05/2018
L01XX	ZYDELIG	Idelalisib	H	SI	18/02/2015	11/09/2015	10/09/2018
L04AX	IMNOVID	Pomalidomide	H	SI	18/02/2015	20/08/2015	19/08/2018
L01XE	IMBRUVICA	Ibrutinib	H	SI	13/07/2015	05/01/2016	04/01/2019
L01XC	OPDIVO	Nivolumab	H	SI	14/09/2015	25/03/2016	24/03/2019
L01XC	KEYTRUDA	Pembrolizumab	H	SI	13/10/2015	11/05/2016	10/05/2019

Current Treatment Paradigm is Evolving



Terminology and definition: coining names for drugs

Most new names consist of three parts: a prefix, an infix and a stem

- **Prefix**: means nothing; differentiates drug from others in class
- **Infix**: used occasionally; further subclassifies
- **Stem**: usually at the end of a name, indicates place in nomenclature scheme; novel stems suggest novel drug action; drugs with the same stem are related

List of drug name stems and affixes [edit]

More comprehensive lists can be found at the National Library of Medicine[7] or in Appendix VII of the USP D

Stem	Drug class	Example
-vir	Antiviral drug[2]	aciclovir
-cillin	Penicillin-derived antibiotics	penicillin, carbenicillin, oxacillin[8]
cef-	Cephem-type antibiotics	cefazolin
-mab	Monoclonal antibodies[2]	trastuzumab, ipilimumab
-ximab	Chimeric antibody that responds to more than one antigen[2]	infliximab
-zumab	humanized antibody[9]	natalizumab, bevacizumab
-tinib	Tyrosine-kinase inhibitors[2]	erlotinib, crizotinib
-vastatin	HMG-CoA reductase inhibitor[2]	atorvastatin
-prazole	Proton-pump inhibitor[2]	omeprazole
-lukast	Leukotriene receptor antagonists[2]	zafirlukast, montelukast
-grel-	Platelet aggregation inhibitor[2]	clopidogrel, ticagrelor
-axine	Dopamine and serotonin–norepinephrine reuptake inhibitor[2]	venlafaxine
-parib	PARP inhibitor	olaparib, veliparib

Dati aggiornati al: 23/06/2016

Elenco in base all'Art.1 comma 1

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Elenco dei farmaci innovativi aggiornato al 23 giugno 2016

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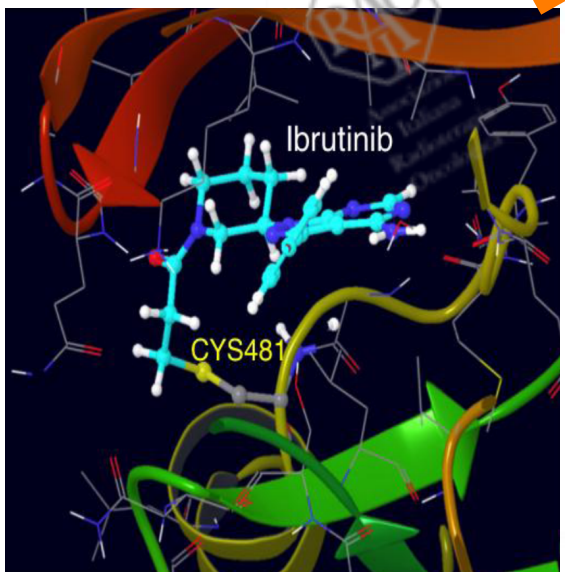
L01XC	KEYTRUDA	Pembrolizumab	H	SI	13/10/2015	11/05/2016	10/05/2019

Targeting B-Cell Receptor Signaling Through Inhibition of Bruton Tyrosine Kinase (BTK)

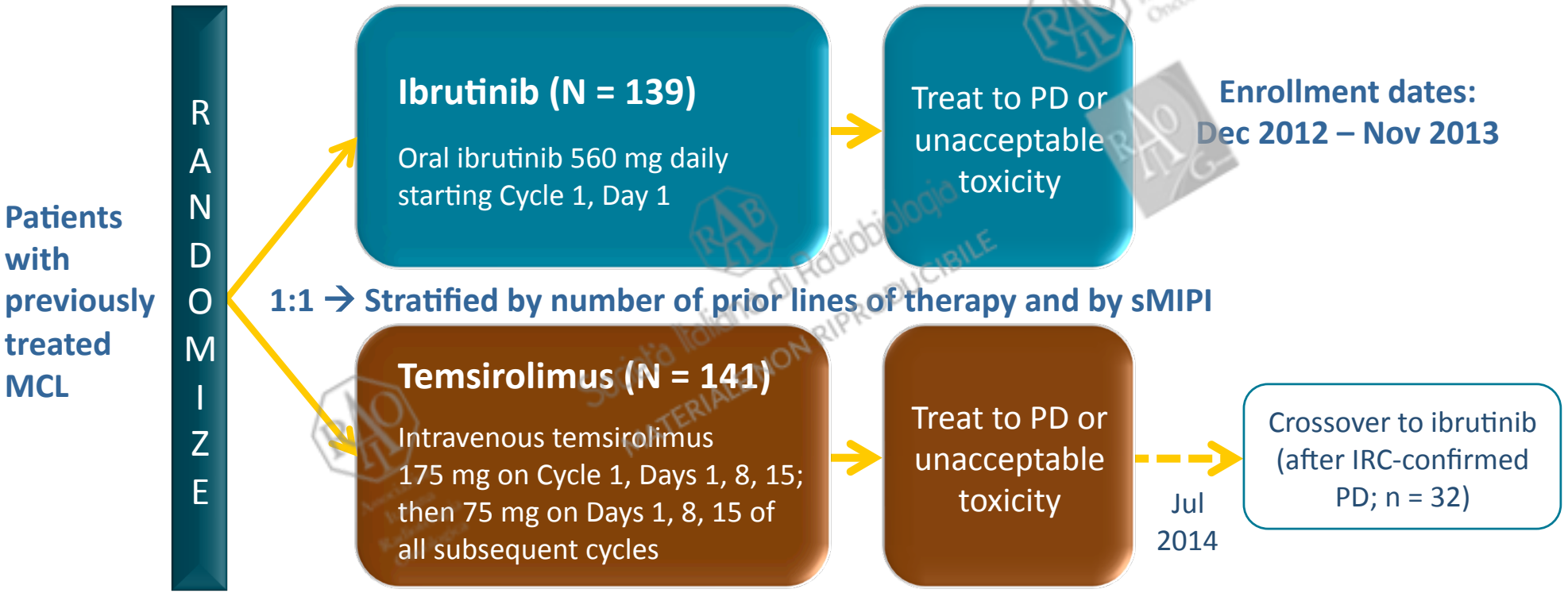


Daily oral dosing produces 24-hour BTK inhibiton

It blocks NF-κB

inhibition of proliferation
adhesion disruption
apoptosis

Ibrutinib Versus Temsirolimus: Results From a Phase 3, International, Randomized, Open-Label, Multicenter Study in Patients With Previously Treated Mantle-Cell Lymphoma



Primary end point:

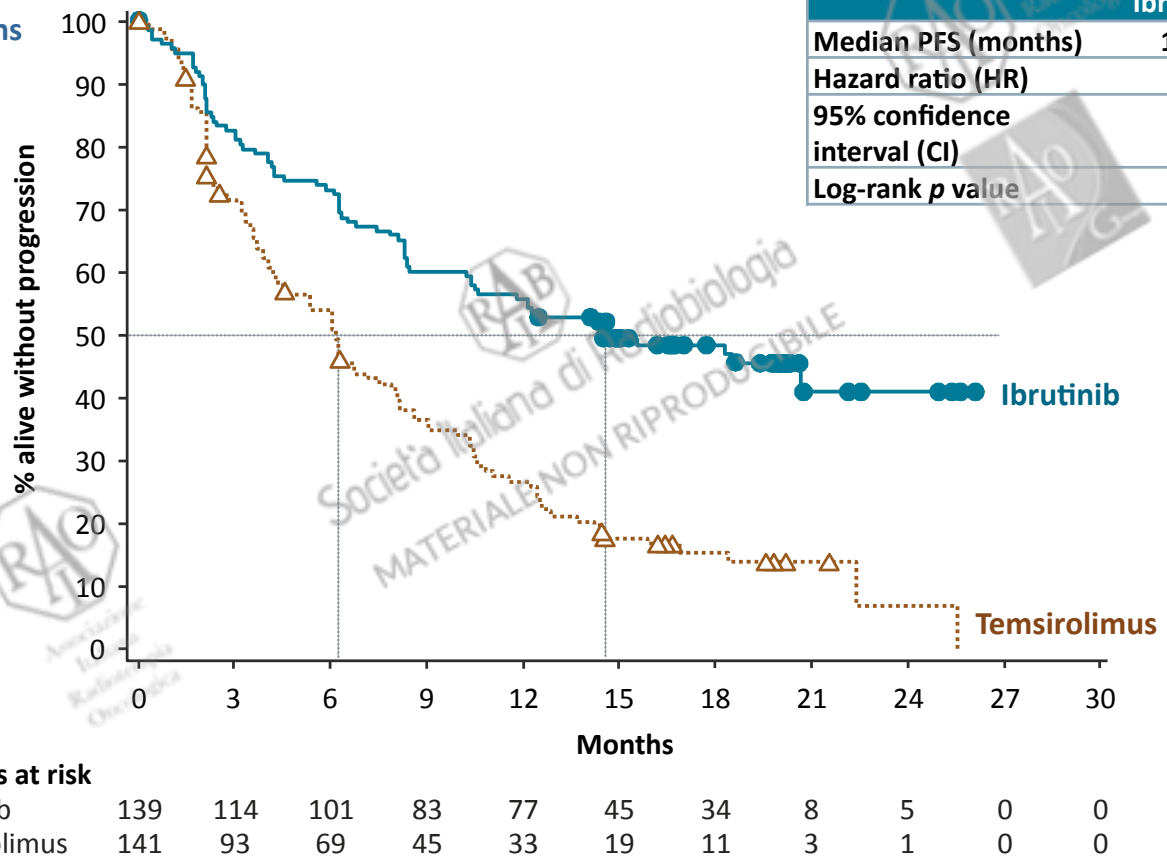
- IRC-assessed PFS

Secondary end points included:

- IRC-assessed ORR (CR + PR)
- Overall survival
- Duration of response
- Time to next treatment
- Safety
- Patient-reported outcomes (FACT-Lym)

Primary End Point: IRC-Assessed PFS

ITT population
Median follow-up: 20 months



	Ibrutinib	Temsirolimus
Median PFS (months)	14.6	6.2
Hazard ratio (HR)	0.43	
95% confidence interval (CI)	0.32-0.58	
Log-rank *p* value	< 0.0001	

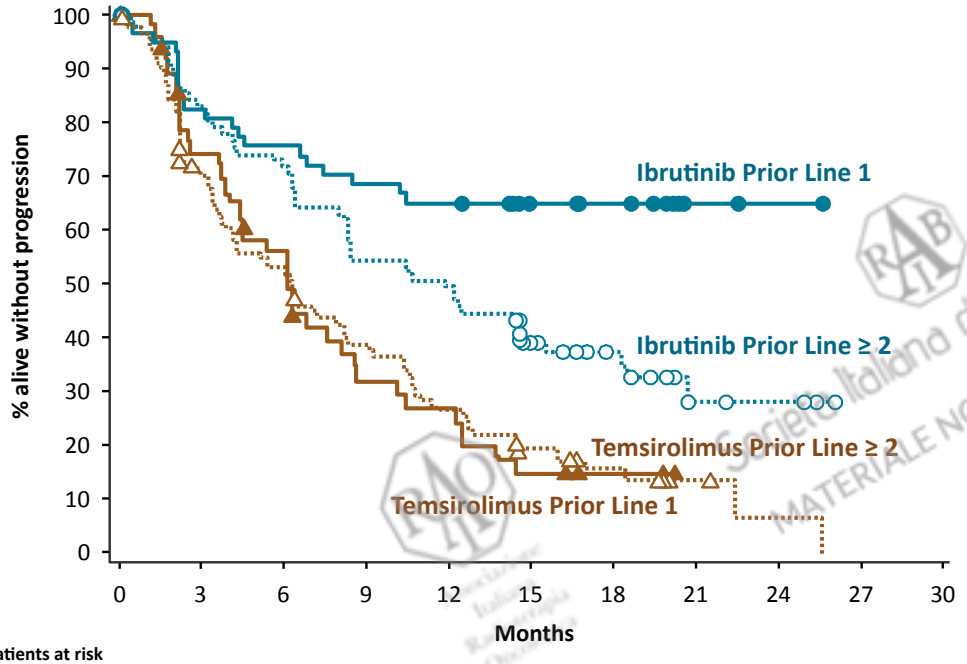
Patients at risk

Ibrutinib	139	114	101	83	77	45	34	8	5	0	0
Temsirolimus	141	93	69	45	33	19	11	3	1	0	0

- At a 2-year landmark, the PFS rate was 41% for ibrutinib versus 7% for temsirolimus
- Investigator-assessed HR for ibrutinib versus temsirolimus was 0.43 (95% CI, 0.32-0.58)

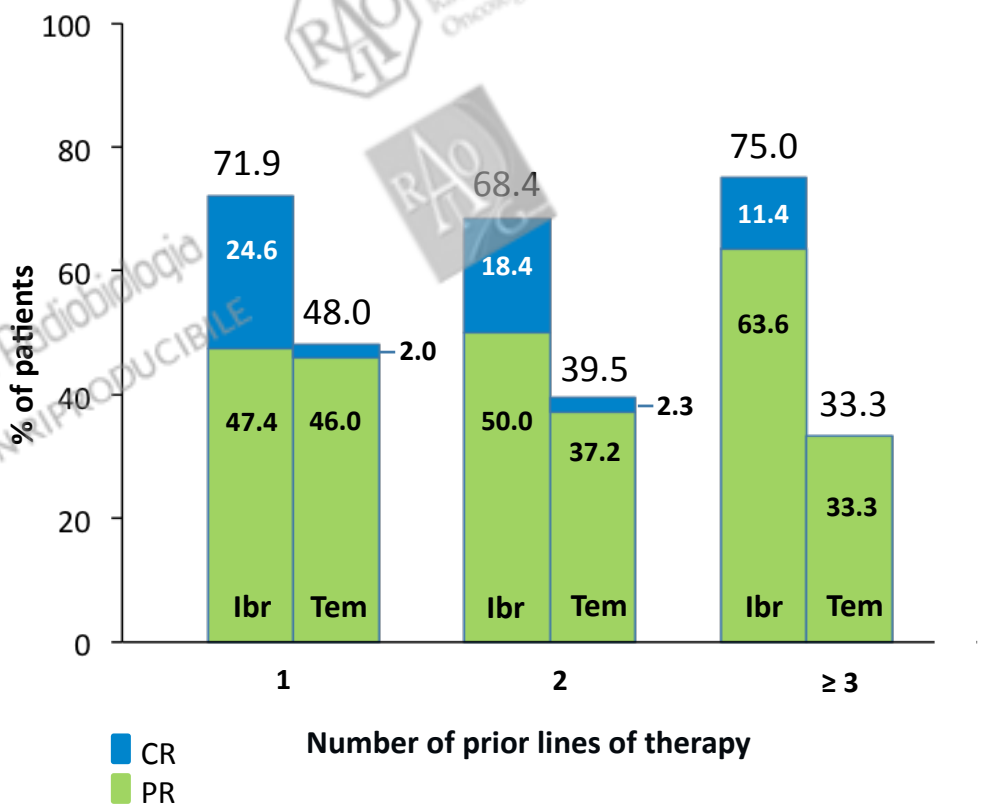
American Society of Hematology 2015, MCL3001, Rule S, et al.

PFS and ORR: Outcomes by Number of Lines of Prior Therapy



Patients at risk

Ibr 1 prior	57	47	43	39	37	21	19	3	2	0	0
Tem 1 prior	50	33	24	13	11	6	4	0	0	0	0
Ibr ≥2 prior	82	67	58	44	40	24	15	5	3	0	0
Tem ≥2 prior	91	60	45	32	22	13	7	3	1	0	0



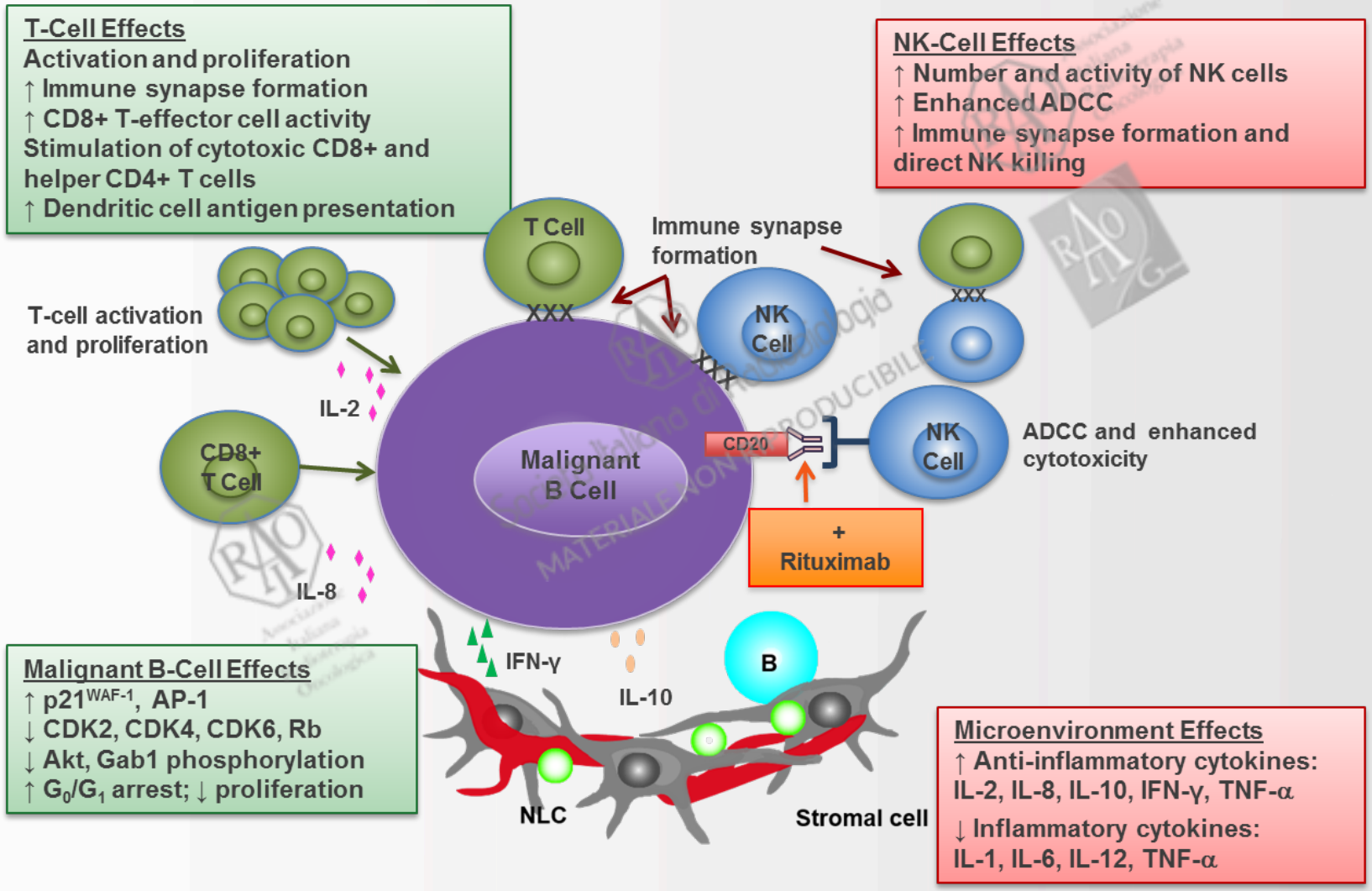
Treatment-Emergent AEs (≥ 20% of Patients)

Safety Population	Ibrutinib (N = 139)		Temsirolimus (N = 139)	
AE, %	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Hematological				
Thrombocytopenia	18.0	9.4	56.1	42.4
Anemia	18.0	7.9	43.2	20.1
Neutropenia	15.8	12.9	25.9	16.5
Nonhematological				
Diarrhea	28.8	2.9	30.9	4.3
Fatigue	22.3	4.3	28.8	7.2
Cough	22.3	0.0	22.3	0.0
Pyrexia	16.5	0.7	20.9	2.2
Nausea	14.4	0.0	21.6	0.0
Peripheral edema	12.9	0.0	22.3	2.2
Epistaxis	8.6	0.7	23.7	1.4
Stomatitis	2.9	0.0	20.9	3.6

Rates shown are not adjusted for differences in exposure.

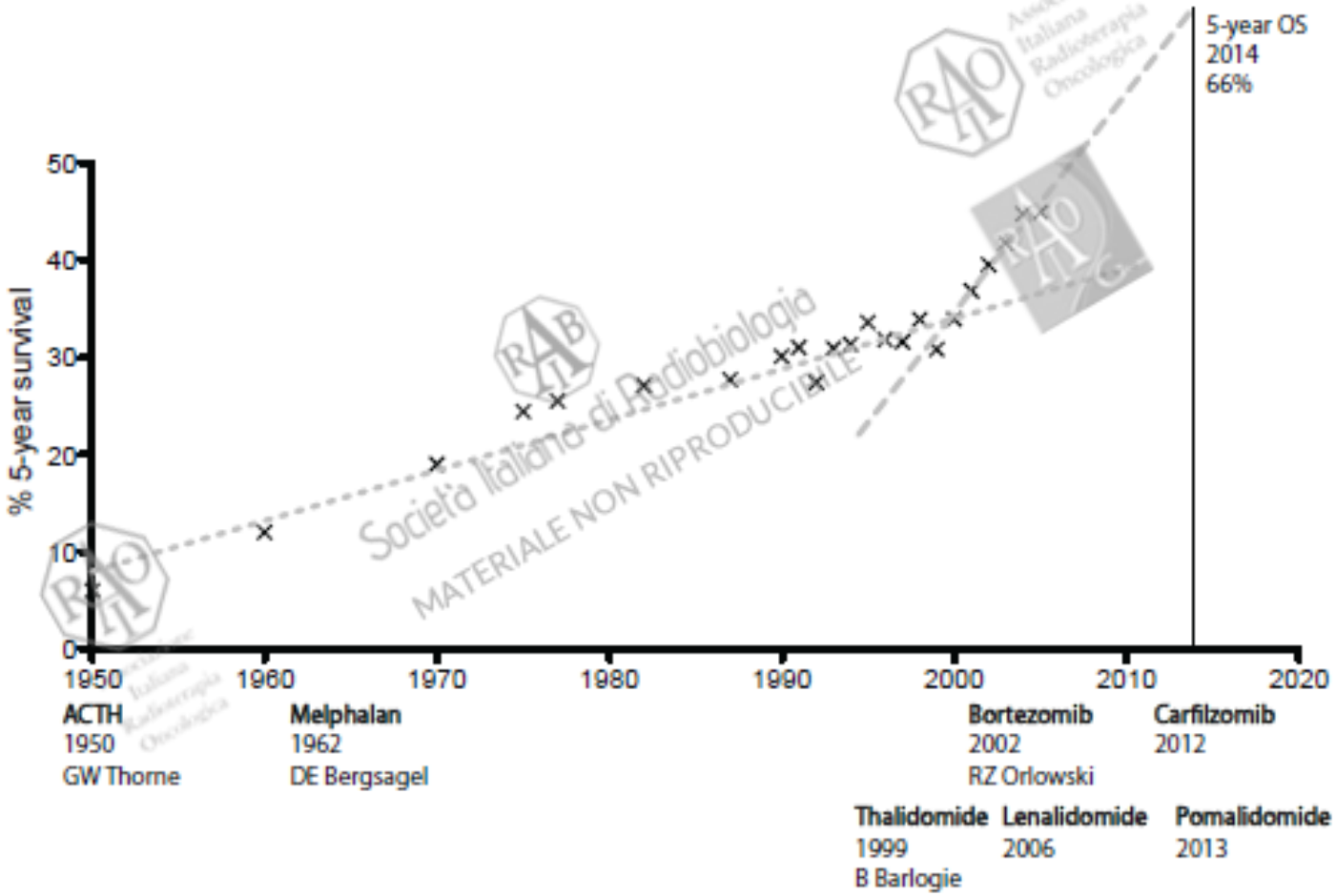
American Society of Hematology 2015, MCL3001, Rule S, et al.

Mechanisms of action of lenalidomide in lymphoma cells and nodal microenvironment



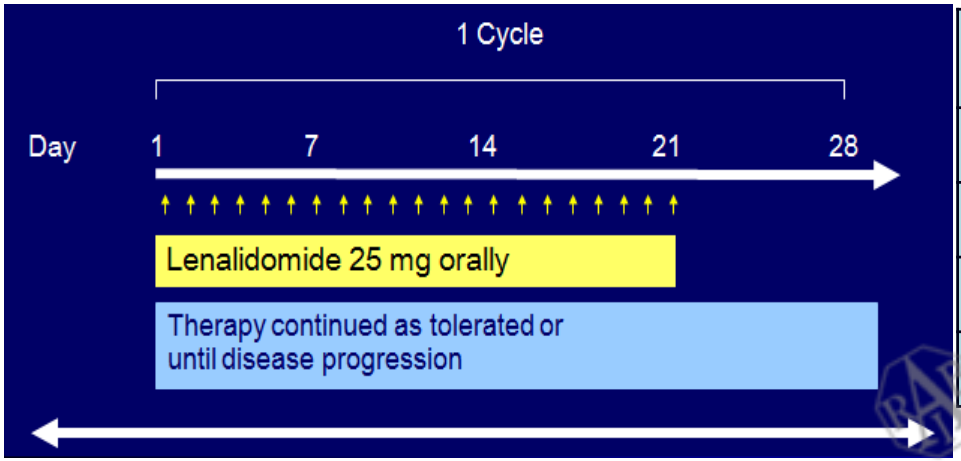
Gribben J., J Clin Oncol 2015.

