

CURRICULUM VITAE

ROBERT CHARLES FREDERICK LEONARD

September 2021

SUMMARY

Posts Held

Lead Cancer Clinician, Imperial College NHS Trust

25 years in senior NHS administrative roles in Edinburgh Swansea and Imperial College NHS Trust London (2006-11)

Founder and ex-Director SW Wales Cancer Institute 2001-6

Ex-Clinical Director, Cancer Services, Swansea NHS Trust 2001-6

Created posts for Chair of Clinical Oncology; Senior Lecturer Medical Oncology and NHS Medical Oncology plus 2 new NHS Clinical Oncology posts

Set up and program director of first medical oncology training scheme for SpRs in Wales.

Co-founder and Medical Director of Maggie's Centres UK (1995-present)

Set up and Chair International Anglo Celtic Collaborative Oncology Group (1994-present)

Author/co-author of more than 300 peer reviewed original papers and reviews

Member of International Research Collaboratives-EORTC,BIG etc

Previously holder/co-holder of science research grants ->£2M

Assessor on Cancer Research UK site visits

Royal College Physicians assessor for SpR training, SAC member

Set up and ran Association of Cancer Physicians Summer Schools over 10 years

Invited speaker international cancer meetings

Lead investigator several previous and current UK NCRI clinical Trials

UK NCRI Breast Cancer Sub-committee member -BCSG

Chair Translational subgroup for BCSG 2004-7

Wales Cancer Trials Network Executive member 2001-6

Wales Breast Cancer Committee member 2001-6

Current activity

Physician in private practice- main interest : breast cancer oncology care at BUPA Cromwell Hospital
Chair Breast MDT BUPA Cromwell Hospital,
Hon. Professor Cancer Studies Imperial College and Swansea University
Medical Director of 'Maggies' Centres UK ; Chair of Professional Advisory board
Ex-Chairman External Review Breast Cancer MDT for Heart of England (Birmingham) NHS Trust concerning ongoing management a large cohort of surgically mis-managed patients
Chairman and Organiser of the Anglo Celtic Collaborative Oncology Group- publications continue

Medico-Legal Work

25 years experience as expert witness in medicolegal cases of malpractice

Expert witness on Trastuzumab in clinical practice for Hospira vs Roche 2013-2014
Adviser to US attorneys in an ongoing patent case.

Address :	Robin Hill Lincoln Road Chalfont St Peter Bucks SL9 9TQ Tel 01753880750 E mail rleonard@ic.ac.uk
Date of Birth :	11th May 1947
Place of Birth :	Merthyr Tydfil, Wales
Marital Status :	Married with three daughters
GMC Reg No :	1488155 (3rd November 1972)
Current Post :	Lead Cancer Clinician, Imperial College Hospitals NHS Trust
Qualifications :	1968 BSc London 1971 MB BS (and Conjoint) London 1974 MRCP(UK) 1980 MD London : "Classification Studies in B-Lymphocyte Neoplasia" 1985 FRCP Edinburgh 1993 FRCP London
Medical School :	1965-1971 Charing Cross Hospital
Undergraduate :	<i>Final Year Prizes :-</i> - Orthopaedic Surgery Prize - Clinical Gold Medal (Prox. Acc)

- Llewellyn Scholar “
- Medicine Prize “
- Surgery Prize “
- Pathology Prize “

Postgraduate : The Oxford Area Health Authority Prize : The Frewin 1978 Research Prize:
“The Gut Mucosa & B-cell Neoplasia”

Cancer Research Campaign Fellowship 1981-1982 : **12 month Travelling Fellowship to the Dana Farber Cancer Institute, Harvard Medical School, Boston, Mass., USA**

PREVIOUS APPOINTMENTS

July 1971 - Dec 1971	<i>House Surgeon</i> Charing Cross Hospital, London Mr A R Makey, Mr J Pendower
Jan 1971 - July 1972	<i>House Physician</i> Charing Cross Hospital, London Dr J T Scott, Professor R N Maini
July 1972 - July 1973	<i>Senior House Officer</i> Charing Cross Hospital, London Professor K D Bagshawe
Aug 1973 - Jan 1974	<i>Senior House Officer</i> Hammersmith Hospital, London Professor Russell Fraser
Feb 1974 - Dec 1976	<i>Registrar in Medicine (Rotation)</i> Radcliffe Infirmary, Oxford Professor P Sleight, Dr J M Holt and Dr D J Lane (Oncology, Cardiology & Chest Medicine as interests on firms)
1976 - 1979	<i>Leukaemia Research Fund Fellowship</i> Nuffield Department of Medicine, Oxford <i>Clinical Research Fellow & Honorary Senior Registrar</i> Professor I C M MacLennan, Professor D J Weatherall
Aug 1979 - Oct 1982	<i>Senior Registrar in Medicine, Oncology</i> Royal Victoria Infirmary, Newcastle upon Tyne Dr R B Thompson, Dr A R Horler, Professor M Shaw

ACADEMIC APPOINTMENTS

1981 - 1982	-	<i>Clinical and Research Fellow</i> Harvard Medical School and Dana Farber Cancer Institute, Boston, Massachusetts, USA
1982 - 1983	-	<i>Clinical Lecturer in Oncology</i> University of Newcastle upon Tyne
1983 - 1993	-	<i>Senior Lecturer (Honorary Consultant Physician)</i> University of Edinburgh, Department of Clinical Oncology
1994 – 2001	-	<i>Part-Time Senior Lecturer</i> University of Edinburgh Department of Clinical Oncology
2001-2006		Professor of Cancer Studies, University of Wales, Swansea , Hon Consultant Medical Oncologist and Director SW Wales Cancer Institute, Clinical Director, Cancer Services, Swansea NHS Trust
2006-2011		Director Cancer services, Chief of Service Medical Oncology Imperial College NHS Trust, Hon Professor Cancer Studies Imperial College
2011-		Professor of Cancer Studies, Imperial college, Hon. Consultant Medical Oncologist, Imperial College NHS Trust

ADMINISTRATIVE RESPONSIBILITIES

Previously	
Head	Professorial Unit of Cancer Studies, Swansea University
Director	South West Wales Cancer Institute
Clinical Director	Cancer Services Division - Clinical Oncology, Haematology, Cancer Genetics and Palliative Care Swansea NHS Trust
Member	Breast International Group
Member	British Breast Group
Member	NCRI Breast Cancer Subcommittee
Member	NTRAC Executive
Member	EORTC Breast group
Member	Executive Board Wales Cancer Trials Network
Member	Nottingham Breast Cancer Symposium Scientific Committee
RCP Assessor	SpR training
Member	RCP SAC Medical Oncology
Medical Advisor	Health care at Home plc
Programme Director	Wales SpR training scheme for Medical Oncology

CRUK site visitor	Laboratory and clinical programme, Dundee 2004
NICE Steering Group	Sarcoma management
NTRAC Advisor	NCRI Breast Committee
NCI Canada	External Review of NCI Programme, Kingston, Ontario
External Reviewer	Gene Therapy Advisory Committee 1998-
Executive Board	Wales Cancer Bank 2002-
Steering Committee	All-Wales Breast Group

Editorial Boards

Editorial Board "*The Breast*" 1990-
Editorial Board "*British Journal of Cancer*" 1987-
Editorial Board "Oncology Times" 2003-
Editorial Board Acta Medica Nagasakiensia 2004-
Editorial Board Cancer Topics 1993-2006
Editorial Board Clinical Oncology 2003-

