New drug-radiotherapy combinations: Current status

Professor Ricky Sharma

Chair of Radiation Oncology, University College London

NCRI
National Cancer
Research Institute

CTRad
Clinical and Translational Radiotherapy
Research Working Group

CANCER RESEARCH UK | CENTRE FOR DRUG DEVELOPMENT

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Disclosures

Honoraria:

- Bayer, BTG, Ipsen, Sirtex, Roche, Cancer Research UK

Advisory Boards/Consultancy:

- Astra Zeneca, DeepMind, Vertex, BTG, Sirtex, Terumo, Affidea, Boston Scientific, Varian, Cancer Research Technology

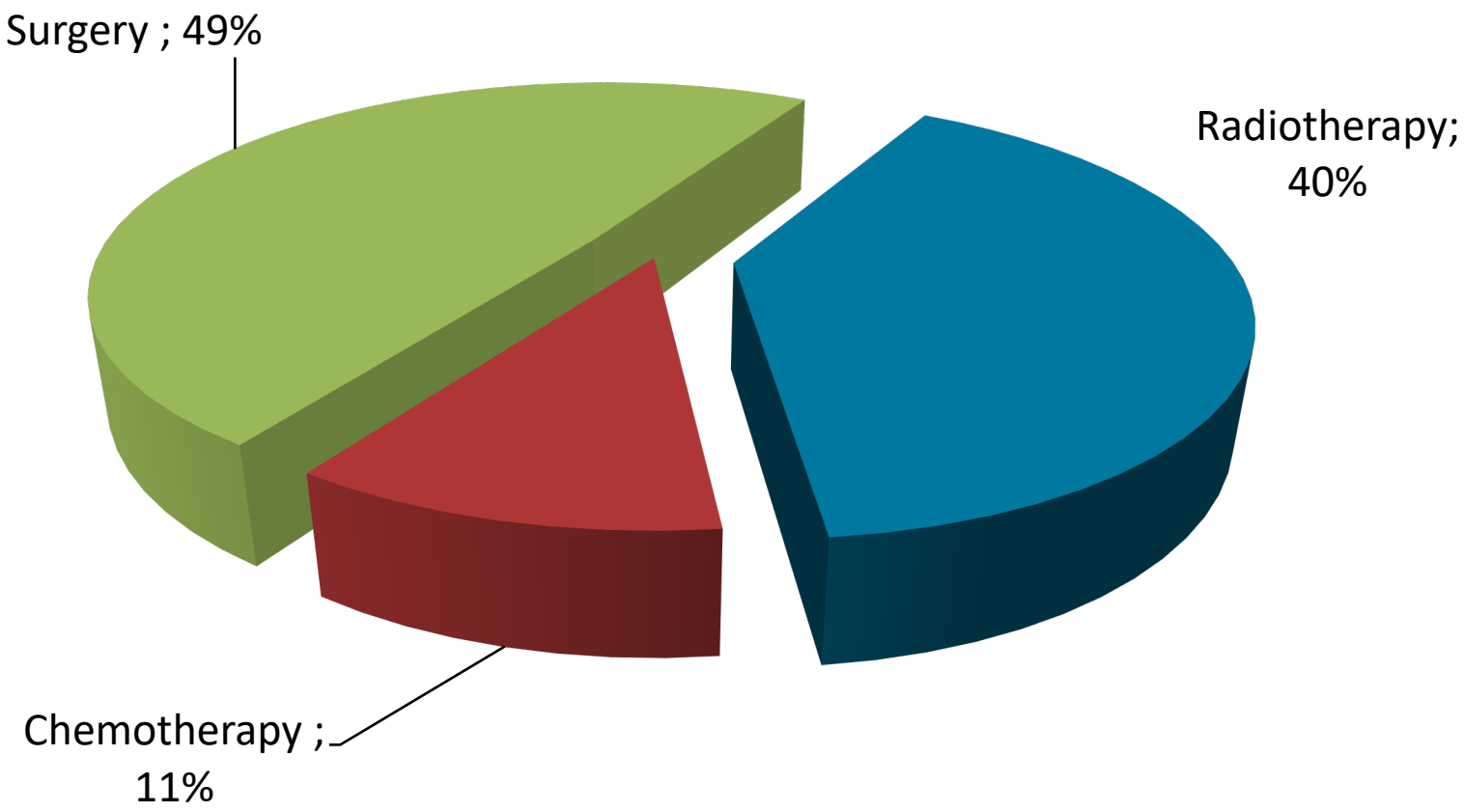
Research Funding:

- Sirtex, BTG, Cancer Research UK

Overview of Talk

1. Why drugs plus radiotherapy?
2. Success stories of drugs combined with radiotherapy
3. Barriers and how to overcome them
4. Exemplar 1: Immunotherapy plus radiotherapy
5. Exemplar 2: DNA damage repair inhibitors

Curative Treatments for All Cancers



Sir Mike Richards,
NCRI Annual Cancer Conference 2011

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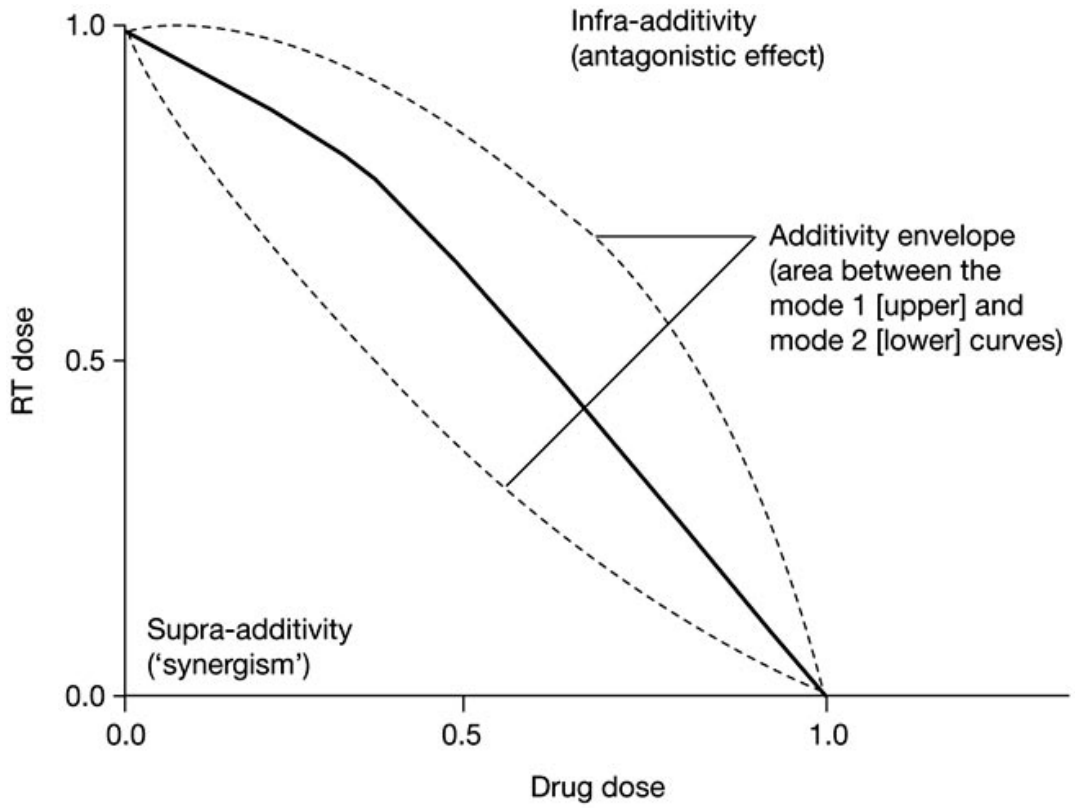
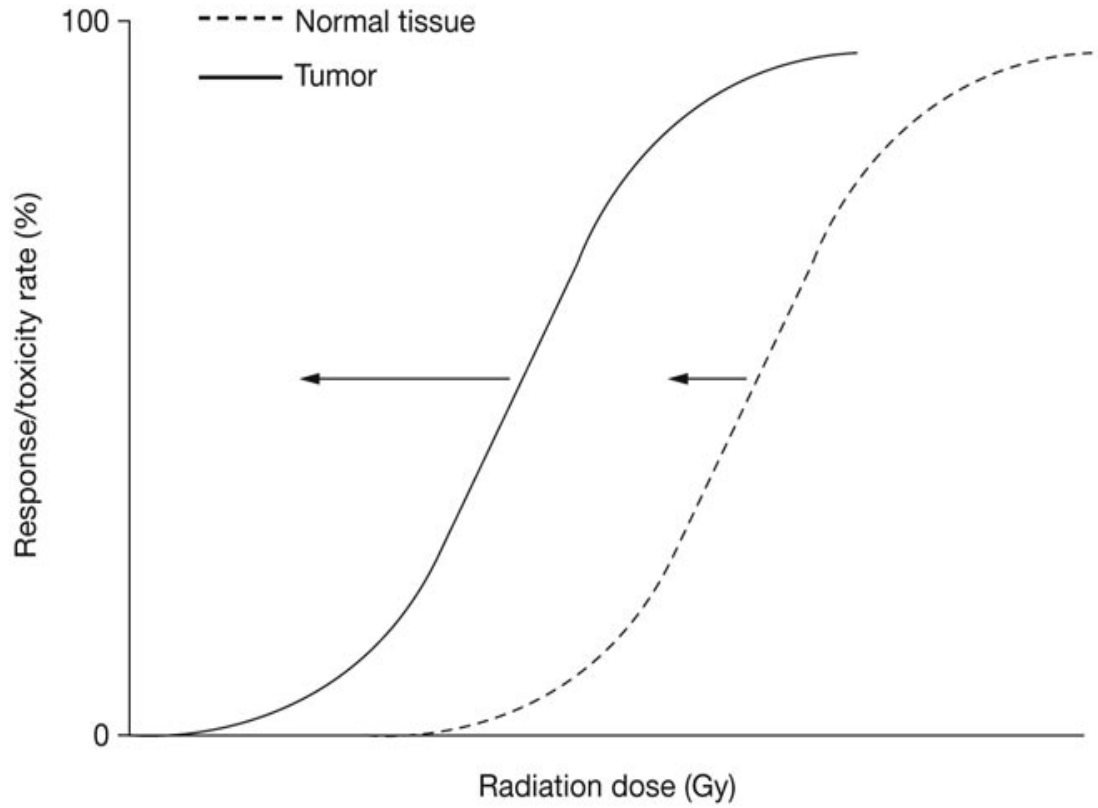
Additivity can Improve the Therapeutic Index





Steel G et al. *Int J Radiat Oncol Biol Phys,* 1979

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Chemo-radiotherapy is an alternative to surgery or an adjunct to surgery for a wide range of cancers in routine clinical practice

Level 1 Evidence for Chemo-radiotherapy

Primary	Systemic agent	Advantage of combined treatment compared with radiation alone
Glioblastoma (brain)	Temozolomide	Improved OS
Head and neck	Cisplatin, cetuximab	Improved OS
Lung	Cisplatin	Improved OS
Esophagus	5FU + cisplatin	Improved OS
Stomach	5FU + leucovorin	Improved OS compared with no treatment
Rectum	5FU	Improved OS
Anus	5FU + mitomycin	Improved local control
Cervix	Cisplatin	Improved OS
Prostate	Androgen deprivation therapy	Improved OS
Bladder	5FU + mitomycin	Improved local control

* OS = overall survival; 5FU = 5-fluorouracil.

Lawrence RY et al. *J Nat Cancer Inst,* 2012

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Rollercoaster of Clinical Trials for Drug-RT Combos

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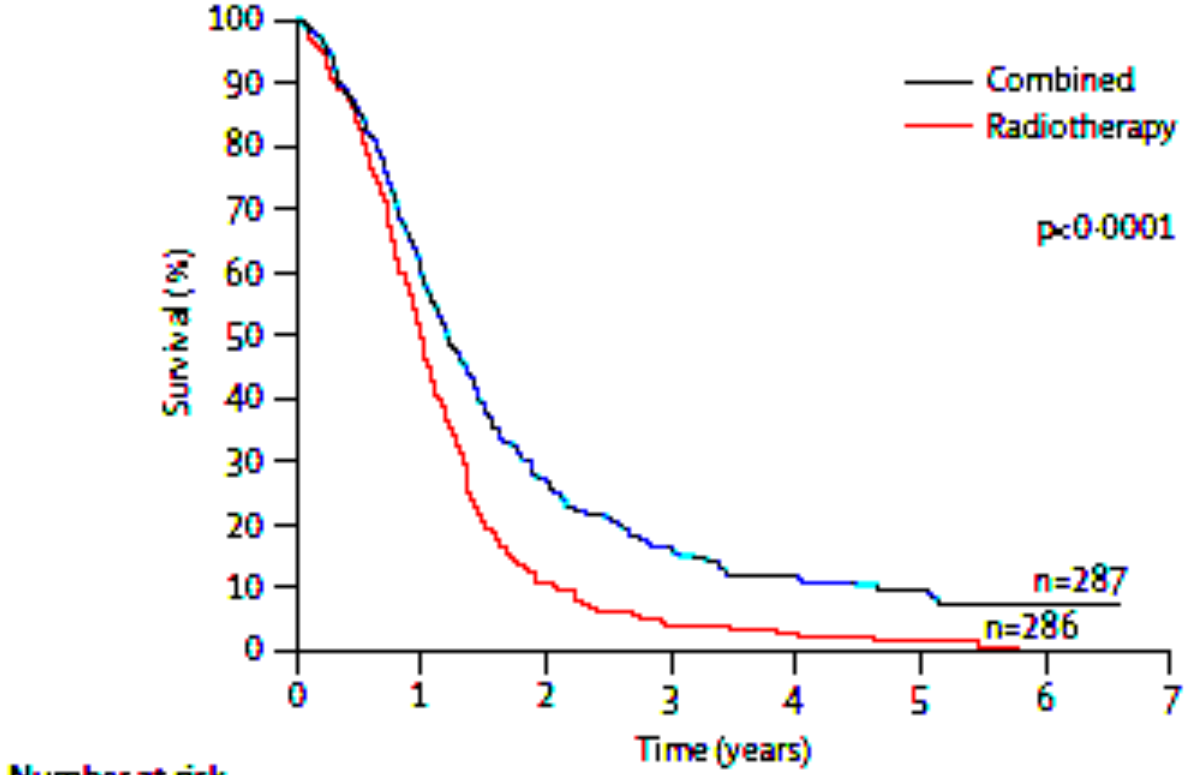
Temozolomide plus RT for Glioblastoma Multiforme