MM: continuous improvement in overall survival



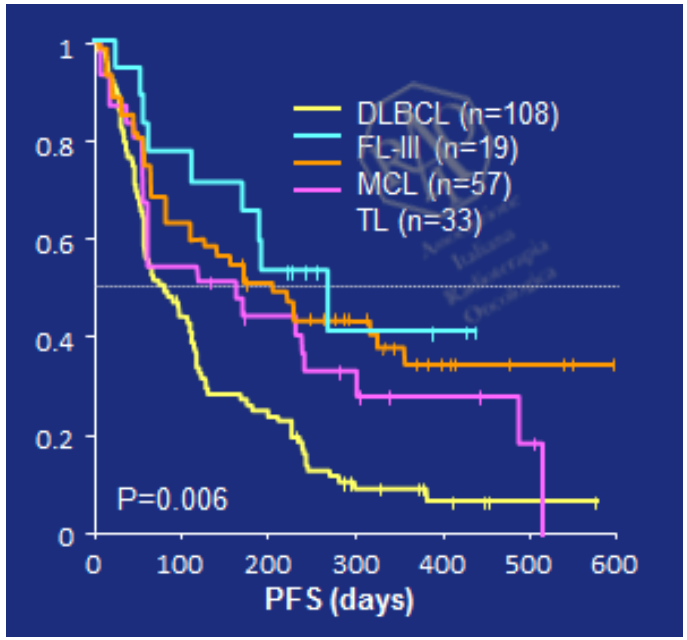
Bergsagel MD 2104 ASCO Educational Book

Lenalidomide in relapsed/refractory DLBCL



Histology, n (%)	ORR
Aggressive NHL, 49 (100%)	17 (35%)
DLBCL, 26 (53%)	5 (19%)
MCL, 15 (31%)	8 (53%)
Follicular g3, 5 (10%)	3 (60%)

Wiernik PH et al, J Clin Oncol 2008.

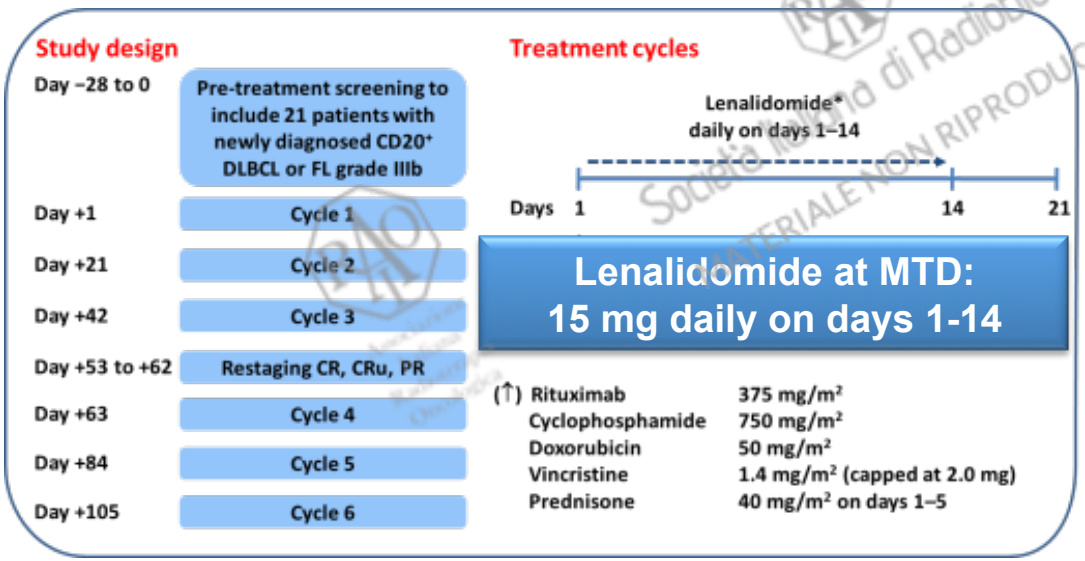


Witzig et al 2011

Author	N.	ORR	CR/ Cru	Median PFS (months)	Median DOR (months)
Wiernik 2008	26	19%	15%	2-3	
Witzig 2011	108	28%	7%	2.7	4.6
REVEAL 2013	77	43%	18%	3.5	

Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial

Umberto Vitolo, Annalisa Chiappella, Silvia Franceschetti, Angelo Michele Carella, Ileana Baldi, Giorgio Inghirami, Michele Spina, Vincenzo Pavone, Marco Ladetto, Anna Marina Liberati, Anna Lia Molinari, Pierluigi Zinzani, Flavia Salvi, Pier Paolo Fattori, Alfonso Zaccaria, Martin Dreyling, Barbara Botto, Alessia Castellino, Angela Congiu, Marcello Gaudiano, Manuela Zanni, Giovannino Ciccone, Gianluca Gaidano, Giuseppe Rossi, on behalf of the Fondazione Italiana Linfomi



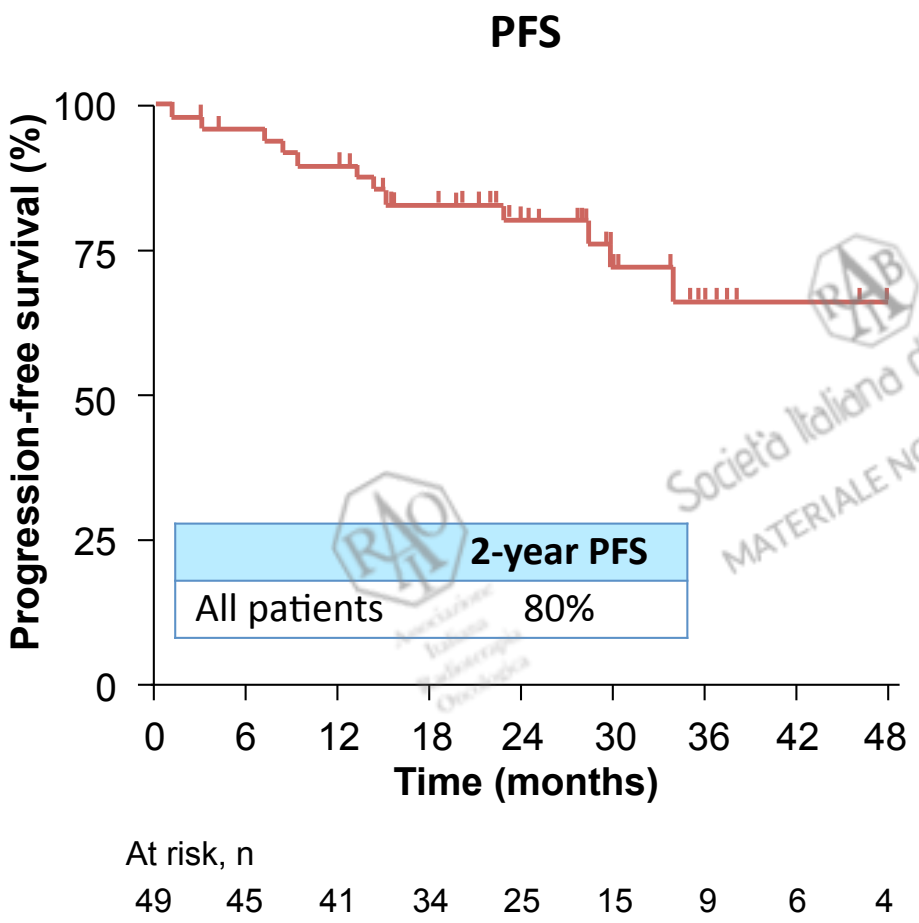
CNS prophylaxis according to Italian Society of Hematology guidelines
Pegfilgrastim or G-CSF as neutropenia prophylaxis
Low Molecular Weigh Heparin as DVT prophylaxis

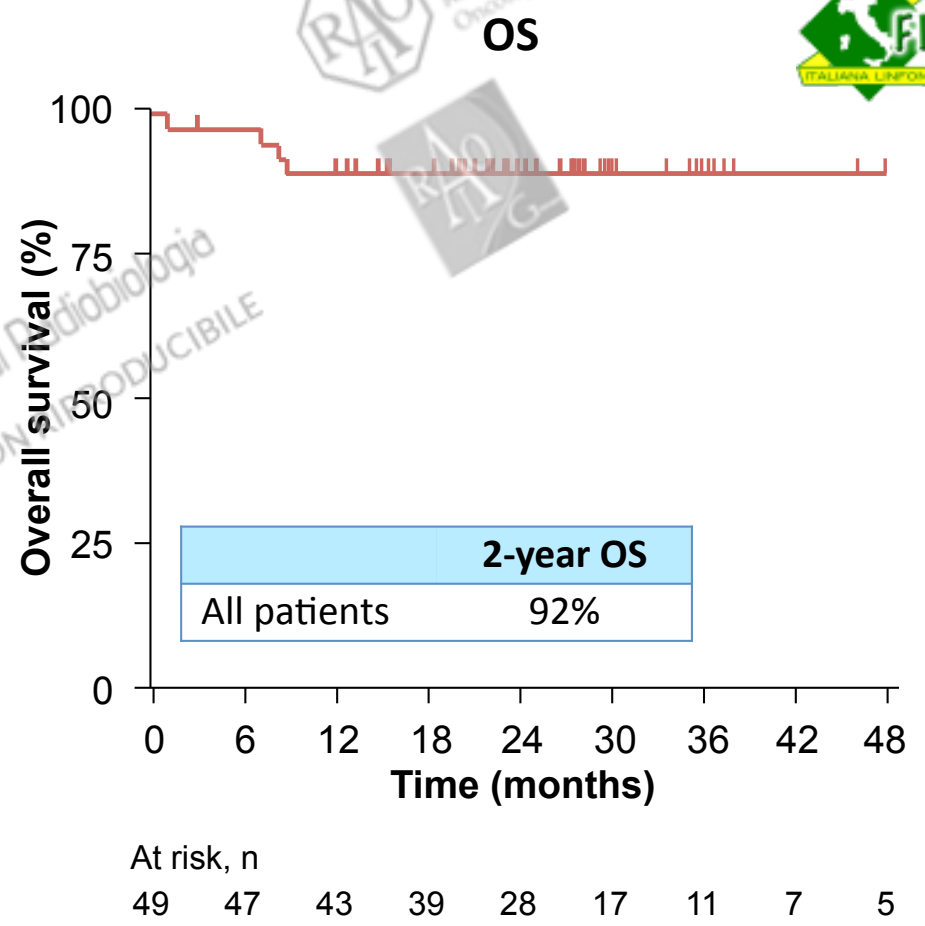
	Enrolled patients (n=49)
Age (years)	69 (64–71)
Sex	
Men	29 (59%)
Women	20 (41%)
Eastern Cooperative Oncology Group performance status	
0–1	42 (86%)
2	7 (14%)
Ann Arbor stage	
II	6 (12%)
III	8 (16%)
IV	35 (71%)
International Prognostic Index risk	
Low-intermediate risk	19 (39%)
High-intermediate or high risk	30 (61%)
Lymphoma type	
Diffuse large B-cell lymphoma	45 (92%)
Follicular lymphoma grade 3b	4 (8%)
Bone marrow involvement	17 (35%)
B symptoms	21 (43%)
Increased lactate dehydrogenase concentration*	22 (45%)
Increased β_2 microglobulin*	34 (69%)

Data are median (IQR) or n (%). *Higher than the upper limit of normal.

Table 1: **Baseline clinical characteristics**

REAL07 phase II R2-CHOP21 in elderly untreated DLBCL: ORR 92%, CR 86%; PFS and OS



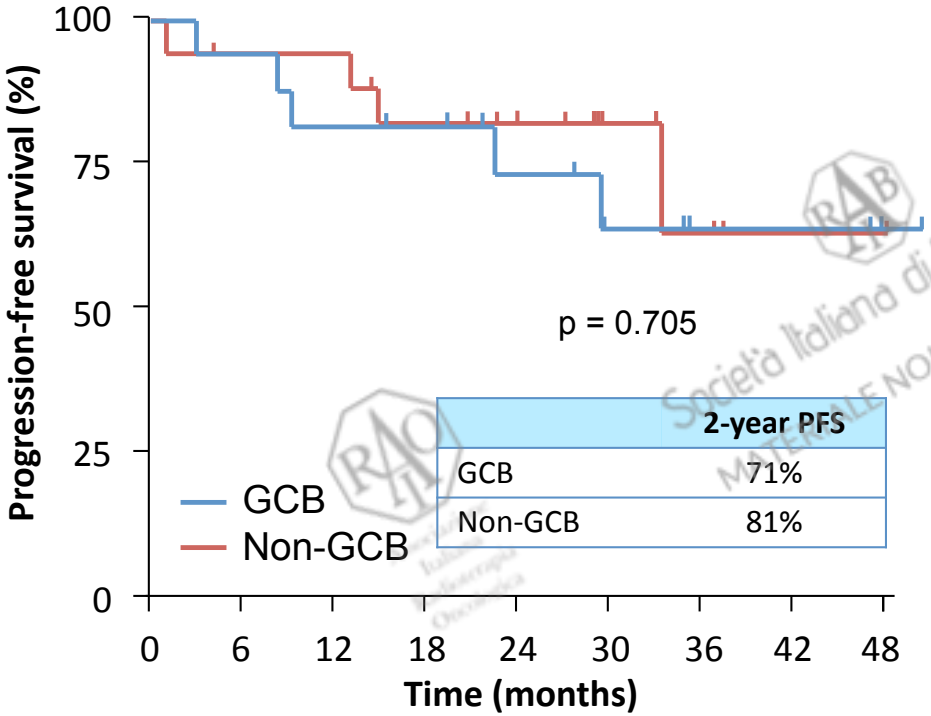


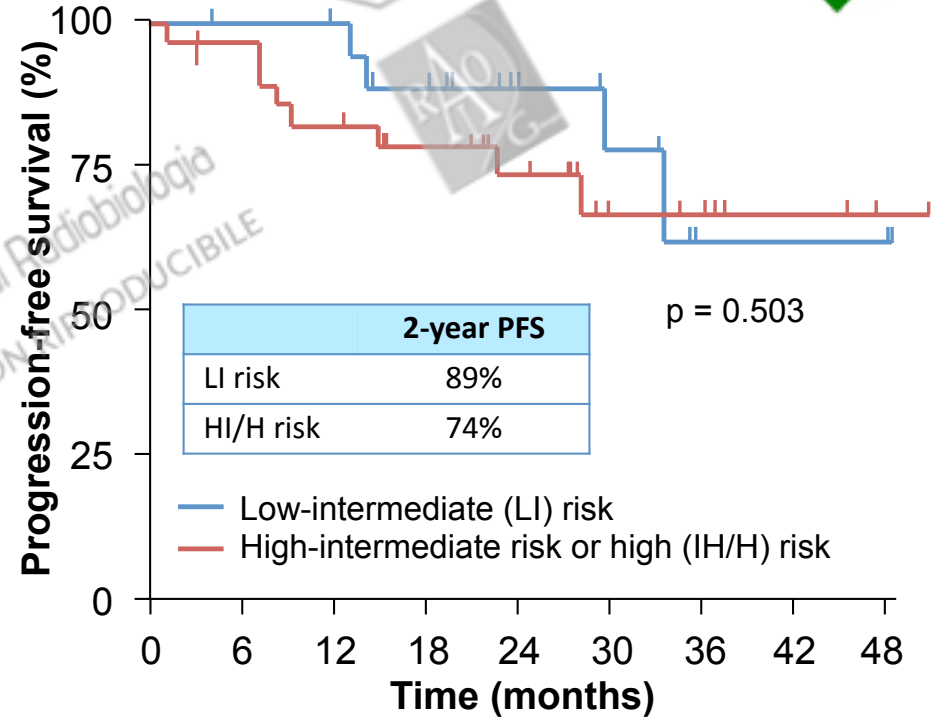
Median follow-up of 28 months. N = 49 elderly DLBCL patients.

DLBCL, diffuse large B-cell lymphoma ; PFS, progression-free survival; OS, overall survival; R2-CHOP, lenalidomide and rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone.

Vitolo U, et al. Lancet Oncol. 2014;15:730-7.

REAL07 phase II R2-CHOP21 in elderly untreated DLBCL: PFS by COO and IPI





At risk, n									
GCB	16	14	12	11	8	6	3	3	
Non-GCB	16	15	15	12	10	5	3	3	1

At risk, n									
LI	20	19	18	15	10	6	2	2	2
HI/H	29	26	23	19	15	9	7	4	4

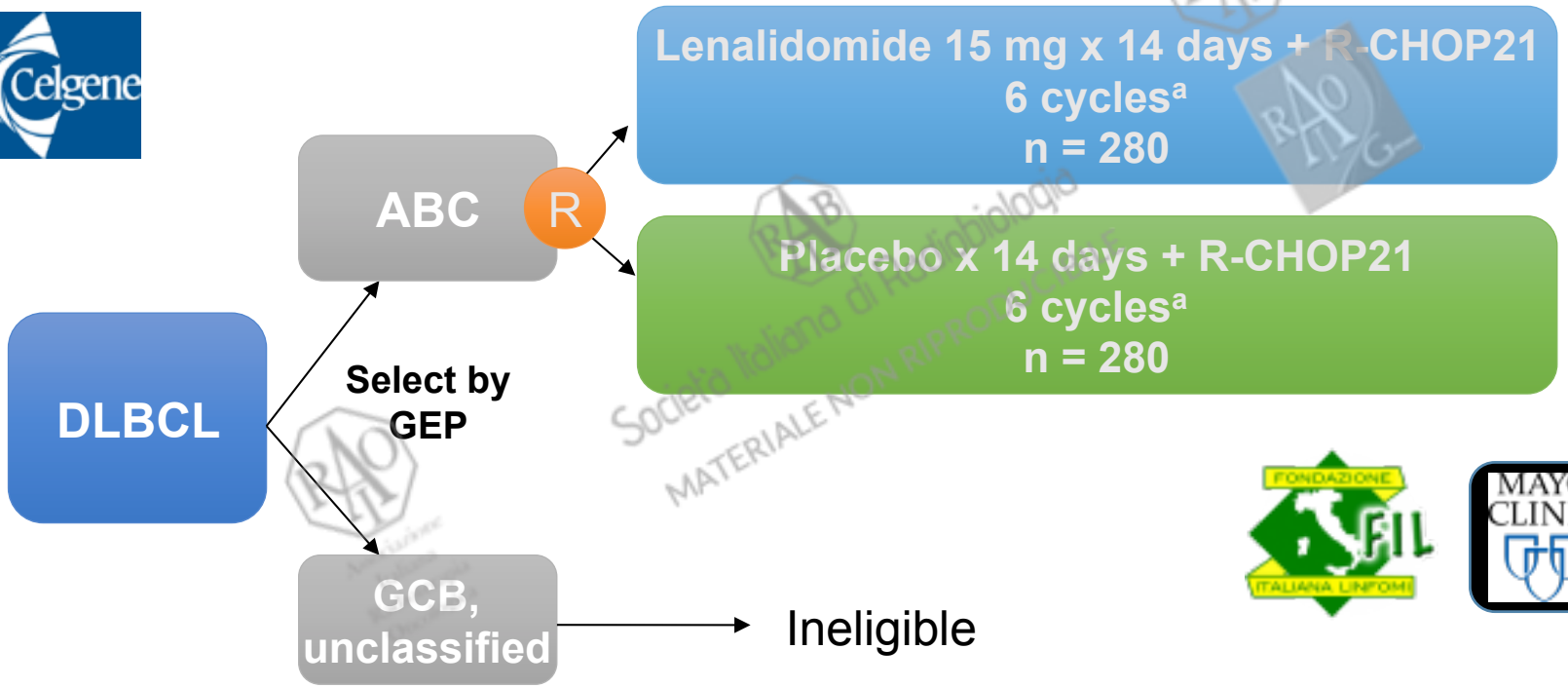
Median follow-up of 28 months.

COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell like; HI/H, high-intermediate or high risk; IPI, International Prognostic Index; LI, low-intermediate risk; PFS, progression-free survival; R2-CHOP, lenalidomide and rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone.

Vitolo U, et al. Lancet Oncol. 2014;15:730-7.

DLC-002 (ROBUST) study design: COO categorization made on nanostring

Sponsor: Celgene Corporation. Team leader: FIL and Mayo Clinic.
PIs: U. Vitolo, T. Witzig.
Writing committee: U. Vitolo, A. Chiappella, M. Spina, T. Witzig, G. Nowakowski.



- Newly diagnosed ABC DLBCL; IPI ≥ 2; ECOG PS ≤ 2; age 18–80 years
- Primary endpoint = PFS; N = 560
- 90% power to detect 60% difference in PFS (control median PFS estimate = 24 months)
- 208 sites expected to be involved

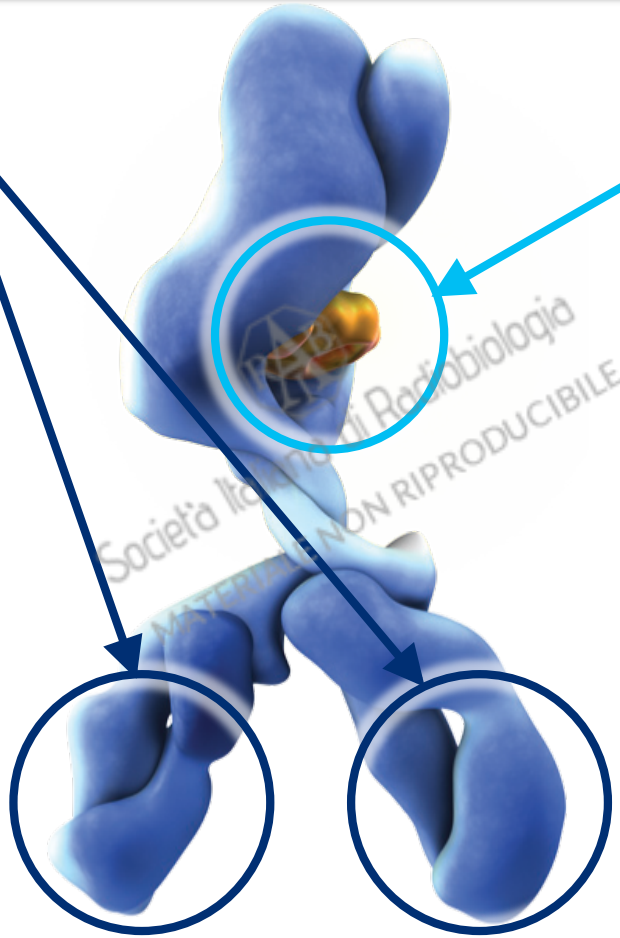
[a]Option for 2 additional rituximab doses after completing treatment regimen (if considered standard of care per local practice). ABC, activated B-cell like; COO, cell of origin ; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal centre B-cell like; GEP, gene expression profile; IPI, International Prognostic Index; PFS, progression-free survival; PI, principle investigator; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone.

NCT02285062.