Previous

Chairman	Scotland and Newcastle Lymphoma Group (1990-1992)
Chairman	Association of Cancer Physicians (ACP) National Education Committee (1985-)
Chairman	Lothian Health Board Ethical Subcommittee, Medicine/Clinical Oncology (1985-91)
Chairman	Subcommittee to assess Tumour Markers in Breast Cancer (SCTO) (1990 -)
Chairman	Investigative Procedures Working Party, East of Scotland & Newcastle Lymphoma Group (1984-91)
Chairman	Division of Clinical Oncology (1992-)
Chairman	Anglo-Celtic Co-operative Oncology Group (1994 -)
Hon. Sec.	Area Medical Committee (Lothian Health Board) (1993-96)
Member	MRC Gynaecological Working Party (1989 -)
Member	MRC Sarcoma Therapy Working Party (1995-)
Member	UKCCCR Breast Advisory Committee (1995-)
Member	New York Academy of Science (1992 -)
Member	Executive Committee British Association for Cancer Research (1984- 1987)
Member	Scottish Breast Cancer Trials Committee (1985-)
Member	Therapy Working Party, East of Scotland & Newcastle Lymphoma Group (1983-)
Member	Executive Committee of the Association of Cancer Physicians (1987-)
Member	Faculty of Medicine, University of Edinburgh (1986-87)
Member	Lothian Health Board Guidelines Committee (1996 -)
Member	Fife Board Breast Cancer Advisory Cancer Group (1996 -)
Member	Specialist Subcommittee of Area Medical Committee (1996 -)
Member	Scottish National Cancer Registry (1995-)
Member	South East Scotland Cancer Advisory Committee (1995-)
Member	MK Jencks Cancer Caring Centre Trust Board (1996-)
Member	Professional Advisory Board Maggie's Centre (1996-)
Member	SE Scotland Breast Cancer Advisory Cancer Group (1996 -)
Member/Co-Author	DHS COG for Purchasing Guidelines Breast Cancer (publ. DHS 1996)
Member	RCGP Committee for the Implementation of Calman Guidelines 1998
Member	ACP Executive Committee 1989-

ADMINISTRATIVE RESPONSIBILITIES (continued)

Examiner	Royal College of Physicians of Edinburgh (1987-)
Examiner	University of Edinburgh, Final MB BS Examinations
Chairman	Grand Rounds, Western General Hospital (1985- 92)
Organiser	Postgraduate Seminars - Department of Clinical Oncology (1984-91)
Organiser	BACR Workshop (Glasgow) " <i>Problems in Drug Resistance</i> " (1985)
Organiser	1st UK Workshop on Antiemetics for Chemotherapy, Edinburgh (1988)
Organiser	1st ACP Symposium for junior training in Clinical Pharmacology, Oxford, (1991)
Organiser	1st ACP Symposium for junior training in Molecular Biology, Glasgow (1990)
Organiser	Summer Schools in Clinical Oncology for the ACP
Co-organiser	BACR Workshop - Tumour Markers in Breast & Ovarian Cancer, Oxford (1991)
Coordinator	UK National Meetings on Lymphoma, Edinburgh, (1984 & 1987)
Others :	Honorary Secretary & Vice Chairman Division of Clinical Oncology Department of Clinical Oncology Western General Hospital Edinburgh (1990 - 92)
	Deputy Head Department Clinical Oncology Western General Hospital Edinburgh (1990 - 92)
	Consultant with Administrative Responsibility Medical Oncology Unit Department of Clinical Oncology Western General Hospital Edinburgh (1990- 2001)
RCP Assessor	SpR Training Glasgow 1989; Leeds 1994 Nottingham 1995 Leeds 2000 Newcastle 2003 and 2004; Leeds 2005
CRC Site Visit	West Midlands Clinical Trials Unit 1993
CRC Site Visit	" " " " " 1998
CRC Site Visit	CRC Communication/Psychosocial Research Unit 1996
CRC Site Visit	Statistics and Epidemiology Unit, Inst. Cancer Res.Lon 1999
CRUK site visit	Psycho-oncology research unit, St Thomas' HMS 2003
CRUK site visit	Laboratory and clinical programme, Dundee 2004
External Reviewer	CRC Trials Unit University Coll Hosp.Lon. 1998
CRUK Site Visit	Sussex Univ. Communication/Psychosocial Research Unit 1996/2001/2006
CRUK site visit	Psycho-oncology research unit, St Thomas' HMS 2009
External Reviewer	Gene Therapy Advisory Committee 1998

Editorial Boards

Editorial Board “*The Breast*” (1990-)
Editorial Board “*British Journal of Cancer*” (1987-)
Editorial Board “*Oncology Times*” (2003-)
Editorial Board “*Clinical Oncology*”(2003-)
Editorial Board “*Cancer Topics*”(1995-)

Book Editor

Key Advances in breast Cancer 2005

Media and Industry

FINALIST 1993 :	<i>Hospital Doctor of the Year</i>
FINALIST 1994 :	<i>Communication Teams In Oncology</i>
2005 Special Commendation	<i>Hospital Doctor of the Year-Oncology Team</i>
Advisory Board Member :	<i>Mediscript Weekends in Oncology</i>
Advisory Board Chairman :	<i>Taxotere Development</i> - Rhône-Poulenc Rorer plc
Advisory Board Member :	<i>Epirubicin Pharmacia</i>
Advisory Board Member :	<i>Aromatase Inhibitor Development</i> - Ciba-Geigy
Advisory Board Member :	<i>Fluconazole</i> - Pfizer
Advisory Board Member :	<i>Antibody Therapy in Lymphoma</i> - Roche
Chairman :	<i>Erythropoietin in Cancer</i> - Janssen-Cilag
Advisory Board Member :	<i>Breast Cancer Trials with Sandostatin</i> - Sandoz
Advisory Board Chairman :	<i>Janssen Cilag International Advisory Board</i>
Advisory Board Member :	<i>Roche Antibody Trials</i>
Advisory Board Member :	<i>Zeneca UK</i>
Advisory Board Member :	<i>Roche UK</i>

Management Experience

Current

See Summary

Previous

Department of Clinical Oncology, Haematology, Palliative Medicine and Cancer Genetics
21 consultants; 14 SpRs and 8 Trust Doctors/Staff Grades

Director, South West Wales Cancer Institute 2001-2006

Lead Clinician, Medical Oncology Unit Western General Hospital Edinburgh 1991-2001

Deputy Clinical Director Clinical Oncology Dept 1998-2001

Chair Division of Oncology 1988-1991 advisory structure

Hon Sec Lothian Health Board Area Medical Committee 1987-91

Chair Lothian Health Board Medicine/Oncology Ethics Committee 1984-92

Expert Witness

Expert advisor to Sanofi-Aventis at ODAC/FDA hearing on Taxotere 1999

UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE PATENT TRIAL AND APPEAL BOARD CELLTRION INC. 2015

Similar UK court expert witness concerning trastuzumab licence amendments in 2014

Working in Wales and in Scotland, I have provided expert witness evidence for more than 20 years. Much of my work has involved cases of breast cancer –see also Summary

Current Research

Molecular markers in breast cancer

Working with Caris Bioscience (Phoenix)

Clinical and translational

Trials of chemotherapy supportive care in young women

Value of ovarian suppression in preserving ovarian function (OPTION trial published 2016)

Assess value of secondary prophylaxis in adjuvant therapy (SPROG trial-published 2015)

Assess role of chemotherapy in the over-70's (ACTION trial- published 2013)

Assess value of molecular profiling to select therapy for advanced cancers (ongoing collaborations)

INVITED LECTURES

2012-2017 MOLECULAR PROFILING AND MANAGEMENT OF ADVANCED CANCER

UK-IRELAND

2013-2015

Bath; North Middlesex H; Leicester; Wolverhampton; Cheltenham; Galway; Southampton; Plymouth; Maidstone

EUROPE -ASIA

ESMO symposiua Sept 2012-2014; ASCO 2012; St Gallen 2013; Madrid 2016

National Society Meetings Moscow 2014; Almaty Kazakhstan 2015; Bucharest 2015; Vienna 2015; Warsaw 2015; Sarajevo 2015; Genoa 2015; Madrid 2016; Istanbul 2016

2011

Johannesburg – South African Oncology Society
Leicester University Oncology course-

Modern Management of Breast Cancer
High dose Chemotherapy

2010

Management of breast cancer in older women Nottingham (January)

Maggies Cancer Caring Centres Open meeting (April)

Athens Hellenic Oncology Society Breast meeting (June)

Nottingham Breast Meeting (September)