Stupp R, et al. *Lancet Oncol,* 2009

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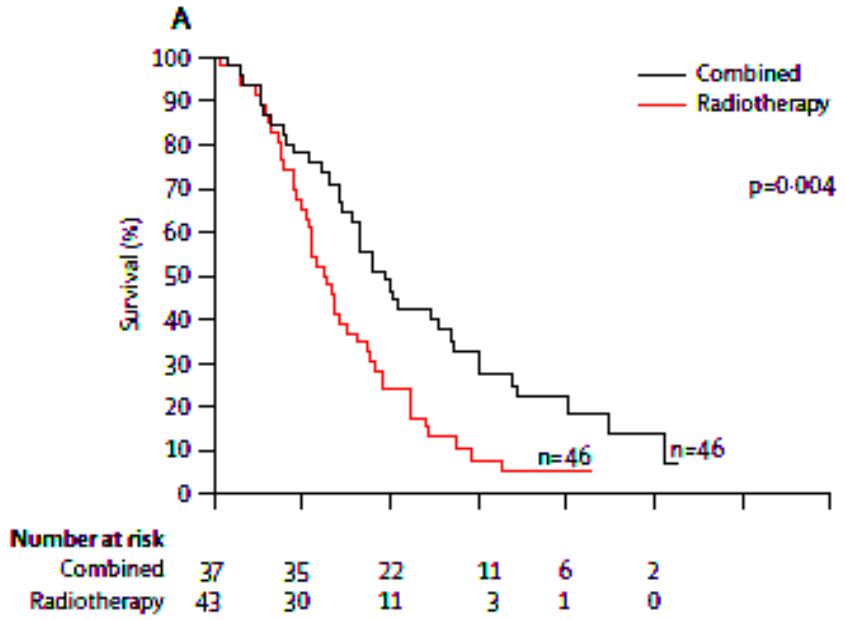
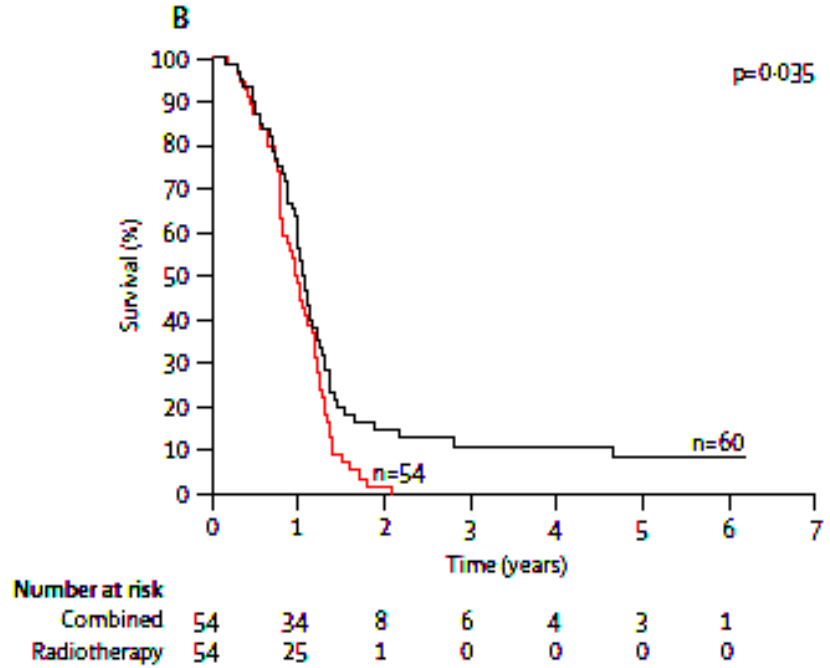
MGMT as a Biomarker for Patient Selection

Promoter region of *O-6-methylguanine-DNA methyltransferase* (*MGMT*) gene

MGMT silenced



MGMT functional



Hegi M, et al. *J Clin Oncol,* 2008

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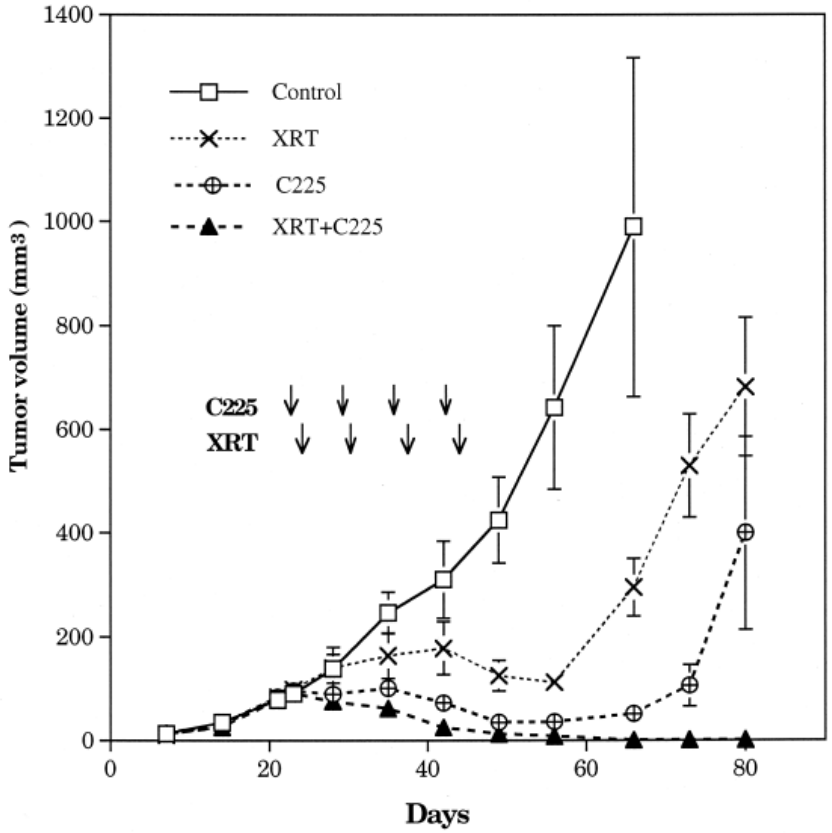
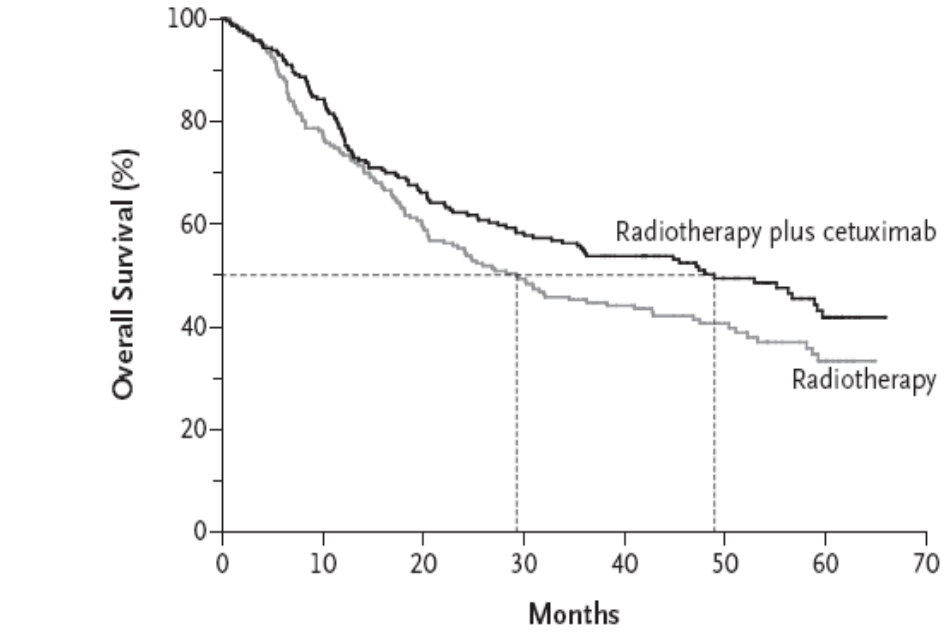
Cetuximab + Radiotherapy in Head and Neck



Harari and Huang. *Int. J. Radiation Oncology Biol. Phys,* 2001



No. at Risk							
Radiotherapy	213	162	122	97	73	47	22
Radiotherapy plus cetuximab	211	177	136	116	98	61	24

Bonner, et al *N Engl J Med,* 2006.

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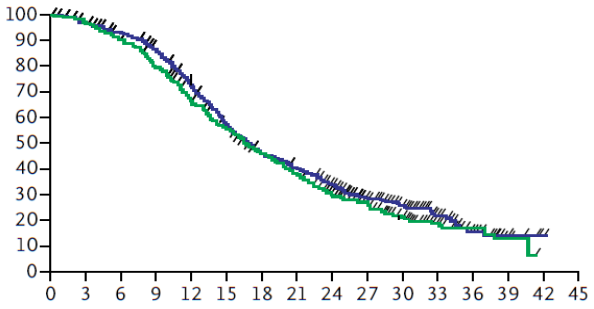
Subsequent High Profile Negative Results

Newly diagnosed GBM: Superior PFS and QoL

- Bevacizumab + RT-TMZ
- Placebo + RT-TMZ

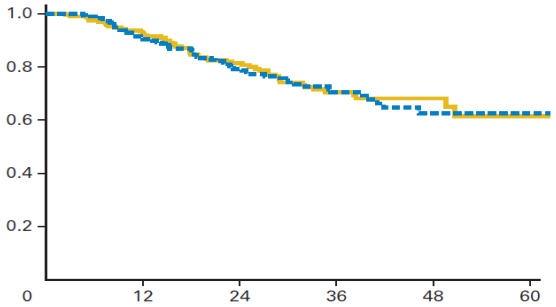


Time (months)

Chinot O et al.
NEJM 2014

Cervical cancer: 3-year OS 70%

- Cis-RT
- Cis-RT + tirapazamine

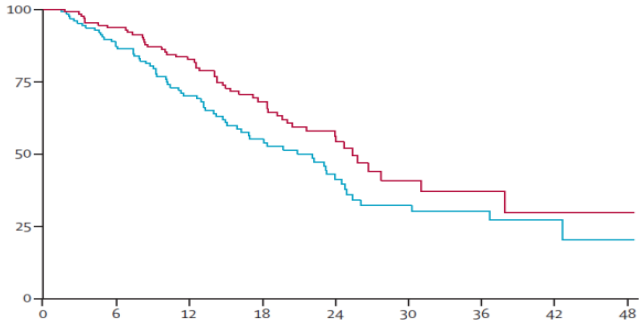


Time (months)

DiSilvestro P et al.
J Clin Oncol 2014

Oesophageal cancer: Stopped early

- Cis-Cape-RT + cetuximab
- Cis-Cape-RT



Time (months)

Crosby T et al.
Lancet Oncol 2013

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What are the barriers to overcome?

Critical Review

The Clinical Development of Molecularly Targeted Agents in Combination With Radiation Therapy: A Pharmaceutical Perspective

Ozlem U. Ataman, MD, PhD,* Sally J. Sambrook, PhD,* Chris Wilks, BSc,† Andrew Lloyd, BSc,* Amanda E. Taylor, PhD,‡ and Stephen R. Wedge, PhD†

*Global Medicines Development, AstraZeneca, Alderley Park, Macclesfield, Cheshire, United Kingdom; †Innovative Medicines, AstraZeneca, Alderley Park, Macclesfield, Cheshire, United Kingdom; and ‡Yellow Delaney Communications Ltd, Wilmslow, Cheshire, United Kingdom

2012; 84: e447-54

Barriers identified:

- Pharmaceutical industry sponsorship is limited
- Phase III studies: mainly sponsored by cooperative groups
- Majority of RT combination trials not initiated until after drug approval
- No consensus on study endpoints

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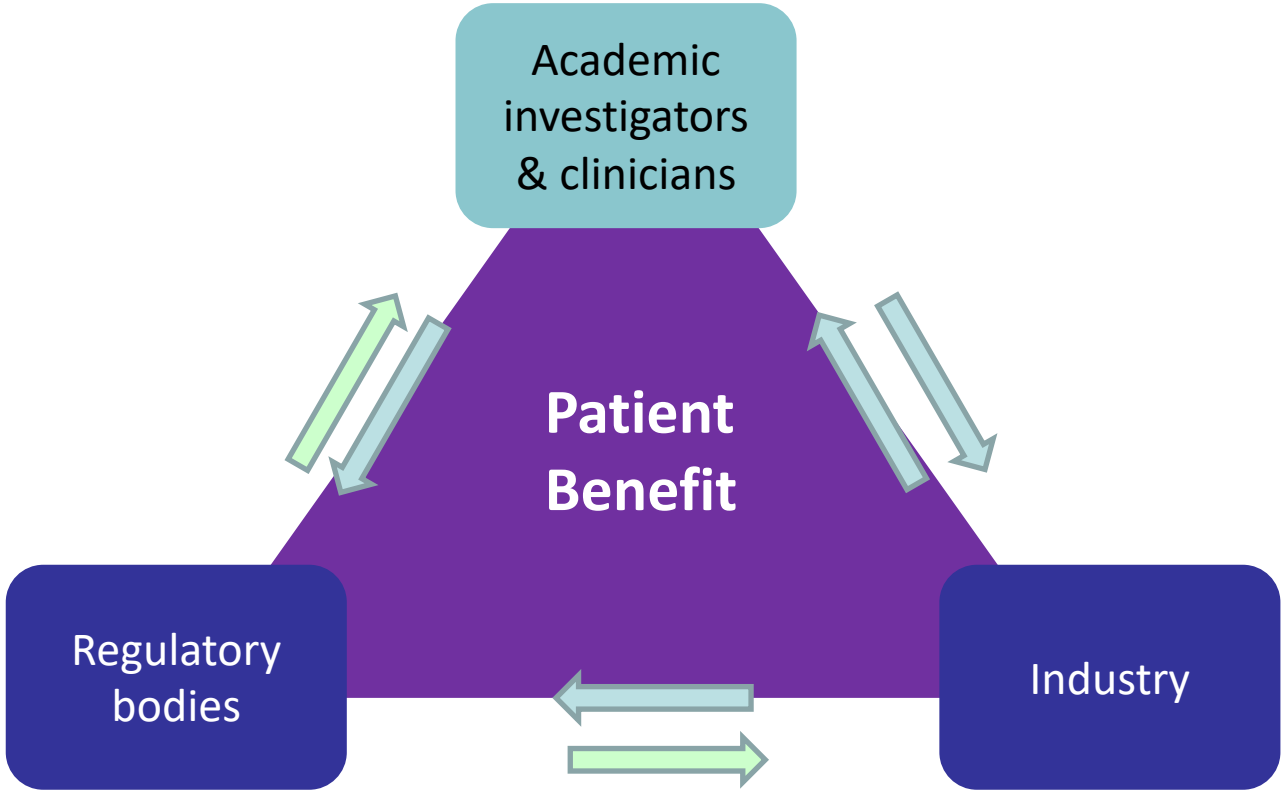
Stakeholders for New Drug-RT Combinations



