Cutaneous lymphomas

Classification and Management

Updates in molecular pathogenesis and biomarkers in MF/SS
(Dr. M. Vermeer)

- Next generation sequencing (NGS)

- Pathways involved:
  - T cell activation/NF-kB
  - JAK/STAT

- Mutations in epigenetic genes
  - DNA metthylation: DNMT3A, SETDB2, TET2
  - Histone modifications: CREBBP, NCOR1
  - Chromatin remodeling: ARID1a, SMARCB1

- Potential diagnostic markers in Sèzary syndrome (CMTM2, PROM1, GNMT)

- Molecular subclassification of patients
  - Diagnostic markers
  - Prognostic markers
  - Selection of treatment

Management of Mycosis fungoides (Dra. Scarisbrick)

Accepted Manuscript

The results of Low dose Total Skin Electron Beam Radiotherapy (TSEB), in patients with mycosis fungoides from the UK cutaneous lymphoma group
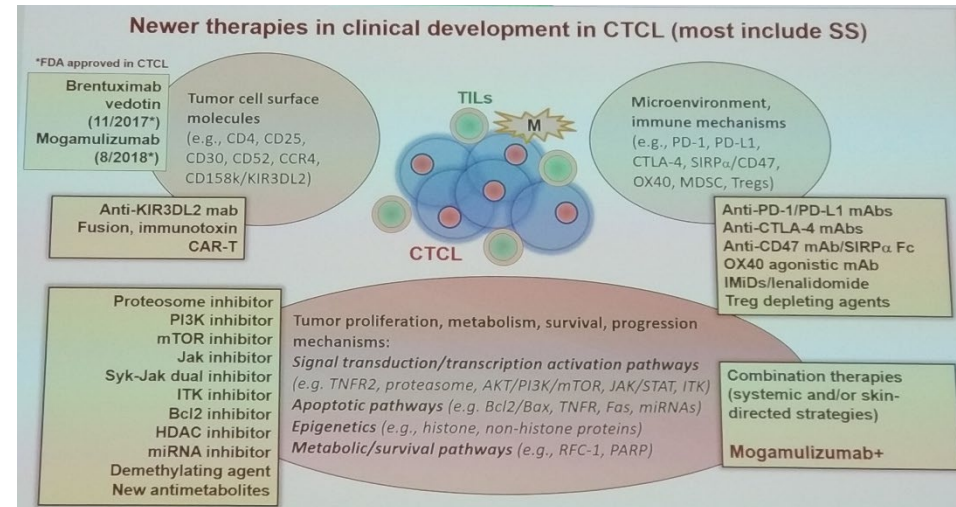
Stephen L. Morris, Julia Scarisbrick, John Frew J, Clive Irwin, Robert Grieve, Caroline Humber, Aleksandra Kuciejewska, Sally Bayne, Sophie Weatherhead, Fiona Child, Marv Wain. Sean Whittaker

- New Low dose Total Skin Electron Beam Radiation
  - Lower dose
  - Shorter treatment
  - Less skin reaction but less duration of response

- Brentuximab vedotin
  - ORR 4 months (56% Vs 13%)
  - CR rate (16% Vs 2%)

Milàn

Management of Sèzary syndrome (Dra. Kim)

- Management is based on compartmental disease burden and biologic activity

- Combined/Sequential strategies
  - Mogamulizumab (last FDA approved agent): High efficacy in Sèzary burden
  - Romidepsin: global efficacy
  - Skin-directed therapies

- KIR3DL2 as promising therapeutic target in CTCL, especially Sèzary syndrome
 - Higher prevalence in Sèzary syndrome
  - Prognostic significance

Newer therapies in clinical development in CTCL (most include SS)

*FDA approved in CTCL

Brentuximab vedotin (11/2017*) Mogamulizumab (8/2018*)

Tumor cell surface molecules (e.g., CD4, CD25, CD30, CD52, CCR4, CD158k/KIR3DL2)

TILs M

Microenvironment, immune mechanisms (e.g., PD-1, PD-L1, CTLA-4, SIRPα/CD47, OX40, MDSC, Tregs)