2009**2008**

Potential for treating liver metastases
with infused radiolabelled spheres

Sirtex International symposium , Rome

Recent advances in the treatment
of early breast cancer
Management of cancer in the elderly

Lecture series in Dailan, Shanghai and Beijing

RCP Edinburgh

2007

Anthracyclines for breast cancer
Molecular medicine and cancer
Review of San Antonio meeting
Limitations of molecular profiling

European Congress, Barcelona
Cancer Agenda 2007
London Oncology Meeting
Debate at ESMO Lugano

2006

Anthracyclines and breast cancer
Liposomal doxorubicin

Hellenic Medical Oncology Soc
Polish Oncological Soc

2005

Adjuvant aromatase inhibitors
Trilostane- dual pathway inhibitor
Trilostane –review of phase 2 trials

St Andrews Symposium
S Wales Symposium
Bioenvision symposium

2004

Teenagers and cancer care delivery
Breast Cancer In Europe
Managing a Consultant Career
Practical Management of Metastatic breast ca
Chair and Speaker
Adjuvant Trials of endocrine therapy
Adjuvant Endocrine Therapy
Adjuvant Endocrine Therapy ASCO review
Bone Disease in breast cancer
Bone health in breast cancer
Adjuvant Endocrine Therapy Trials 2004
Management of advanced breast cancer
HER2 positive breast cancer, management
Management of her2-negative metastatic bc
Critique of IES Exemestane trial
Chair, Organiser, Anglo Celtic Group

UK Teenage Cancer Trust Meeting, RCP London
C.O.E.Radiation Biology Workshop, Nagasaki
New Consultants Group, Meriden
Lilly Symposium, London
ASCO Breast Cancer Education Symposium ,
New Orleans
AZ UK Breast Symposium Gleneagles Hotel, Scotland
S Wales SpR training day, Cardiff
Romania Cancer Society, Constantse
Roche symposium, Jersey
Pfizer UK Breast symposium, Oxford
Scottish Breast Cancer Symposium, Perth
E Midlands Cancer Group, Notts
Belgian Cancer Soc.,Inst Gustave Roussy, Brussels
UK NCRI Meeting, London
Breast Cancer Scientific Symposium, Edinburgh

2003

Trials in the elderly
New Developments In Breast Cancer
Ovarian Protection trial
BRAVE trial
Eurpoean studies in neutropenia
UK Breast Cancer Symposium
Neutropenia audit in the UK
Oral Chemotherapy for breast cancer
Cancer Care in the elderly
Chair Key Advances in Breast Cancer
NCRN 6th National Meeting
Trilostane for breast cancer

NCRN Breast trials Group
RCP Education Symposium, Edinburgh
TANGO trialists meeting London
Investigators meeting, Nice
Swiss/Austrian/German Annual Oncology Symposium
Practical Management of metastatic breast cancer
Roche Cambridge symposium
Roche South American Breast Symp., Dominican Rep.
BOA nad BASO meeting, Cambridge
ACP symposium RCP London
Overview of Trials In Elderly Breast Cancer
Nottingham Int Breast Meeting

Management of chemotherapy neutropenia	ECCO, Copenhagen
Liposomal anthracyclines	UK/Ireland breast cancer symposium, Dublin
Neutropenia management	Italian Medical Oncology Society, Rome
New Developments in Breast cancer Care	Chinese Society of clinical Oncology, Beijing
Elderly breast cancer	NCRN National Breast Meeting, London
2002	
Trials in breast cancer	UK National trials meeting, Birmingham
HER2 and endocrine therapy	Roche International symposium Dublin
Elderly breast cancer	UK NCRN Annual symposium London
Adjuvant chemotherapy review	Breakthrough Breast Cancer National Meeting
Oral chemotherapy for breast cancer	Cambridge Oncology Society
2001	
Current clinical research in breast cancer	South Humberside Breast Group
Elderly patients with breast cancer	NCRI National Meeting RCP Nov 2001
Evolution of treatment of breast cancer	Wilfred Card Lecture Edinburgh
Taxoids in the treatment of breast cancer	Advanced Medicine Course RCP 3/2001
Adjuvant chemotherapy for breast cancer	Royal College of Surgeons Advanced teaching course
2000	
Trastuzumab in clinical practice	Herceptin symposium London 9/2000
High Dose Chemotherapy	Controversies in Breast Cancer London 6/2000
Management of Advanced Breast Cancer	RCP Edinburgh 9/2000
Herceptin Symposium Netherlands Cancer Institute	Amsterdam 1/2000
Adjuvant chemotherapy and its management	Neutropenia workshop
Cork, Ireland 1/2000	
1999	
Neutropenia in adjuvant chemotherapy and its management	NorthWest Region Breast Group
Neutropenia in adjuvant chemotherapy and its management	Nottingham 2nd International Breast Cancer Mtg
New agents for advanced breast cancer	Nottingham 2nd International Breast Cancer Mtg
Primary Medical Management of Large tumours of breast	All Wales Cancer Group
Cutaneous metastases from breast cancer	Phillipines Oncology Society Manila
High Dose Chemotherapy for Node Positive Breast Cancer	Leicester Breast Cancer Group
Oral fluoropyrimidines for breast cancer	Argentinian Breast Cancer Society Punta Del Este
Anthracyclines and High Dose Chemotherapy for High Risk Breast Cancer	7th Japanese Breast Cancer Symposium Nagoya
Chemotherapy for breast cancer in the elderly	RCP London June 1999
1998	
New Developments in chemotherapy for breast cancer	RCP London June 1998
Alkylating Therapy with Treosulfan for breast cancer	German Cancer Society Meeting Berlin

New Developments in chemotherapy for breast cancer	1st European Congress on Breast Cancer, Florence
Breast cancer-The Case for Chemotherapy	Debate-Nottingham Breast Cancer Meeting
New Developments in adjuvant chemotherapy for breast cancer	Advances in breast Cancer, RCP Edinburgh
1997	
Intensive chemotherapy for breast cancer	6th European Bone Marrow Transplantation Meeting ,Aix-les Bains
Hormonal therapy for breast cancer	Irish Cancer Nursing Soc. Dublin
High dose chemotherapy for breast cancer	Cancer Chemoprevention Meeting, Bruges
Primary medical therapy for breast cancer	Northwest cancer group Manchester
High dose chemotherapy for breast cancer	Merseyside oncology Meeting,Clatterbridge
High dose chemotherapy for breast cancer	Belfast Medical Society
Hormonal therapy for breast cancer	South American Breast Cancer Congress, Venezuela
High dose chemotherapy for breast cancer	Mastology congress of South America, Sao Paulo
Docetaxel -long term survival analysis of open access programme	Nottingham Breast Meeting
1996	
Update on Medical Therapy for Breast Cancer	South American Cancer Society, Montevideo
The advancement of high dose chemotherapy and intensification schedules	ESMO symposium Vienna
High Dose Chemotherapy:Australian Oncology Association Meeting	Noosa Australia
Hormonal Therapy of Breast Cancer:	UK National Nursing Congress, Brighton
Timely Dose Intensification for Breast Cancer:	European School of Oncology, Milan
New Developments in Hormonal Treatment of Breast Cancer :	UKCCCR National Meeting,Birmingham
High Dose Chemotherapy for Metastatic Breast Cancer :	Brit Soc Haematol. AGM Birmingham
Dose -Intensive Chemotherapy for Metastatic Breast Cancer :	2nd Edinburgh Royal College of Physicians
Symposium Stem Cell Therapy	
1995	
Multiple High Dose Chemotherapy for Solid Cancers-	European School Task Force Milan
The current place of high dose chemotherapy in breast cancer	European School Med Onc Course
High Dose Chemotherapy for Breast Cancer	Royal Society of Medicine London
The Place of Chemotherapy in the Management of Breast Cancer-	Nottingham/EORTC Breast Cancer Meeting
1994	