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Strengths of 37 members:
Diversity, knowledge and expertise

10 Radiation Oncologists

3 Medical Oncologists

2 Scientists from Academia

1 Clinical Radiologist

3 Regulatory Experts

2 Consumer representatives

13 Scientists/ Clinicians from Pharma

3 Statisticians

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Open access paper in *Nature Reviews Clinical Oncology*

CONSENSUS STATEMENT

OPEN

Clinical development of new drug–radiotherapy combinations

Ricky A. Sharma[1], Ruth Plummer[2], Julie K. Stock[3], Tessa A. Greenhalgh[4], Ozlem Ataman[5], Stephen Kelly[6], Robert Clay[7], Richard A. Adams[8], Richard D. Baird[9], Lucinda Billingham[10], Sarah R. Brown[11], Sean Buckland[6], Helen Bulbeck[12], Anthony J. Chalmers[13], Glen Clack[14], Aaron N. Cranston[15], Lars Damstrup[16], Roberta Ferraldeschi[17], Martin D. Forster[1], Julian Golec[18], Russell M. Hagan[19], Emma Hall[20], Axel-R. Hanauske[21], Kevin J. Harrington[20], Tom Haswell[12], Maria A. Hawkins[4], Tim Illidge[22], Hazel Jones[3], Andrew S. Kennedy[23], Fiona McDonald[20], Thorsten Melcher[24], James P. B. O'Connor[22], John R. Pollard[18], Mark P. Saunders[22], David Sebag-Montefiore[11], Melanie Smitt[25], John Staffurth[8], Ian J. Stratford[22] and Stephen R. Wedge[2] on behalf of the NCRI CTRad Academia-Pharma Joint Working Group

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Sharma RA et al. *Nat Rev Clin Oncol* 2016; 13: 627-42

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Consensus Statements

Collaboration between industry and academia is essential

Occur as early as possible in drug development

Consider drug-radiotherapy combinations as important as drug-drug combinations

Robust scientific basis for the combination in preclinical models

Line of sight to registration

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Consumer involvement and raising awareness

Patients/consumers should be involved from the concept stage of development

Patients/consumers need to define what will or will not be acceptable to trial participants

Include clear statements about the potential benefit for future patients from conducting this research

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American Association for Cancer Research

FINDING CURES TOGETHER℠

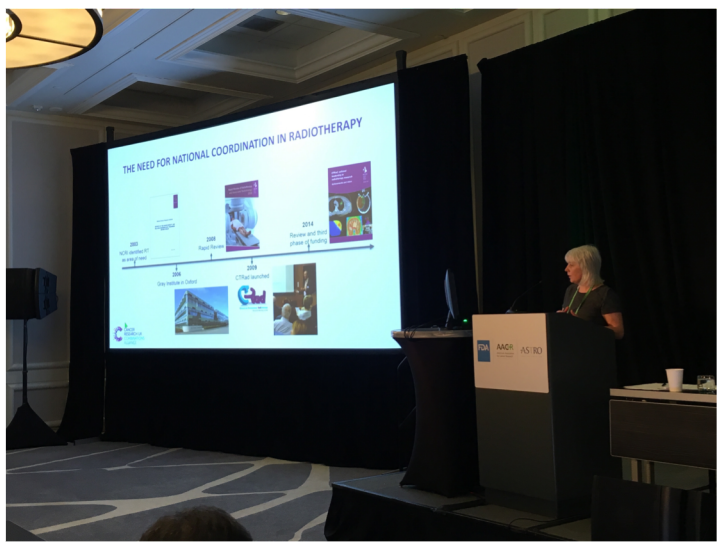
ASTRO

AMERICAN SOCIETY FOR RADIATION ONCOLOGY

FDA-AACR-ASTRO Clinical Development of Drug-Radiotherapy Combinations Workshop

with support from Cancer Research UK Combinations Alliance

February 22-23, 2018 | Bethesda, MD



Clinical Cancer Research

CCR Perspectives in Regulatory Science and Policy - INVITED

Clinical Development of Novel Drug-Radiotherapy Combinations

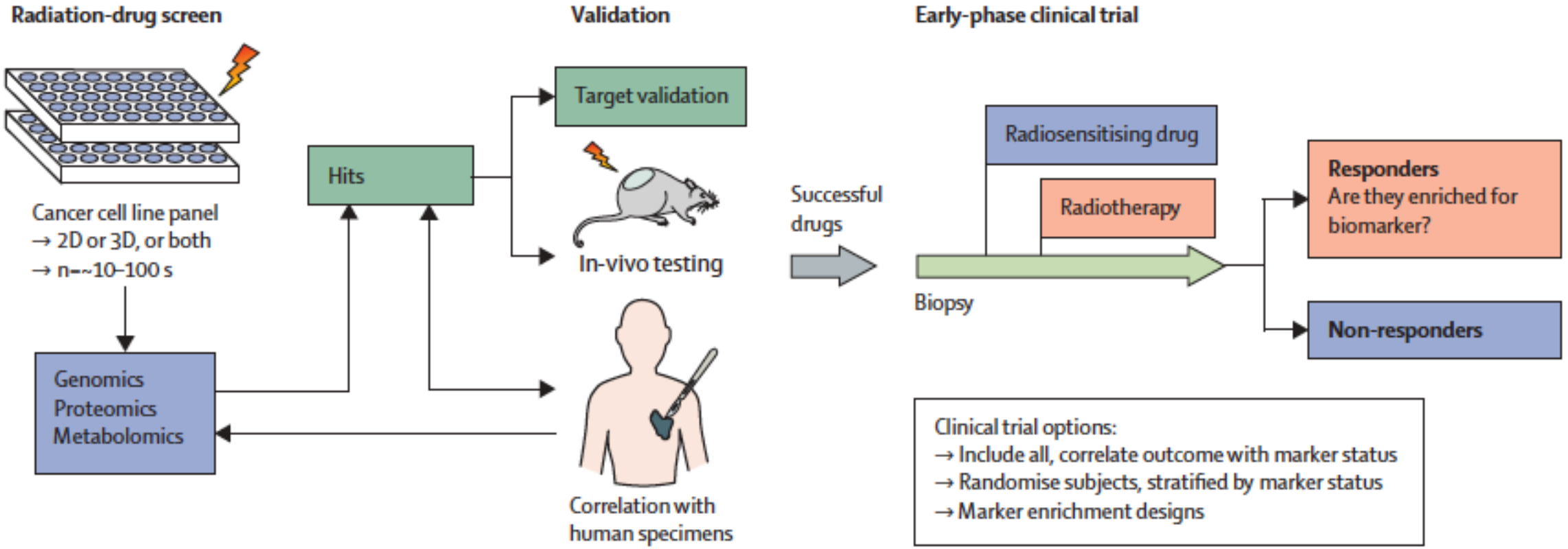
Saif S Ahmad, Marka R Crittenden, Phuoc T. Tran, Paul G. Kluetz, Gideon M. Blumenthal, Helen Bulbeck, Richard D Baird, Kaye J Williams, Timothy Illidge, Stephen Hahn, Theodore S. Lawrence, Patricia A Spears, Amanda J. Walker, and Ricky A Sharma

DOI: 10.1158/1078-0432.CCR-18-2466 Check for updates

Combining precision radiotherapy with molecular targeting and immunomodulatory agents: a guideline by the American Society for Radiation Oncology

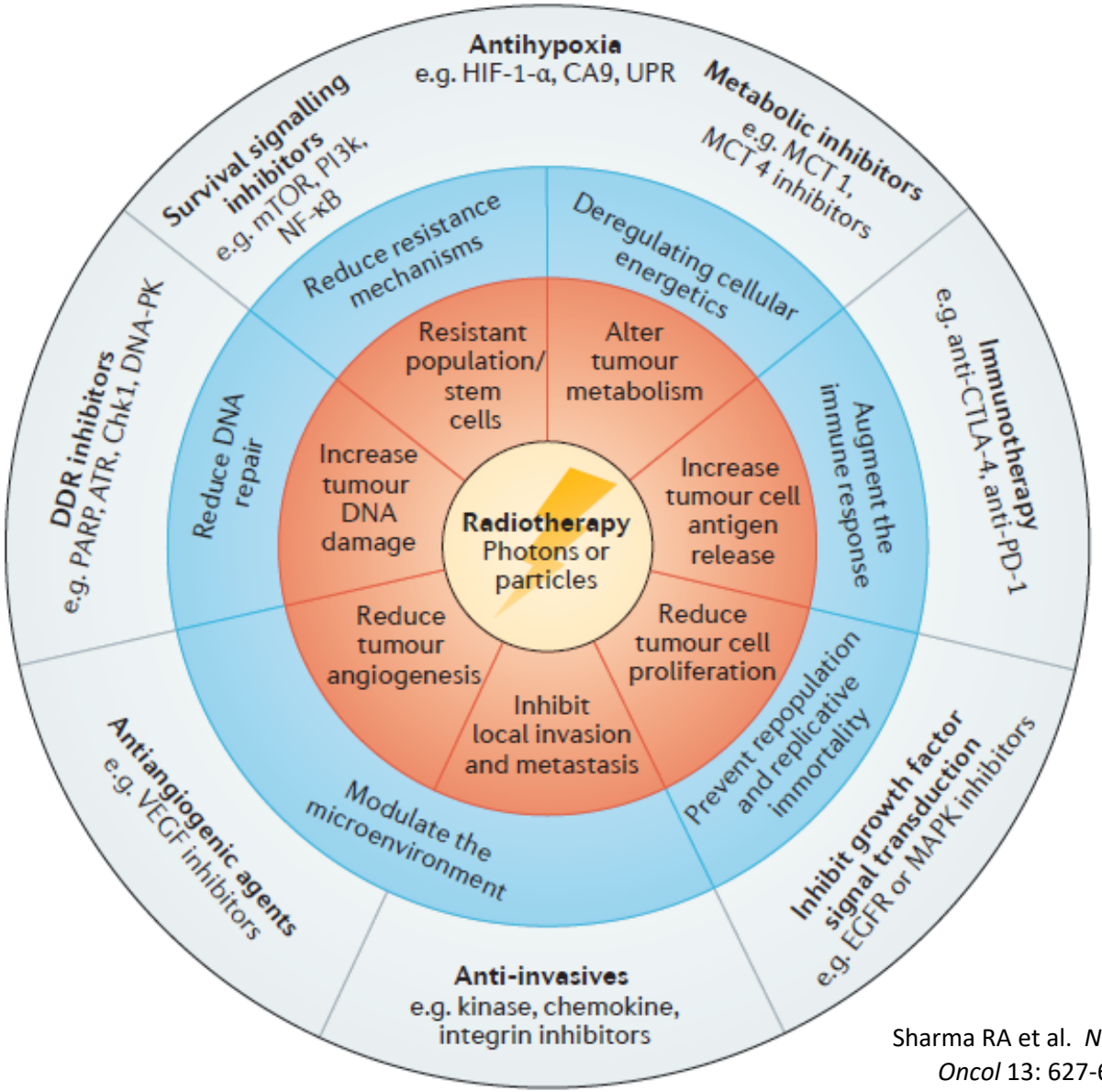
Lancet Oncol 2018; 19: e240–51

Robert G Bristow, Brian Alexander, Michael Baumann, Scott V Bratman, J Martin Brown, Kevin Camphausen, Peter Choyke, Deborah Citrin, Joseph N Contessa, Adam Dicker, David G Kirsch, Mechthild Krause, Quynh-Thu Le, Michael Milosevic, Zachary S Morris, Jann N Sarkaria, Paul M Sondel, Phuoc T Tran, George D Wilson, Henning Willers, Rebecca K S Wong, Paul M Harari



Defining the Line of Sight for a New Combination

Strong Basic Science



Sharma RA et al. *Nature Rev Clin Oncol* 13: 627-642, 2016

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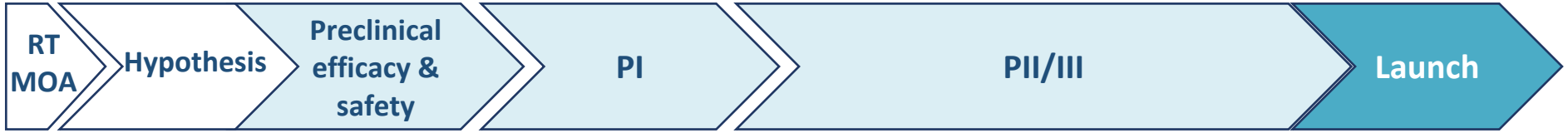
Core Programme

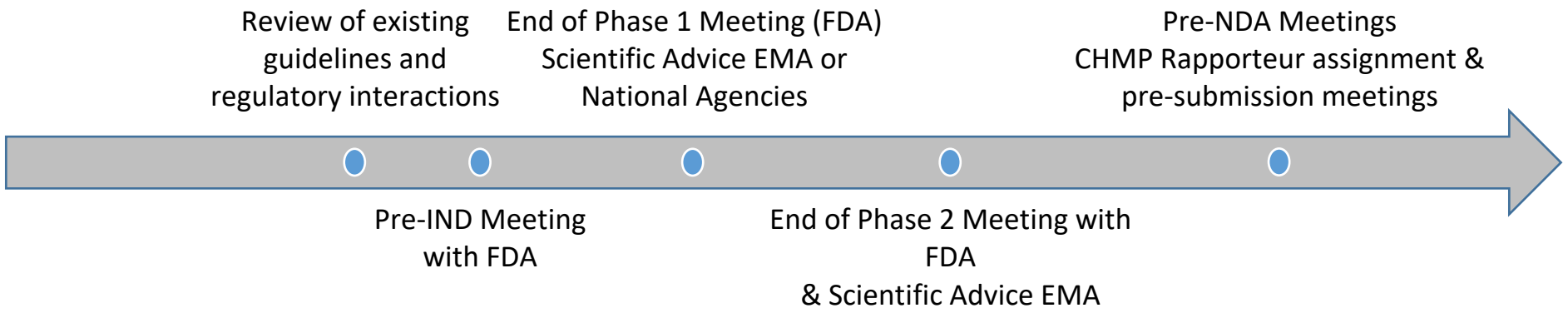
Monotherapy/ chemo MTD

Radiotherapy Program



RT-combined MTD

Potential Regulatory Interactions



Changing the standard of care

The treatment intent and the current standard of care for each disease being treated must be defined by the investigators, including any potential variation across countries. Potential changes in the standard of care must be predicted by clinical experts if the path to registration is to succeed.