Anti-KIR3DL2 mab Fusion, immunotoxin CAR-T

CTCL

Anti-PD-1/PD-L1 mAbs Anti-CTLA-4 mAbs Anti-CD47 mAb/SIRPα Fc OX40 agonistic mAb IMiDs/lenalidomide Treg depleting agents

Proteosome inhibitor PI3K inhibitor mTOR inhibitor Jak inhibitor Syk-Jak dual inhibitor ITK inhibitor Bcl2 inhibitor HDAC inhibitor miRNA inhibitor Demethylating agent New antimetabolites

Tumor proliferation, metabolism, survival, progression mechanisms: Signal transduction/transcription activation pathways (e.g. TNFR2, proteasome, AKT/PI3K/mTOR, JAK/STAT, ITK) Apoptotic pathways (e.g. Bcl2/Bax, TNFR, Fas, miRNAs) Epigenetics (e.g., histone, non-histone proteins) Metabolic/survival pathways (e.g., RFC-1, PARP)

Combination therapies (systemic and/or skin-directed strategies)

Mogamulizumab+

Single-cell heterogeneity in Sézary syndrome

Terkild Brink Buus,[1] Andreas Willerslev-Olsen,[1] Simon Fredholm,[1] Edda Blümel,[1] Claudia Nastasi,[1] Maria Gluud,[1] Tengpeng Hu,[1] Lise M. Lindahl,[2] Lars Iversen,[2] Hanne Fogh,[3] Robert Gniadecki,[3] Ivan V. Litvinov,[4] Jenny L. Persson,[5,6] Charlotte Menné Bonefeld,[1] Carsten Geisler,[1] Jan Pravsgaard Christensen,[1] Thorbjørn Krejsgaard,[1] Thomas Litman,[1] Anders Woetmann,[1] and Niels Ødum[1]

- Single cell RNAseq

- Individual patients with Sèzary syndrome contain several distinct malignant subpopulations and show marked single-cell heterogeneity

- Malignant subpopulations exhibit differences in their sensivity to treatment warranting precision therapy