GA101 (Obinutuzumab): Designed for increased antibody-dependent cellular cytotoxicity (ADCC) and Direct Cell Death

Type II anti-CD20 mAb[1]

Increased Direct Cell Death[2]



Glycoengineered Fc region[2]

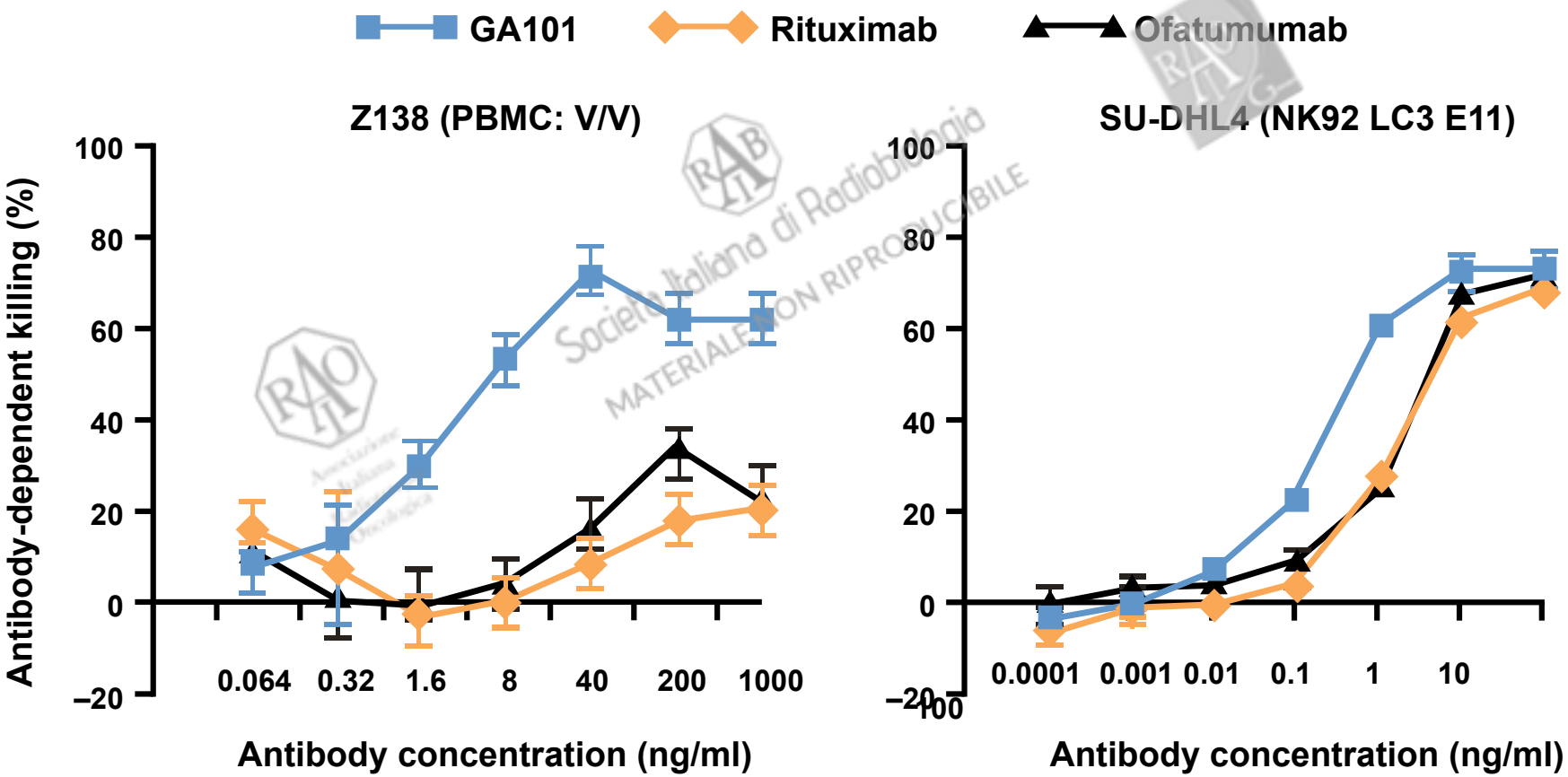
Increased antibody-dependent cellular cytotoxicity (ADCC)[2]

Extensive clinical development program to evaluate the superiority of GA101 over rituximab in multiple head-to-head trials

1. Niederfellner G, et al. Blood 2011; 118:358–367. 2. Mössner E, et al. Blood 2010; 115:4393–4402.

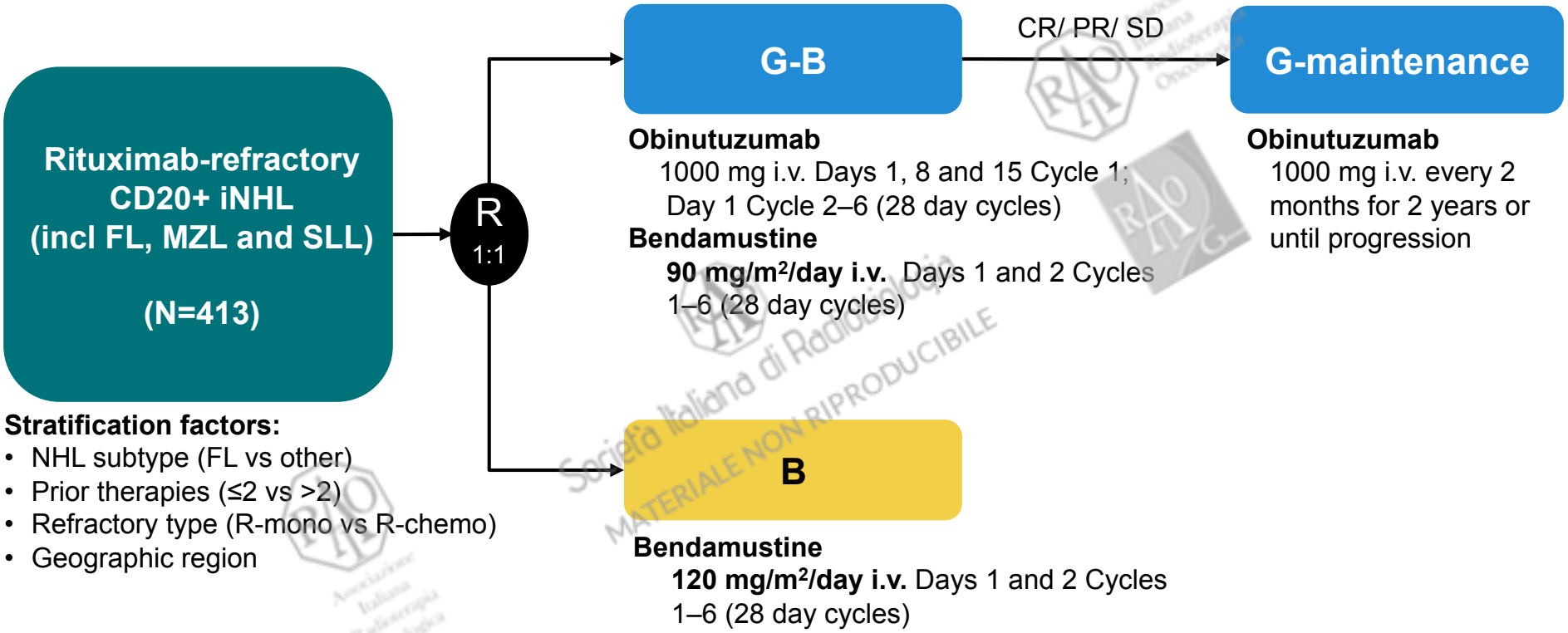
GA101-induced ADCC

GA101 exhibited up to 100-fold higher ADCC potency than rituximab and ofatumumab on Z138 and SU-DHL4 cell lines



ADCC, antibody-dependent cell-mediated cytotoxicity; PBMC, peripheral blood mononuclear cells
Herter S, *et al.* Poster presentation at ASH 2010 (Abstract 3925).

GADOLIN: Study design (NCT01059630)



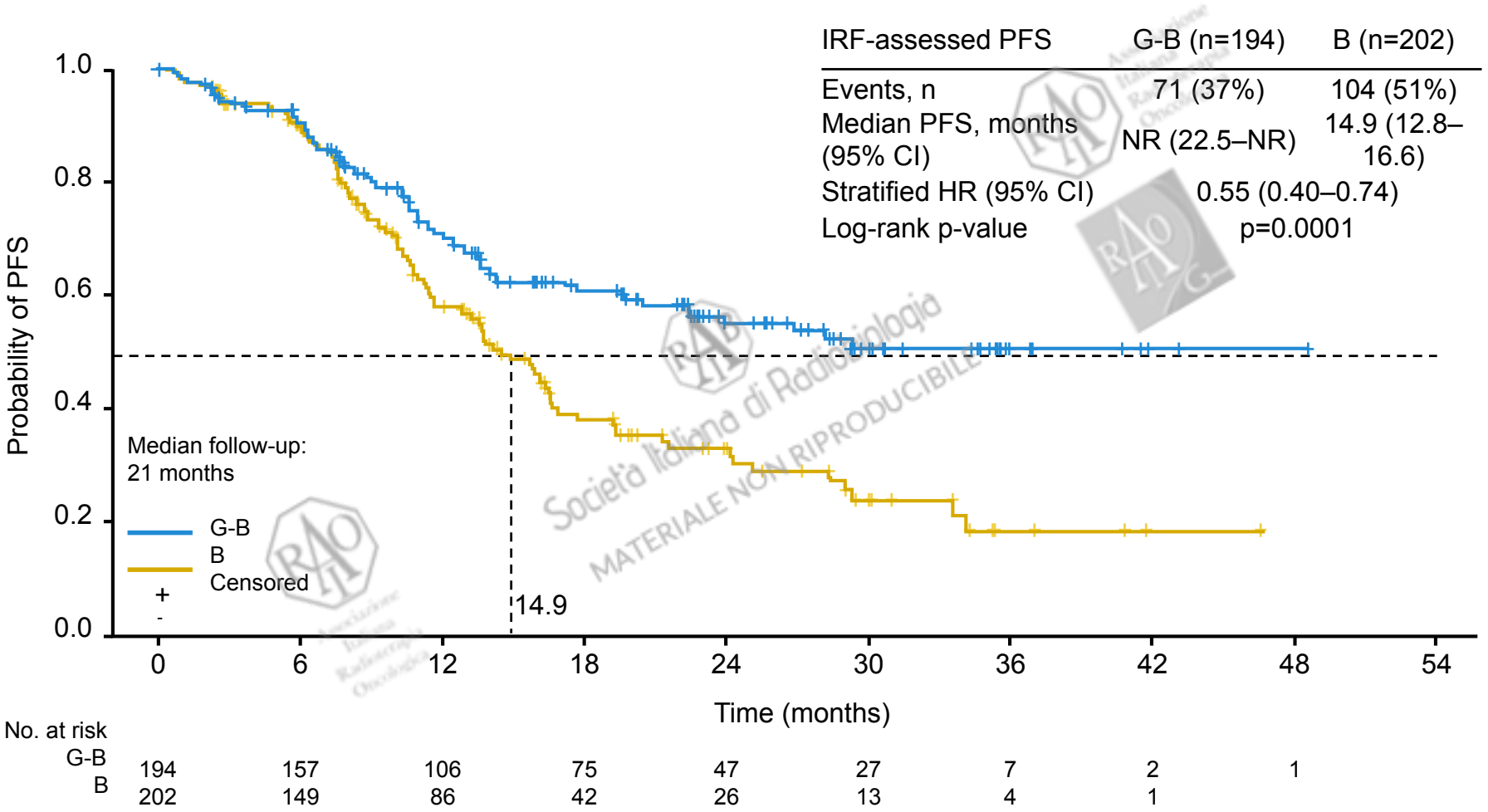
Stratification factors:

- NHL subtype (FL vs other)
- Prior therapies (≤2 vs >2)
- Refractory type (R-mono vs R-chemo)
- Geographic region

- International, randomized, open-label study
- Response monitored by CT scan post-induction, then every 3 months for 2 years, then every 6 months

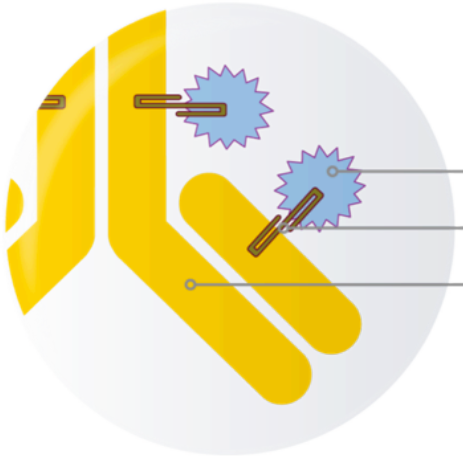
iNHL, indolent non-Hodgkins lymphoma; G-B, obinutuzumab plus bendamustine; G, obinutuzumab.

GADOLIN primary outcome: IRF-assessed PFS



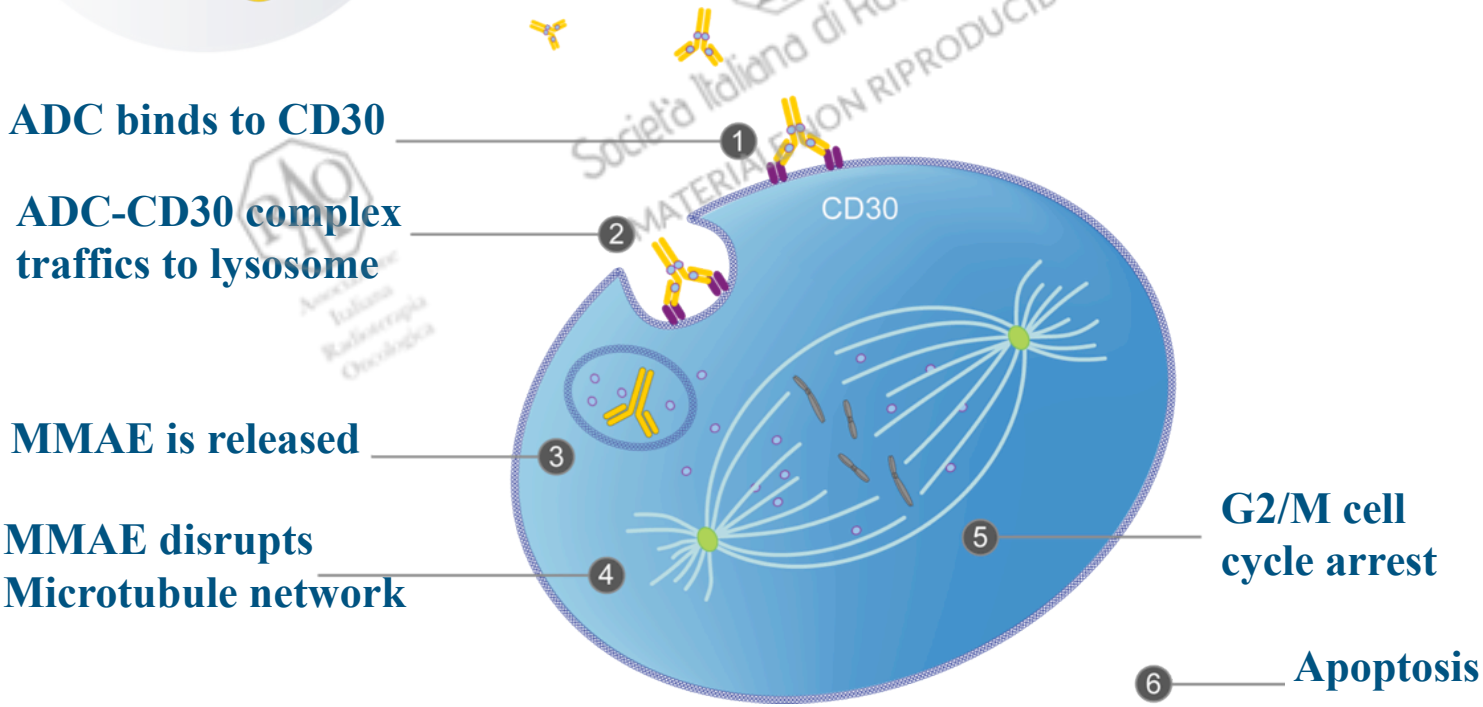
IRF, independent radiology facility; HR, hazard ratio; CI, confidence interval; NR, not reached.

Brentuximab Vedotin (SGN-35)
Mechanism of action



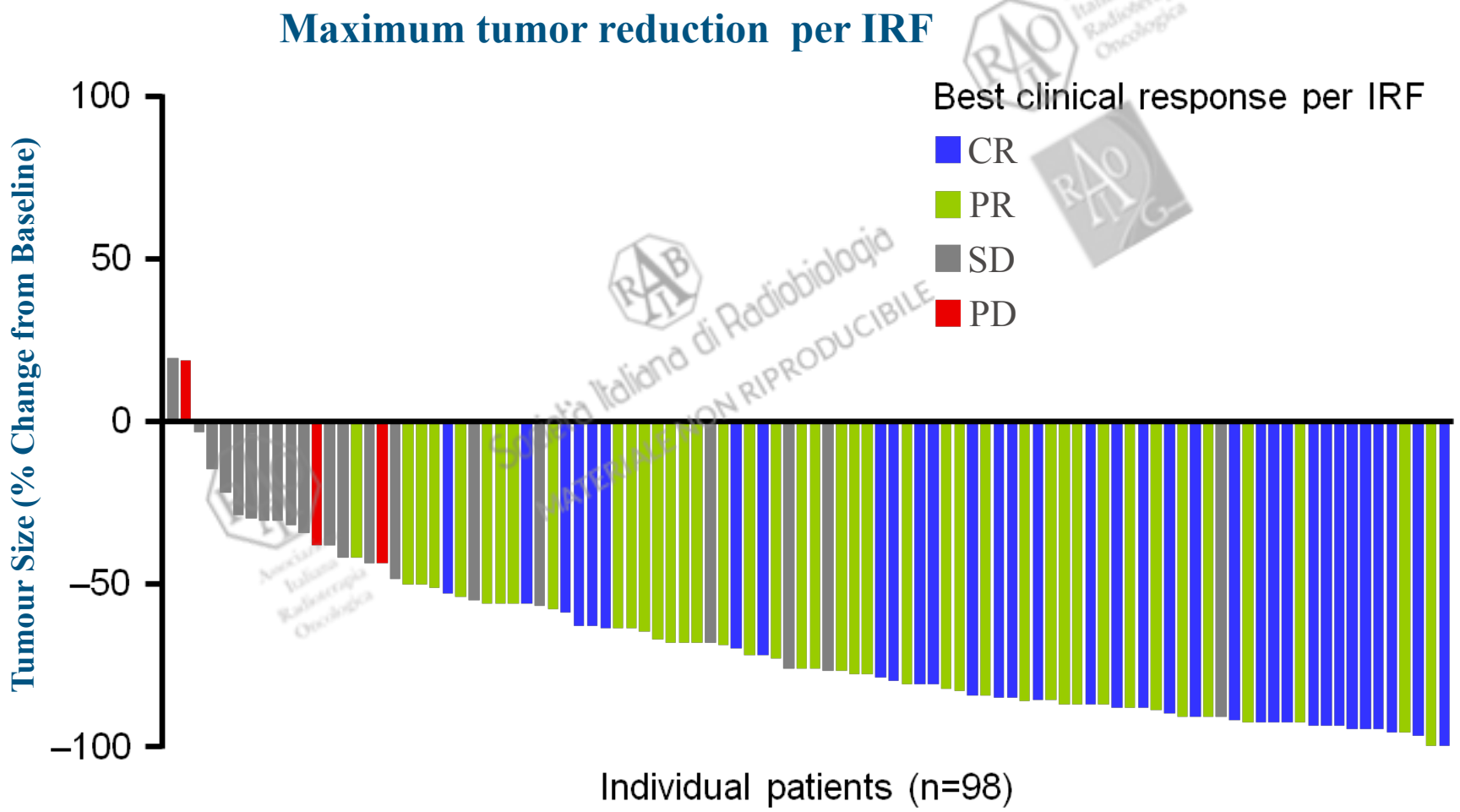
Brentuximab vedotin (SGN-35) ADC

- monomethyl auristatin E (MMAE), potent antitubulin agent
- protease-cleavable linker
- anti-CD30 monoclonal antibody



1. ADC binds to CD30
2. ADC-CD30 complex traffics to lysosome
3. MMAE is released
4. MMAE disrupts Microtubule network
5. G2/M cell cycle arrest
6. Apoptosis

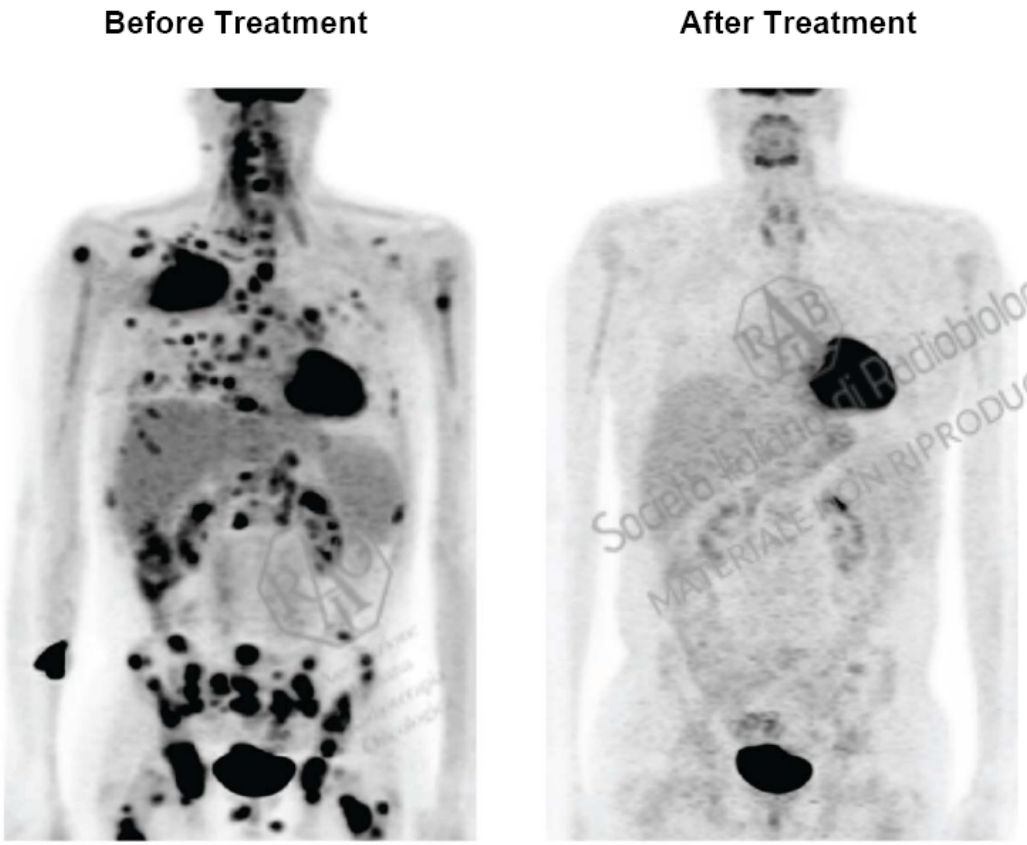
Phase II Pivotal Study of BV
Patients with R/R HL post ASCT



Younes A et al, J Clin Oncol 2012;30: 2183-2189.

SG035-0001: Phase 1 dose-escalation study in patients with rel/ref CD30+ lymphoma

Case study



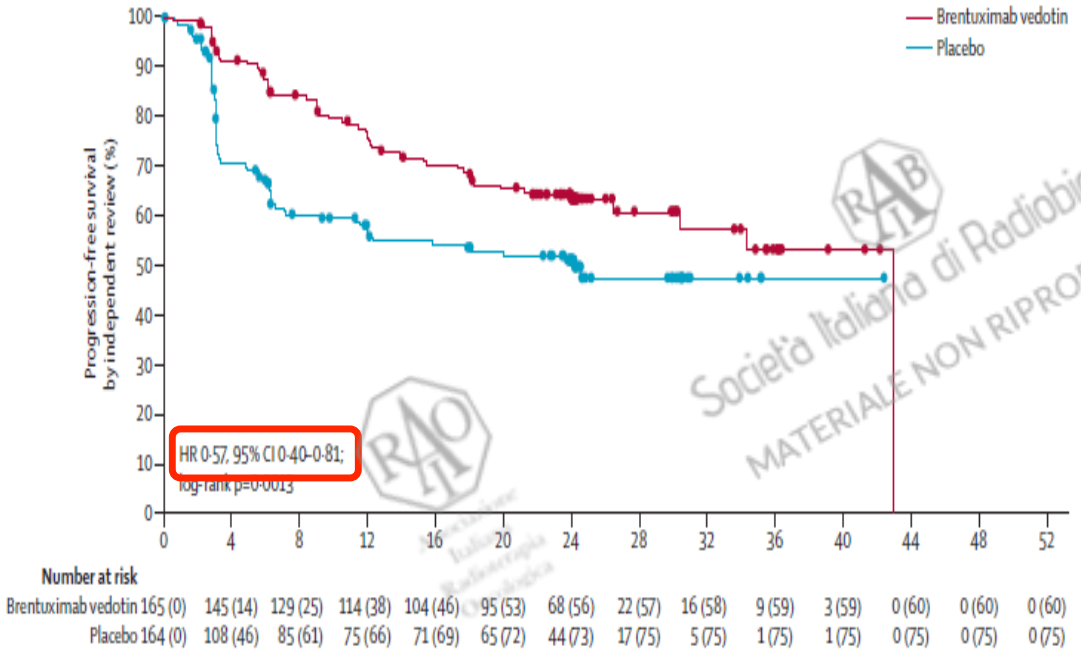
- 37-yr-old male diagnosed with HL
- Prior treatment:
  - Five chemotherapy regimens
  - Two radiotherapy regimens
  - ASCT
  - Rituximab
- Cycle 2 restaging: CR

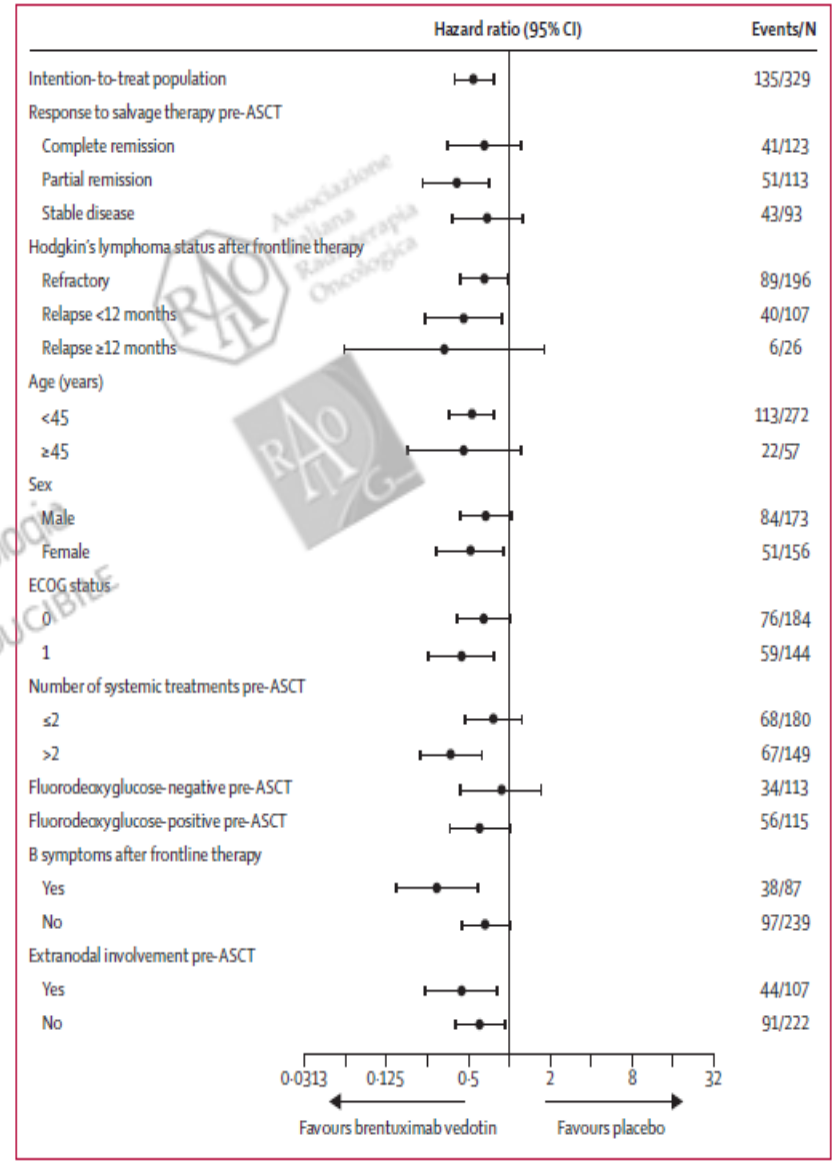
From New England Journal of Medicine, Younes A, et al. Brentuximab Vedotin (SGN-35) for Relapsed CD30 Positive Lymphomas, 363;1812–21;Suppl Appendix.