Define the current standard of care

Predict how the standard of care might change

The line of sight should take potential changes into account

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What can we do now?

AIRO Overview: Efficacy of drug-RT combinations

Small molecule inhibitors
Erlotinib, Gefitinib, Afatinib
Sunitinib, Sorafenib
PARP inhibitors
Everolimus
Vemurafenib, Dabrafenib
Vismodegib, Inidegib

Androgen Receptor Pathway
Abiraterone
Enzalutamide
Apalutamide
Darolutamide
Orteronel
Galeterone

Monoclonal antibodies/Immune checkpoint blockade
Cetuximab, Panitumumab
Trastuzumab, Pertuzumab
Bevacizumab
PD-1 and PDL-1 antagonists
CTLA-4 antagonists

Arcangeli S et al. *Crit Rev Oncol Hematol* 2019; 134: 87-103

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Drug/radiation interaction

Harnessing drug/radiation interaction through daily routine practice: Leverage medical and methodological point of view (MORSE 02-17 study)

A. Vallard [a,b], C. Rancoule [a,b], S. Espenel [a,b], M.-A. Garcia [c], J. Langrand-Escure [a], M.Y. He [a], M. Ben Mrad [a], A. El Meddeb Hamrouni [a], S. Ouni [a], J.-C. Trone [a], A. Rehailia-Blanchard [a], E. Guillaume [a], N. Vial [a], C. Riocreux [a], J.-B. Guy [a,b], N. Magné [a,b,*]

[a] *Radiotherapy Department, Lucien Neuwirth Cancer Institute, 42270 St Priest en Jarez;* [b] *Cellular and Molecular Radiobiology Laboratory, CNRS UMR 5822, IPNL, 69622 Villeurbanne; and* [c] *General Health Department, Hygée Institute, Avenue Albert Raimond, BP 60008, 42271 Saint-Priest en Jarez, France*

ARTICLE

DOI: 10.1038/s41467-018-04278-6 OPEN

Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis

Sean P. Pitroda[1,2], Nikolai N. Khodarev[1,2], Lei Huang[3], Abhineet Uppal[4], Sean C. Wightman[4], Sabha Ganai[5], Nora Joseph[6], Jason Pitt[7], Miguel Brown[7], Martin Forde[7], Kathy Mangold[6], Lai Xue[4], Christopher Weber[8], Jeremy P. Segal[8], Sabah Kadri[8], Melinda E. Stack[4], Sajid Khan[9], Philip Paty[10], Karen Kaul[6], Jorge Andrade[3], Kevin P. White[7,11], Mark Talamonti[12], Mitchell C. Posner[4], Samuel Hellman[1,2] & Ralph R. Weichselbaum[1,2]

	Subtype 1 canonical	Subtype 2 immune	Subtype 3 stromal
Frequency	33%	28%	39%
Molecular signatures	↓Immune and stroma E2F/MYC signaling DNA damage and cell cycle	↑Immune Interferon signaling p53 pathway	↑Stroma KRAS signaling EMT and angiogenesis
Specific mutations	*NOTCH1* and *PIK3C2B*	*NRAS*, *CDK12*, and *EBF1*	*SMAD3*
Metastatic recurrences	Many	Few	Many
Overall survival	Intermediate	Favorable	Unfavorable

Clinical end points: Recommendations

Include clinically relevant early and intermediate end points

End points must be pragmatic, relevant to patients and applicable in a 'real world' setting

Loco-regional control matters to patients

Secondary end points should include normal tissue toxicity

Sharma RA et al. *Nature Rev Clin Oncol* 13: 627-642, 2016

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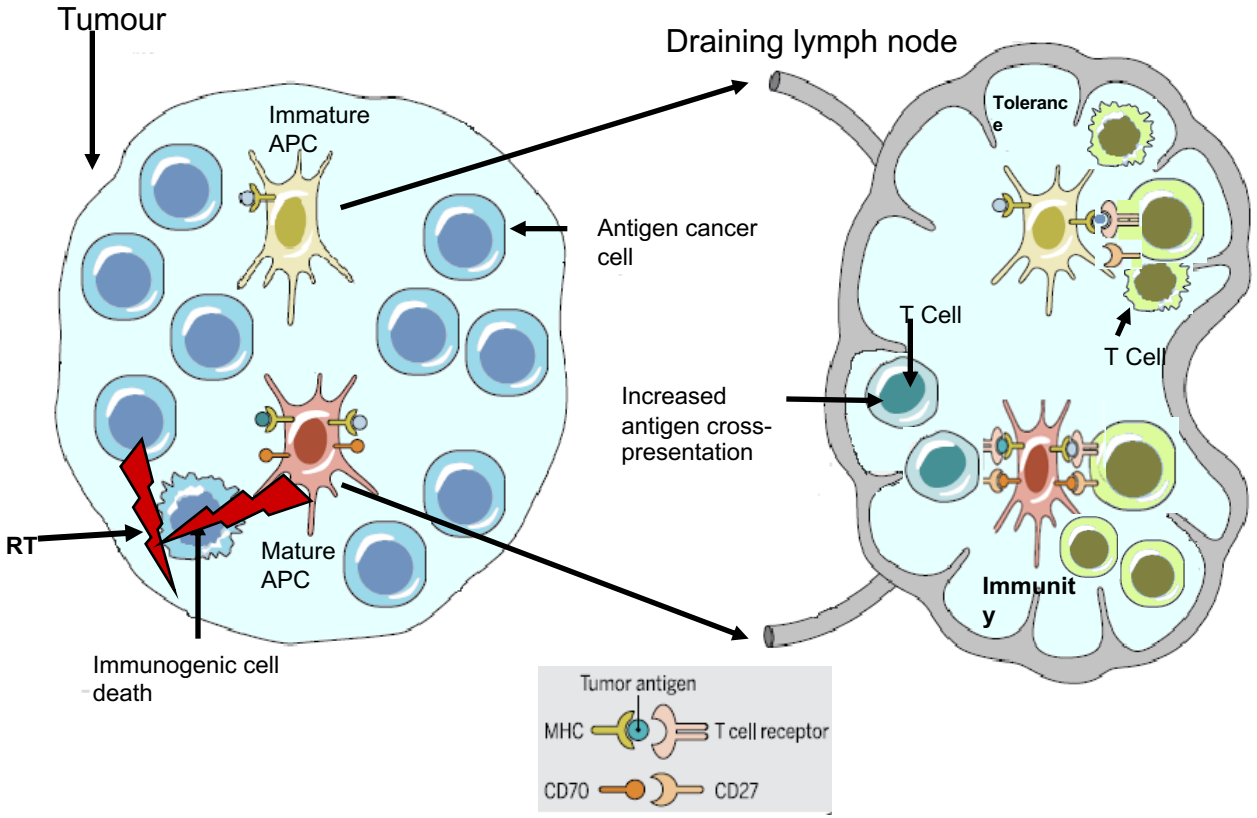
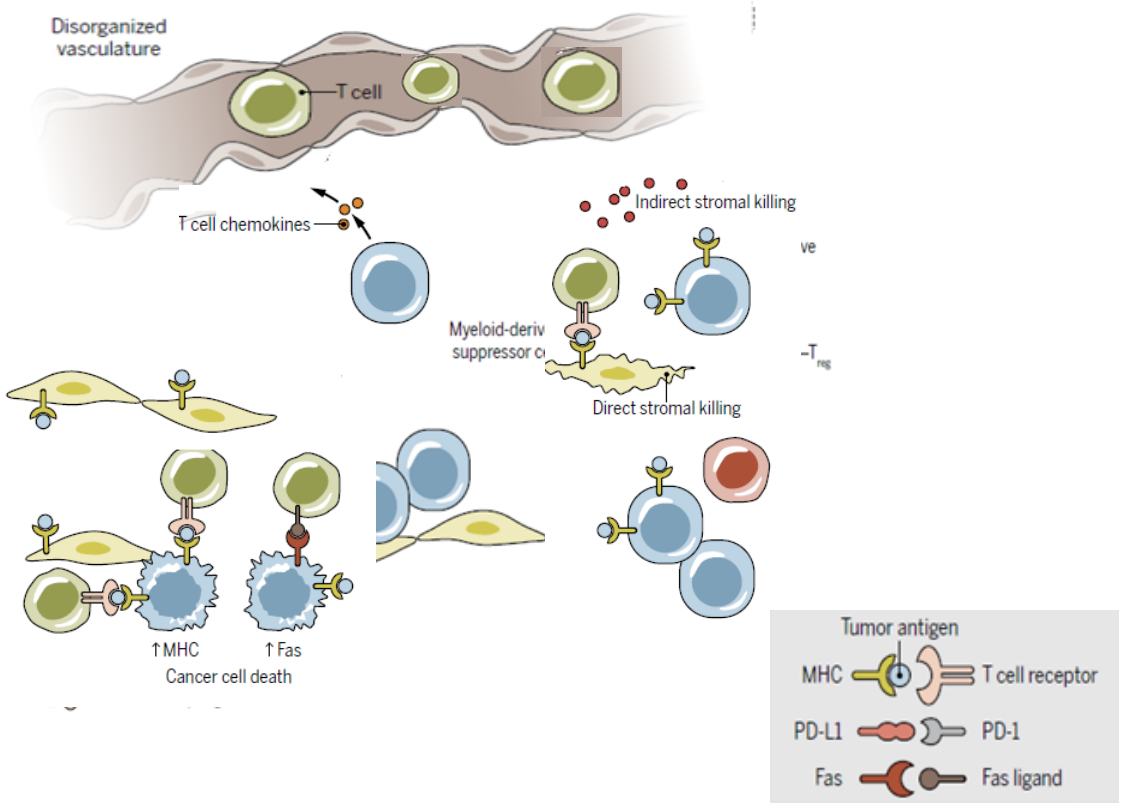
Exemplar 1: Immunotherapy

Radiation Induces T-cell Priming



Spiotto M et al. Sci. Immunol. 1, eaag1266 (2016)

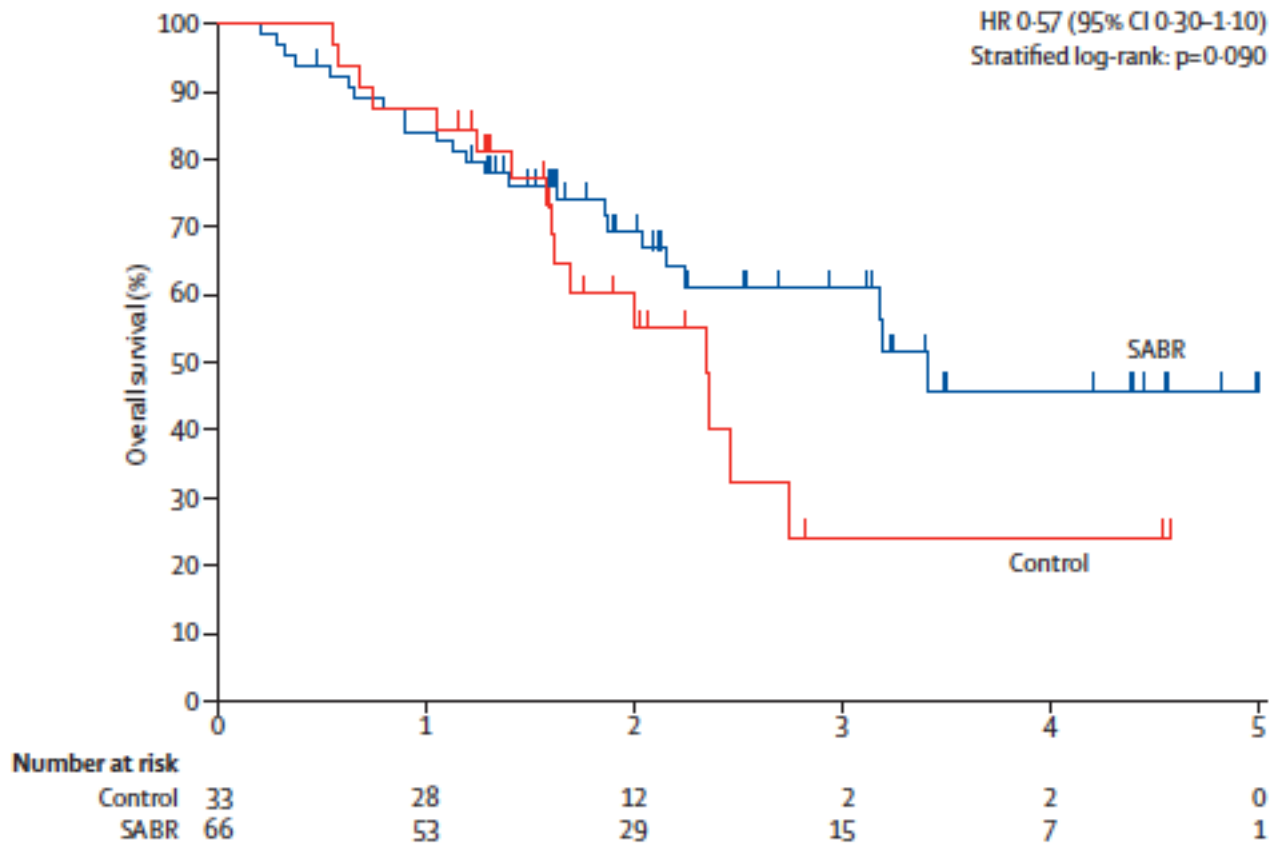
Irradiated Tumor: Effector T-cell Responses