Mìlàn

# CD52 negative escape variant emerges during Alemtuzumab treatment
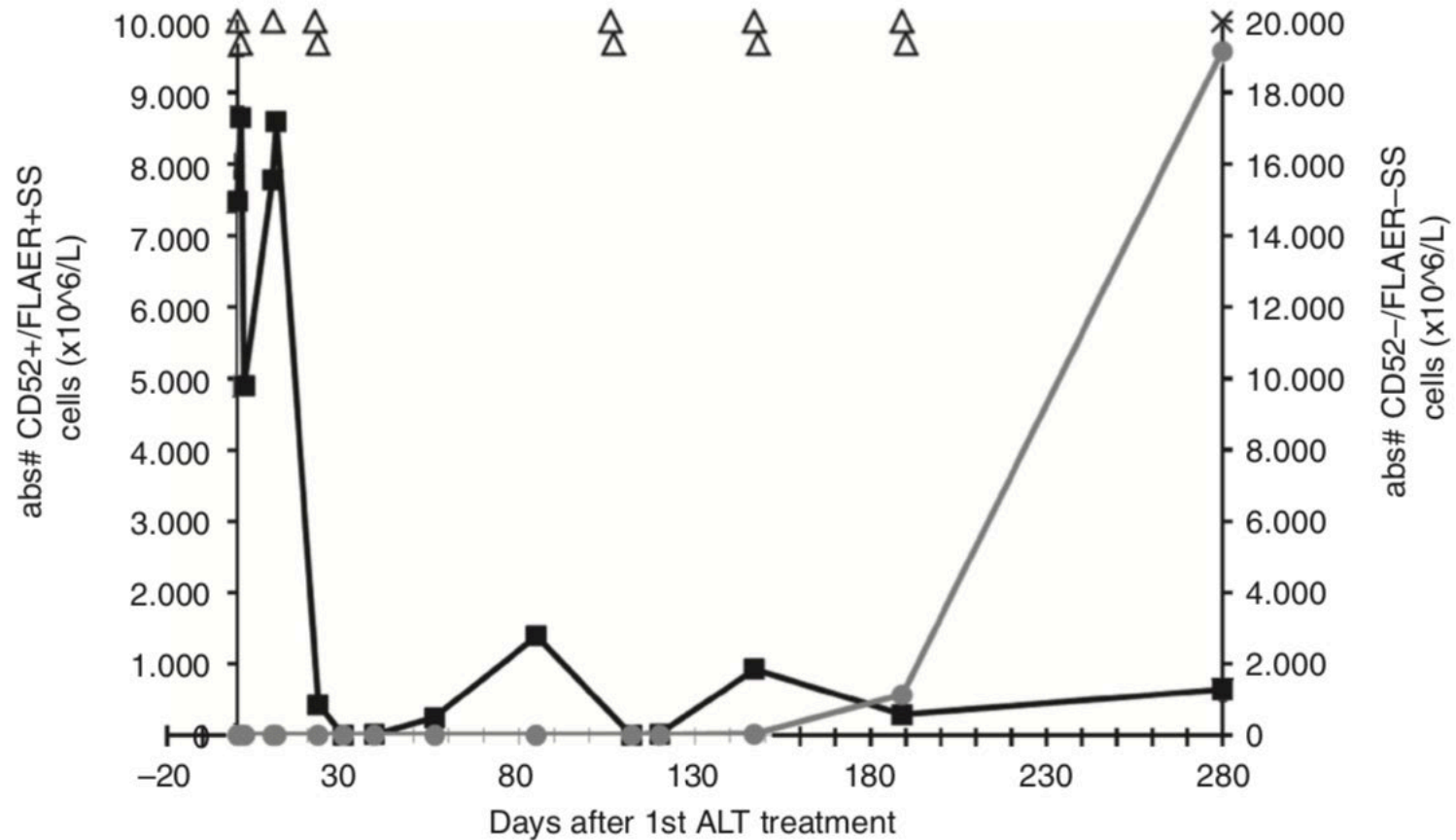
Breast implant-asssociated anaplastic large cell lymphoma

- Subcutaneous lesions adjacent to breast implant
- EMA positive ALK negative
- In situ/infiltrative
- Indolent/aggressive
- Anaplastic cells limited to fibrous capsule
- Reed-Stemberg-like cells and eosinophils
- Implant removal/additional (chemo)therapy
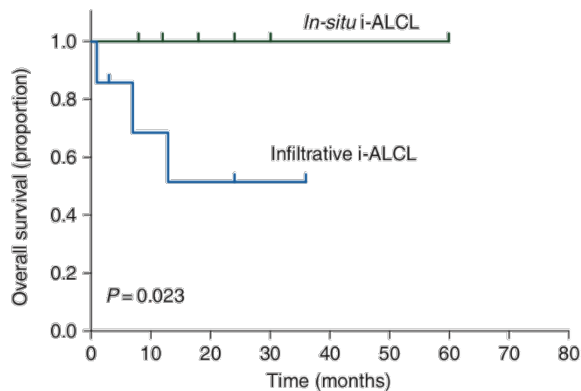
Breast implant-associated anaplastic large cell lymphoma: two distinct clinicopathological variants with different outcomes

C. Laurent[1,2]*, A. Delas[1], P. Gaulard[3,4], C. Haioun[4,5], A. Moreau[6], L. Xerri[7], A. Traverse-Glehen[8], T. Rousset[9], I. Quintin-Roue[10], T. Petrella[11], J. F. Emile[12], N. Amara[1], P. Rochaix[1], M. P. Chenard-Neu[13], A. M. Tasei[14], E. Menet[15], H. Chomarat[16], V. Costes[9], L. Andrac-Meyer[17], J. F. Michiels[18], C. Chassagne-Clement[19], L. de Leval[20], P. Brousset[1,2], G. Delsol[1,2] & L. Lamant[1,2]