Brentuximab vedotin & Hodgkin Lymphoma

- ***Approved indications***
  - Post-ASCT recurrences
  - After 2 lines of therapy if ASCT is not a therapeutic option

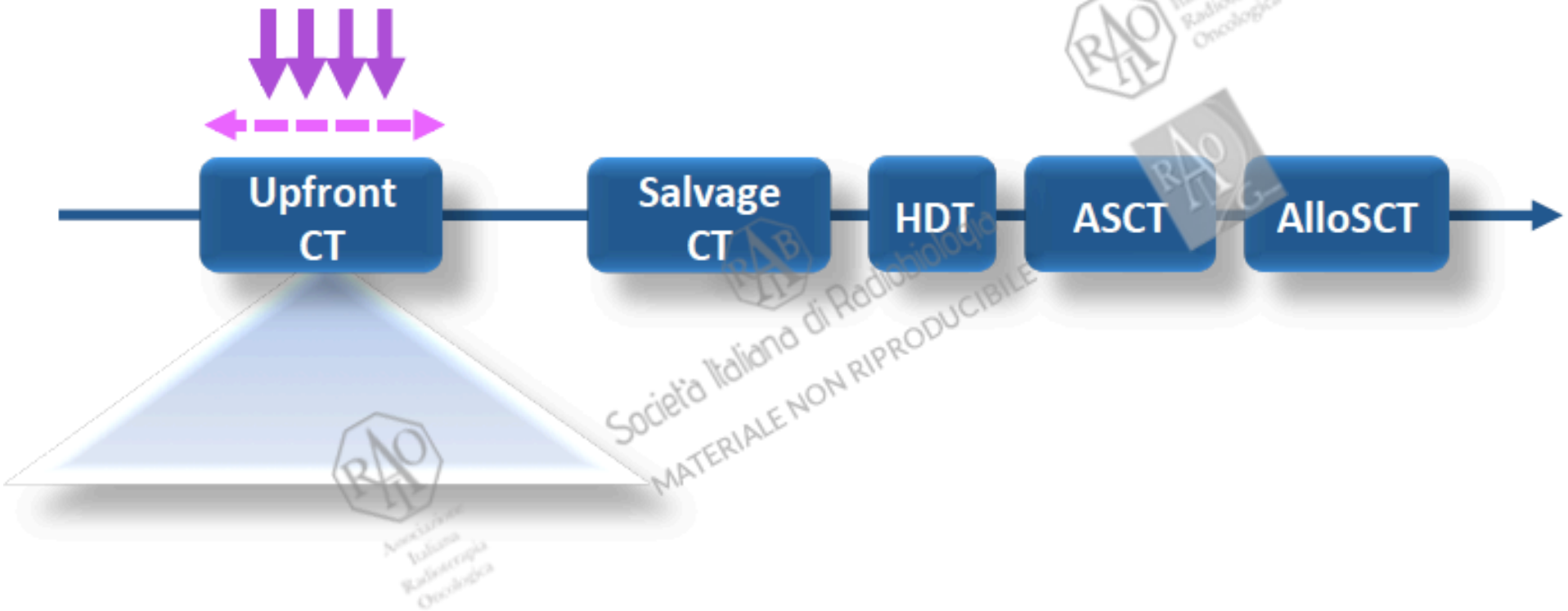
Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial





Moskowitz C.H. et al., The Lancet, 2015

Hodgkin Lymphoma: treatment sequence



Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study

Anas Younes, Joseph M Connors, Steven I Park, Michelle Fanale, Megan M O'Meara, Naomi N Hunder, Dirk Huebner, Stephen M Ansell

	Brentuximab vedotin and ABVD group (n=25)	Brentuximab vedotin and AVD group (n=26)
Any event	11 (44%)	0
Pulmonary toxic effects	9 (36%)	0
Interstitial lung disease	1 (4%)	0
Pneumonitis	1 (4%)	0

Table 3: Patient incidence of pulmonary toxic effects

- 12 mo.s PFS
- BV-ABVD: 85% (range 64–100
- BV-AVD): 95% (range 85–100
- Estimated median PFS: not reached

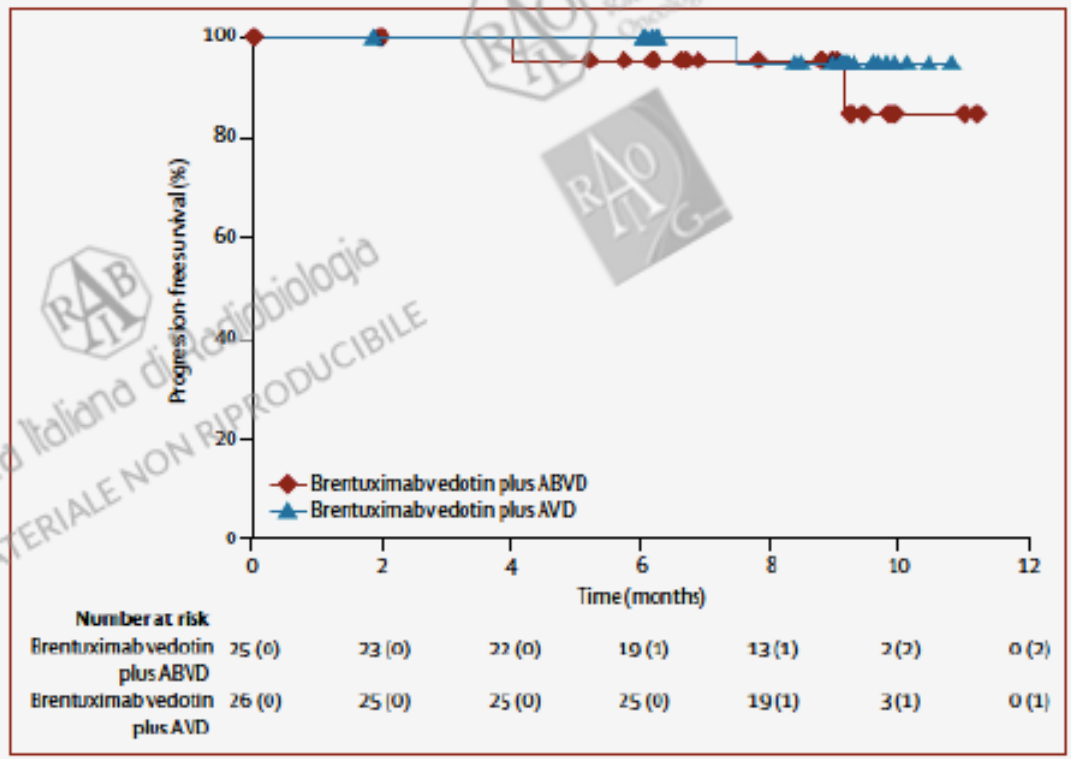


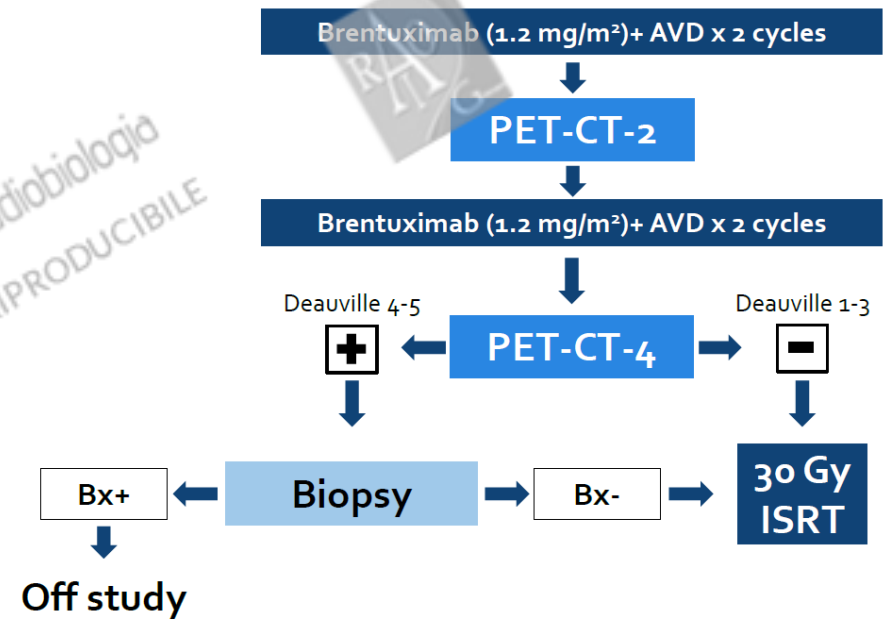
Figure 2: Progression-free survival per investigator assessment

Lancet Oncol 2013; 14: 1348–56

Pilot study of brentuximab vedotin plus AVD/ISRT in previously untreated early-stage, unfavorable-risk HL

Objectives: *Primary:* safety, pulmonary toxicity; *Secondary:* prognostic significance of interim PET (Deauville criteria), preliminary efficacy

Pt Characteristics, N=30	
Median age, yrs (range)	31 (18–59)
CD30+ HL, %	100
CD20+	13
EBV +, n=27	11
Stage II, %	100
Unfavorable risk features, ≥1 (%)	100
B symptoms, %	47
ESR >50 or ESR >39 with B-symptoms, %	67
Nodal sites >2, %	67
Extranodal involvement, %	47
Bulk ≥10 cm, %	47
Anterior mediastinal mass >10 cm, n=14; median size, cm (range)	13 (10–16.9)
Bulky by MSK definition*, n=28 (%)	86

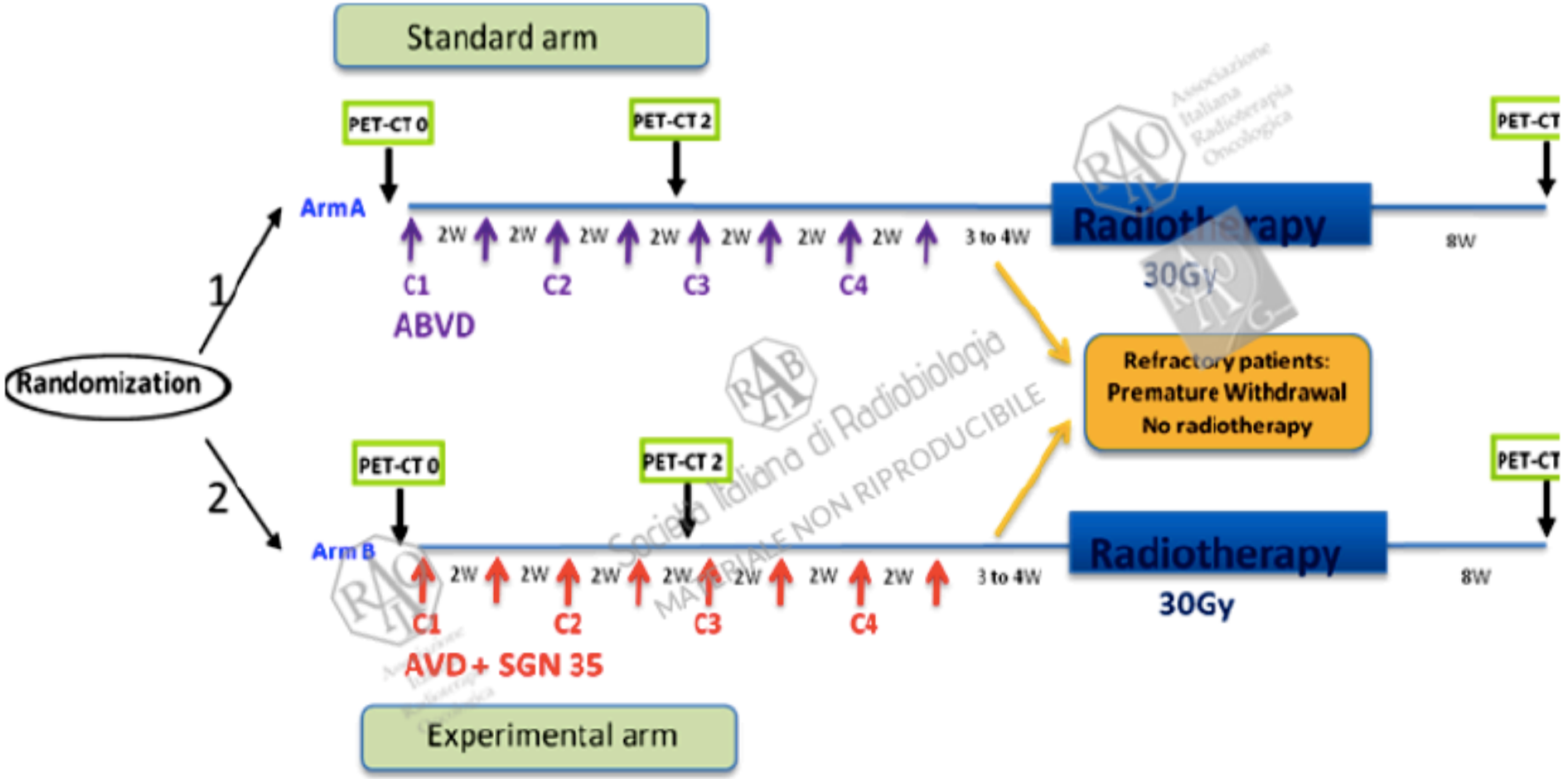


* >7 cm in MTD or >7 cm in MCD

Kumar A et al. ICML 2015, Oral presentation from Abstract #88

Supra-diaphragmatic stage I –II unfavorable EORTC/GELA

BREACH



Primary end point

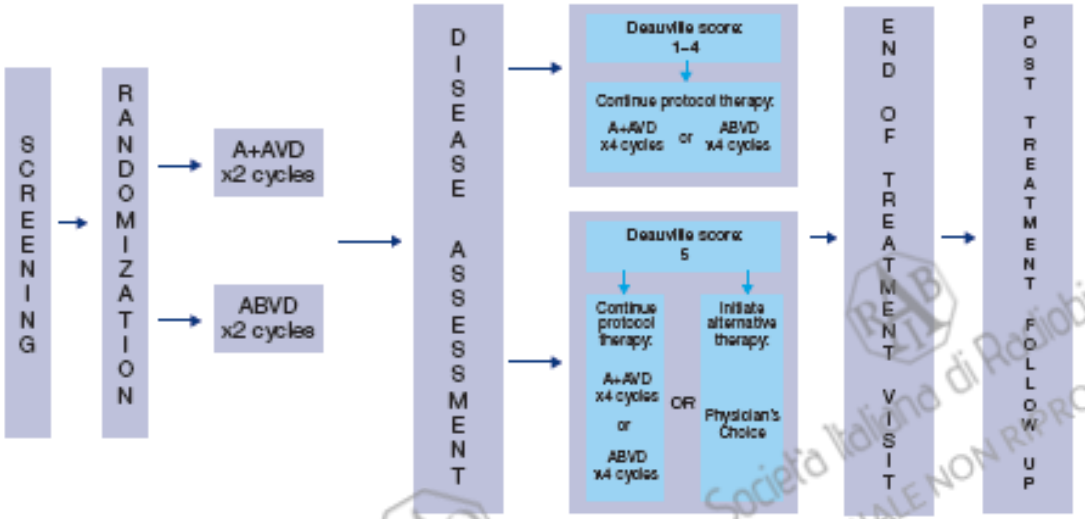
- PET2 negativity (score 1 and 2): A^{2}VD >75% of PET negativity

Secondary end points

- CR rate ; PFS; OS; Safetyf of Brentuximab vedotin in a combined modality treatment

ECHELON-1: Ongoing phase 3 trial of brentuximab vedotin and AVD vs. ABVD in frontline advanced HL

Schema:



Objectives:

- Primary: PFS
- Secondary:
  - Overall survival
  - Others: CR rate, safety, EFS, DFS, ORR, DOR, duration of CR, rate of irradiation for those not in CR, CR at the end of front-line therapy, rate of cycle 2 PET negativity, HRQOL, PK, immunogenicity

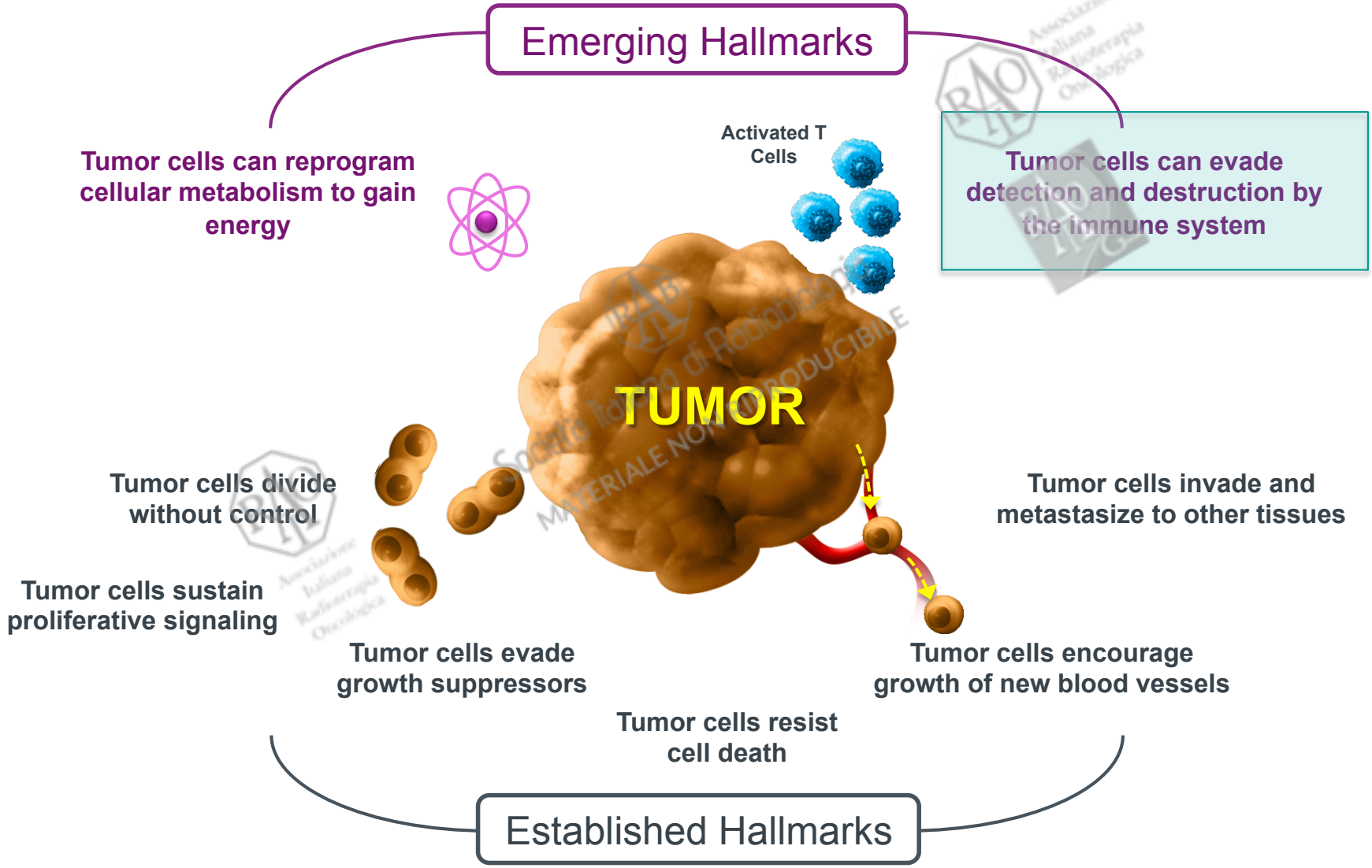
Treatment regimen:

- Brentuximab vedotin + AVD (up to 6 cycles):
  - Brentuximab vedotin 1.2 mg/kg IV infusion on days 1 and 15 of each 28-day cycle
  - Doxorubicin 25 mg/m^2 IV infusion on days 1 and 15 of each 28-day cycle
  - Vinblastine 6 mg/m^2 IV infusion on 1 days and 15 of each 28-day cycle
  - Dacarbazine (DTIC) 375 mg/m^2 on days 1 and 15 of each 28-day cycle
- ABVD (up to 6 cycles):
  - Doxorubicin 25 mg/m^2 IV infusion on days 1 and 15 of each 28-day cycle
  - Bleomycin 10 units/m^2 IV infusion on Days 1 and 15 of each 28-day cycle
  - Vinblastine 6 mg/m^2 IV infusion on 1 days and 15 of each 28-day cycle
  - Dacarbazine (DTIC) 375 mg/m^2 on days 1 and 15 of each 28-day cycle

PFS = Progression-free Survival, IRF = Independent review facility, EFS = Event-free survival, DFS= Disease-free survival, DOR= Duration of response, HRQOL= Health-related quality of life, PK= Pharmacokinetics

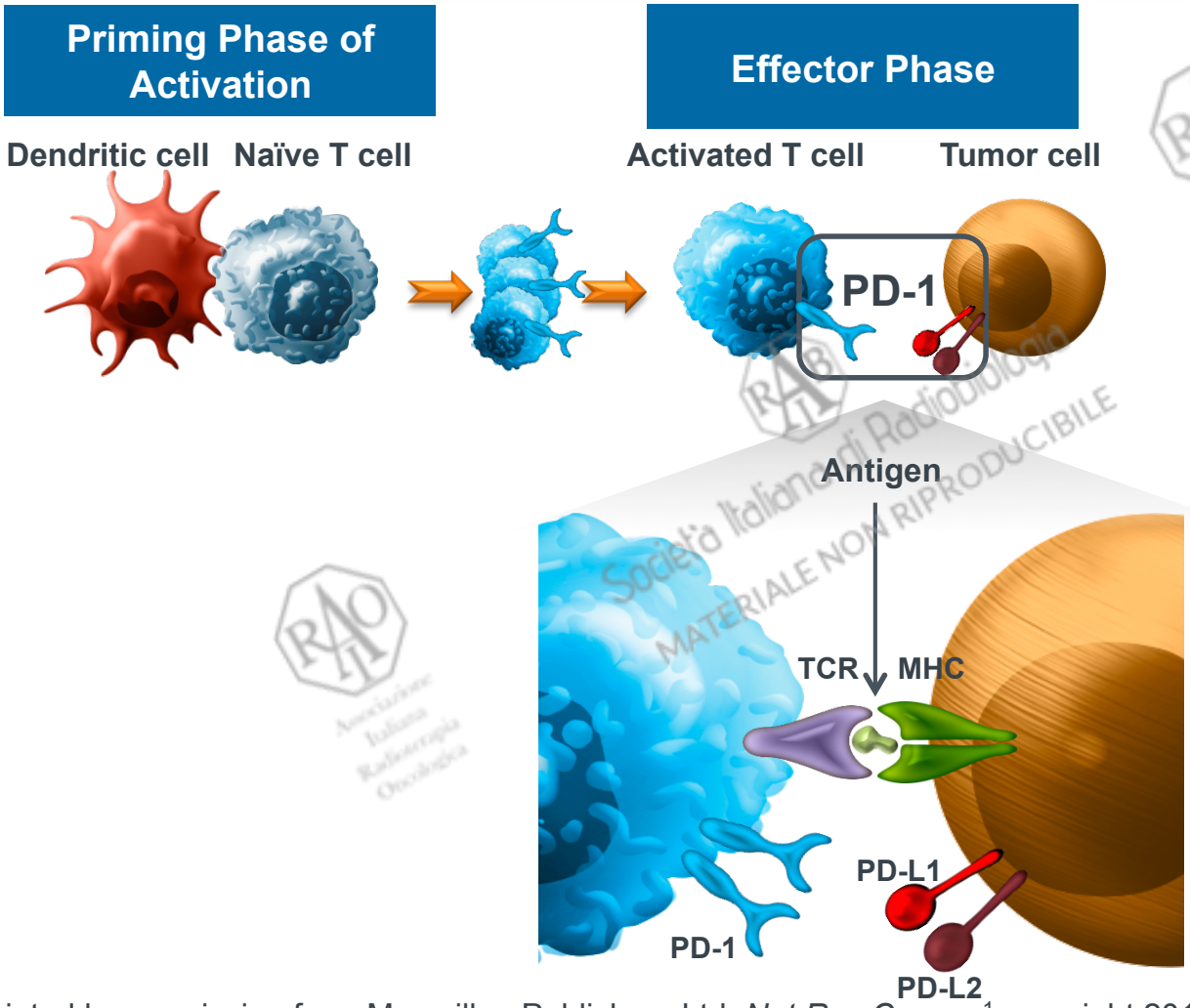
Radford, et al. ISHL 2013; Cologne, Germany (P017)

Evasion of the Immune Response Is One of the Emerging Hallmarks of Cancer[1]



1. Hanahan D et al, *Cell*. 2011;144:646–674.

Exploiting the PD-1 Immune Checkpoint Pathway[1]



- Emerging research has identified PD-1 as an immune checkpoint pathway that tumor cells may exploit to evade immune surveillance
- Tumor cells may block immune responses via the PD-1 immune checkpoint pathway by expressing the dual PD-1 ligands, PD-L1 and PD-L2