Intensive Chemotherapy for Breast Cancer	Perth Royal Infirmary Scotland
1993	
"Serum Tumour Markers " May 1993	Edinburgh Royal College of Surgeons Symposium
"Adjuvant Systemic Therapy in Breast Conservation" May 1993	Royal College of Surgeons Symposium
"High Dose Chemotherapy and Transplant in Patients with Breast Cancer"	Study Day St John's Hospital Howden
1992	
"Primary Chemotherapy of Locally Advanced Breast Cancer".	Medical Oncology Group of Australasia ,Canberra,
"Meet The Expert" Issues in Breast Cancer Chemotherapy.	Medical Oncology Group of Australasia ,Canberra,
Seminar - "Molecular Genetics of Ovarian Cancer"	Prince of Wales Oncology Department, Sydney
"Prognostication in Low Grade Non Hodgkin's Lymphoma".	Visiting Professor, University of Nebraska,
"Molecular Genetics of Ovarian Cancer"	Visiting Professor, Duke University
"Dose Intensive Chemotherapy for Breast Cancer".	Visiting Professor, Duke University
"Place of Chemotherapy in Gastrointestinal Cancer".	Moynihan Chirurgical Society Edinburgh
"Do Clinical Trials Influence Practice?"	British Organisation of Data
Managers -	
"Studies on Phenotypic Variation of Small Cell Lung Cancer Micrometastases".	3rd International Symposium on Lung Cancer, Lon Gdansk
1991	
"Designing Chemotherapy".	Fourth Simpson Symposium. Hormones, Cancer and The Reproductive System
1990	
"Management of Advanced Breast Cancer".	Symposium of Preventive Medicine, Perth.
1989	
"Immunological Markers and Bone Marrow Disease in Small Cell Lung Cancer".	Second UKCCCR Lung Cancer Workshop.Lon
Prognosis in High and Intermediate grade non-Hodgkins Lymphoma".	Dana Farber Cancer Institute, Boston M.A.
"Cellular and Genetic Markers of Common Ovarian Cancer".	Seminar Duke University Cancer Centre .
"Chromosome 17 Deletions in Breast Cancer A Lead for Other Cancers?"	Dana Farber Breast Cancer Group.
1988	

"The Immunology of Small Cell Lung Cancer and Implications for Treatment Polish Pneumological Society, Gdansk.

1986

"Intensive Therapy for Small Cell Lung Cancer".

EORTC Lung Cancer Group.Nice

1984

"Current Management of Small Cell Lung Cancer".

Polish Pneumological Society, Gdansk.

Grants

Oct 2007-

TRICC study of tissue from ACTION trial (TRansACTION)
£300k

April 2003 –

Wales Cancer Bank/NTRAC Wales
Welsh Assembly Government
£459,000 annually

held jointly with Professors Mason, Maughan, Sampson, Wynford-Thomas (all UWCM), Stuart (UWB) and Dr Thomas (USwan)

February 2004-Jan 2009

Translating molecular knowledge into early breast cancer management:
building on the BIG (Breast International Group) network for improved
treatment tailoring - TRANS-BIG
EC Network of Excellence

Total value: €6M
Imperial College (contractor) £192,661

November 2003- Oct 2007

Wales Cancer Trials Network
CRUK
£3,000,000
held jointly with Professors T Maughan, M Mason (UWCM) and N Stuart (UWB) and Dr Thomas (USwan)

March 2004 – Feb 2010

Ovarian protection in hormone receptor negative pre-menopausal breast cancer patients receiving adjuvant or neo-adjuvant chemotherapy. (OPTION)
CRUK
£450,000

March 2009

£350,000 for investigator initiated trial in metastatic breast cancer

Industry combined

£750,000

Original Papers/Letters

2020

Leonard R, Yellowlees A, Mansi J, Fallowfield L, Jenkins V

The affect of goserelin on the QoL of women having chemotherapy for EBC: results from the OPTION trial

The Breast Aug 2020 52 122-131

PII: S0960-9776(20)30116-8

DOI: <https://doi.org/10.1016/j.breast.2020.05.009>

2019

Leonard Cameron Verrill et al

Randomised controlled Trial of Weekly vs. 3 Weekly Paclitaxel- for Metastatic and locally advanced breast cancer: the Anglo Celtic Will Weekly Win Trial **in preparation 2021**

Stavraka C,,,,, Leonard R and Mansi J et al

Ten-year outcome for women randomized in a Phase III trial comparing Doxorubicin and Cyclophosphamide with Doxorubicin and Docetaxel as primary medical therapy in early breast cancer- an Anglo - Celtic cooperative Oncology Group study P-2-16-15 Sana Antonio Breast Cancer Symposium 2019

Leonard R¹, Yellowlees A², Fallowfield L³, Jenkins V³

Does goserelin have an effect on Quality of Life in women who have chemotherapy for early breast cancer? Results from OPTION Sana Antonio Breast Cancer Symposium 2019

2018

271 Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data

Matteo Lambertini, Halle C.F. Moore, Robert C.F. Leonard

J Clin Oncol 2018 36 19 • 1981-1990

2017

270 R Leonard¹, D Adamson², A Yellowlees³, J Dunlop⁴, G Thomas¹, and RA Anderson⁵, for the Anglo Celtic Collaborative Oncology Group and NCRI trialists

GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: the OPTION trial. Annals of Oncology 2017 28 1811–1816,

269 Addition of gemcitabine to paclitaxel, epirubicin, and cyclophosphamide adjuvant chemotherapy for women with early-stage breast cancer (tAnGo): final 10-year follow-up of an open-label, randomised, phase 3 trial **Helena M Earle, ...Robert C Leonard, MD,....of the tAnGo trial collaborators**

Lancet Oncology Volume 18, No. 6, p755–769, June 2017

265 Refining the role of pegfilgrastim (a long-acting G-CSF) for prevention of chemotherapy-induced febrile neutropenia: consensus guidance recommendations

Matti Aapro, Ralph Boccia, **Robert Leonard** et al

Support Care Cancer DOI10.1007/s00520-017-3842-1

264 First-in-human study of a new class of anti-cancer agent, the ProTide NUC-1031, in patients with advanced solid tumours

Sarah P. Blagden^{1,7}....., Robert Leonard¹, ...

British Journal of Cancer (2018) 119:815–822;

2017

263 Collins K, Reed M, Lifford K, ...Leonard R

Bridging the age gap in breast cancer: evaluation of decision support interventions for older women with operable breast cancer: protocol for a cluster randomised controlled trial

BMJ Open 2017;7:e015133. doi: 10.1136/bmjopen-2016-015133

2016

262 Wilson C Gossiel F Leonatrd R et al Goserelin, as an ovarian protector during (neo)adjuvant breast cancer chemotherapy, prevents long term altered bone turnover J Bone Oncol 2016 43-49

261 Giovanni Ussia¹, Robert Leonard², Jaak Janssens³ Multi-platform tumour profiling delivers the highest clinical utility and improves patient outcomes in today's routine clinical practice.
Int J Surg Surgical Proced 2016, 1: 107

Wyld L(R.Leonard) et al Bridging the Age Gap in Breast Cancer Protocol submitted to Brit J Cancer

2015

G Arpino¹, F Marmé², J Cortés³, E Ricevuto⁴, R Leonard⁵, A Llombart-Cussac

Tailoring the dosing schedule of nab-paclitaxel in metastatic breast cancer according to patient and disease characteristics: Recommendations from a panel of experts
Crit Rev Oncol Hematol 2016 Mar;99:81-90.

260 Leonard RC, Mansi JL, Keerie C, Yellowlees A, Crawford S, Benstead K, Matthew R, Adamson D, Chan S, Grieve R; Anglo-Celtic Collaborative Oncology Group. A randomised trial of secondary prophylaxis using granulocyte colony-stimulating factor ('SPROG' trial) for maintaining dose intensity of standard adjuvant chemotherapy for breast cancer by the Anglo-Celtic Cooperative Group and NCRN. Ann Oncol. 26 2437-2441 2015

259 Leonard R¹, Hennessy BT, Blum JL, O'Shaughnessy J

Dose-adjusting capecitabine minimizes adverse effects while maintaining efficacy: a retrospective review of capecitabine for metastatic breast cancer..