Milàn
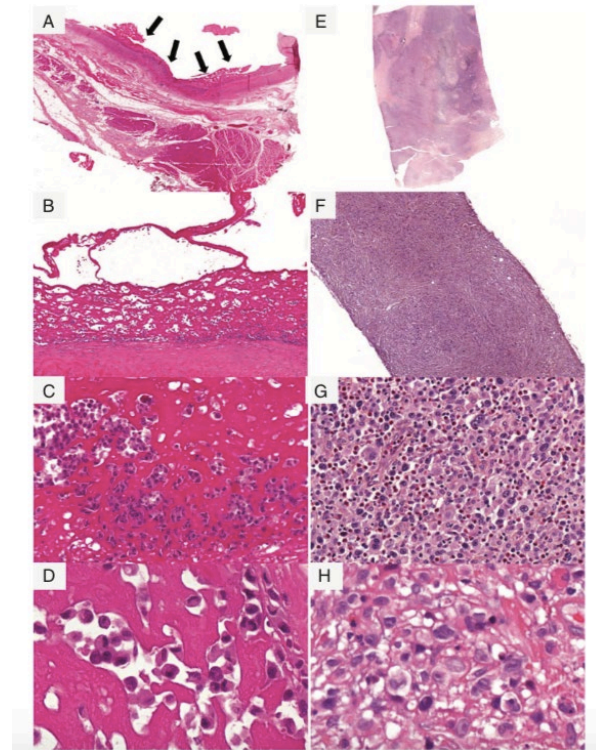
# Breast implant-asssociated anaplastic large cell lymphoma

- PD-L1 and PD-L1 amplification
- 9p24.1 alteration common
- ↑ ↑ PD-L1
- In microenvironment ↑ ↑ PD-1 TILs
- ↑ ↑ PD-L1 TAMs
- Active PD-1/PD-L1 axis?
- Potential target in advanced stage?

ACCEPTED MANUSCRIPT

Recurrent PDL1 expression and *PDL1* (*CD274*) copy number alterations in breast implant-associated anaplastic large-cell lymphomas.

Running head: *PDL1 expression in BI-ALCL: mechanisms and therapeutic potential.*

Valentina Tabanelli MD,[1] Chiara Corsini BS,[2] Stefano Fiori MD,[1] Claudio Agostinelli MD PhD,[3] Angelica Calleri BS PhD,[1] Stefania Orecchioni BS PhD,[2] Federica Melle BS PhD,[1] Giovanna Motta BS PhD,[1] Anna Rotili MD,[4] Arianna Di Napoli MD[5]* and Stefano A. Pileri MD PhD[1]*
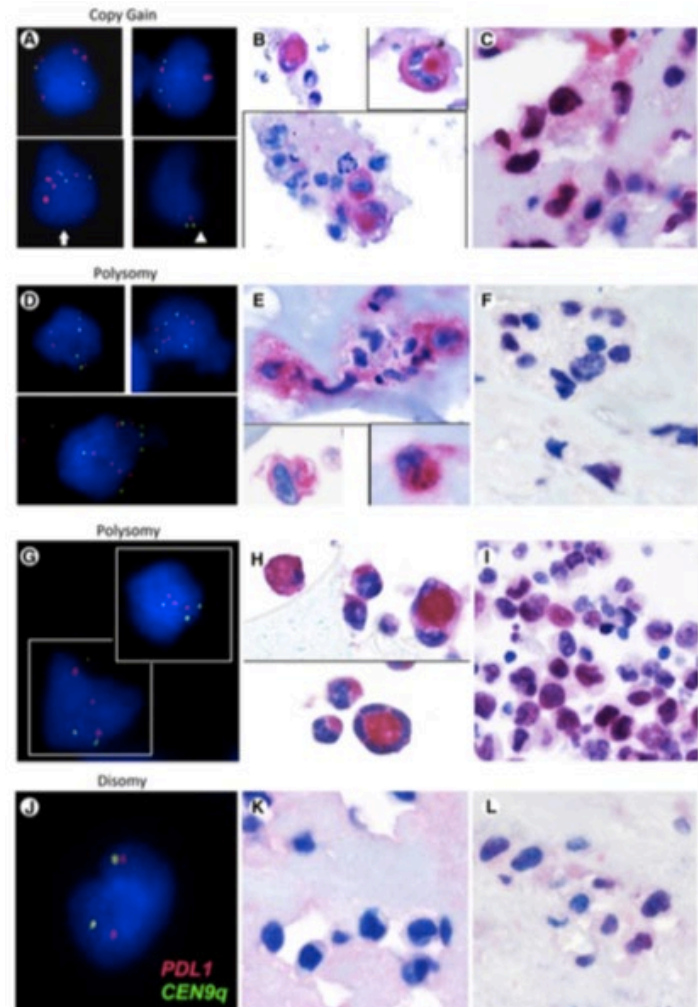
B-cell cutaneous lymphoma (Dr. Guitart)