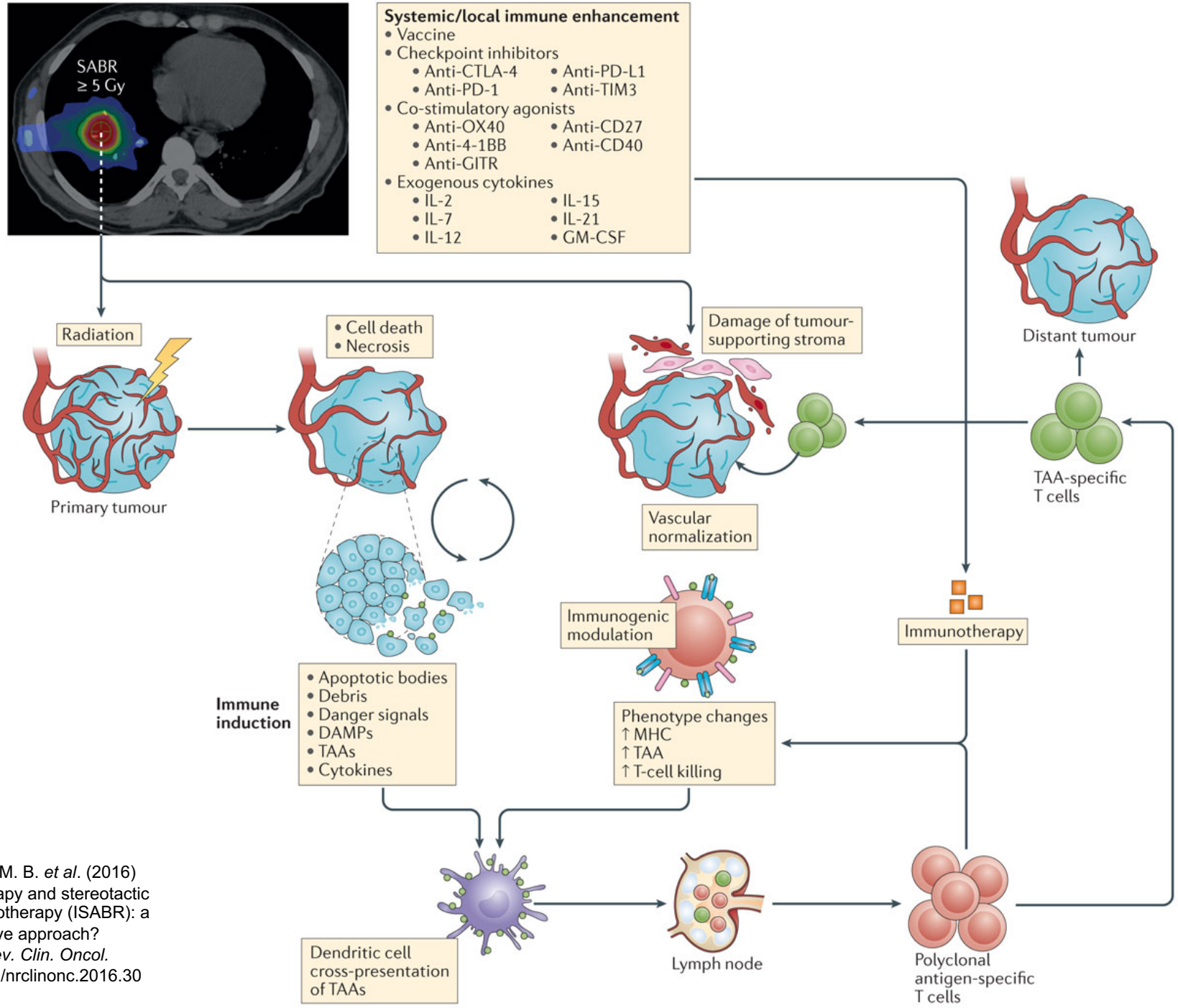


Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

Lancet 2019; 393: 2051–58

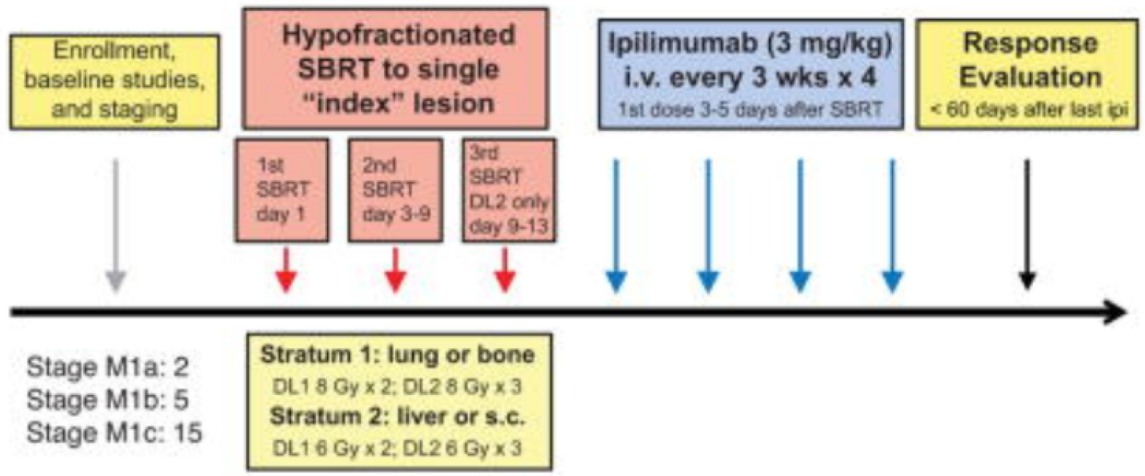
David A Palma, Robert Olson, Stephen Harrow, Stewart Gaede, Alexander V Louie, Cornelis Haasbeek, Liam Mulroy, Michael Lock, George B Rodrigues, Brian P Yaremko, Devin Schellenberg, Belal Ahmad, Gwendolyn Griffioen, Sashendra Senthi, Anand Swaminath, Neil Kopek, Mitchell Liu, Karen Moore, Suzanne Currie, Glenn S Bauman, Andrew Warner, Suresh Senan

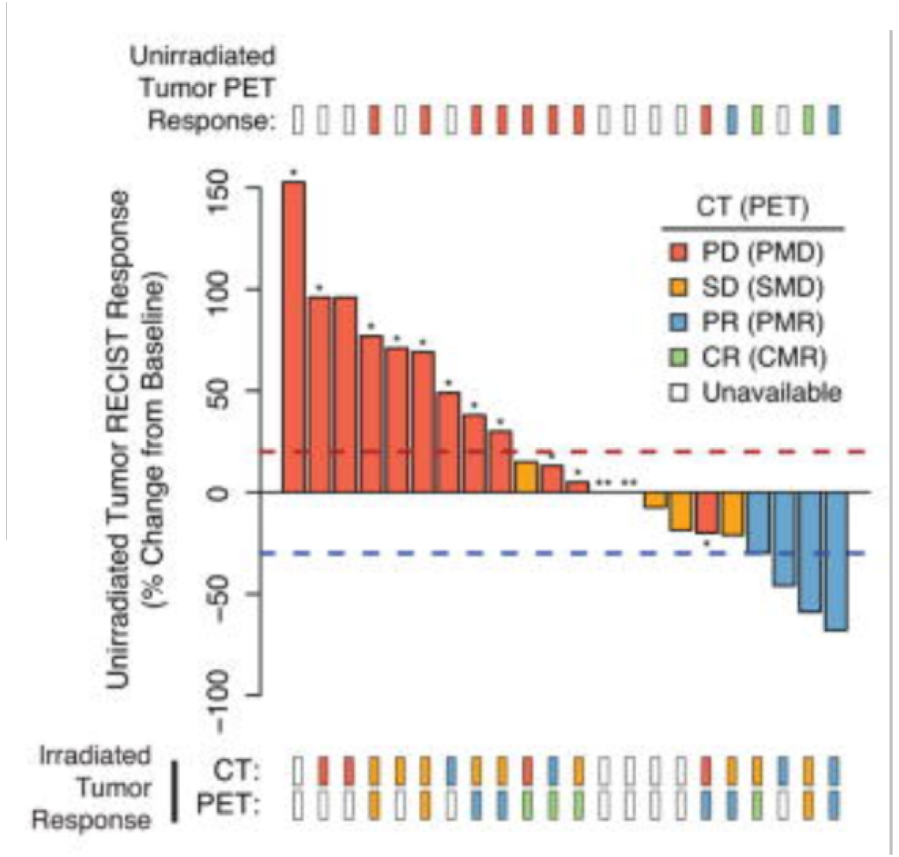




Bernstein, M. B. *et al*. (2016)
Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach?
Nat. Rev. Clin. Oncol.
doi:10.1038/nrclinonc.2016.30

Translational Exemplar: SBRT + Anti-CTLA4





- Study demonstrated the safety of addition of SBRT to ipilumumab
- ~18% abscopal responses in immunocompetent mice and in patients with melanoma

Twyman Saint-Victor, et al, Nature 2015

Clinically relevant model systems

Immunocompromised models

- Human origin of cancer cells
- Fast growth
- Features close to original tumor

Genetically-engineered models

- These mice develop tumors driven by oncogenic mutations
- To some extent reproduce the carcinogenic process in a more physiological way

Syngeneic models

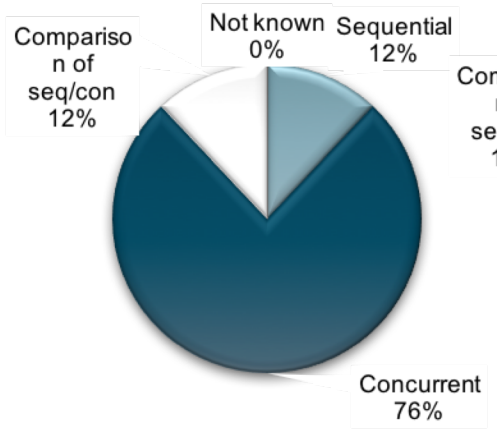
- Experimental mouse tumors injected in fully immune competent syngeneic mice
- Have provided the data leading to development of immunotherapy in the clinic

Humanized mice

- These mice can provide the best opportunity to study the interaction of human tumors with the human immune system

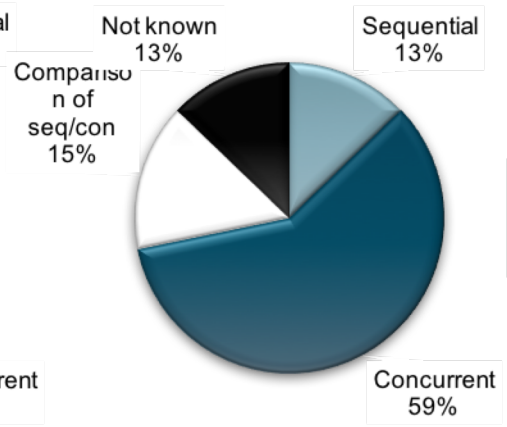
Tidal wave of new Trials of RT + Immunotherapy

Trials of RT + αCTLA-4 mAb



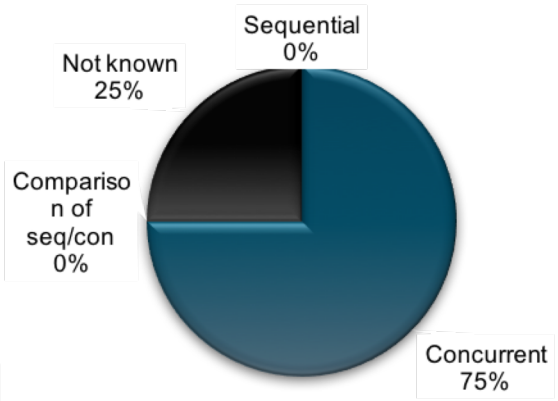
25 trials
PhI 8, PhI/II 8, PhII 8, PhIII 1

Trials of RT + αPD-1 / αPD-L1 mAb



39 trials
PhI 18, PhI/II 4, PhII 16, PhIII 1

Trials of RT + αCTLA-4 + αPD-1 / αPD-L1 mAb



4 trials
(PhII)