Clin Breast Cancer. 2011 Dec;11(6):349-56. doi: 10.1016/j.clbc.2011.06.005.

258 Krell J, James CR, Shah D, Gojis O, Lim A, Riddle P, Ahmad R, Makris A, Cowdray A, Chow A, Babayev T, Madden P, Leonard R, Cleator S, Palmieri C. Human epidermal growth factor receptor 2-positive breast cancer relapsing post-adjuvant trastuzumab: pattern of recurrence, treatment and outcome. Clin Breast Cancer. 2011 Jun;11(3):153-60.

257: Coleman RE, Marshall H, Cameron D, Dodwell D, Burkinshaw R, Keane M, Gil M, Houston SJ, Grieve RJ, Barrett-Lee PJ, Ritchie D, Pugh J, Gaunt C, Rea U, Peterson J, Davies C, Hiley V, Gregory W, Bell R; AZURE Investigators. Breast-cancer adjuvant therapy with zoledronic acid. N Engl J Med. 2011 Oct 13;365(15):1396-405. Epub 2011 Sep 25. PubMed PMID: 21995387.

256: Leonard R, Ballinger R, Cameron D, Ellis P, Fallowfield L, Gosney M, Johnson L, Kilburn LS, Makris A, Mansi J, Reed M, Ring A, Robinson A, Simmonds P, Thomas G, Bliss JM. Adjuvant chemotherapy in older women efficacy: a retrospective review of capecitabine for metastatic breast cancer. Clin Breast Cancer. 2011 Dec;11(6):349-56. Review. PubMed PMID: 21856245.

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REVIEWS, REPORTS, CHAPTERS AND EDITORIALS

Optimising the management of primary breast cancer in older women e A report of a multi-disciplinary study day
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Expert opinion on the use of anthracyclines in patients with advanced breast cancer at cardiac risk
P. J. Barrett-Lee^{1*}, J. M. Dixon², C. Farrell³, A. Jones⁴, R. Leonard⁵, N. Murray⁶, C. Palmieri⁷, C. J. Plummer⁸, A. Stanley⁹ & M. W. Verrill
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.

Declaration of Prof. Robert Charles Frederick Leonard (MD)

I, Prof. Robert Charles Frederick Leonard declare and state as follows:

I. Background

1. I am Professor of Cancer Studies and consultant medical oncologist at Imperial College, London. Before I retired in 2011, I held the positions of the Director of Cancer Services at Healthcare NHS Trust, as well as the Chief of Service for Medical Oncology at Imperial College. I held senior NHS administrative roles in Edinburgh, Swansea and Imperial College NHS Trust for 25 years, including founder and Director of the Southwest Wales Cancer Institute and Clinical Director of Cancer Services at Swansea NHS Trust. I chaired different oncological advisory and scientific boards, was a senior advisor to Cancer Research UK and am lead investigator of several previous and current UK clinical trials in the field of tumour therapy. A copy of my *curriculum vitae* including a publication list accompanies this declaration.
2. As a medical oncologist, professor and clinical investigator, my major interest is the management of breast cancer. However, my areas of expertise also include other tumour entities including gynaecological cancer, sarcoma, lymphomas, and colon cancer. My clinical research has focused on the biology and treatment of human cancer, as can be seen from the more than 300 peer reviewed original papers and reviews I have (co-)authored.
3. I have 25 years of experience as expert witness in medicolegal cases of malpractice and have acted as an expert witness in various patent litigation cases in the UK and US.
4. Consequently, I believe that I am qualified to provide an opinion as to what a person of ordinary skill in the art would have known and concluded as of the claimed priority date and the filing date of EP 3 288 980 B1 (April 28, 2015 and April 28, 2016, respectively).

II. Instructions

5. I am familiar with European Patent EP 3 288 980 B1 (hereinafter referred to as "EP'980") for which the claims relate to nivolumab for use in melanoma treatment wherein nivolumab is to be administered at a dose of 480 mg once every four weeks.
6. I have been asked by the Opponent's representative to review the FDA approval document "*Clinical Pharmacology and Biopharmaceutics Review(s)*" (D2) and the research article by Brahmer et al. 2010 (D3) in the light of the following questions and from the perspective of a skilled person treating cancer patients with an antibody such as nivolumab **before April 2015**:

- (a) Which dosing parameters of antibody treatment would the skilled person modify and within what limits?
 - (b) Would the skilled person consider changing a body-weight-based dose to a flat dose based on the knowledge available in the relevant time frame (April 2015)?
 - (c) How would the skilled reader interpret the data regarding receptor occupancy and half-life (cf. **D3**) and how would he/she apply these findings when trying to modify a treatment schedule for an antibody, in particular, nivolumab?
7. I have further been asked to comment on whether or not a person of ordinary skill in the art at the filing date would have considered the claimed dosing regimen, wherein nivolumab is administered at a flat dose of 480 mg once every four weeks in the treatment of melanoma.

III. Incentive to change the body weight-based dose of nivolumab to a flat dose in April 2015

8. The skilled person working with antibody treatments in the relevant time frame (April 2015) would have appreciated that dosing antibodies by body weight may over-adjust for the body size effect, since aside from body weight there are many potential covariates which is why pharmacokinetics are rarely proportional to body size (Bai et al. 2012 (**D4**), p. 120, left col., 2nd para., last sent.).
9. Administering a flat dose and thus the same amount of drug to each patient regardless of the patient's body weight offers advantages of convenience, compliance, cost effectiveness and safety due to less risk of dosing errors. Furthermore, most monoclonal antibodies (mAbs) are target-specific with a relatively **large therapeutic window** and generally a small contribution of body size to pharmacokinetic variability. Thus, flat dosing should be the approach of choice if there is no rigorous scientific rationale for body weight-based dosing (cf., e.g., Wang et al. 2009 (**D5**), p. 1023, "Other Factors"; **D4**, Abstract, and Figure 6).
10. Consequently, the answer to the question of whether the skilled person who worked in the relevant time frame (April 2015) and whose goal is to provide a more convenient and flexible treatment schedule would consider changing a body-weight-based dose to a flat dose is **yes, he/she would do so**. Being aware of the numerous advantages of a flat dose and the fact that nivolumab has a wide therapeutic window (see below, sections IV.2.1 to IV.2.3), the skilled person would seriously consider the use of a flat dose. Indeed, flat dosing is the **recommended** option for mAbs with a wide therapeutic window, like nivolumab (**D4**, p. 133, left col., last para.). This is particularly true for the antibody nivolumab due to the dosing schedules used in nivolumab clinical trials that were known to the skilled person in the relevant time frame.
11. Before April 2015, the body weight-based dose for nivolumab monotherapy was 3 mg/kg as can be seen from the following exemplary phase II and III clinical trials conducted in melanoma patients (see ClinicalTrials.gov; the NCT numbers listed below are ClinicalTrials.gov identifiers):