- Cutaneous B-cell marginal zone lymphoma
    - Is it really a lymphoma?
    - Secondary to local stimulus (tatto, vaccines, surgery…)
    - Related with autoinmmunity disorders, GI disorders, borreliosis…

- Leg types lymphomas have worse prognostic regardeless their fenotype (B or T)

- T-cell systemic lymphomas could produce B-cell cutaneous proliferative disorders.

Advances in the management of Melanoma

New molecular tecniques for cutaneous melanoma diagnosis (Dr. Gerami)

- 31-GEP add prognostic information independent from staging factors
- Improves prediction over SLNB negative status for distant metastasis-free survival
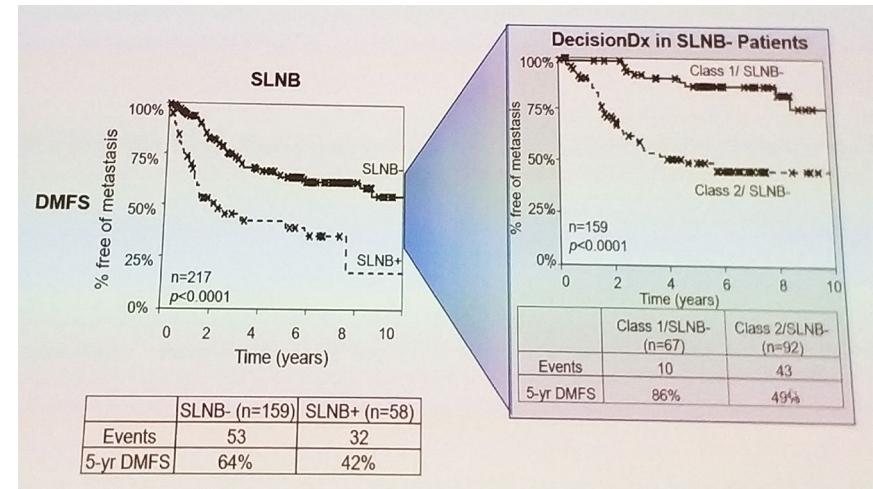
31-GEP result	Probabilty of a positive sentinel lymph node for T1-T2 patients		
	<55 years (n=370)	55-64 years (n=247)	>65 years (n=448)
Class 1A	7.6%	4.9%	1.6%
Class 1B/2A	19.6%	7.7%	6.9%
Class 2B	**24.0%**	**30.8%**	**11.9%**

- New adhesive tape stripping for melanoma diagnosis

Artificial intelligence for cutaneous melanoma detection (Dra. Swetter)