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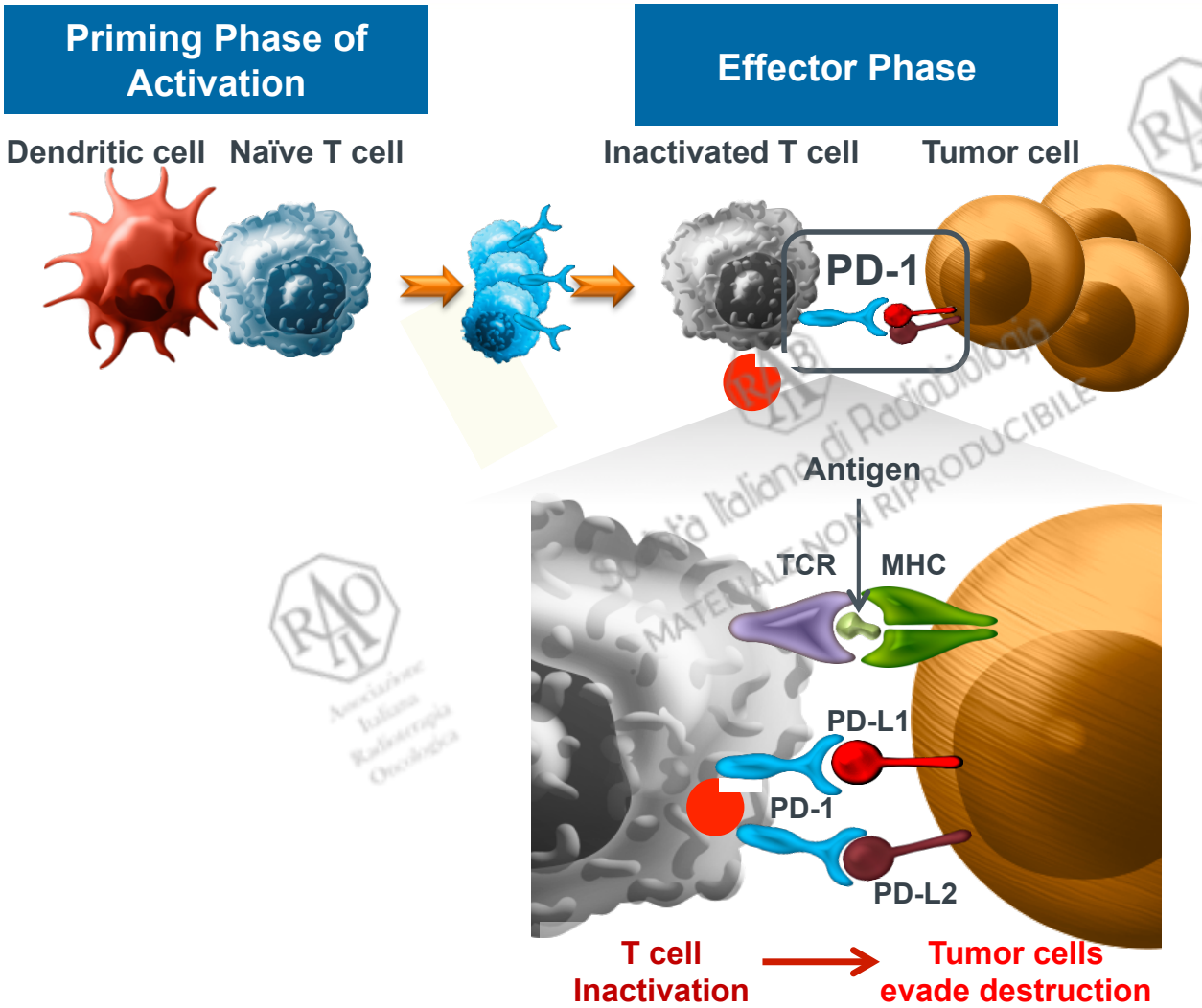
PD-1 = programmed cell death protein 1; TCR = T-cell receptor; MHC = major histocompatibility complex; PD-L1 = programmed cell death ligand 1; PD-L2 = programmed cell death ligand 2.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–64.

3. Exploiting the PD-1 Immune Checkpoint Pathway[1]



- PD-1 is upregulated on activated T cells during the effector phase of the immune response
- PD-L1 and PD-L2 engage the PD-1 receptor on T cells to downregulate T-cell activity in the effector phase

Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Cancer,*[1] copyright 2012.

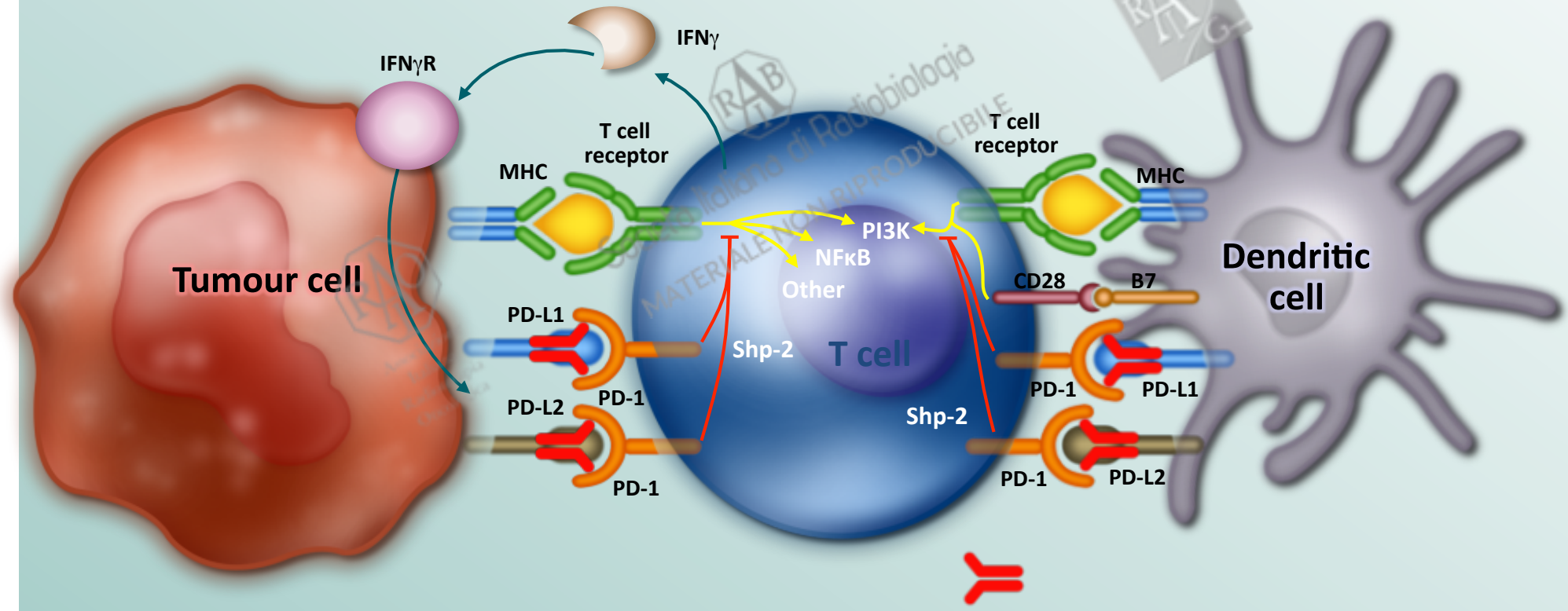
PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PD-L2 = programmed cell death ligand 2.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

PD-1 inhibitors: mechanism of action

Recognition of tumour by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 upregulation on tumour

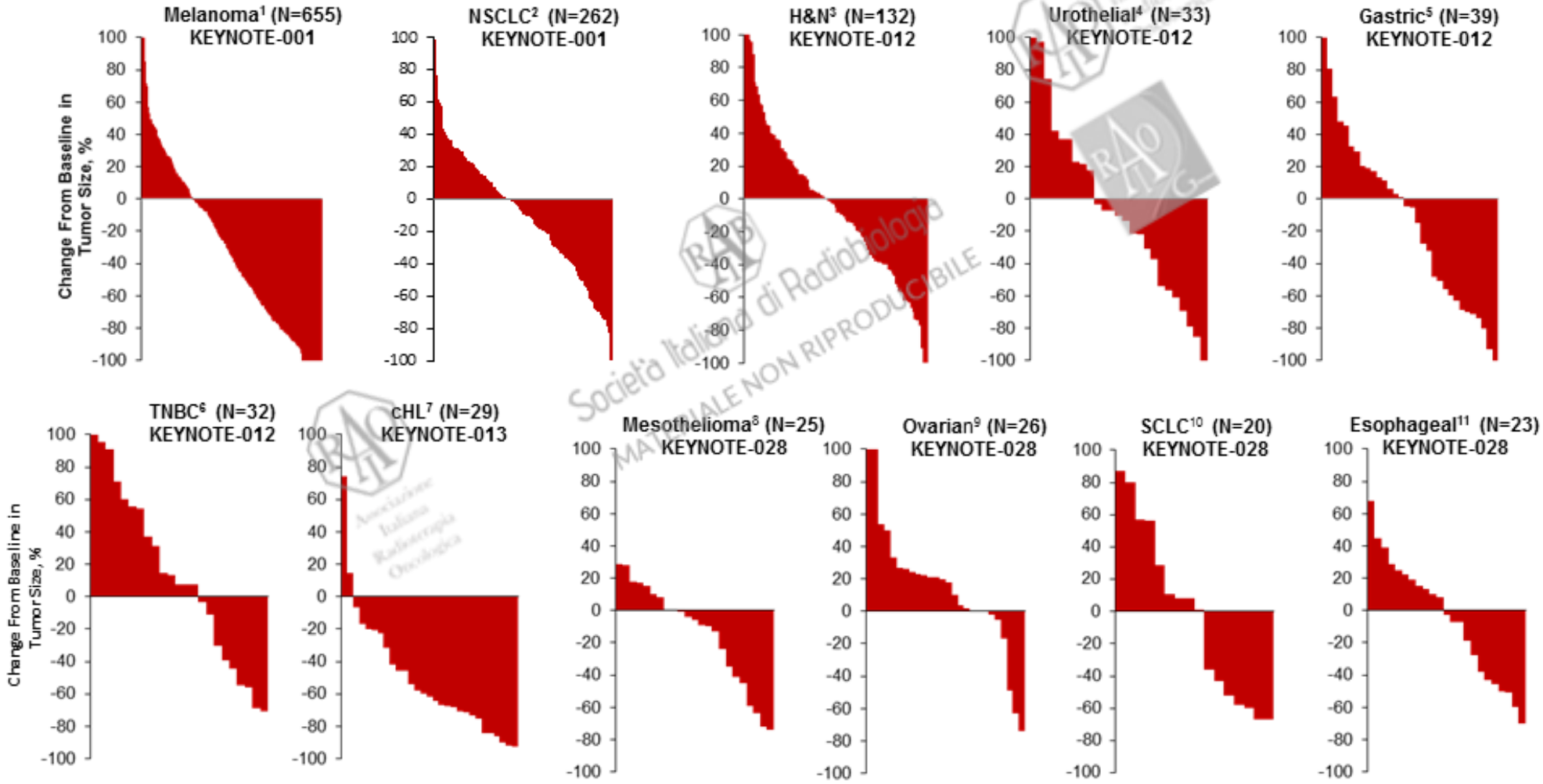
Priming and activation of T cells through MHC/antigen and CD28/B7 interactions with antigen-presenting cells



PD-1 receptor-blocking Ab

restoring anti-tumour T cell activity

Pembrolizumab Antitumor Activity



cHL = classical Hodgkin's lymphoma; H&N = head and neck; NSCLC = non-small cell lung cancer; TNBC = triple-negative breast cancer.

1. Daud A et al. 2015 ASCO; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. 2015 ASCO; 4. Plimack E et al. 2015 ASCO; 5. Bang YJ et al. 2015 ASCO; 6. Nanda R et al. SABCS 2014; 7. Moskowitz C et al. 2014 ASH Annual Meeting; 8. Alley EA et al. 2015 AACR; 9. Varga A et al. 2015 ASCO; 10. Ott PA et al. 2015 ASCO; 11. Doi T et al. 2015 ASCO.

CLINICAL DEVELOPMENT OF PD-1 AND PD-L1 INHIBITORS

PD-1	**Nivolumab**	Fully human IgG4 mAb	BMS	ph III
	Pidilizumab	Humanized IgG1 mAb	Cure Tech	ph II
	Pembrolizumab	Humanized IgG4 mAb	Merck	ph III
	AMP-224	Recombinant PD-L2 Fc fusion protein	GSK	ph I
PD-L1	BMS-936559	Fully human IgG4 mAb	BMS	ph I
	MEDI4736	Engineered human IgG1 mAb	MedImmune	ph III
	MPDL3280A (Atezolizumab)	Engineered human IgG1 mAb	Genentech	ph III
	MSB0010718C	Engineered human IgG1 mAb	EMD Serono	ph II

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D., Caroline Dutriaux, M.D., Michele Maio, M.D., Laurent Mortier, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Catriona McNeil, M.D., Ph.D., Ewa Kalinka-Warzocha, M.D., Ph.D., Kerry J. Savage, M.D., Micaela M. Hernberg, M.D., Ph.D., Celeste Lebbé, M.D., Ph.D., Julie Charles, M.D., Ph.D., Catalin Mihalcioiu, M.D., Vanna Chiarion-Sileni, M.D., Cornelia Mauch, M.D., Ph.D., Francesco Cognetti, M.D., Ana Arance, M.D., Ph.D., Henrik Schmidt, M.D., D.M.Sc., Dirk Schadendorf, M.D., Helen Gogas, M.D., Lotta Lundgren-Eriksson, M.D., Christine Horak, Ph.D., Brian Sharkey, Ph.D., Ian M. Waxman, M.D., Victoria Atkinson, M.D., and Paolo A. Ascierto, M.D.

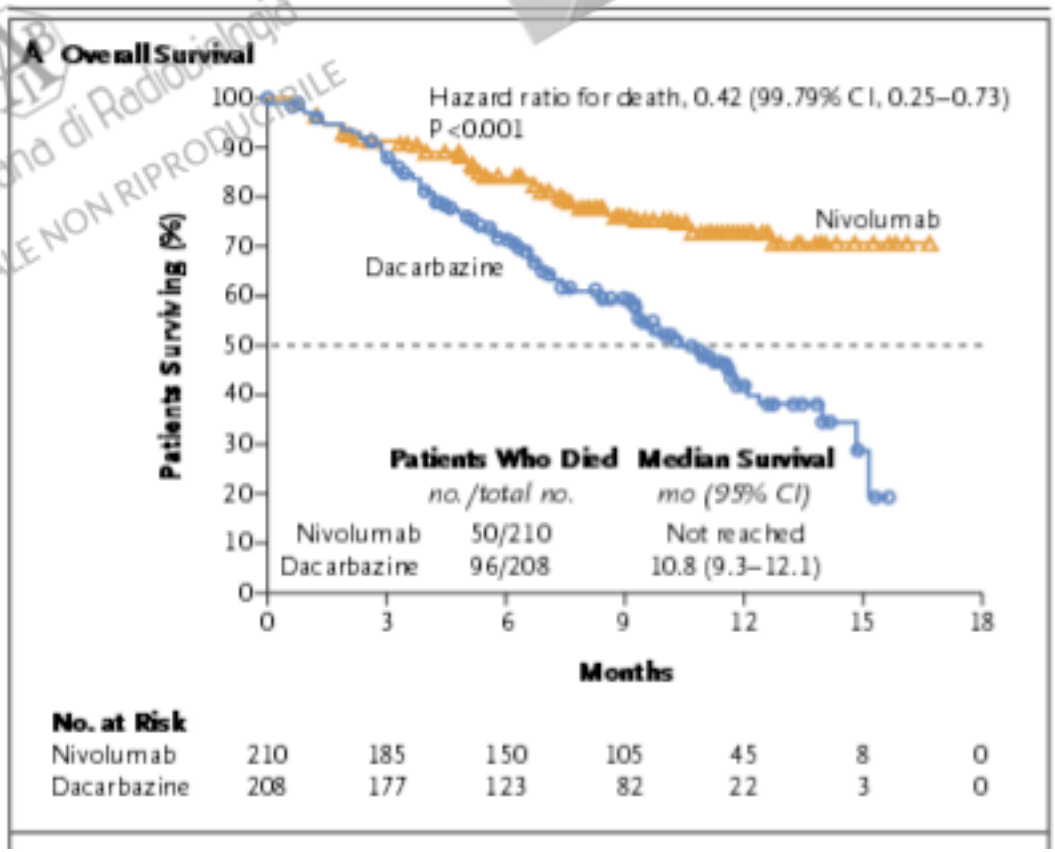
ABSTRACT

N Engl J Med. 2015 Jan 22;372(4):320-30.

CheckMate 066 ClinicalTrials.gov number, NCT01721772.

Table 2. Response to Treatment.*

Response	Nivolumab (N=210)	Dacarbazine (N=208)
Best overall response — no. (%)†		
Complete response	16 (7.6)	2 (1.0)
Partial response	68 (32.4)	27 (13.0)
Stable disease	35 (16.7)	46 (22.1)
Progressive disease	69 (32.9)	101 (48.6)
Could not be determined	22 (10.5)	32 (15.4)
Objective response‡		
No. of patients (% [95% CI])	84 (40.0 [33.3–47.0])	29 (13.9 [9.5–19.4])
Difference — percentage points (95% CI)	26.1 (18.0–34.1)	
Estimated odds ratio (95% CI)	4.06 (2.52–6.54)	
P value	<0.001	
Time to objective response — mo		
Median	2.1	2.1
Range	1.2–7.6	1.8–3.6
Mean	2.6±1.3	2.5±0.7
Duration of response — mo§		
Median (95% CI)	Not reached	6.0 (3.0–not reached)
Range	0.0–12.5	1.1–10.0



n engl j med 372;21, 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

Michael A. Postow, M.D., Jason Chesney, M.D., Ph.D., Anna C. Pavlick, D.O., Caroline Robert, M.D., Ph.D., Kenneth Grossmann, M.D., Ph.D., David McDermott, M.D., Gerald P. Linette, M.D., Ph.D., Nicolas Meyer, M.D., Jeffrey K. Giguere, M.D., Sanjiv S. Agarwala, M.D., Montaser Shaheen, M.D., Marc S. Ernstoff, M.D., David Minor, M.D., April K. Salama, M.D., Matthew Taylor, M.D., Patrick A. Ott, M.D., Ph.D., Linda M. Rollin, Ph.D., Christine Horak, Ph.D., Paul Gagnier, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and F. Stephen Hodi, M.D.

ABSTRACT

CheckMate 067
ClinicalTrials.gov
NCT01844505.

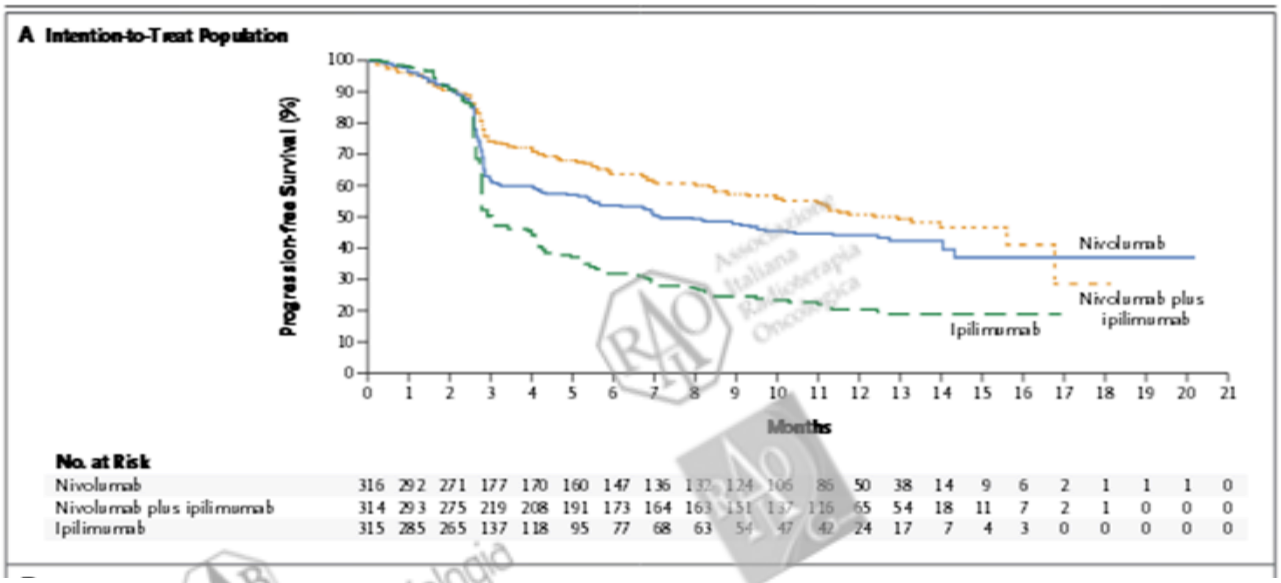
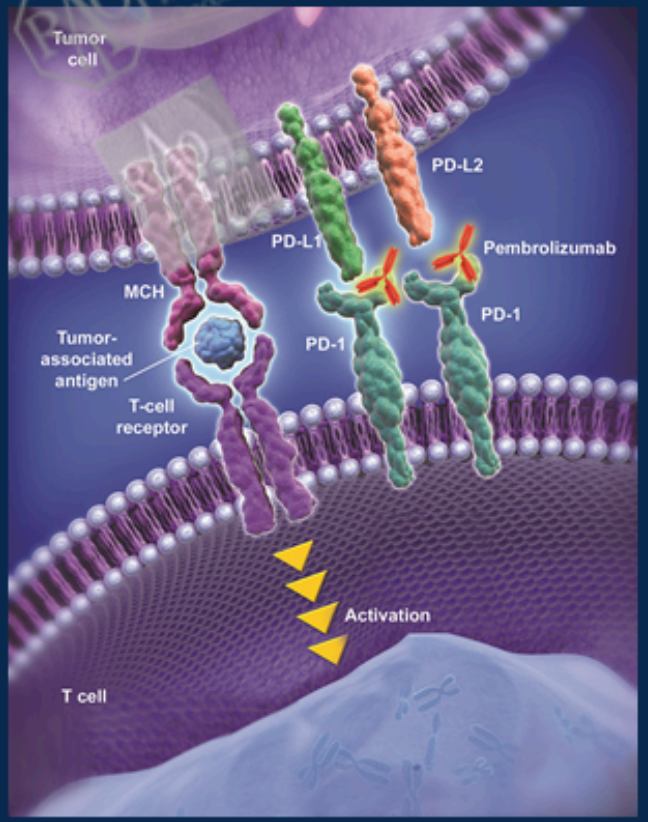


Table 2. Response to Treatment.

Variable	Nivolumab (N=316)	Nivolumab plus Ipilimumab (N=314)	Ipilimumab (N=315)
Best overall response — no. (%)*			
Complete response	28 (8.9)	36 (11.5)	7 (2.2)
Partial response	110 (34.8)	145 (46.2)	53 (16.8)
Stable disease	34 (10.8)	41 (13.1)	69 (21.9)
Progressive disease	119 (37.7)	71 (22.6)	154 (48.9)
Could not be determined	25 (7.9)	21 (6.7)	32 (10.2)
Objective response†			
No. of patients with response	138	181	60
% of patients (95% CI)	43.7 (38.1–49.3)	57.6 (52.0–63.2)	19.0 (14.9–23.8)
Estimated odds ratio (95% CI)‡	3.40 (2.02–5.72)	6.11 (3.59–10.38)	—
Two-sided P value	<0.001	<0.001	—
Time to objective response — mo			
Median	2.78	2.76	2.79
Range	2.3–12.5	1.1–11.6	2.5–12.4

Pembrolizumab and Advanced Melanoma

- Anti–PD-1 monoclonal antibody approved in >50 countries for treating advanced melanoma
  - Dose: 2 mg/kg administered IV over 30 min every 3 wk
- Studied as monotherapy in 3 trials
  - KEYNOTE-001 (phase 1b): initial evidence of efficacy (N = 655)[1]
  - KEYNOTE-002 (phase 2): PFS superiority over chemotherapy for ipi-refractory disease (N = 540)[2]
  - KEYNOTE-006 (phase 3): PFS and OS superiority over ipi (N = 834)[3]



1. Daud A et al. Presented at: 2015 ASCO Annual Meeting; May 29-June 2, 2015; Chicago, IL; abstr 9005.
2. Ribas A et al. *Lancet Oncol*. 2015;16:908-918.
3. Robert C et al. *N Engl J Med*. 2015;372:2521-2532.