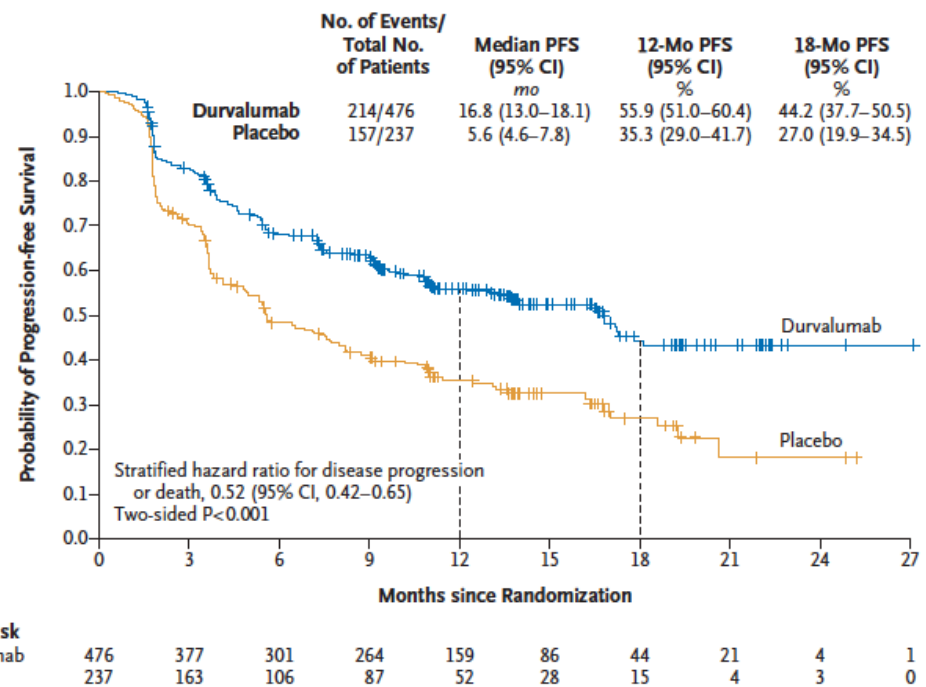
Data from clinicaltrials.gov

The NEW ENGLAND JOURNAL of MEDICINE

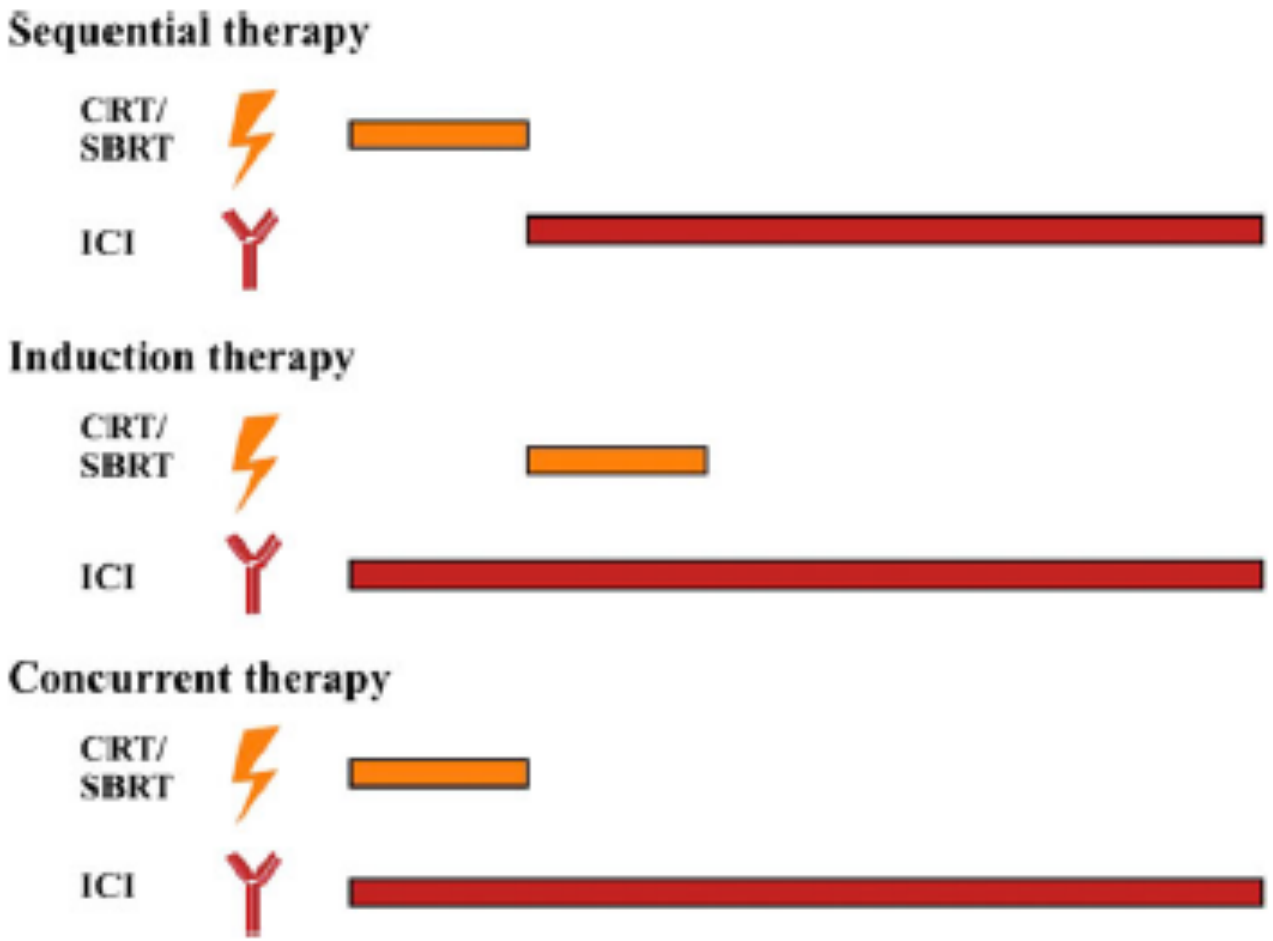
ORIGINAL ARTICLE

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*



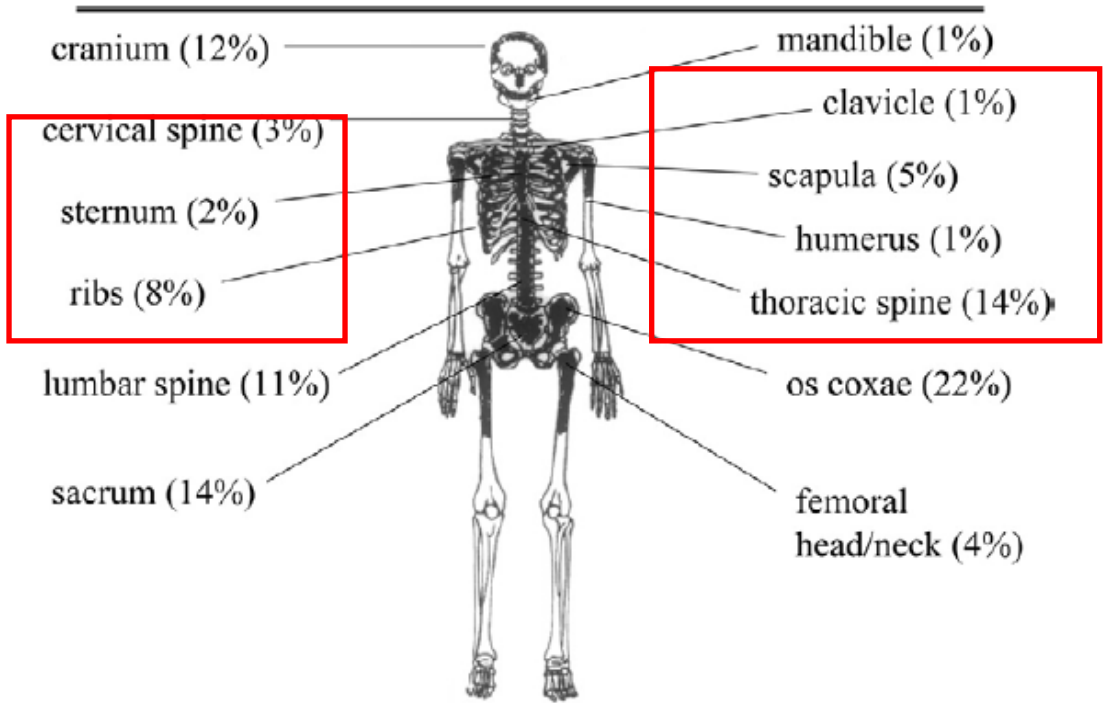
Sequencing of Immunotherapy plus Radiotherapy



Ongoing clinical trials of Immunotherapy plus Radiotherapy for Stage III NSCLC

NCT number	Reference	Radiation	Sequencing	Radiation dose	Immunotherapy	Stage	Phases	Enrollment
Resectable stage III NSCLC								
NCT03217071	53	SBRT	Induction	12 Gy/1 fx	Pembrolizumab	I–IIIA	2	40
NCT02987998	54	cCRT	Concurrent	45 Gy/25 fx	Pembrolizumab	IIIA	1	20
NCT03053856	56	cCRT	Adjuvant	44 Gy//22 fx	Pembrolizumab	IIIA	2	37
NCT03237377	55	TRT	Concurrent	45–50 Gy/25 fx	Durvalumab (+tremelimumab)	IIIA	2	32
Unresectable stage III NSCLC								
NCT02768558	60	cCRT	Sequential	60 Gy	Nivolumab	III	3	13
NCT03285321	61	cCRT	Sequential	59.4–66.6 Gy	Nivolumab (+ipilimumab)	III	2	108
NCT02434081[a]	62	cCRT	Concurrent	NM	Nivolumab	III	2	78
NCT02525757[a]	58	cCRT	Sequential/ concurrent	60–66 Gy/30–32 fx	Atezolizumab	III	2	52
NCT03102242	63	cCRT	Induction	60 Gy/30 fx	Atezolizumab	III	2	63
NCT02125461[a]	57	cCRT	Sequential	54–66 Gy	Durvalumab	III	3	713
NCT03509012	64	cCRT	Concurrent	NM	Durvalumab	III	1	300
NCT02343952[a]	59	cCRT	Concurrent	59.4–66.6 Gy	Pembrolizumab	III	2	93
NCT02621398	65	cCRT	Concurrent	30 fx (dose NM)	Pembrolizumab	II–IIIB	1	30

Distribution of Adult Bone Marrow



Thorax - Thoracic Spine + Ribs + Clavicle + Sternum = 25% of BM reserve

Part of these areas are included in the treatment volume, especially for patients with locally advanced disease

Exemplar 2: DNA Damage Repair

Radiobiology

The Gray – the unit of absorbed dose

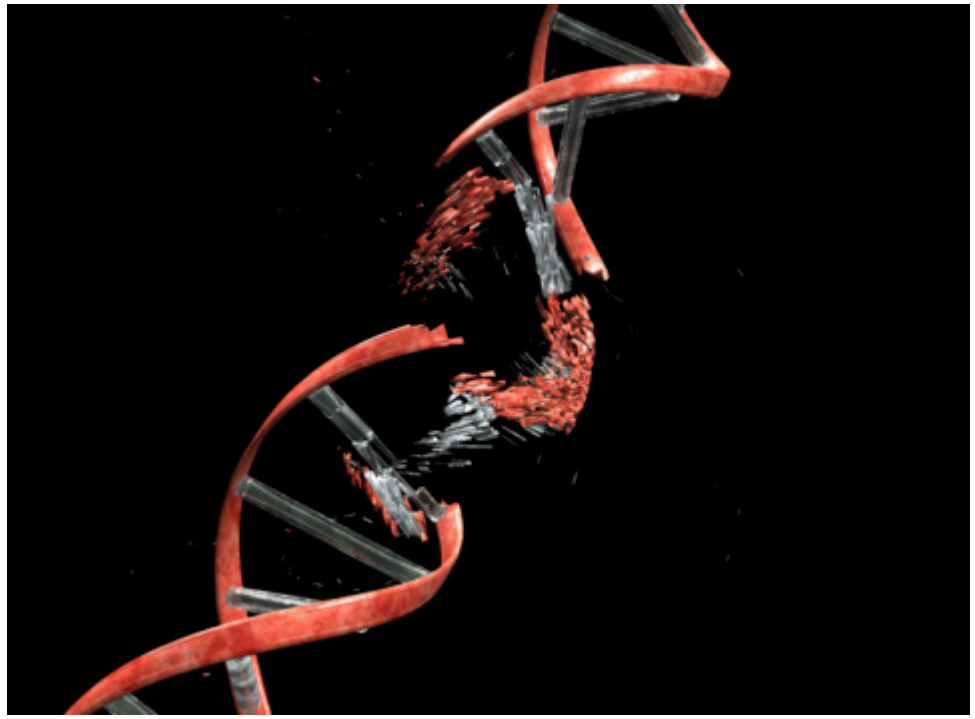
1 Gy is the deposit of one joule of (radiation) energy in one kg of matter or tissue

1 Gy exposure in cells causes

>10,000 damaged DNA bases

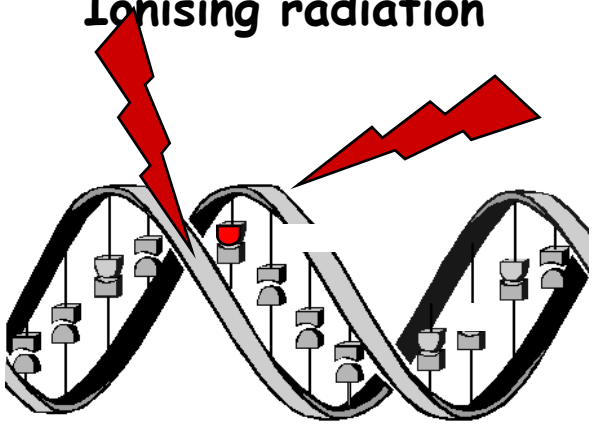
~ 1000 single stranded DNA breaks

~ 40 double stranded breaks



Radiation causes DNA damage

Ionising radiation



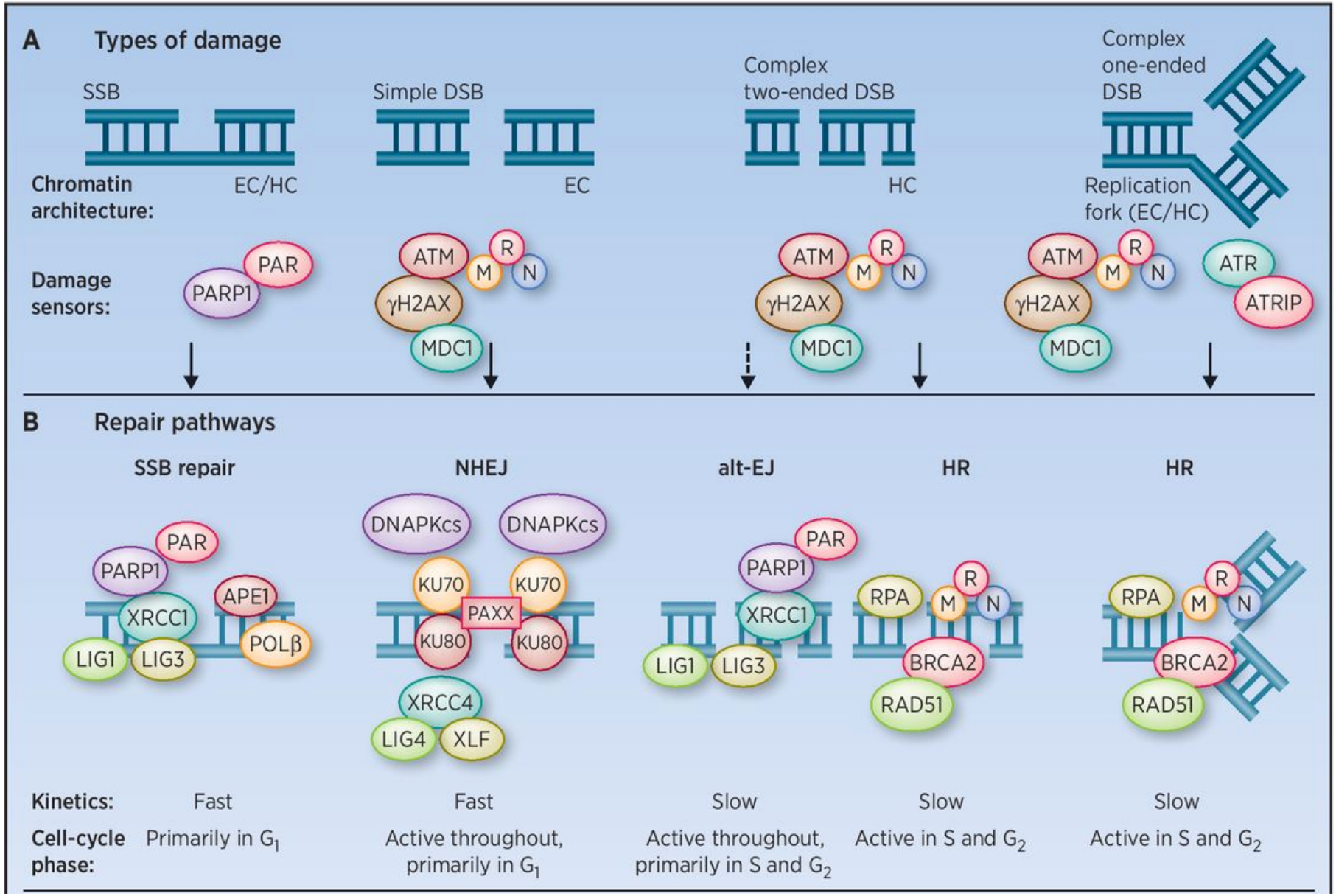
Double strand breaks
Single strand breaks
Base damage
Reactive oxygen species and other free radicals