- Results for CNN VS Dermatologists
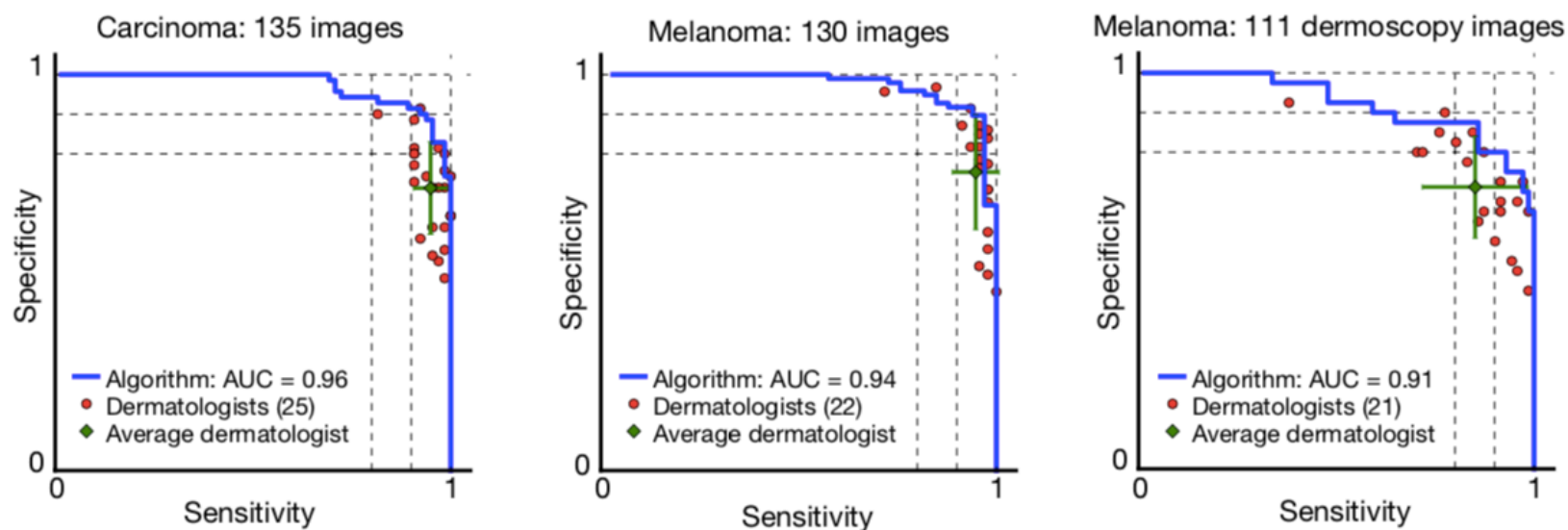
- CNN performed at least as well as dermatologists as a whole

Advanced imaging technology in early melanoma detection (Dr. Soyer)

- Transform melanoma early detection using total body surveillance to enhance individual lesion management
  - Diagnostic intelligence
  - Health service evaluation
  - Informatics

- World´s largest most comprenhensive skin imaging database
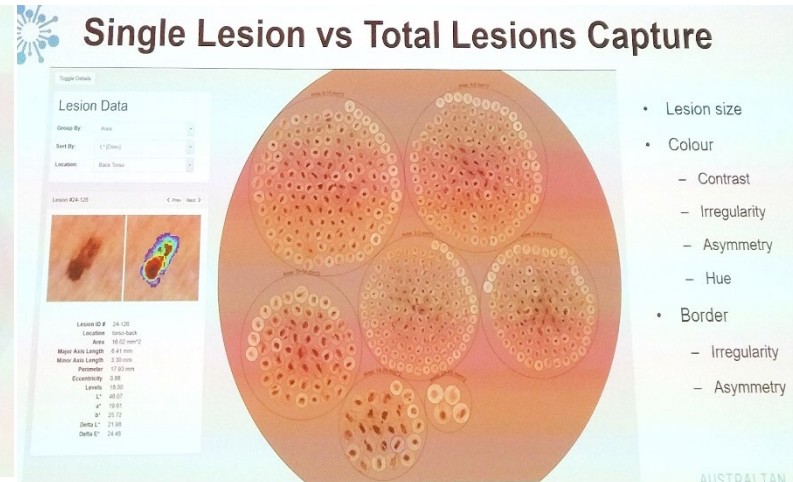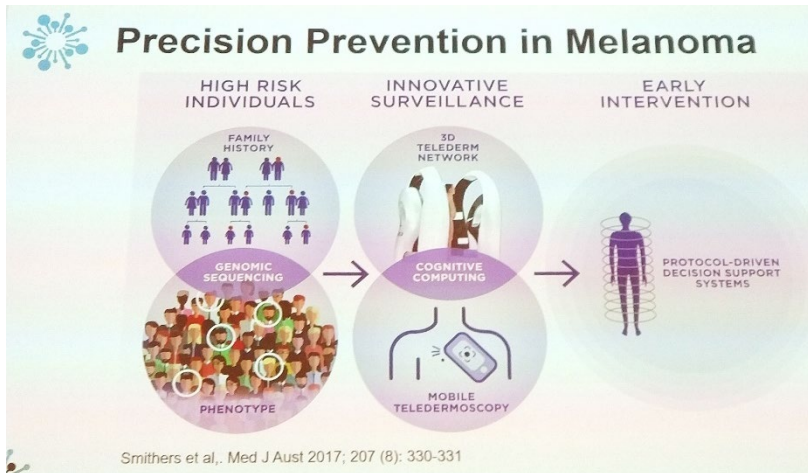
Mutations, metastasis and the importance of multidisciplinary management (Dra. Mar)