- NCT01721746 (“CheckMate 037”) first posted on November 6, 2012 (D6);
 - NCT01721772 (“CheckMate 066”) first posted on November 6, 2012 (D7);
 - NCT01844505 (“CheckMate 067”) first posted on May 1, 2013 (D8);
 - NCT02156804 (“CheckMate 172”) first posted on June 5, 2014 (D9);
 - NCT02374242 first posted on February 27, 2015 (D10).
12. To calculate the flat dose that is equivalent to a certain body weight-based dose, the latter is multiplied by the median patient body weight (cf., e.g., D5, p. 1014, right col., last para., 1st sent.). Generally, a median body weight of about 80 kg is used for this purpose (cf. D5, p. 1015, left col.: median = 75,7 kg; D4, p. 124, left col., l. 3: median = 78 kg). Of note, the patient cohort enrolled in the clinical studies summarized in D2 has a mean body weight of 81 kg (D2, p. 18, section 2.3.2.3, l. 2). Following this approach, the skilled person would easily derive the equivalent flat dose of **240 mg Q2W** from the known **3 mg/kg Q2W** body weight-based dose.
13. Notably, as of October 2013, a **flat dose of 240 mg Q2W** was already planned for the administration of nivolumab in a clinical trial sponsored by Bristol-Myers Squibb (BMS) (NCT01968109 (first posted in October 2013), see arm B; D11). As of October 2014, the study had been updated to indicate that a flat dose of nivolumab at 80 or **240 mg Q2W** would be administered as part of a combination therapy to **melanoma** patients (NCT01968109 (update posted in October 2014), see Inclusion Criteria for part B; D12). Therefore, in the case of nivolumab, the skilled person had the incentive to proceed from the weight-based dose to the flat dose.
14. Taken together, the skilled person would consider the use of a **flat dose** for nivolumab and would readily derive **240 mg Q2W** from the known body weight-based dose.
- IV. Incentive to change the dose of nivolumab and extend the dosing interval from 240 mg every two weeks (Q2W) to 480 mg every four weeks (Q4W)**
15. In considering whether a longer dosing interval is feasible for nivolumab, the skilled person would look at the available safety and efficacy data for the antibody.
- IV.1 Analysis of data in Brahmer et al. 2010 (D3)
16. I have carefully read the research article by Brahmer et al. 2010 (D3). In the following, I will summarise the relevant data and explain how the skilled person would interpret and apply this data when modifying a treatment regimen.
17. In this article, the authors report the results of a phase I dose-escalation study, in which the anti-PD1 monoclonal antibody MDX-1106 (i.e., **nivolumab**; cf., D8, p. 10, “Arms and Interventions”, right col.) was administered to 39 patients with different types of solid tumours including melanoma. In

the study, cohorts of six patients received a single infusion of nivolumab at **0.3, 1, 3 or 10 mg/kg** and were evaluated for toxicities on a weekly basis for 8 weeks. Fifteen additional patients received a single infusion of 10 mg/kg nivolumab to confirm safety. Patients with evidence of clinical benefit (n = 12) were retreated with 2 additional doses spaced by 4 weeks at 12-week intervals (i.e, at weeks 0, 12, 16, 28, 32, etc.; **D3**, p. 3168, right col., “*Study Design and Procedures*”; see also Table 2 and Fig. 4B). In order to select a dose and schedule, the clinician would consider the following data and information:

IV.1.1 *Pharmacokinetics: safety and efficacy*

18. Nivolumab was well-tolerated over the dose range of 0.3 to 10 mg/kg (**D3**, p. 3169, left col., 2nd para.) and no grade 3+ AE occurred within the 28-day period following the first dose of the antibody, thereby demonstrating a **promising safety profile** of the antibody (**D3**, p. 3172, left col., 1st para. and right column, final para.). A **Maximum Tolerable Dose (MTD)** was not defined in this study (**D3**, p. 3169, left col., 2nd para.).
19. A larger, follow-up phase I trial reported similar results. In particular, as of January 2011, data had been presented on 126 patients, showing that a twice-weekly treatment in the dosage range of 1 to 10 mg/kg was generally well-tolerated and an MTD was also not reached in this study (Flies et al. 2011 (**D13**), p. 417, left col., last para.).
20. While efficacy was not a primary end point of the trial reported in **D3**, similar response rates were observed for the different treatment groups (**D3**, Table 2; reproduced and commented below).

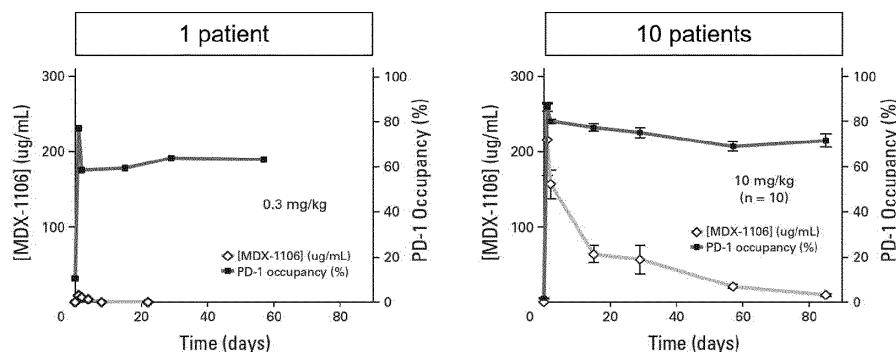
Dose (mg/kg)	No. of Patients	Total No. of Doses					Best Response (duration in months)*	response rate (%)
		1	2	3	5	11		
0.3	6	6	0	0	0	0	N/A	N/A
1	6	3	1	1	1	0	1 MXR (1)	16.6 (1/6)
3	6	3	0	2	1	0	1 CR (21+) [†]	16.6 (1/6)
10	21	15	1	4	0	1	2 PR (3+, 16+) ^{‡§} 1 MXR (1)	14.3 (3/21)
Total	39	27	2	7	2	1	1 CR, 2 PR, 2 MXR	15.2 (5/33)

Abbreviations: N/A, not applicable; MXR, mixed response defined as regression in some lesions but concomitant progression in others; CR, complete response; PR, partial response.
^{*}CR and PR by Response Evaluation Criteria in Solid Tumors 1.0 criteria.
[†]This patient with stage IV colorectal cancer had previously shown progressive disease after receiving chemotherapy regimens including bevacizumab and cetuximab.
[‡]PR duration of 3+ months was preceded by an MXR in this patient with melanoma lasting 20 months. Previous therapies that were ineffective included high-dose interleukin-2 and temozolomide.
[§]PR duration of 16+ months was preceded by an MXR in this patient with renal cell carcinoma lasting 4 months. Previous therapies that were ineffective included sunitinib, sorafenib, and an experimental histone deacetylase inhibitor.

21. This is **evidence of durable clinical activity** within the dose range of 1 to 10 mg/kg, which was subsequently supported by the larger follow-up study (**D13**, p. 417, left col., last para.).

IV.1.2 *Pharmacodynamics: half-life and receptor occupancy*

22. **D3** mentions an approximate serum half-life ($t_{1/2}$) of 12 days for the doses up to 3 mg/kg, and 20 days for the 10 mg/kg dose. According to the “*Patients And Methods*” section serum samples were collected serially before and up to 85 days (i.e., 12 weeks) after the first dose. Consequently, said serum half-life values refer to single dose administration only and do not allow any conclusions for multiple dosing regimens (see section IV.2.4 below).
23. The *receptor occupancy theory* is that the response to a therapeutic is proportional to its receptor binding, i.e., maximal response is achieved when all receptors are occupied. Receptor occupancy assays are designed to quantify the binding of therapeutics to their targets. When combined with the pharmacokinetic profile, receptor occupancy data can establish PK/PD relationships, which are crucial for informing dose decisions.
24. According to the data disclosed in **D3**, PD-1 receptor occupancy after one infusion appeared to be dose-independent, wherein the mean peak occupancy was 85% and the mean plateau occupancy observed up to 57 days or longer was 72% (cf., **D3**, Fig 4A; exemplary graphs are depicted below).



NOTE: MDX-1106 = nivolumab

25. In line with these data, the authors report a high affinity of nivolumab to the PD-1 receptor, wherein *in vitro* assays have shown that a nivolumab serum concentration of 0.04 µg/mL is sufficient to occupy more than 70% of PD-1 molecules on T cells. The authors point out that even when serum levels are undetectable (below 1.2 µg/mL), sufficient serum concentrations persist to maintain plateau PD-1 receptor occupancy. This is in line with the observation that the different treatment groups had similar response rates.
26. Consequently, the receptor occupancy data further support nivolumab's **durable clinical activity** including at the lowest dose tested.