DNA DAMAGE REPAIR PATHWAYS

Cell death

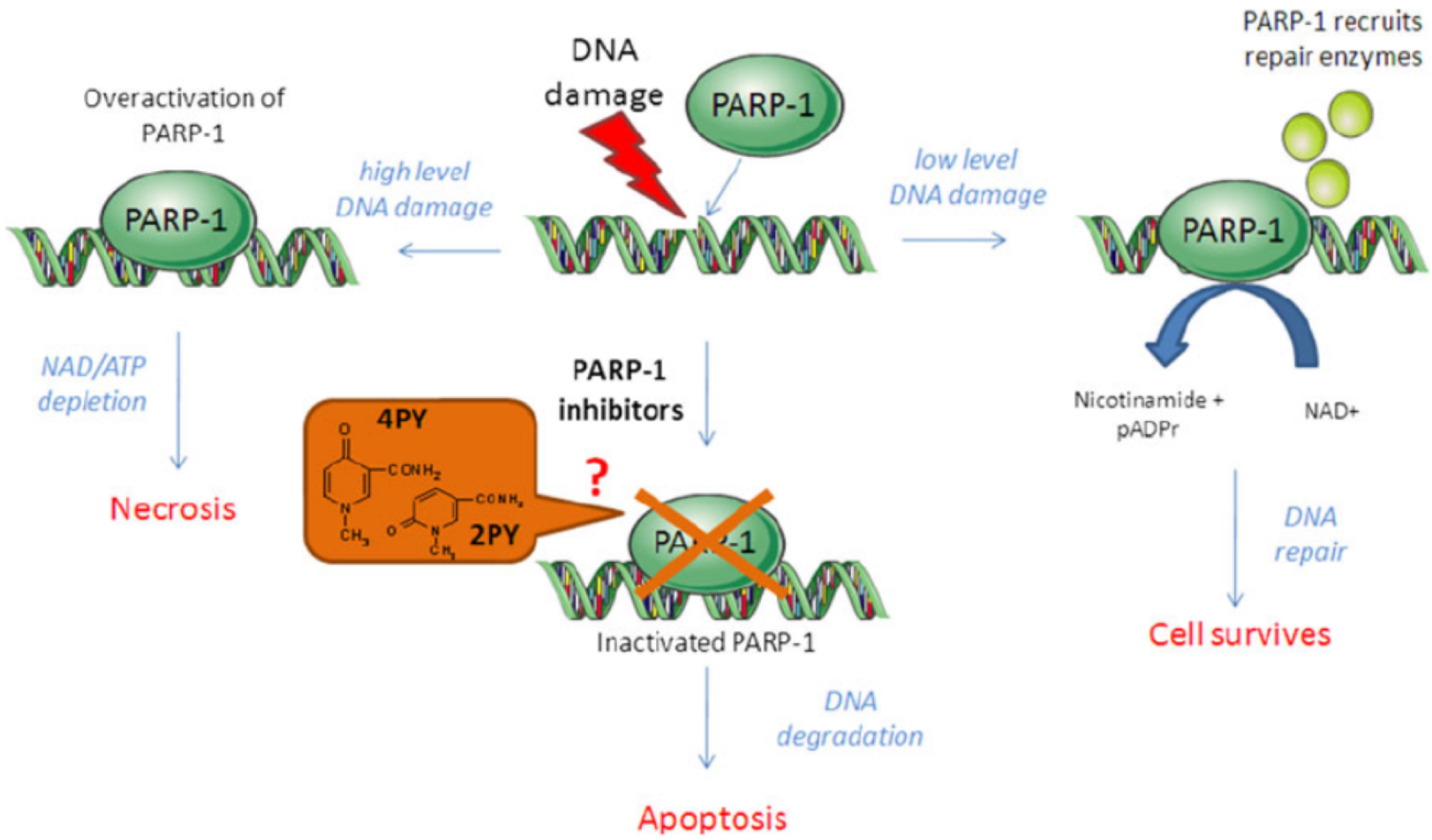
DNA Damage

Single and clustered damage sites	Double strand breaks (prompt DSB)
single strand break	simple DSB
base damage/sugar damage	complex DSB
clustered damage	



CCR Molecular Pathways, 2015

Combined PARP inhibitor and radiation treatment



Lenglet et al, 2013, Drugs in R&D.