- Mutation status might stratify risk in SLNB – patients
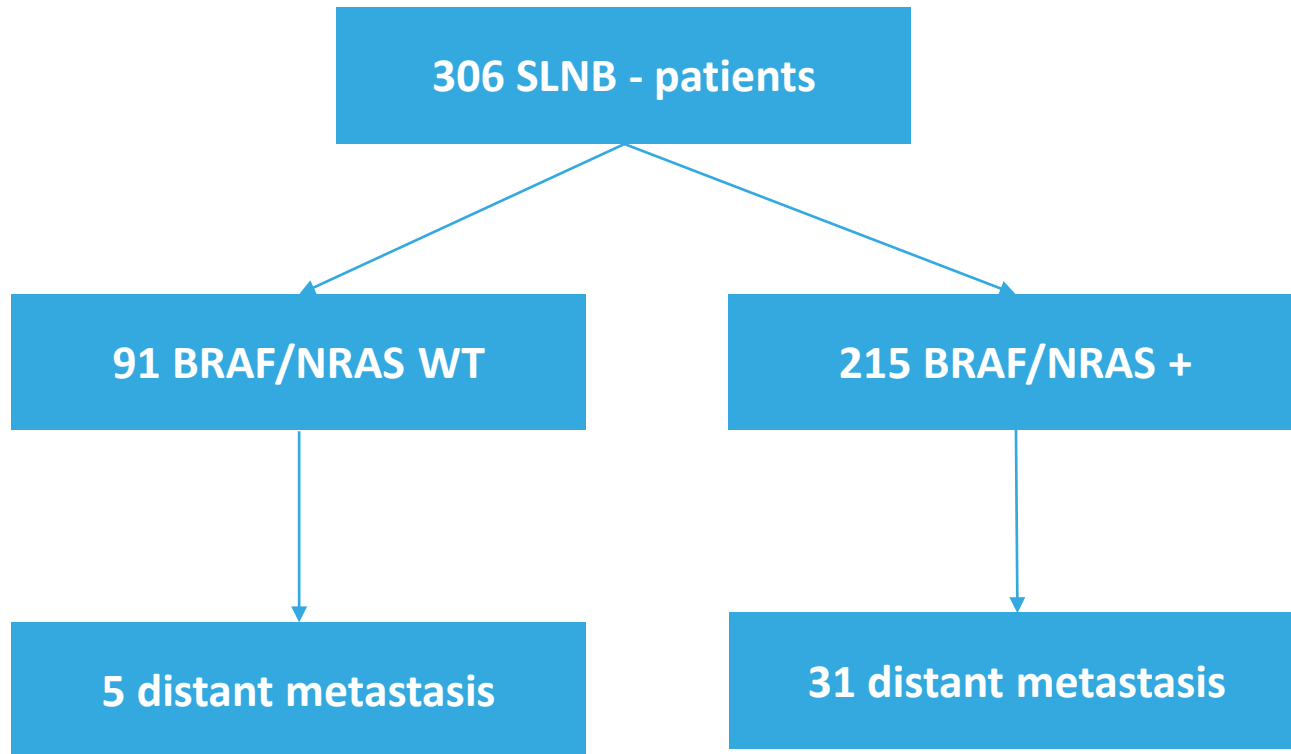
Mutations, metastasis and the importance of multidisciplinary management (Dra. Mar)