IV.2 Analysis of data “Clinical Pharmacology and Biopharmaceutics Review(s)” (D2)

27. I have carefully read the “Clinical Pharmacology and Biopharmaceutics Review(s)” (D2) published by the FDA as part of the drug approval package for nivolumab. In the following, I will summarise the relevant data and explain how the skilled person would interpret and apply these data when modifying a treatment regimen.
28. The pharmacokinetic data provided in the FDA document are based on several clinical (pharmacology) studies involving 909 patients who received **0.1 to 20 mg/kg of nivolumab** as a single dose or multiple doses every 2 or 3 weeks (**Q2W** or **Q3W**; cf. D2, Tables 1 and 2 on p. 8-9). These patients suffer from different types of solid tumours including melanoma. In order to select a dose and schedule, the clinician would look at the following data:

IV.2.1 Exposure-response relationship of safety and efficacy

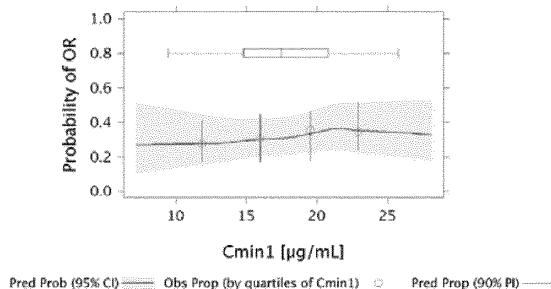
29. Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs. Exposure refers to drug levels achieved in the body. Response can be assessed in terms of either efficacy or safety. Understanding the relationship between exposure and response is critical to finding a dose that optimally strikes a balance between drug efficacy and adverse events.
30. Table 4 and Figure 1 of the FDA document (D2, p. 11; reproduced below) show that the overall response rate does not change much over the dose range of 0.1 to 10 mg/kg (Table 4) and across the trough concentration range of 7 to 28 µg/mL for the first 3 mg/kg Q2W dose (Figure 1).

Table 4. Overview of ORR of nivolumab in advanced melanoma in study MDX1106-03

Dose (mg/kg)	0.1	0.3	1	3	10	Overall
Melanoma	35.3 (14.2, 61.7) N=17	27.8 (9.7, 53.5) N=18	31.4 (16.9, 49.3) N=35	41.2 (18.4, 67.1) N=17	20.0 (5.7, 43.7) N=20	30.8 (22.3, 40.5) N=107

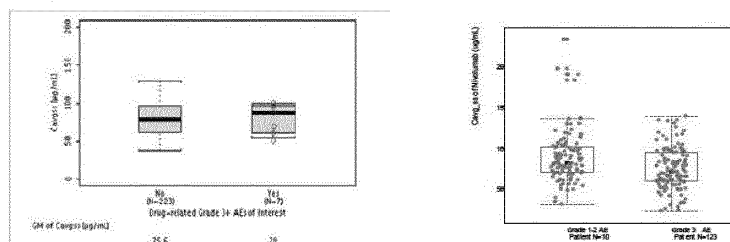
Source: Tables 7.2.1-1, 7.3.1-1 and 7.4.1-1 of MDX1106-03 CSR

Figure 1. Flat exposure-response relationship of ORR versus nivolumab C_{min1} at 3 mg/kg Q2W for patients with advanced melanoma



31. Thus, the response rate is largely independent of the dose or plasma exposure (**no dose or exposure-efficacy relationship**). Consequently, in terms of efficacy, the **dose can be chosen very flexibly** within the range of 0.1 to 10 mg/kg.
32. Figure 2 of **D2** (**D2**, p. 12; reproduced below) shows that patients with serious adverse events (AEs) (right bar of left panel: drug-related grade 3+ AEs; right bar of right panel: all grade 3+ AEs) have comparable nivolumab steady-state average concentrations ($C_{avg,ss}$) to patients with no (left bar of left panel) or less serious AEs (left bar of right panel). Thus, the safety risk did not increase with exposure in the dose range of 0.1 to 10 mg/kg Q2W, i.e. the occurrence of serious AEs was independent of plasma exposure (**no exposure-safety relationship**). Consequently, also in terms of safety, the **dose can be chosen very flexibly** within the range of 0.1 to 10 mg/kg.

Figure 2. No exposure-response relationship between drug-related or all grade 3+ adverse events and steady-state average concentration ($C_{avg,ss}$) of nivolumab at 3 mg/kg Q2W in study CA209037



Left: Drug-related 3+ AEs of interest; Right: All grade 3+ AEs.
Source: Pharmacometrics Review, Figure 2 and 3

33. Such **flat exposure-response** relationships for the safety and efficacy over a large range of plasma exposure support a **wide therapeutic window** of nivolumab.

IV.2.2 Maximum tolerable dose (MTD)

34. The **Maximum Tolerable Dose (MTD)** is defined as the dose that produces an “*acceptable*” level of toxicity or that, if exceeded, would put patients at “*unacceptable*” risk of toxicity, i.e., the dose that most patients (generally at least two thirds) can tolerate without experiencing a grade 3 or higher adverse event. Establishing the MTD is one of the main objectives of Phase I clinical trials in cancer treatment in which relatively high doses of drugs are usually chosen to achieve the greatest possible beneficial anti-tumour effect, while minimizing toxicity.
35. According to the FDA document, the MTD of nivolumab was not reached at 10 mg/kg, i.e., nivolumab is **well-tolerated** over the dose range of 0.1 to 10 mg/kg Q2W (**D2**, p. 12, last para., l. 5-7).

IV.2.3 Receptor binding

36. The response to nivolumab is the result of its competition with the endogenous ligands PD-L1 and PD-L2 for PD-1 receptor binding. How well a drug performs in such competition (its potency) depends on its affinity and efficacy:
- **Affinity** describes how well a drug can bind to a receptor. Faster or stronger binding is represented by a higher affinity, or equivalently a lower dissociation constant.
 - **Efficacy** is the relationship between receptor binding and the ability to initiate a response at the molecular, cellular, tissue or system level.
37. A measure of a drug's potency is the EC_{50} which is the concentration required to obtain a 50% effect (**half maximal effective concentration**). Nivolumab has an EC_{50} of **0.1 µg/mL** (D2, p.31, penultimate para.).
38. In the Phase I multiple dose PK study in human (MDX1106-03), the trough concentrations after the first dose ranged from 0.3 to 56.5 µg/mL depending on the dose of nivolumab administered. Thus, the trough concentration was at least 3 times the EC_{50} (D2, p. 16, Table 7, 3rd col.). This is in line with the observation that over the dose range of 0.1 to 10 mg/kg the response rate was largely independent of the nivolumab dose or plasma exposure (cf., para. 30 above).
39. Consequently, these data further support nivolumab's **therapeutic efficacy** at doses as low as 0.1 mg/kg.

IV.2.4 Terminal half-life ($t_{1/2}$)

40. Terminal half-life is the time it takes for the drug concentration in plasma/blood to be reduced by half after reaching steady-state equilibrium and is an index of drug persistence in the body. The main clinical application of terminal half-life is to **select an appropriate length for the dosing interval** in circumstances of multiple dose administration because it relates to the degree of drug accumulation and concentration fluctuations; and controls the time to reach steady-state equilibrium.
41. Nivolumab's terminal half-life was estimated to be **26.7 days** which requires about 12 weeks to achieve steady state, and which leads to a near three-fold accumulation at a dosing interval of 14 days (cf. D2, p.13, 1st para., l. 6; p. 15, Table 6; p. 16, Figure 6). Even at an interval equal to nivolumab's half-life of 26.7 days (i.e., about Q4W) one would have to expect a two-fold accumulation (cf., e.g., Toutain et al. 2004 (D14), Table 2). Thus, the equilibrium concentration of nivolumab at this dosing interval is expected to be roughly twice the plasma concentration obtained after the first administration. Based on the flat response rate for safety and efficacy reported in D2, this accumulation level is expected to be safe and efficacious.