The UK CONCORDE Study

Sarah Brown
Lead Statistician

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Clin Onc CI

Alastair Greystoke
Med Onc CI

Anderson Ryan
Lead Scientist

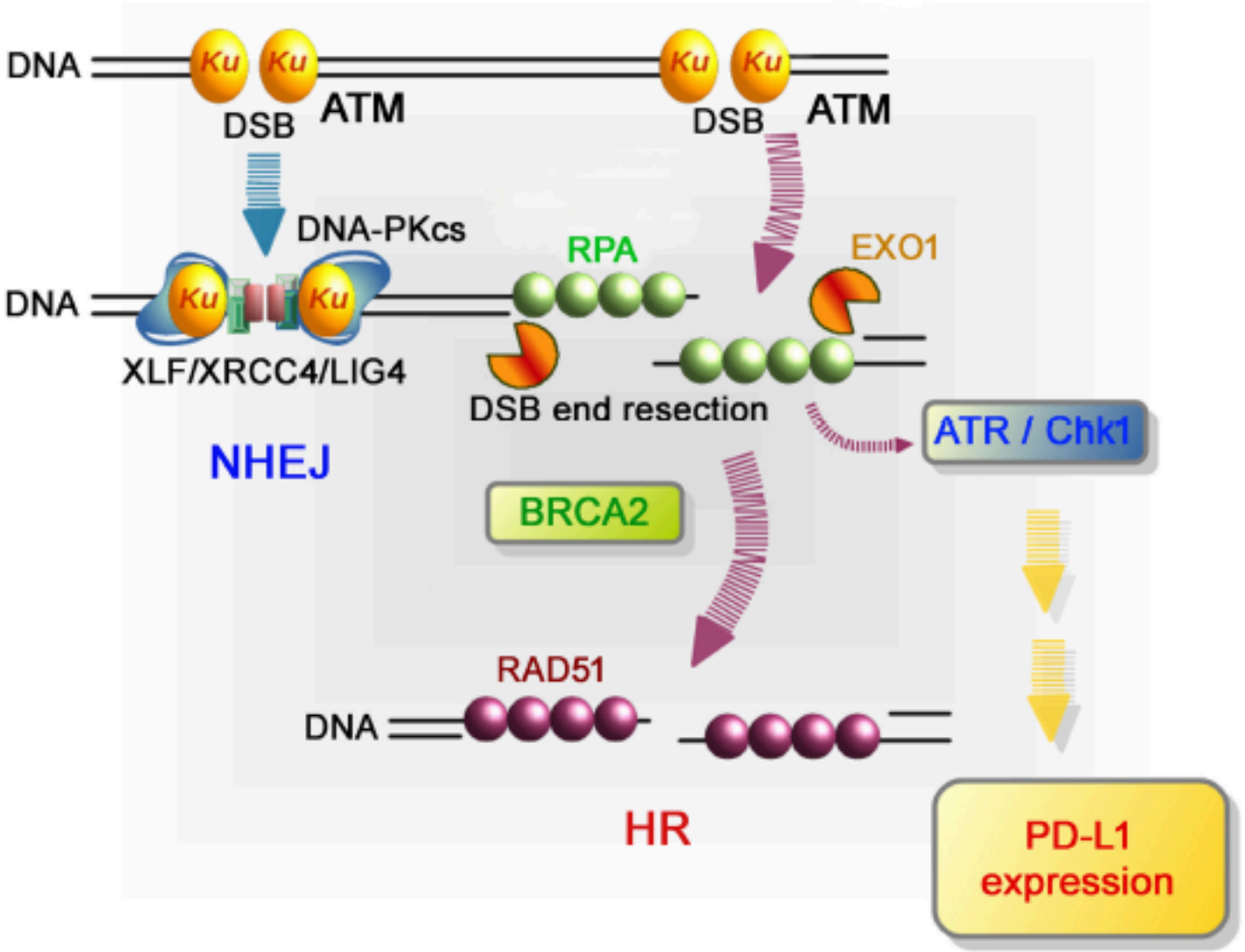
David Sebag-Montefiore
Co-Investigator

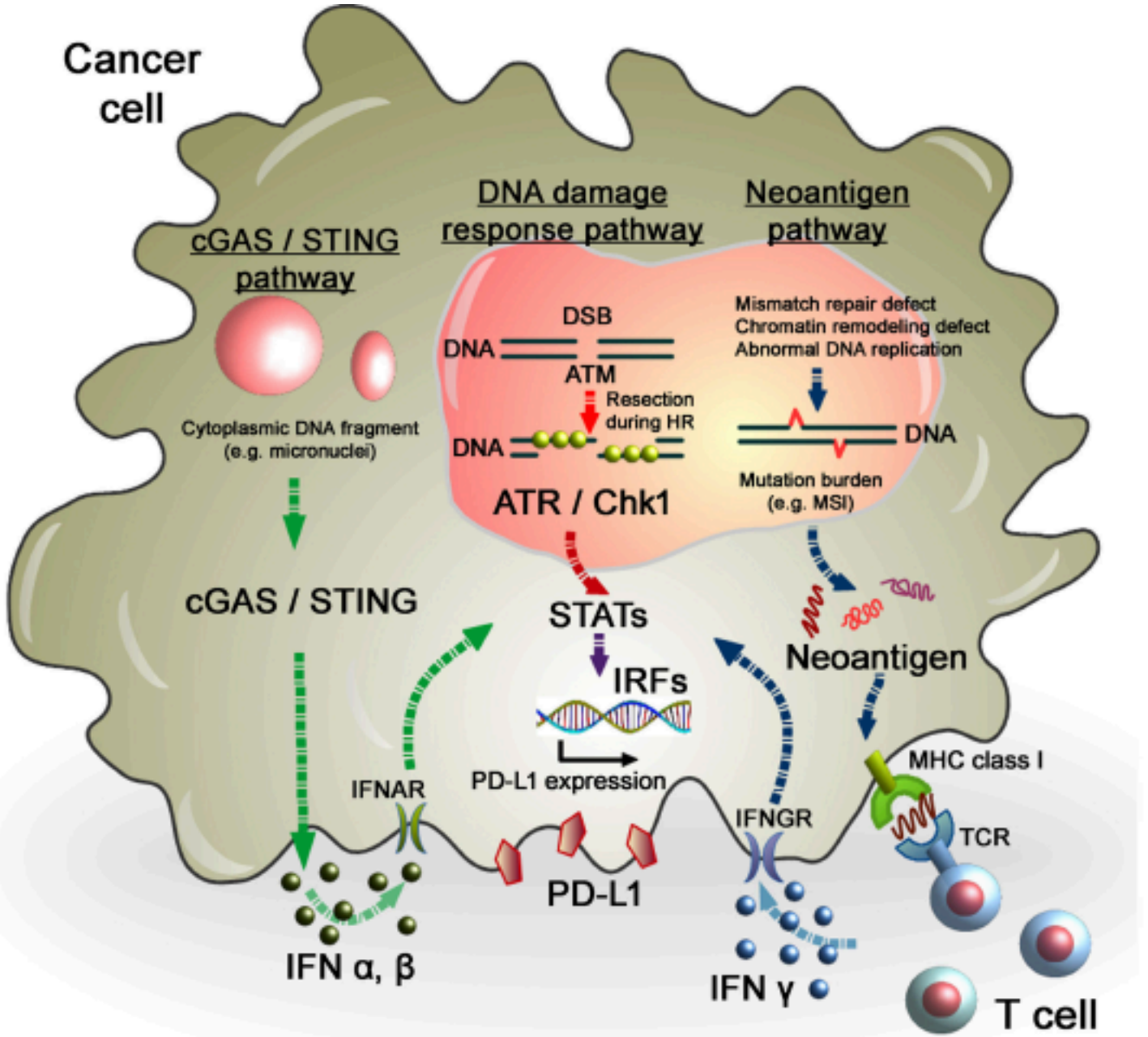
Anthony Chalmers
Co-Investigator

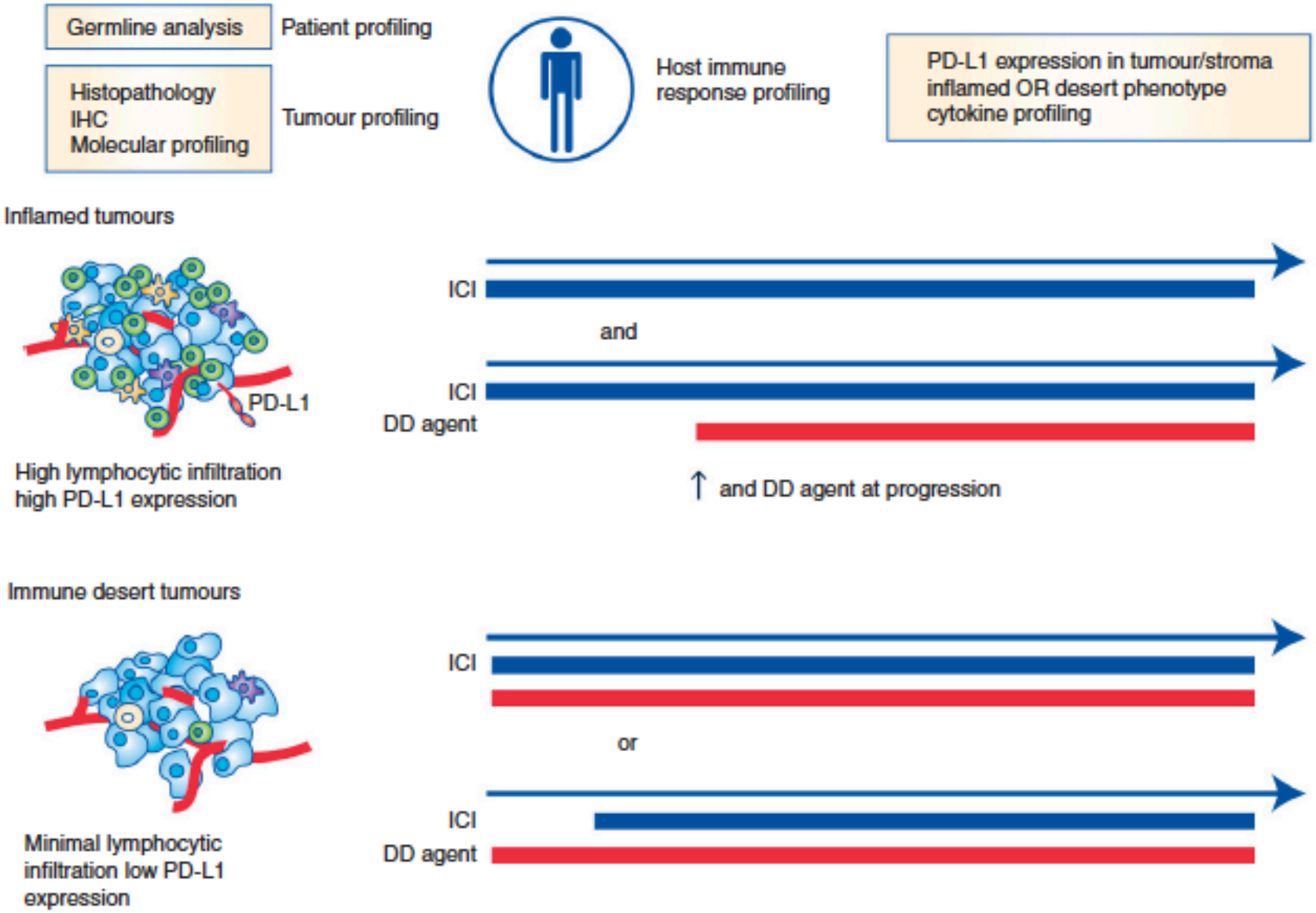
Stage IIB/III NSCLC fit for radical dose RT
Not suitable for concurrent CRT or surgery
(n= 40 per arm)

Randomise 3:1	Randomise 3:1	Randomise 3:1	Randomise 3:1	Randomise 3:1
RT + Olaparib (PARP) / RT	RT + AZD1775 (Wee1) / RT	RT + AZD6738 (ATR) / RT	RT + AZD7648 (DNAPK) / RT	RT + AZD1390 (ATM) / RT
Study Arm Leads: Kevin Franks (Chris Twelves)	Study Arm Leads: Andrew Hudson (Matthew Krebs)	Study Arm Leads: Paul Shaw (Rob Jones)	Study Arm Leads: Crispin Hiley (Martin Forster)	Study Arm Leads: Stephen Harrow (Anthony Chalmers)

Critical balance of DDR in PD-L1 expression

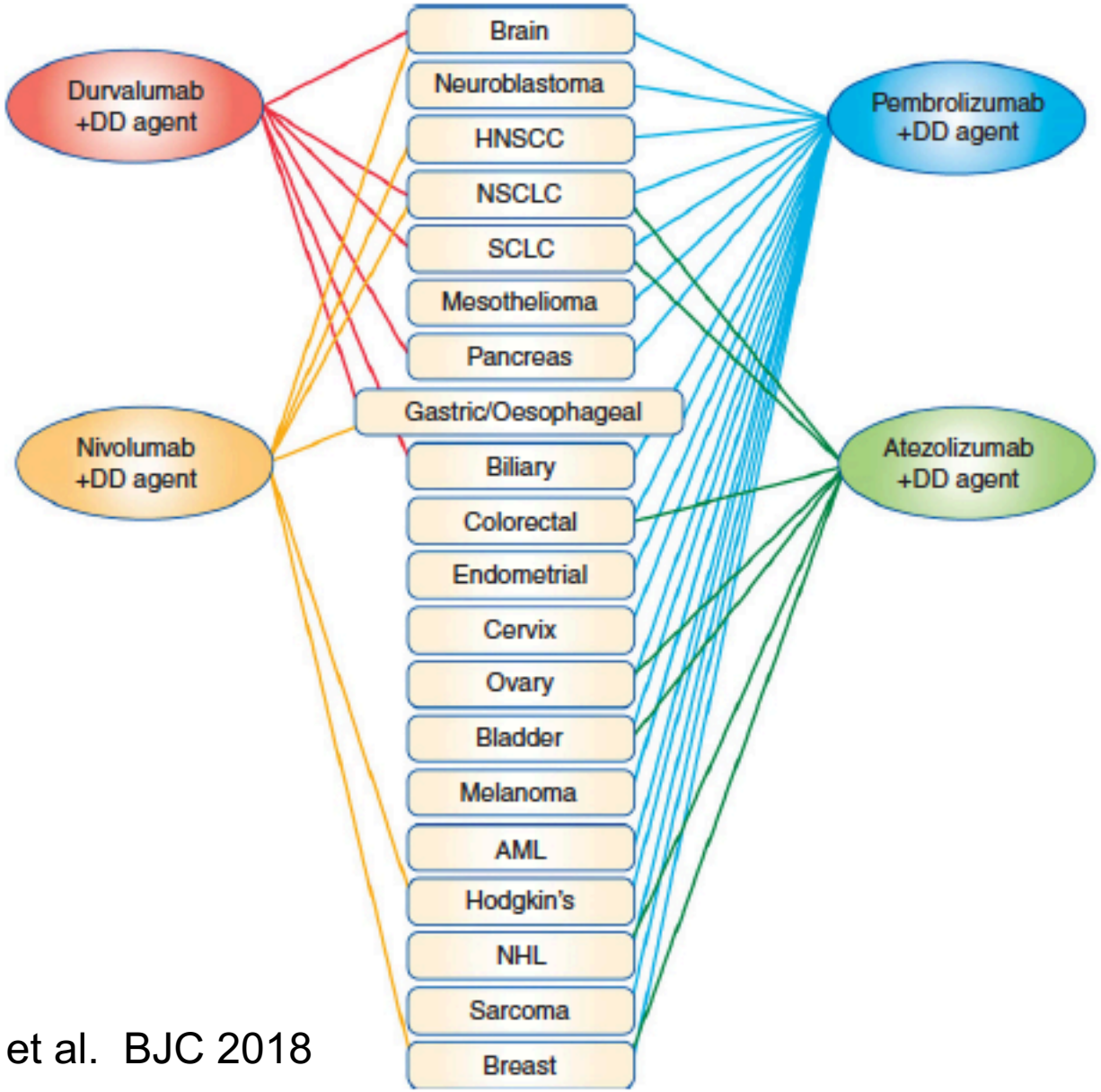



Cancer cell
cGAS / STING pathway
DNA damage response pathway
Neoantigen pathway
Cytoplasmic DNA fragment (e.g. micronuclei)
DSB
DNA
ATM
Resection during HR
DNA
ATR / Chk1
Mismatch repair defect
Chromatin remodeling defect
Abnormal DNA replication
DNA
Mutation burden (e.g. MSI)
cGAS / STING
STATs
IRFs
PD-L1 expression
Neoantigen
MHC class I
TCR
IFNAR
IFNGR
PD-L1
IFN α, β
IFN γ
T cell



Brown JS et al. BJC 2018

Trials of immunotherapy plus DNA damaging agent



Brown JS et al. BJC 2018

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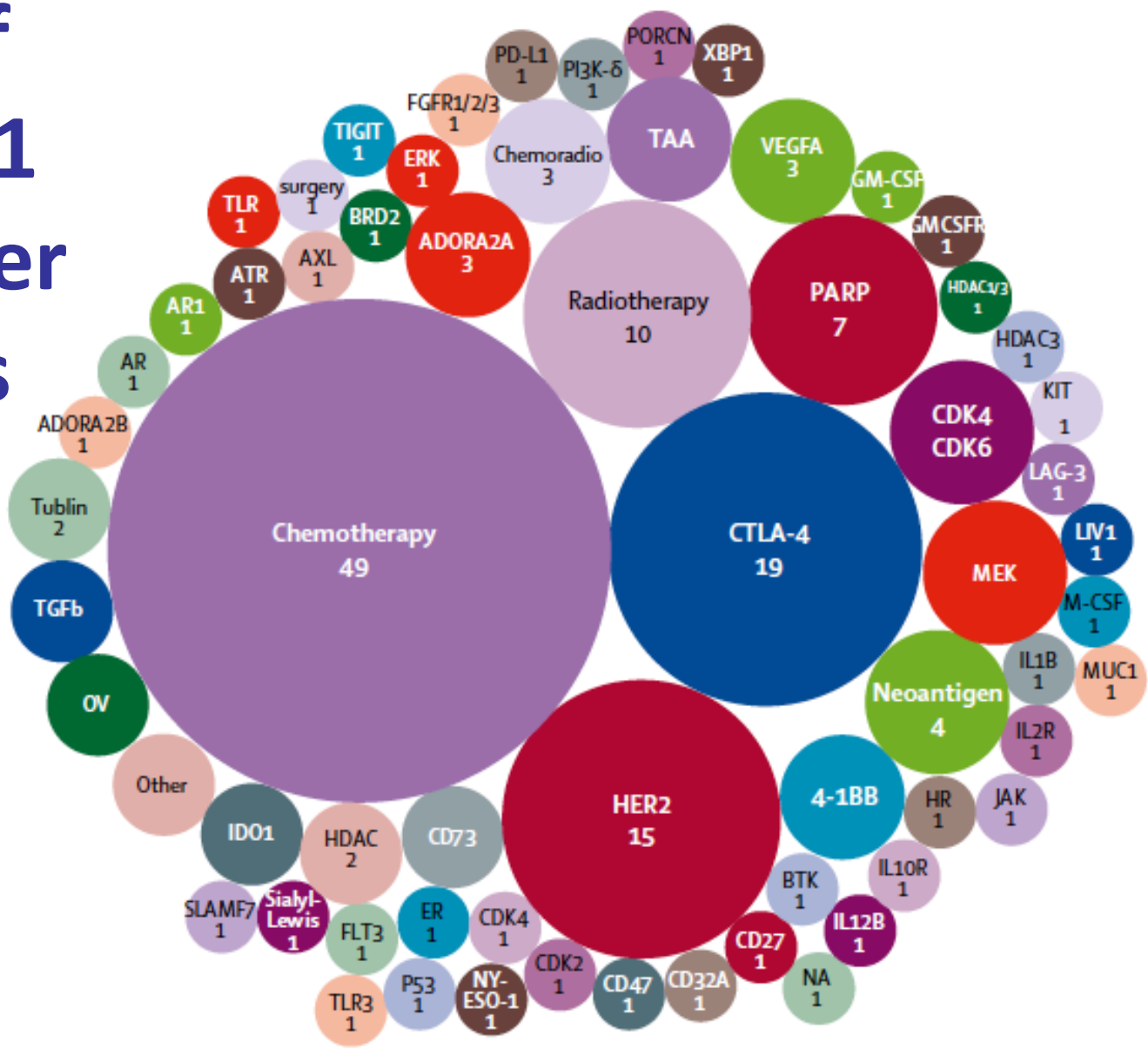
Current clinical trials of anti-PD-1 and anti-PDL-1 in combination with other treatments for patients with breast cancer

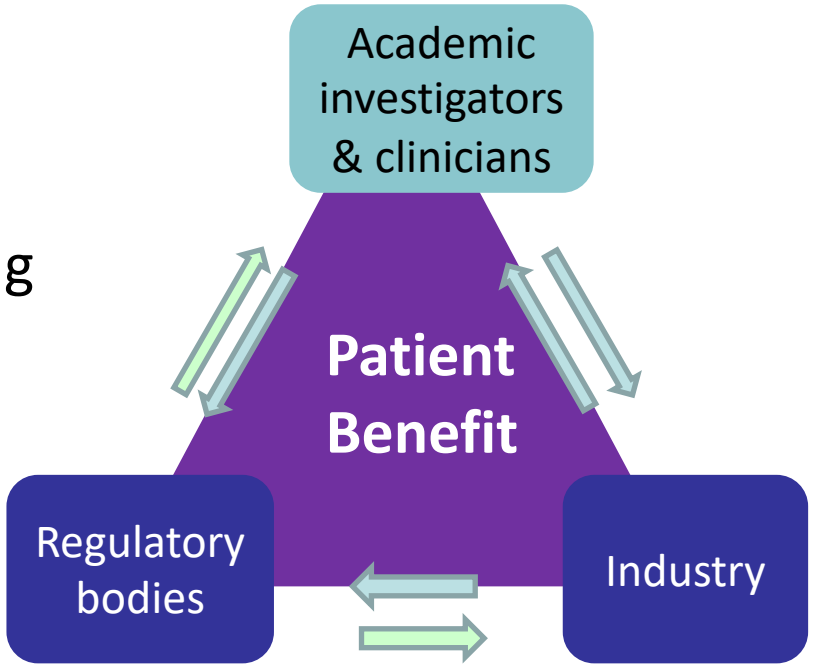


Esteva FJ et al. *Lancet Oncol* 2019; 20: e175-86

Conclusions

Recommendations for future drug-RT combinations

1. Increase number of clinical trials, incorporating modern clinical trial designs
2. Individualisation of treatment based on genetic/biological features and/or imaging, including mathematical biological systems models
3. Dialogue with pharma industry, including timely preclinical development
4. Discussions with regulators, including consumer representation
5. Collaboration across radiobiology laboratories



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Sharma RA et al. *Nature Rev Clin Oncol*, 2016 Bristow RG et al. *Lancet Oncol*, 2018 Ahmad SS et al. *Clin Cancer Res*, 2018

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  - PROVIDING NECESSARY PRECLINICAL EVIDENCE FOR EARLY PHASE CLINICAL TRIALS

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CTRad Clinical and Translational Radiotherapy Research Working Group

CANCER RESEARCH UK COMBINATIONS ALLIANCE

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