Review

Radiotherapy and immune checkpoints inhibitors for advanced melanoma

Andrea Riccardo Filippi [a,*], Paolo Fava [b], Serena Badellino [a], Chiara Astrua [b], Umberto Ricardi [a], Pietro Quaglino [b]

Radiotherapy and Oncology xxx (2016)

Immunogenic hub

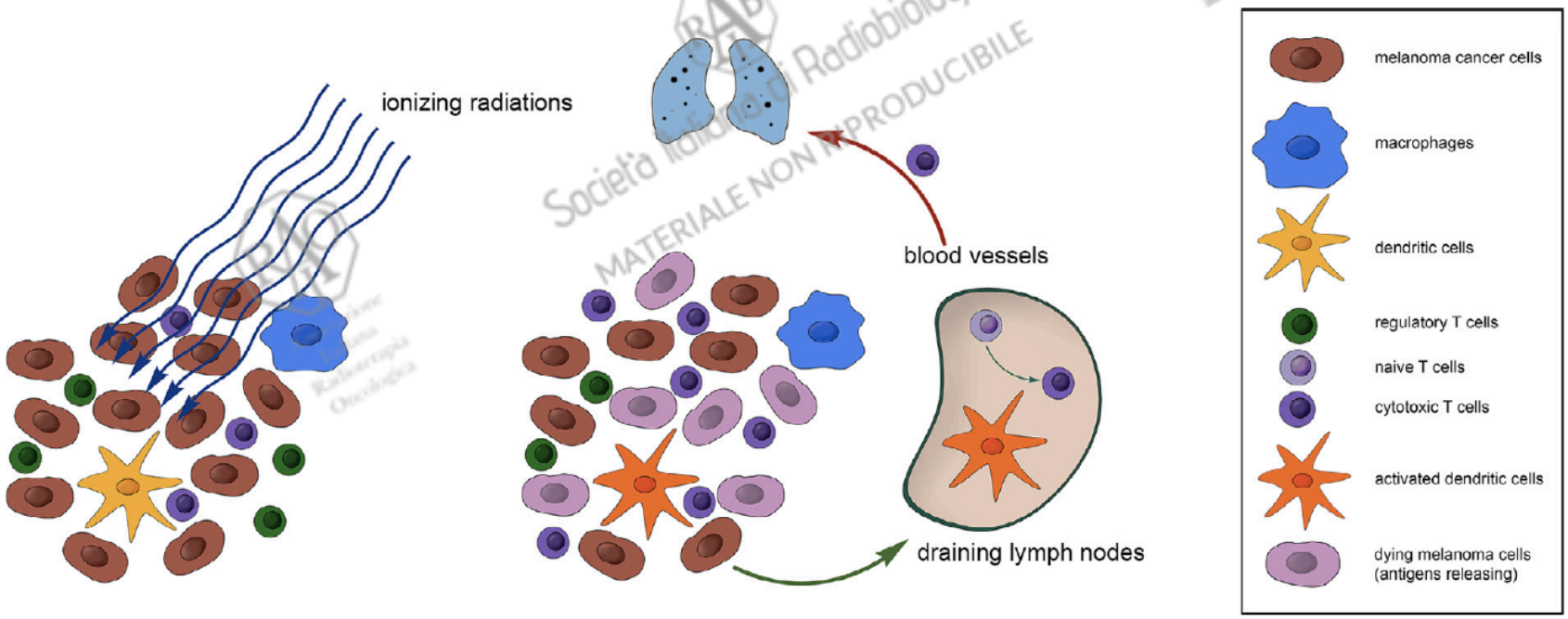
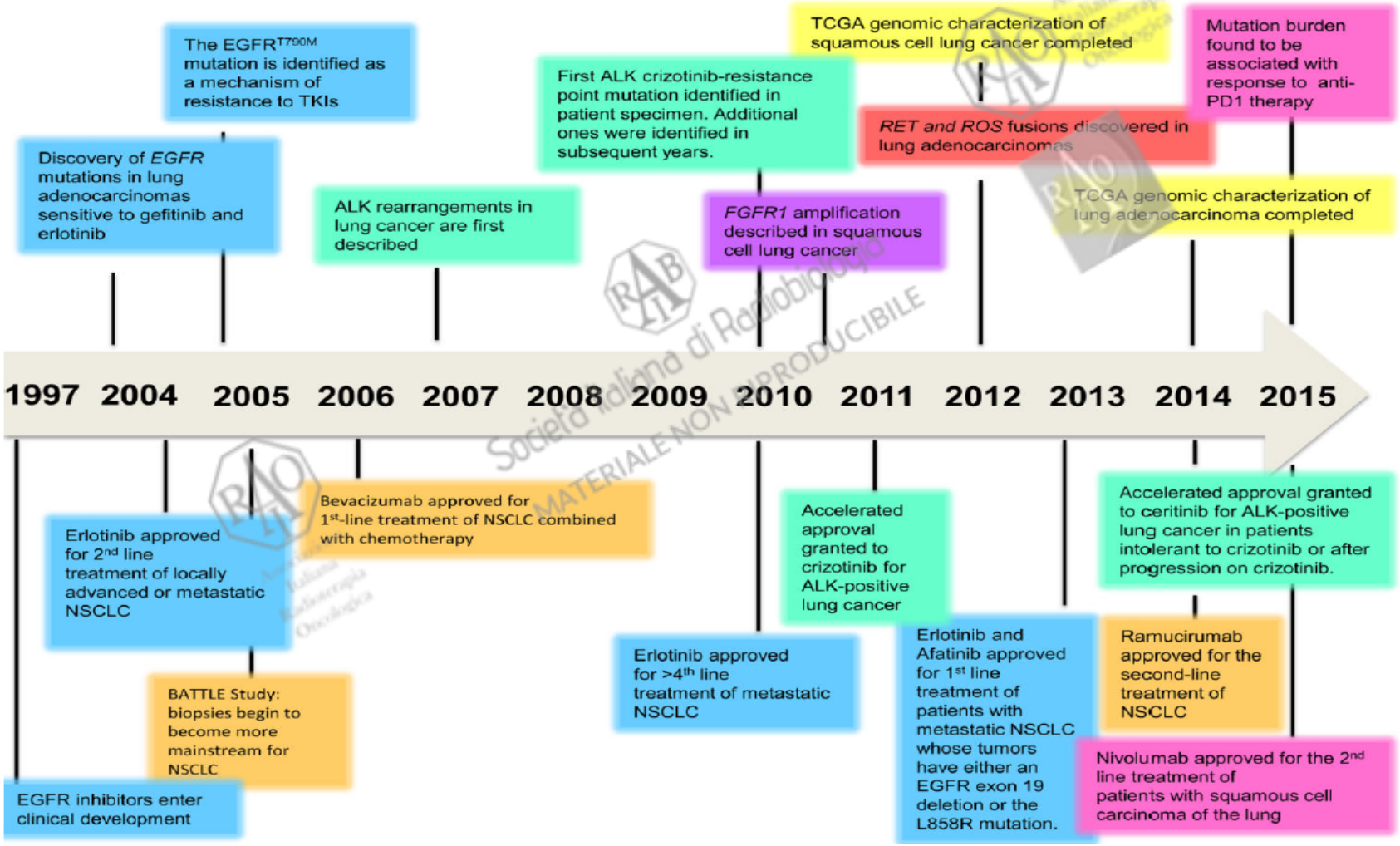


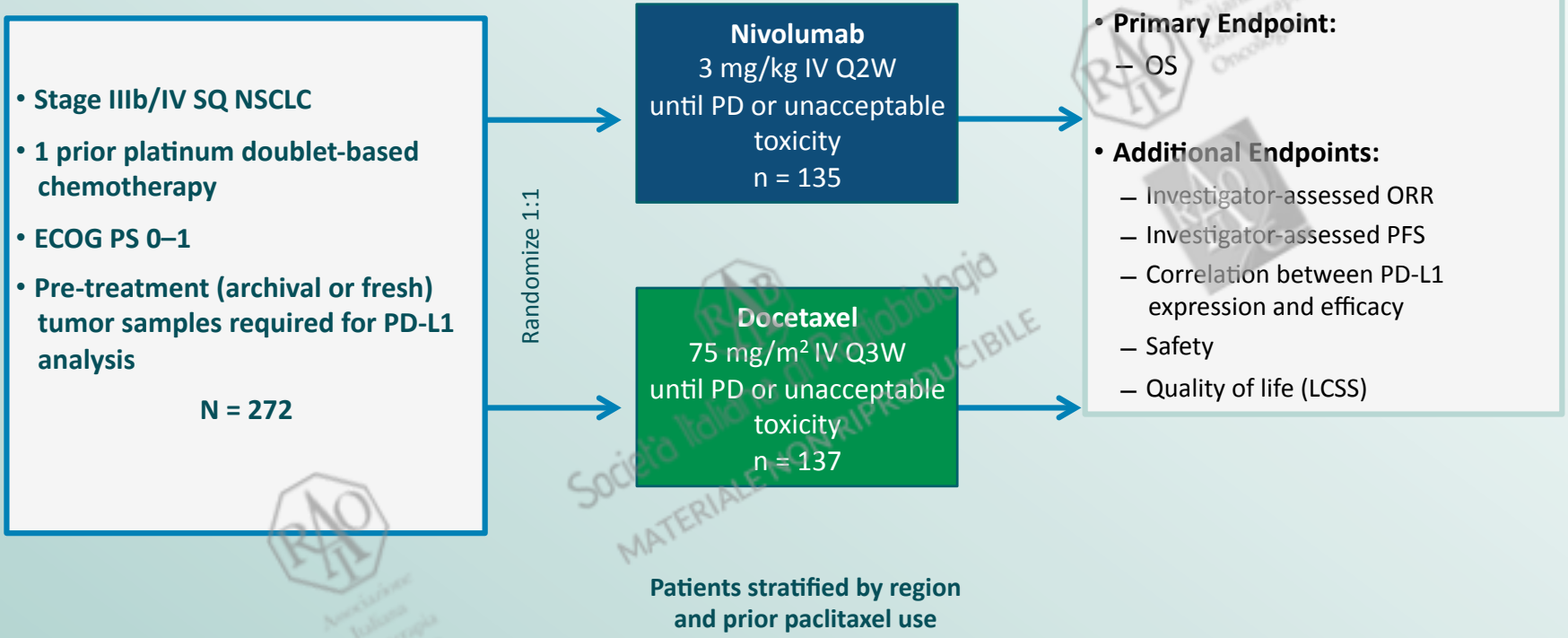
Fig. 1. The "in situ vaccination" concept: ionizing radiation may increase antigens release from dying cancer cells, activate dendritic cells, expand specific anti-melanoma cytotoxic T cells (CTCs) through cross-priming in draining lymph nodes and increase immune response at both local and distant sites [modified from Ref. 52].

Timeline of major discoveries in Lung Cancer



Politi K & Herbst R. Clin. Cancer Res. 2015; 21:2213

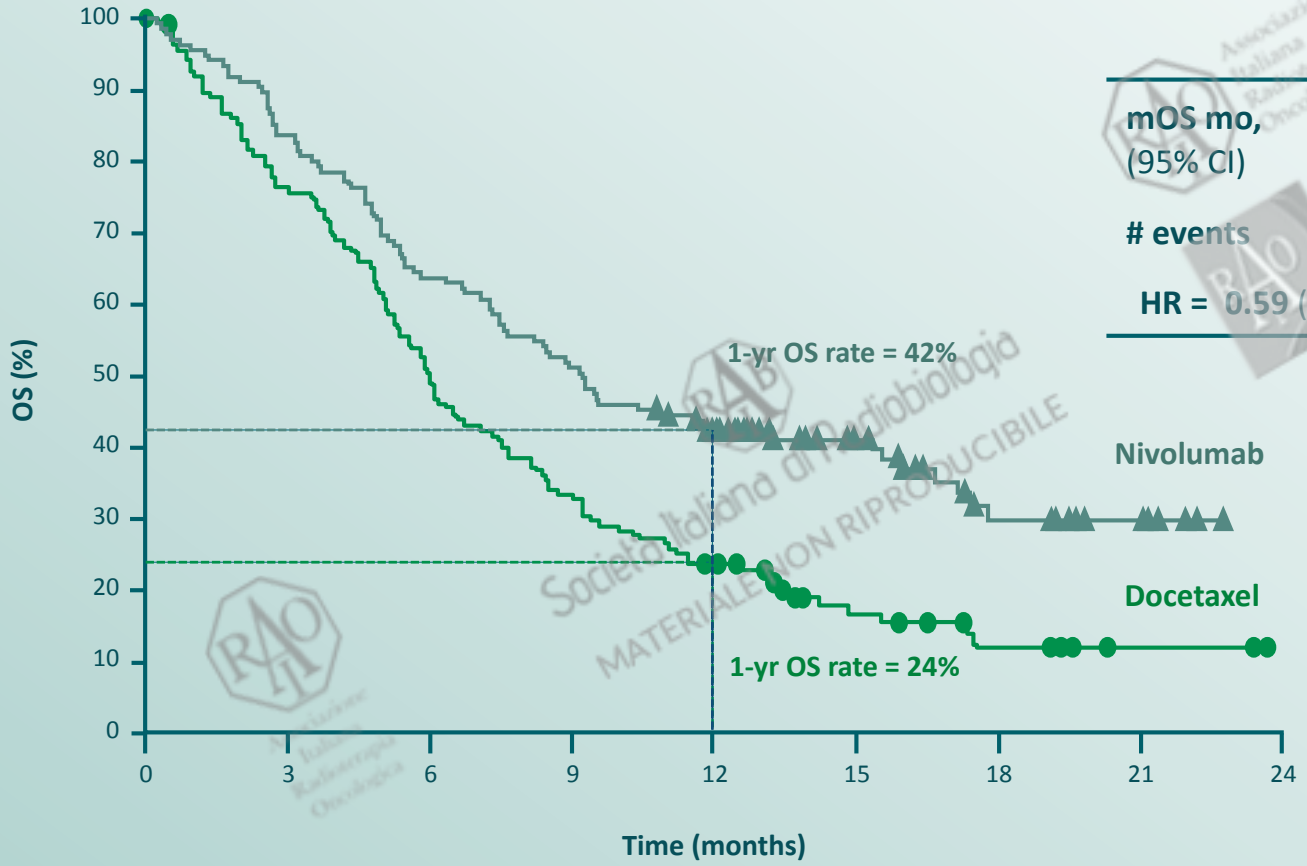
CheckMate 017 (NCT01642004) - Study Design



- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was *P* <0.03

LCSS = Lung cancer symptom scale

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

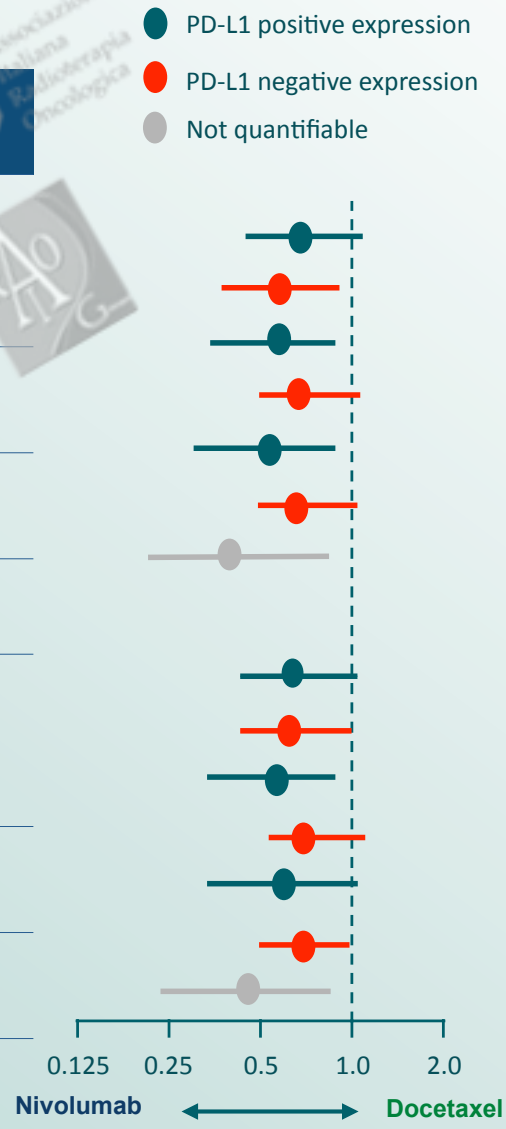
Symbols represent censored observations

OS and PFS by PD-L1 Expression

Nivolumab benefit was independent of PD-L1 expression

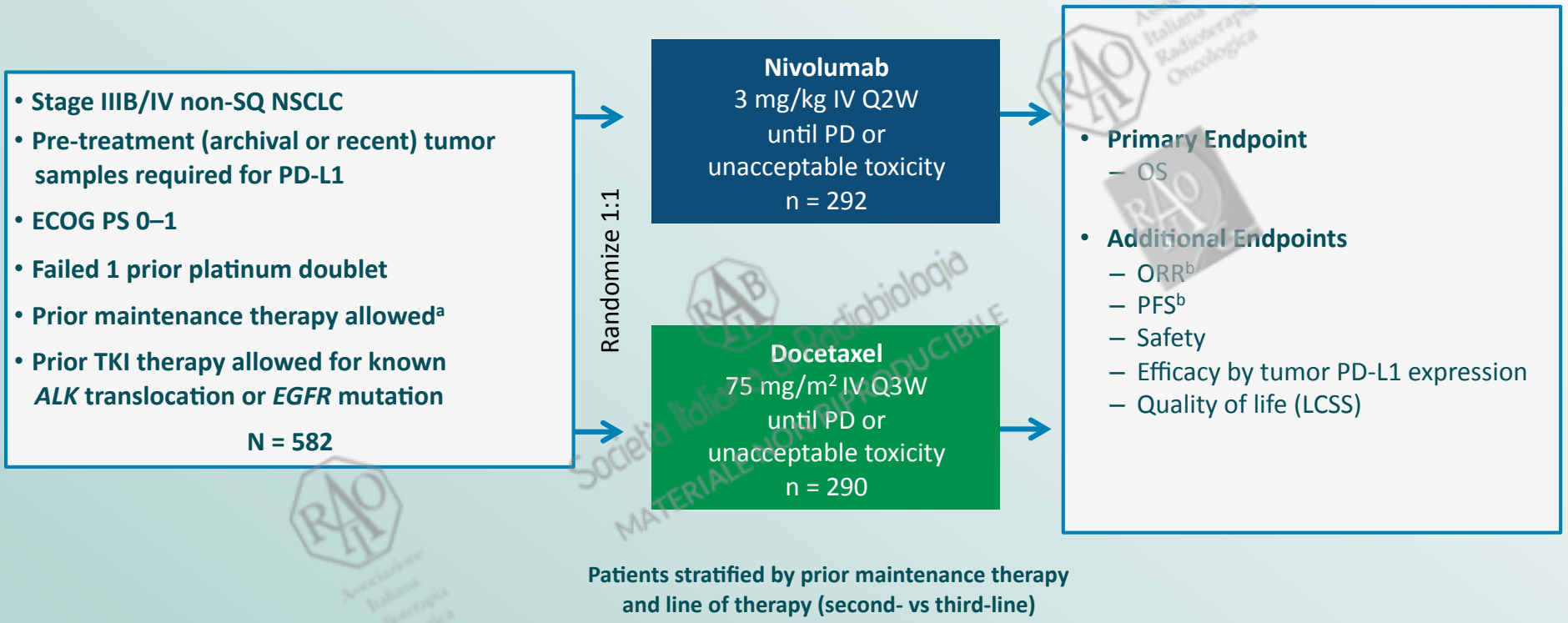
•Survival benefit with nivolumab was independent of PD-L1 expression level

PD-L1 expression	Patients, n		Unstratified HR (95% CI)	Interaction *P*-value
	Nivolumab	Docetaxel		
OS				
≥1%	63	56	0.69 (0.45, 1.05)	**0.56**
<1%	54	52	0.58 (0.37, 0.92)	
≥5%	42	39	0.53 (0.31, 0.89)	**0.47**
<5%	75	69	0.70 (0.47, 1.02)	
≥10%	36	33	0.50 (0.28, 0.89)	**0.41**
<10%	81	75	0.70 (0.48, 1.01)	
Not quantifiable	18	29	0.39 (0.19, 0.82)	
PFS				
≥1%	63	56	0.67 (0.44, 1.01)	**0.70**
<1%	54	52	0.66 (0.43, 1.00)	
≥5%	42	39	0.54 (0.32, 0.90)	**0.16**
<5%	75	69	0.75 (0.52, 1.08)	
≥10%	36	33	0.58 (0.33, 1.02)	**0.35**
<10%	81	75	0.70 (0.49, 0.99)	
Not quantifiable	18	29	0.45 (0.23, 0.89)	



• PD-L1 expression was measured in pre-treatment tumor biopsies (DAKO automated IHC assay)[15]

CheckMate 057 (NCT01673867) Study Design

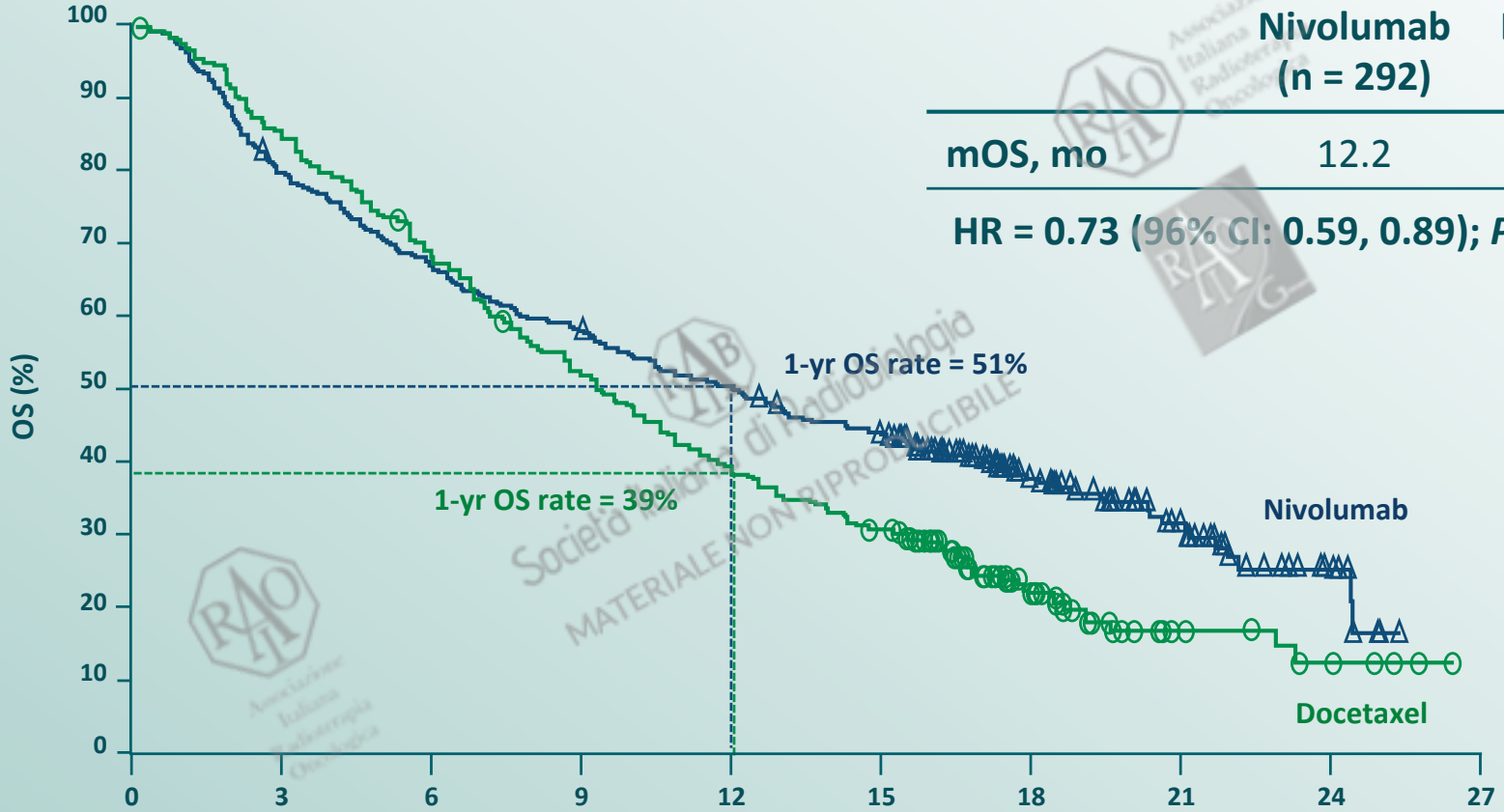


Patients stratified by prior maintenance therapy and line of therapy (second- vs third-line)

- **PD-L1 expression measured using the Dako/BMS automated IHC assay[14,15]**
  - Fully validated with analytical performance having met all pre-determined acceptance criteria for sensitivity, specificity, precision, and robustness

[a] Maintenance therapy included pemetrexed, bevacizumab, or erlotinib (not considered a separate line of therapy); [b] Per RECIST v1.1 criteria as determined by the investigator.

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

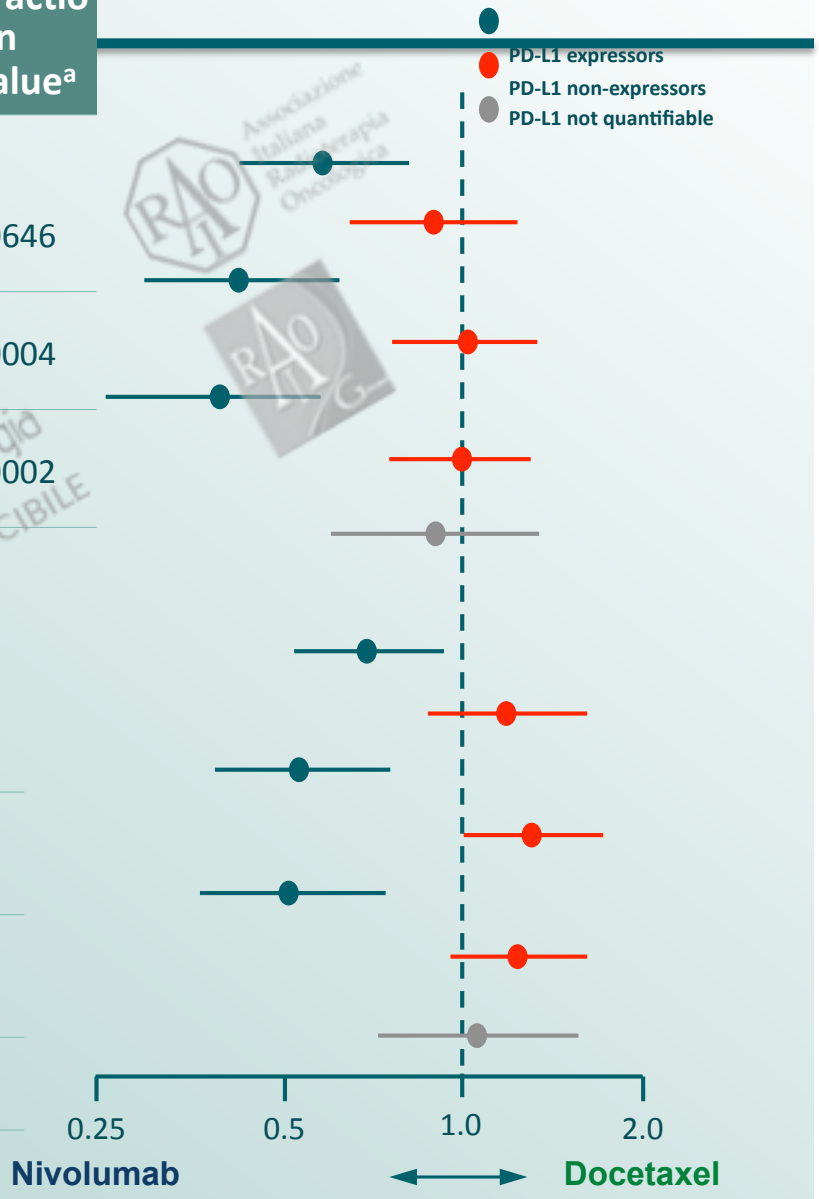
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations.