42. Additionally, the relationship between terminal half-life and dosing interval determines the amplitude of fluctuations in drug plasma concentrations during the dosing intervals. If the dosing interval is large relative to terminal half-life, there will be wide fluctuations in concentrations with possible side-effects ($C_{\max}$ too high) or lack of efficacy ($C_{\min}$ too low). Accordingly, a dosing interval should be selected such that the plasma concentrations fluctuate within the therapeutic window of the drug (cf. D14, see the equation at the top of p. 432 and Table 2).
43. In the light of the facts that the efficacy at the lowest dose tested, i.e. 0.1 mg/kg, was more or less the same as at any other dose in the dose range of 0.1 to 10 mg/kg (cf. section IV.2.1 above) and that nivolumab was very well-tolerated up to at least 10 mg/kg (cf. section IV.2.2 above), the **dosing interval can be chosen very flexibly** without fear of toxicity or loss of efficacy. Specifically, the lowest and highest acceptable steady-state concentrations observed for nivolumab $C_{\min,ss}$ (**0.3 µg/mL**) and $C_{\max,ss}$ (**475 µg/mL**), respectively, provide a reasonably large therapeutic window in which the plasma concentrations may comfortably fluctuate (D2, Tables 6 and 7 on p. 15 + 16).
44. Taken together, the data disclosed in the FDA document (D2) show that it is safe and effective to vary **the dose** within the range of 0.1 to 10 mg/kg (i.e., 8 mg and 800 mg, assuming a median 80 kg weight), wherein the lowest trough and the highest peak concentrations cover a serum concentration range of **0.3 µg/mL up to 475 µg/mL**.
45. Given that nivolumab has a rather long terminal half-life of 26.7 days, the **dosing interval** can also be chosen very flexibly without fear of toxicity or loss of efficacy as long as the peak-to-trough fluctuations are within the limits mentioned above.

IV.3 Adapting the dose and interval for nivolumab would have been a routine measure in light of the disclosures of D2 or D3 or a combination thereof

46. As outlined above, with respect to nivolumab, the skilled person would easily derive the flat dose of **240 mg Q2W** from the known body weight-based dose of **3 mg/kg Q2W**. As I will explain in the following, in view of the available information relating to nivolumab, the skilled person would further easily derive the flat dose of **480 mg Q4W** and expect this dose to provide a similar response to the flat dose of **240 mg Q2W**.

IV.3.1 The claimed dosing regimen of 480 mg Q4W is obvious in view of D3

47. As I stated above, the answer to the question of whether the skilled person would consider the flat dose of **480 mg Q4W** as an alternative to the flat dose of **240 mg Q2W** for nivolumab with regard to D3 is **yes, he/she would do so**.
48. The highest dose tested was **10 mg/kg** which is equivalent to a flat dose of **800 mg** for the median 80 kg patient. Since the **480 mg** dose is well below said maximum dose tested and no excessive

accumulation is to be expected at an interval of Q4W, the skilled person would not expect toxicity issues when increasing the dose from 240 mg to 480 mg (cf. e.g., **D14**, Table 2).

49. The skilled person would additionally expect that extending the dosing interval from Q2W to Q4W to be unproblematic in the light of the efficient and durable receptor occupancy (no risk of loss of efficacy). Indeed, **D3** shows that receptor occupancy is maintained for up to 57 days, which is well beyond 4 weeks.
50. Accordingly, the skilled person who aims at providing a more convenient and flexible treatment schedule for nivolumab would consider changing the known treatment schedule of **240 mg Q2W** to a dosing regimen of **480 mg Q4W**.

IV.3.2 The claimed dosing regimen of 480 mg Q4W is obvious in view of D2

51. At the filing date of EP'980, it was common general knowledge that a change in the interval (e.g., Q2W to Q4W) at constant dose per time unit (e.g., 480 mg within 4 weeks) only affects the amplitude of fluctuations at steady state. Both the steady-state average concentration and the time to reach steady state concentration remain the same (**D14**, p. 431, left col., last para., and Figure 7).
52. Consequently, the sole difference between the two dosing regimens of **240 mg Q2W** and **480 mg Q4W** is the extent of peak-to-trough fluctuations around the steady state. These fluctuations may be relevant in terms of safety and efficacy for drugs exhibiting a narrow therapeutic window. However, since nivolumab has a wide therapeutic window, the skilled person would consider these two dosing regimens as **equivalent alternatives**. In particular, both of these dosing regimens will fluctuate within the limits mentioned above.
53. Accordingly, the skilled person who aims at providing a more convenient and flexible treatment schedule would consider changing the known treatment schedule for nivolumab of **240 mg Q2W** to its equivalent dosing regimen of **480 mg Q4W** – this is routine in the art.

IV.3.3 The claimed dosing regimen of 480 mg Q4W is obvious in view of the combination of D2 and D3

54. As outlined above, already in view of either **D2** or **D3**, the skilled person would easily derive the claimed dosing regimen of **480 mg Q4W** from the known body weight-based treatment schedule of **3 mg/kg Q2W**.
55. Furthermore, the data of the two documents support each other: the FDA approval document (**D2**) underpins the wide therapeutic window of nivolumab based on the results of various clinical studies, which is already apparent from the phase I dose-escalation study with 39 patients disclosed in the Brahmer paper (**D3**). The high potency of nivolumab described in **D2** (EC50 = 0.1 µg/mL) can be attributed, among other things, to the efficient and long-lasting receptor occupancy known from **D3**.

Both the efficient and long-lasting receptor occupancy and the knowledge of nivolumab's terminal half-life (cf. **D2**) support the clinician in selecting an appropriate length for the dosing interval.

56. Consequently, the combined teaching of **D3** and **D2** inevitably leads the skilled person to the claimed treatment regimen.

IV.3.4 The claimed dosing regimen of 480 mg Q4W is obvious in view of any one of the clinical trials (D12, D15, D16 or D17) in combination with any one of D3 or D2

57. As noted above, **melanoma** patients were indicated to receive a **flat dose** of 80 or **240 mg Q2W** of nivolumab as part of a combination therapy as of October 2014 (**D12**, see arm B; and Inclusion Criteria for part B).
58. Flat doses of **240 mg Q2W** and **480 mg Q4W** were subsequently indicated for nivolumab in further BMS-sponsored clinical trials. As I understand, these additional trials published the flat-dose indications after April 2015, but before April 28, 2016. In particular,
- As of October 6, 2015, **NCT02046733** indicated that SCLC patients were to receive nivolumab in the maintenance phase at a dose of **240 mg Q2W** (**D15**, see the arms and interventions).
 - As of March 21, 2016, **NCT02713867** indicated that patients with advanced or metastatic NSCLC were to receive nivolumab at **240 mg Q2W** and **480 mg Q4W** in (**D16**, see Title and Study Identification).
 - As of April 15, 2016, **NCT02335918** indicated that tumour patients (including those with **melanoma**) were to receive a combination therapy including nivolumab at a dose of **240 mg Q2W** (**D17**, see the arms and interventions).
59. In view of these clinical trials, it is quite apparent that the skilled person would easily derive flat doses of nivolumab, such as **240 mg Q2W** or **480 mg Q4W** based on the previously indicated body weight-based dose.
60. In particular, the skilled person simply had to select the flat dose from any one of these trials. As explained in detail above, the skilled person could have selected either the **240 mg Q2W** or the **480 mg Q4W** to replace the known body weight-based dose of 3 mg/kg and expected them to be **equally** safe and effective in view of the data in either **D3** or **D2**.
61. Consequently, a flat dose regimen could easily have been selected from any one of the BMS-sponsored clinical trials that were on-going between October 2014 and April 2016. The choice between **240 mg Q2W** and **480 mg Q4W** would merely have been a matter of convenience to the patient and the practitioner.

V. Summary

62. For the reasons explained above, I believe that based on the results reported in the prior art discussed above, a person of ordinary skill in the art would have considered the flat dose of **480 mg Q4W** as an **equivalent alternative** to the known **240 mg Q2W** dosing regimen.
63. Indeed, the fact that these two regimens may be considered equivalent alternatives is confirmed by the FDA label for nivolumab, which indicates that either regimen may be used for the treatment of melanoma (**D18**, page 1, Dosage and Administration; and sections 2.1 and 2.2).
64. I declare that the foregoing statements are true and correct, to the best of my expert and personal knowledge.

Executed on November 23rd, 2021 in my home.



Prof. Robert Charles Frederick Leonard (MD)

Enclosures
Curriculum Vitae