OS and PFS Hazard Ratios by Baseline PD-L1 Expression

PD-L1expression level	Nivolumab n	Docetaxel n	Unstratified HR (95% CI)	Interaction *P*-value[a]
OS				
≥1%	123	123	0.59 (0.43, 0.82)	0.0646
<1%	108	101	0.90 (0.66, 1.24)	
≥5%	95	86	0.43 (0.30, 0.63)	0.0004
<5%	136	138	1.01 (0.77, 1.34)	
≥10%	86	79	0.40 (0.26, 0.59)	0.0002
<10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable at baseline	61	66	0.91 (0.61, 1.35)	
PFS				
≥1%	123	123	0.70 (0.53, 0.94)	0.0227
<1%	108	101	1.19 (0.88, 1.61)	
≥5%	95	86	0.54 (0.39, 0.76)	<0.0001
<5%	136	138	1.31 (1.01, 1.71)	
≥10%	86	79	0.52 (0.37, 0.75)	0.0002
<10%	145	145	1.24 (0.96, 1.61)	
Not quantifiable at baseline	61	66	1.06 (0.73, 1.56)	

[a] Interaction p-value from Cox proportional hazard model with treatment, PD-L1 expression and treatment by PD-L1 expression interaction.



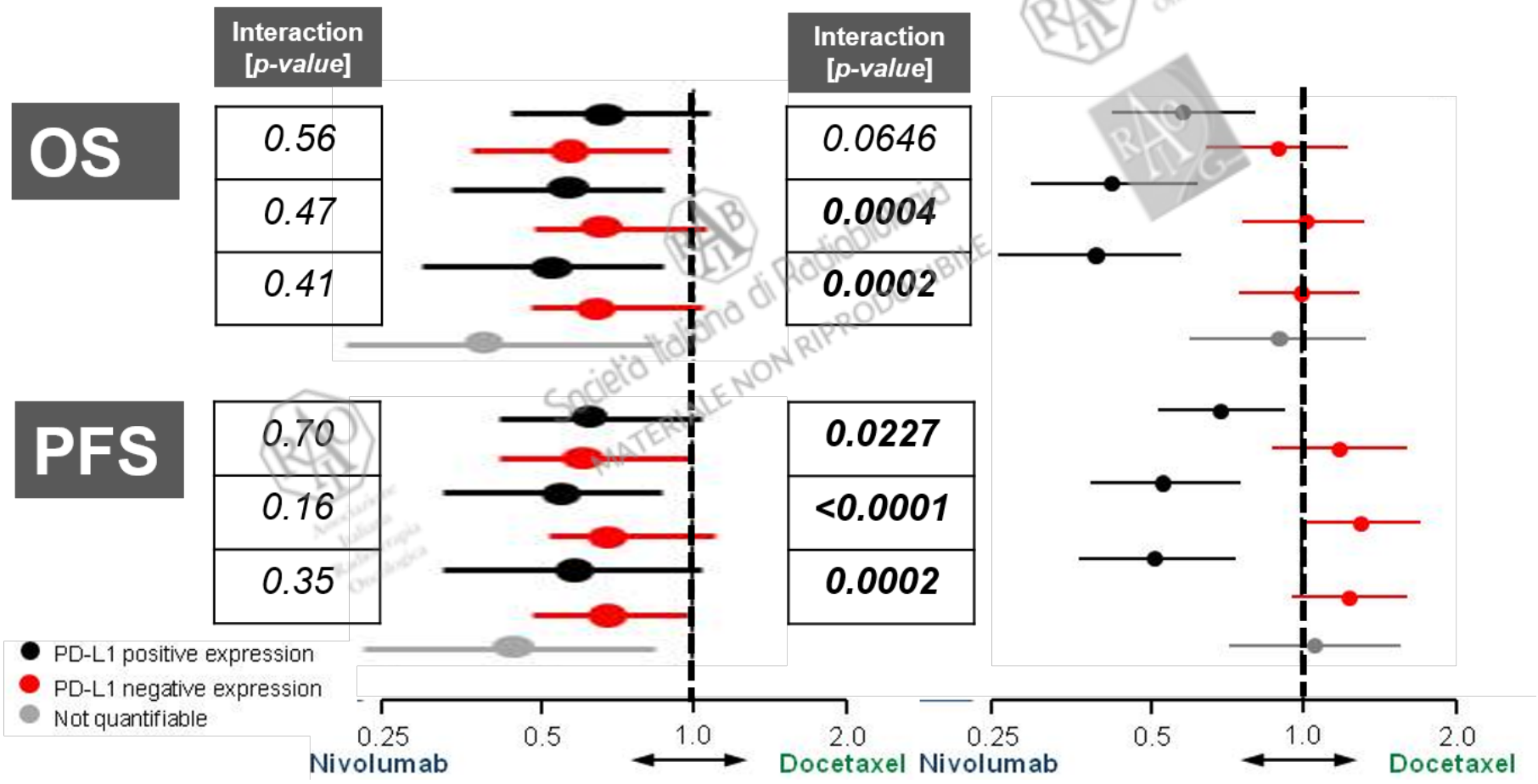
ORR by PD-L1 Expression

	ORR,[a] %		
PD-L1 expression level	Nivolumab	Docetaxel	Interaction *P*-value
≥1%	31	12	0.0019
<1%	9	15	
≥5%	36	13	0.0020
<5%	10	14	
≥10%	37	13	0.0021
<10%	11	14	
Not quantifiable	13	9	

- Median DOR was longer with nivolumab vs docetaxel in both PD-L1 expressors and non-expressors across all expression levels

[a] CR+PR as per RECIST v1.1 criteria. Confirmation of response required (investigator assessment)

The Biomarker Issue: PD-L1 & Histology



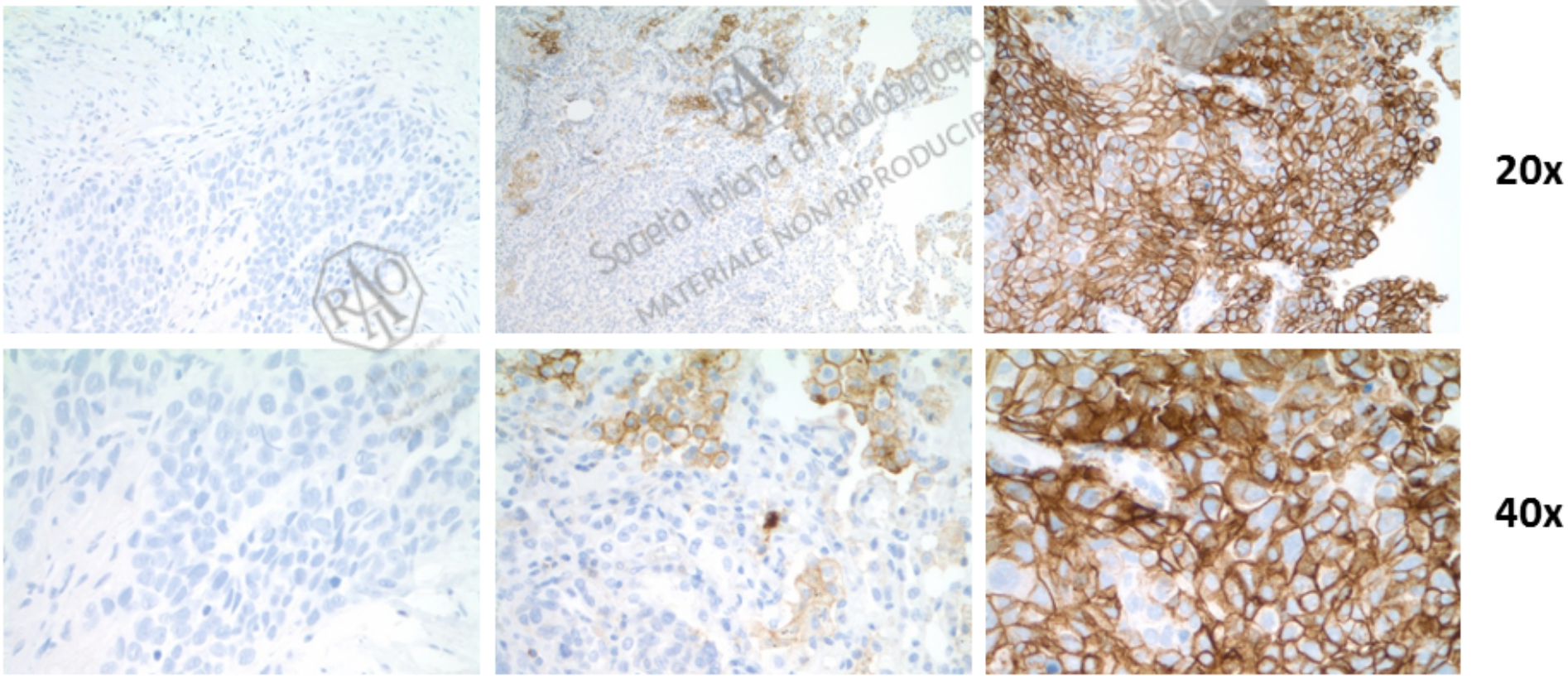
Modified – Spigel ASCO 2015; Paz-Ares ASCO 2015

PD-L1 as a predictive immune biomarker: assays, sample collection and analysis in NSCLC studies

	Pembrolizumab Merck	Nivolumab Bristol-Myers Squibb	MPDL3280A Roche/Genentech	MEDI4736 AstraZeneca
PD-L1 Assay	• Prototype or clinical trial IHC assay (22C3 Ab)[1]	• Dako automated IHC assay (28-8 Ab)[3,4]	• Ventana automated IHC assay	• 1st generation or Ventana automated IHC (BenchMark ULTRA) assay (Ventana PD-L1 (SP263) clone)[7,8]
Sample Source and Collection	• Surface expression of PD-L1 on tumor specimen* • Ph I: Fresh tissue • Ph II/III: Archival or fresh tissue[2]	• Surface expression of PD-L1 on tumor cells* • Archival[4] or fresh tissue	• Surface expression of PD-L1 on TILs[5] • Archival or fresh tissue	• Surface expression of PD-L1 on TILs • PhI: Fresh tissue
Definition of Positivity†	**IHC Staining:** • Strong vs weak expression[2] • PD-L1 expression required for NSCLC for enrollment[2] • Note that one arm of KEYNOTE 001 trial requires PD-L1⁻ tumors[1] **Tumor PD-L1 expression:**[1] • ≥50% PD-L1⁺ cut-off: 32% (41/129) • 1-49% PD-L1⁺ cut-off: 36% (46/129)	**IHC Staining:** • Strong vs weak expression[3,4] • Patients not restricted in PD-L1 status in 2nd- & 3rd-line[4] • Ph III 1st-line trial in PD-L1+[3] **Tumor PD-L1 expression:**[4] • 5% PD-L1⁺ cut-off: 49% (33/68)[4]	**IHC Staining intensity (0, 1, 2, 3):** • IHC 3 (≥10% PD-L1⁺): Ph III trial[5] • IHC 2,3 (≥5% PD-L1⁺)[5] • IHC 1,2,3 (≥1% PD-L1⁺)[5] • IHC 1, 0, or unknown • PD-L1 expression required for NSCLC for enrollment **TIL PD-L1 expression:**[5,6] • IHC 3 (≥10% PD-L1⁺): 11% (6/53) • PD-L1 low (IHC 1, 0): 75% (40/53)	**IHC Staining intensity:** • Not presented to date[7,8,9] **TIL PD-L1 expression:** • Not presented to date[7,8,9]

PD-L1 Expression Associated with Favorable Outcome With Pembrolizumab

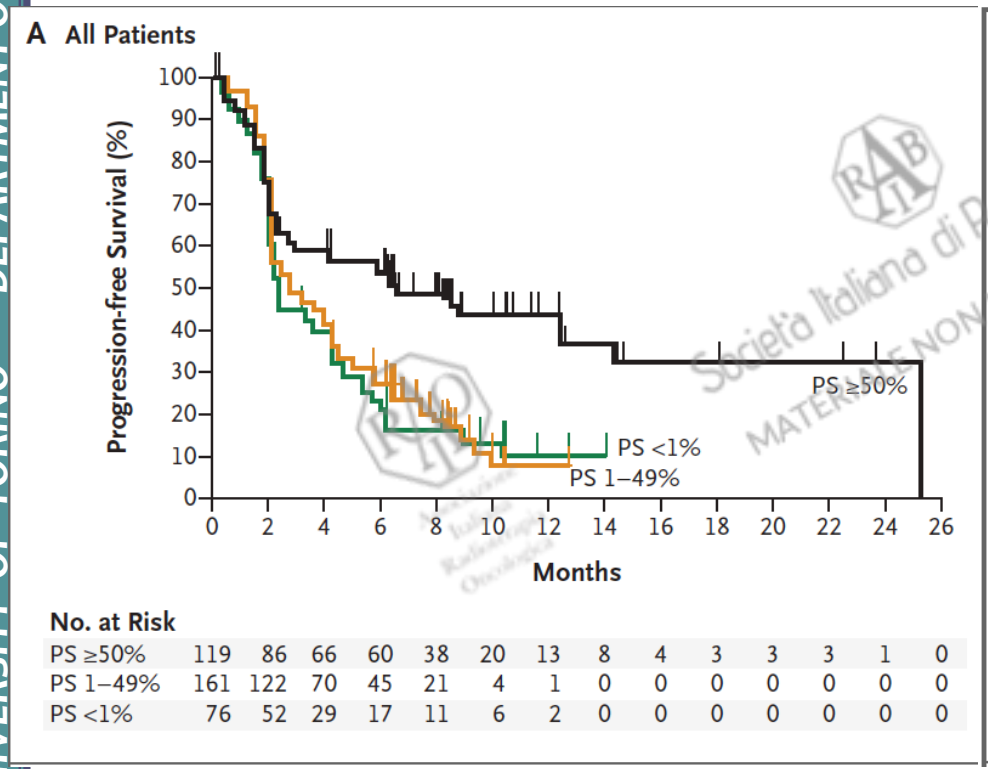
- TPS ≥50% cutpoint rigorously determined using independent training and validation sets derived from KEYNOTE-001[1]
- PD-L1 IHC 22C3 pharmDx (Dako) approved in the US as a companion diagnostic for pembrolizumab



1. Garon EB et al. *N Engl J Med* 2015;372:2018-28.

Keynote001: outcomes on the basis of PD-L1 staining

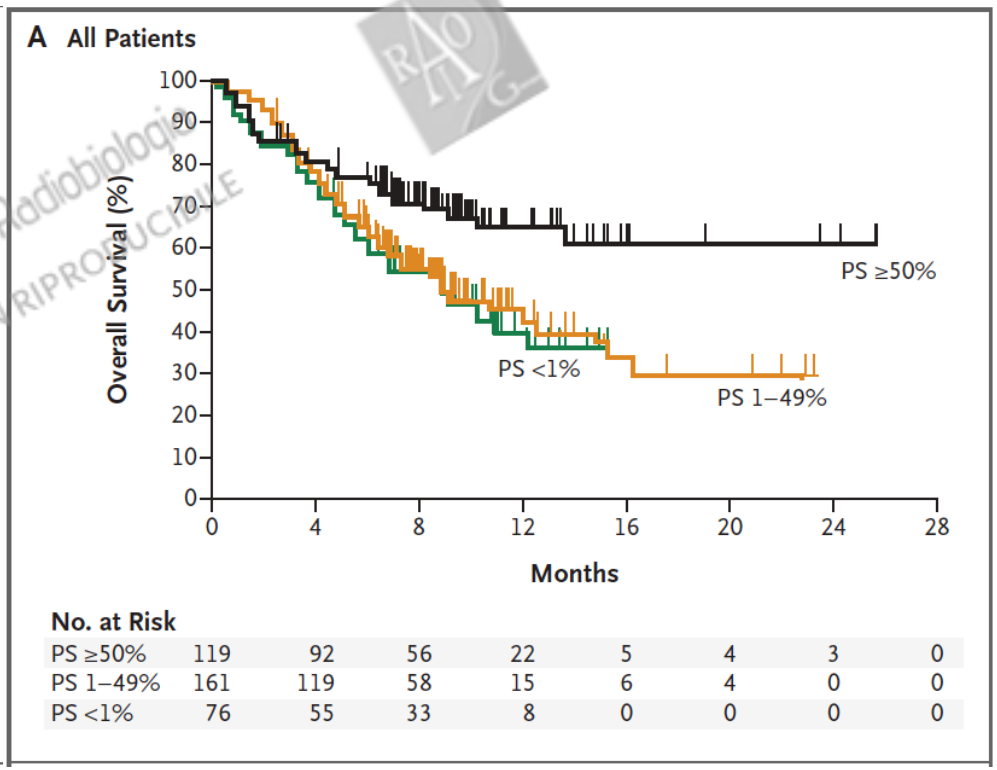
PFS



No. at Risk

PS ≥50%	119	86	66	60	38	20	13	8	4	3	3	3	1	0
PS 1–49%	161	122	70	45	21	4	1	0	0	0	0	0	0	0
PS <1%	76	52	29	17	11	6	2	0	0	0	0	0	0	0

OS



No. at Risk

PS ≥50%	119	92	56	22	5	4	3	0
PS 1–49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

Garon EB et al , NEJM Apr 19 2015

Updated Efficacy From IMvigor210: Atezolizumab in Platinum-Treated Locally Advanced/Metastatic Urothelial Carcinoma (mUC)

Robert Dreicer,[1] Jean Hoffman-Censits,[2] Thomas Flaig,[3] Enrique Grande,[4] Ani Balmanoukian,[5] Gunhild von Amsberg,[6] Christine Theodore,[7] Simon Chowdhury,[8] Sergio Bracarda,[9] Jessica M. Clement,[10] Evan Y. Yu,[11] Arash Rezazadeh Kalebasty,[12] Günter Niegisch,[13] Stephane Culine,[14] Michael S. Gordon,[15] Beiying Ding,[16] Sanjeev Mariathasan,[16] Fatema Legrand,[16] Oyewale O. Abidoye[16] and Daniel P. Petrylak[17]

[1]Division of Hematology/Oncology, University of Virginia, Charlottesville, VA; [2]Sidney Kimmel Cancer Center, Thomas Jefferson University Hospital, Philadelphia, PA; [3]University of Colorado Cancer Center, Aurora, CO; [4]Hospital Universitario Ramón y Cajal, Madrid, Spain; [5]The Angeles Clinic and Research Institute, Los Angeles, CA; [6]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [7]Hôpital Foch, Suresnes, France; [8]Sarah Cannon Research Institute, London, UK; [9]USL8 Ospedale San Donato, Arezzo, Italy; [10]Neag Comprehensive Cancer Center, UConn Health, Farmington, CT; [11]University of Washington and Seattle Cancer Care Alliance, Seattle, WA; [12]Norton Cancer Institute, Louisville, KY; [13]Heinrich Heine University Düsseldorf, Düsseldorf, Germany; [14]Hôpital Saint-Louis, Paris, France; [15]Pinnacle Oncology Hematology, Scottsdale, AZ; [16]Genentech, Inc., South San Francisco, CA; [17]Yale Cancer Center, New Haven, CT, USA.

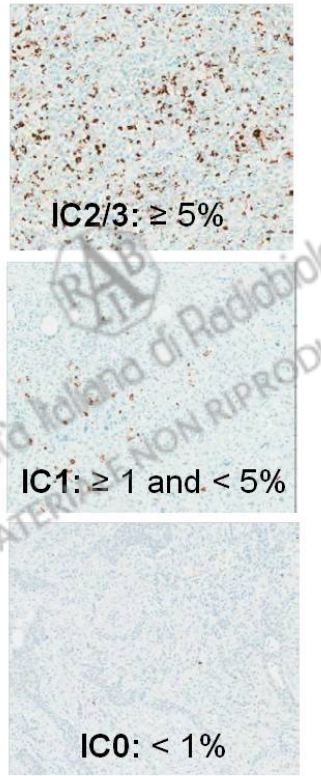
PRESENTED AT: ASCO ANNUAL MEETING '16

Presented By Robert Dreicer at 2016 ASCO Annual Meeting

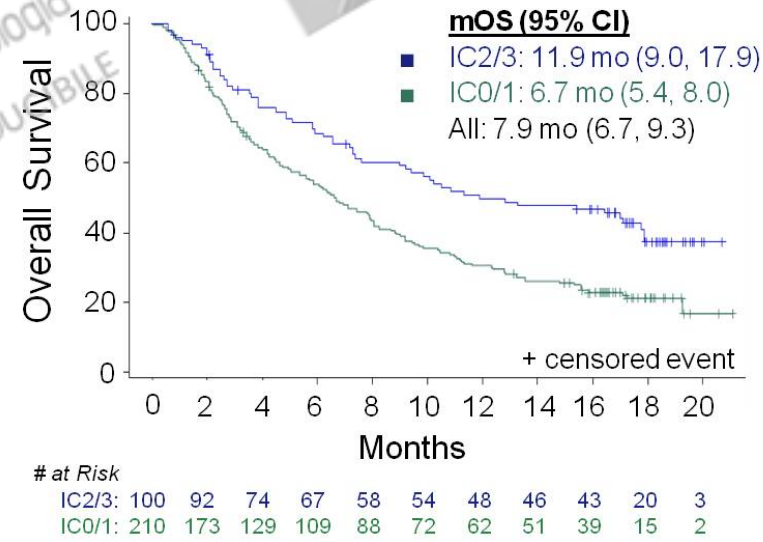
PD-L1 Expression on Immune Cells and Efficacy

- IMvigor210 samples were evenly distributed in PD-L1 IC expression (VENTANA SP142 IHC assay)
- Atezolizumab efficacy in cohort 2 was associated with PD-L1 on IC[2]
  - Responses occurred in all IC subgroups, but ORR increased with higher PD-L1 expression
  - Longer OS was observed with higher PD-L1 status

PD-L1 IHC[1]



PD-L1 Status	ORR (95% CI)
IC2/3 (n = 100)	28% (19, 38)
IC0/1 (n = 210)	10% (6, 15)
All (N = 310)	16% (12, 20)



IC, tumor-infiltrating immune cell. NE, not estimable. Data cutoff: March 14, 2016. Median follow up: 17.5 mo. 1. Rosenberg ECC 2015 [abstract 21LBA]. 2. Dreicer ASCO 2016 [abstract 4515].

THE LANCET

Articles

Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward B Garon

Summary

Background Despite recent advances in the treatment of advanced non-small-cell lung cancer, there remains a need for effective treatments for progressive disease. We assessed the efficacy of pembrolizumab for patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer.

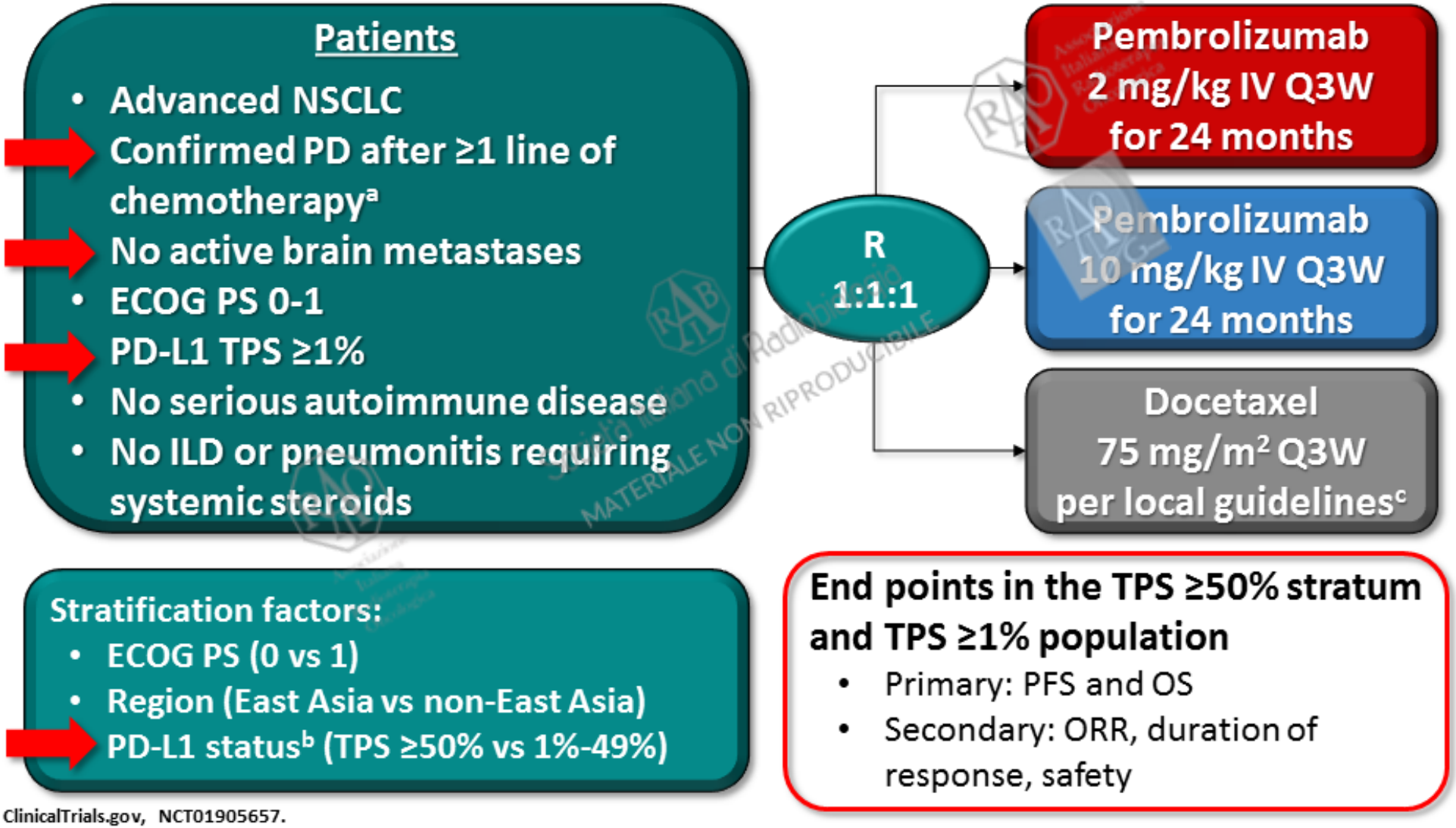
Methods We did this randomised, open-label, phase 2/3 study at 202 academic medical centres in 24 countries. Patients with previously treated non-small-cell lung cancer with PD-L1 expression on at least 1% of tumour cells were randomly assigned (1:1:1) in blocks of six per stratum with an interactive voice-response system to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m² every 3 weeks. The primary endpoints were overall survival and progression-free survival both in the total population, and in patients with PD-L1 expression on at least 50% of tumour cells. We used a threshold for significance of p<0·00825 (one-sided). This trial is registered at ClinicalTrials.gov, number NCT01905657.

Published Online
December 19, 2015
http://dx.doi.org/10.1016/S0140-6736(15)01281-7

See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(15)01308-2

Yale School of Medicine, Yale Cancer Center, and Smilow Cancer Hospital, New Haven, CT, USA (Prof R S Herbst MD); The Netherlands Cancer Institute and The Academic Medical Hospital Amsterdam,

KEYNOTE-010 Study Design



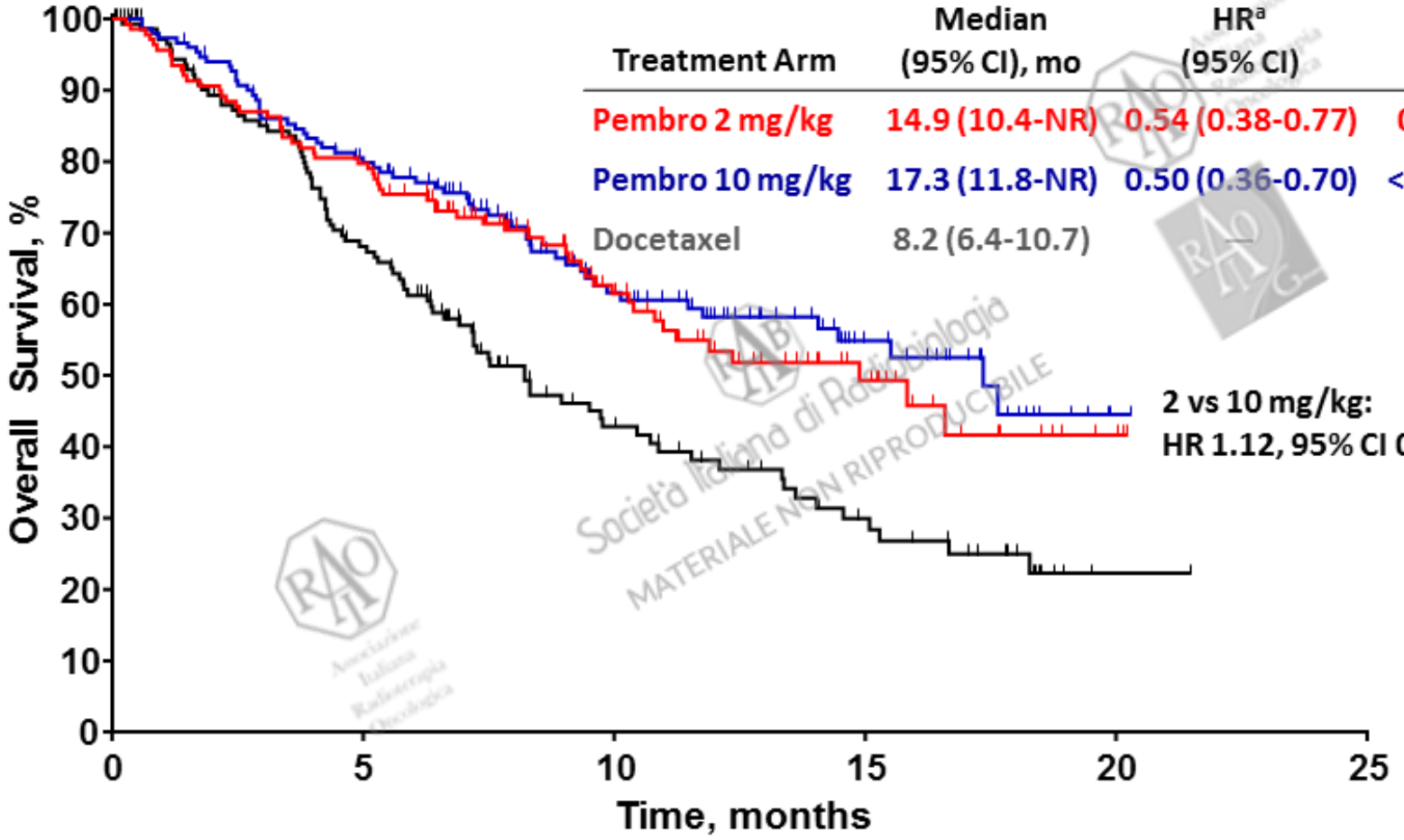
ClinicalTrials.gov, NCT01905657.

[a]Prior therapy must have included ≥2 cycles of platinum-doublet chemotherapy. An appropriate tyrosine kinase inhibitor was required for patients whose tumors had an *EGFR* sensitizing mutation or an *ALK* translocation.

[b]Added after 441 patients enrolled based on results from KEYNOTE-001 (Garon EB et al. *N Engl J Med*. 2015;372:2018-28).

[c]Patients received the maximum number of cycles permitted by the local regulatory authority.

OS, PD-L1 TPS ≥50% Stratum



Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	14.9 (10.4-NR)	0.54 (0.38-0.77)	0.0002
Pembro 10 mg/kg	17.3 (11.8-NR)	0.50 (0.36-0.70)	<0.0001
Docetaxel	8.2 (6.4-10.7)	—	—

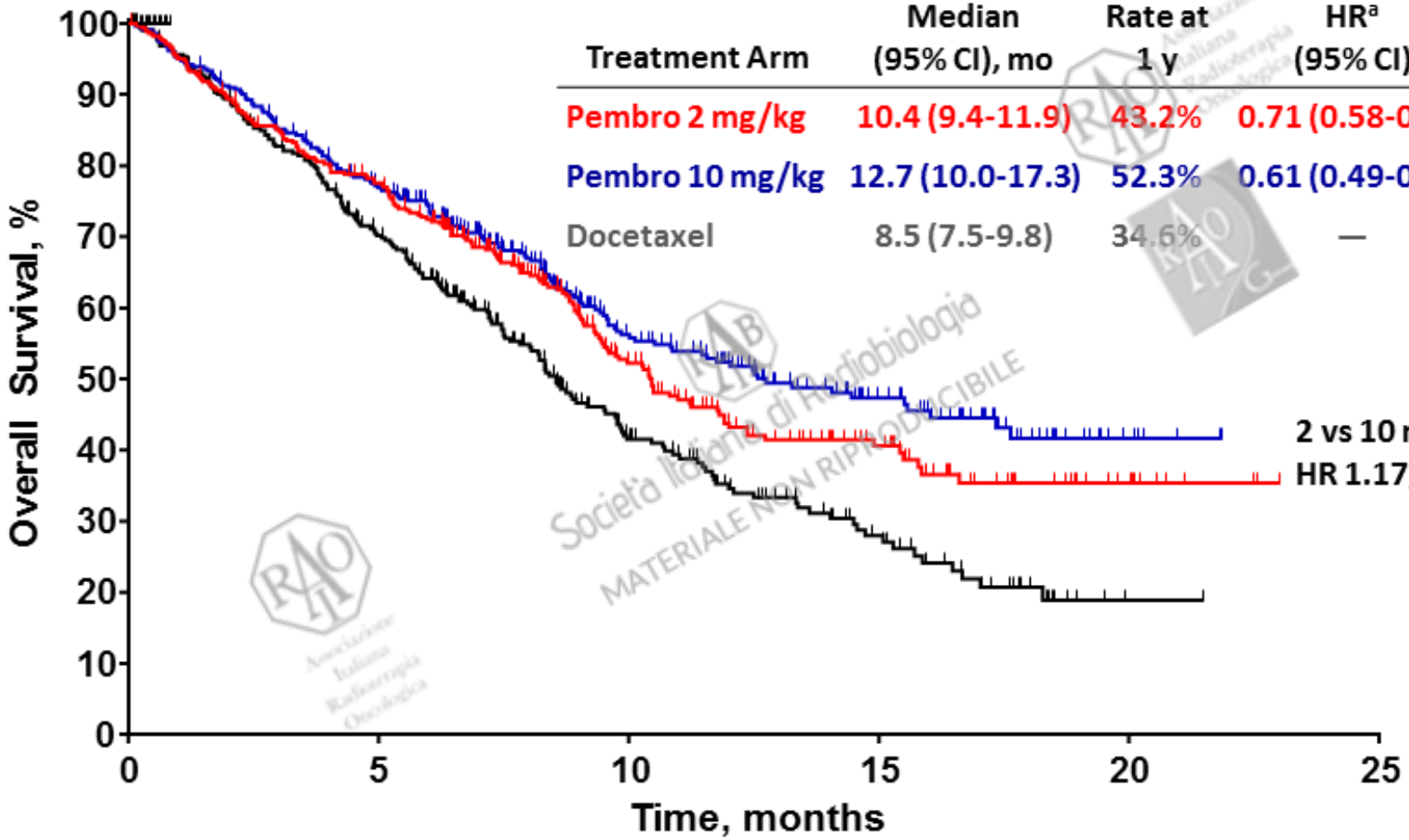
2 vs 10 mg/kg:
HR 1.12, 95% CI 0.77-1.62

139	110	51	20	3	0
151	115	60	25	1	0
152	90	38	19	1	0

Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

OS, PD-L1 TPS ≥1% (Total Population)



Treatment Arm	Median (95% CI), mo	Rate at 1 y	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	10.4 (9.4-11.9)	43.2%	0.71 (0.58-0.88)	0.0008
Pembro 10 mg/kg	12.7 (10.0-17.3)	52.3%	0.61 (0.49-0.75)	<0.0001
Docetaxel	8.5 (7.5-9.8)	34.6%	—	—

2 vs 10 mg/kg:
HR 1.17, 95% CI 0.94-1.45

Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

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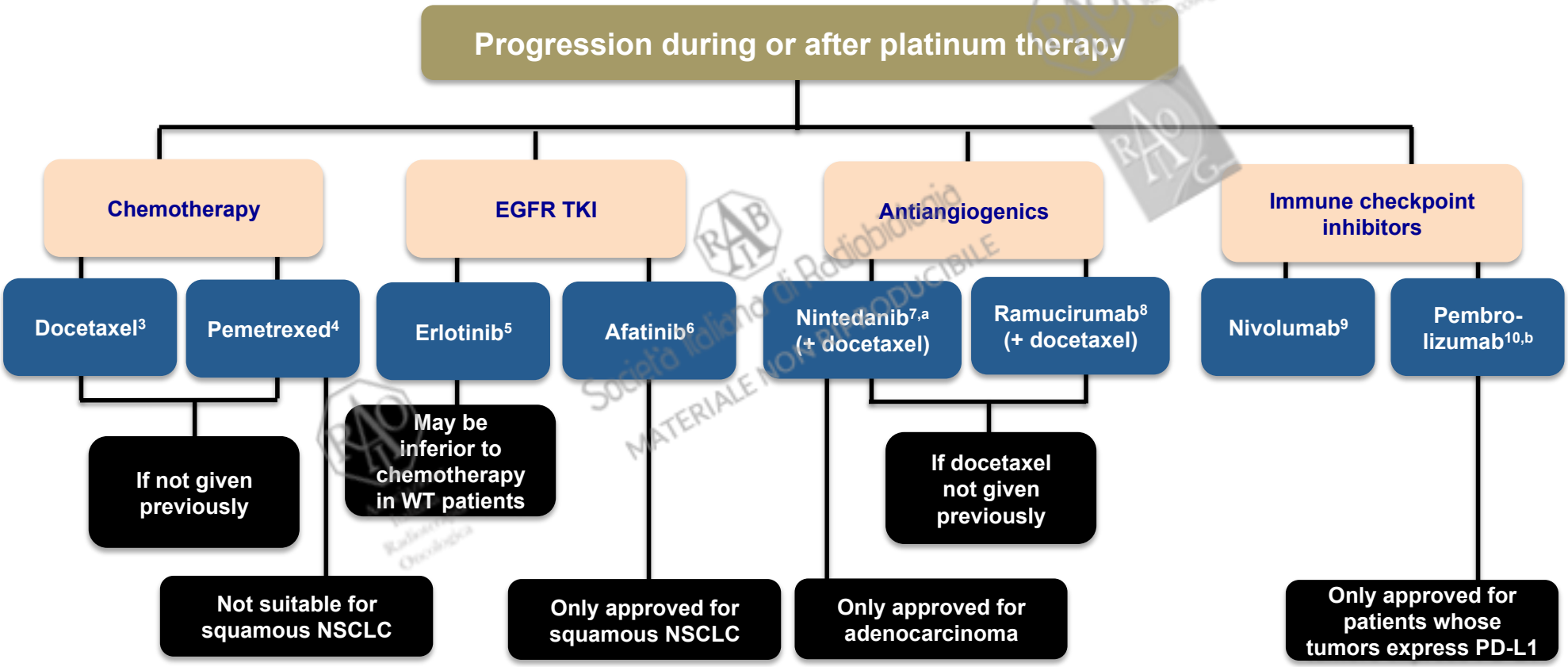
Treatment Options in Second Line: Overview



[a]Approved in EU only; [b]Approved in US only

1. NCCN Clinical Practice Guidelines for Non-Small Cell Lung Cancer, V.4.2016
2. Reck M et al. *Ann Oncol* 2014;25(Suppl 3):27-39

MERCK

News Release

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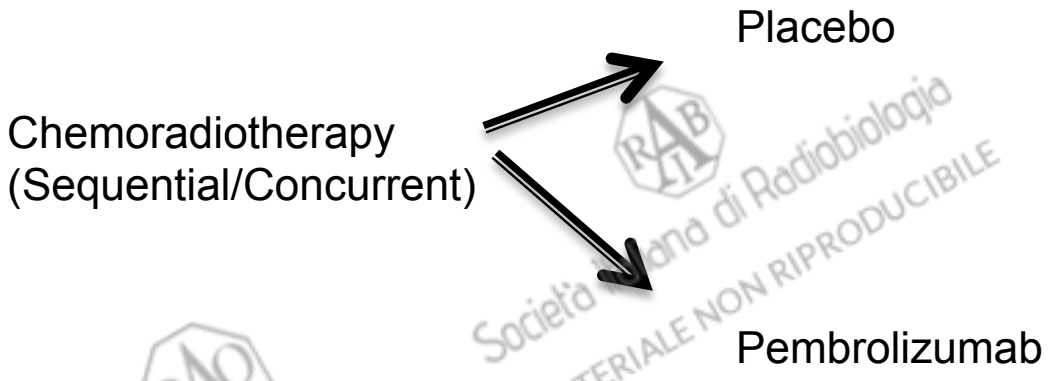
Merck's KEYTRUDA® (pembrolizumab) Demonstrates Superior Progression-Free and Overall Survival Compared to Chemotherapy as First-Line Treatment in Patients with Advanced Non-Small Cell Lung Cancer

KEYNOTE-024 Studied Patients Whose Tumors Expressed High Levels of PD-L1

KENILWORTH, N.J., June 16, 2016 – Merck (NYSE: MRK), known as MSD outside the United

Global MSD Phase II Randomized Trial

PI: G. Scagliotti, U. Ricardi



Immune Related Adverse Events (IRAEs)

System	Adverse Events
Gastrointestinal	Colitis (Diarrhea, perforation)
Renal	Acute Interstitial Nephritis (Increased serum Creatinine)
Pulmonary	Pneumonitis (dyspnea, cough)
Dermatologic	Dermatitis (Lichenoid/ spongiotic dermatitis, rash), Vitaligo
Hepatic	Hepatitis (elevated LFTs)
Neurologic	Central and Peripheral (Aseptic Meningitis, Guillan-Barre Syndrome, Myasthenia Gravis
Endocrine	Hypophysitis, thyroiditis, adrenal insufficiency
Ocular	Uveitis, Iritis

Immune Related Adverse Events (IRAEs)

- Average time to onset of irAEs is 6-12 weeks after initiation of therapy
  - Within days of the first dose
  - After several months of treatment
  - After discontinuation of therapy
- Severity: Can be mild and asymptomatic to severe and life threatening

ABOUT THE SCHOOL

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COMBINED DRUG-RADIATION TREATMENT: BIOLOGICAL BASIS, CURRENT APPLICATIONS AND PERSPECTIVES

15-18 June, 2017
Milan, Italy

TARGET GROUP

The course is aimed at radiation oncologists and medical oncologists involved in the multidisciplinary treatment of cancer.

FACULTY

Course director

Barbara Jereczek-Fossa, *Radiation Oncologist and Clinical Oncologist, European Institute of Oncology and University of Milan, Milan (IT)*

ESTRO VISION 2020

Every cancer patient in Europe will have access to state of the art radiation therapy, as part of a multidisciplinary approach where treatment is individualized for the specific patient's cancer, taking into account the patient's personal circumstances

Radiotherapy & Oncology 103(2012) 99-101

Precision Medicine

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The unit in Precision Medicine is a "biomarker ensemble"

- Assumption : *"Treatment T is effective for condition C, as defined by testing positive for biomarker B, where B is determined by diagnostic assay A."*
- A biomarker, hypothesized to play a crucial role in the disease pathway
- A diagnostic assay, used to determine a patient's biomarker status; and
- A therapeutic agent, intended to be more effective for patients who are "biomarker-positive."

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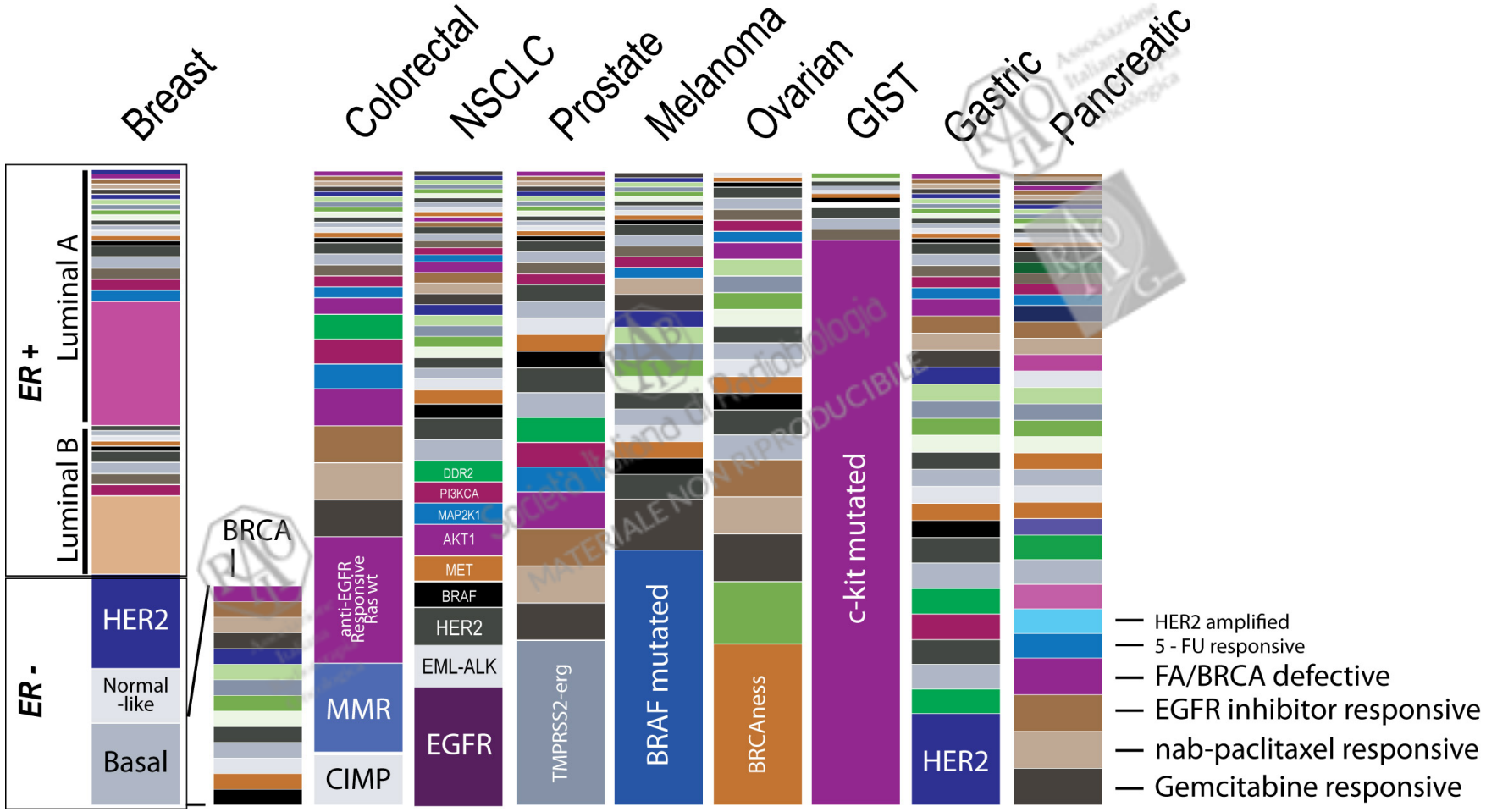
Sub-Classification of Cancers
"Molecular heterogeneity"



even the most frequent tumors are a collection of rare diseases based on their molecular characteristics

Biankin AV , Hudson TJ Hum. Genet. 2011; 130: 79-91

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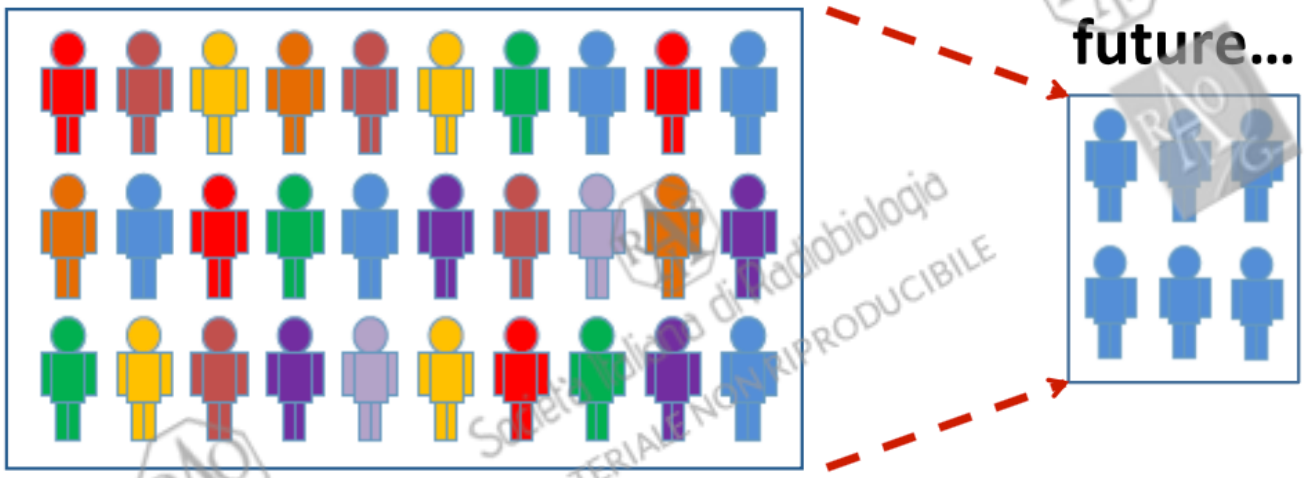
The Implications of Precision Medicine for Pharmaceuticals



Non-stratified large-volume administration of "blockbuster" pharmacotherapies with maximum return on investment

Stratified delivery of pharmacotherapies to specific target groups requiring new investment and pricing models

Darzi A. World Ecomonic Forum , November 2012

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