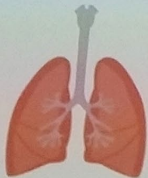## Mutation status and risk of melanoma death

- **BRAF** vs BRAF/NRAS WT   aHR 2.95, P=0.001   (MSS)
- **NRAS** vs BRAF/NRAS WT   aHR 3.08   P=0.001   (MSS)

*adjusted for age, sex, ulceration, Breslow thickness, histologic subtype and mitotic rate

Sites of Metastasis

CNS   **BRAF** aOR= 4.65, **NRAS** aOR=4.03 compared to WT (p<0.001)

Lung   **NRAS** aOR=2.44 p=0.013   (BRAF aOR=1.78 p=0.06)

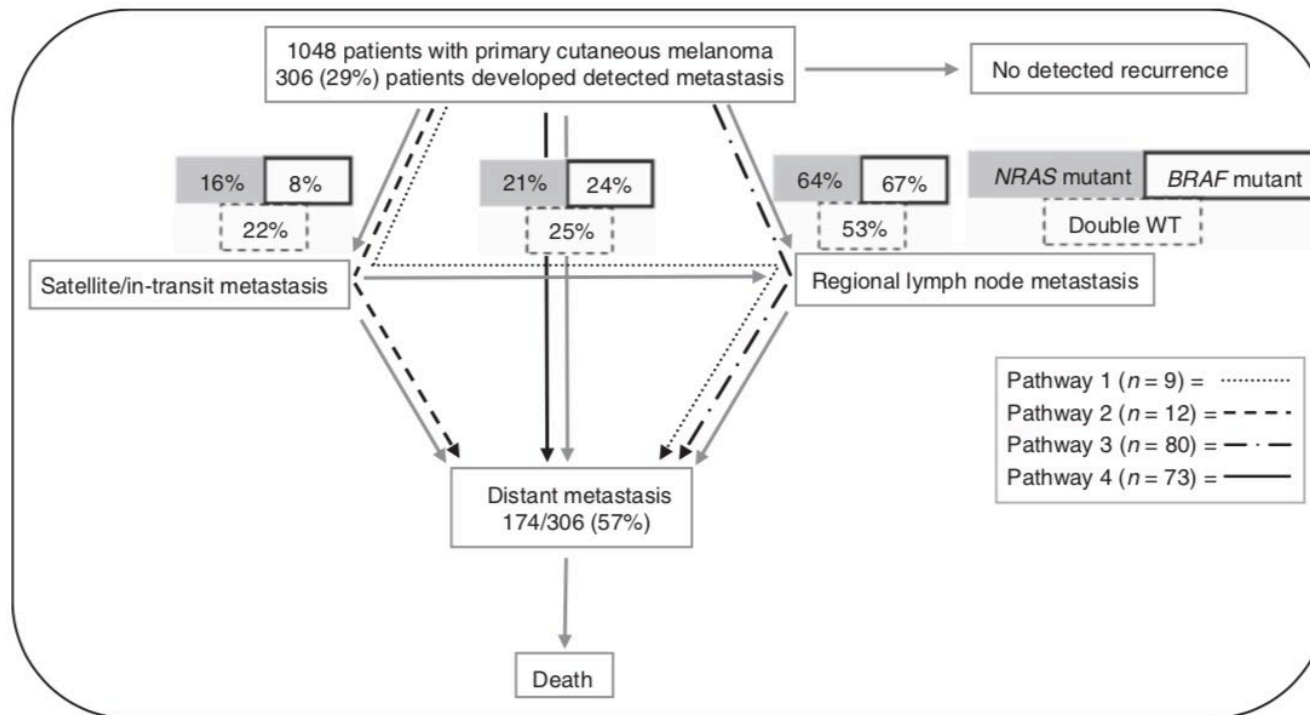Liver   **BRAF** aOR=3.09, P=0.003; **NRAS** aOR=3.17 (p=0.01)

Mutations, metastasis and the importance of multidisciplinary management (Dra. Mar)

Mutations, metastasis and the importance of multidisciplinary management (Dra. Mar)

- Circulating tumor DNA in blood samples
- 133 melanoma patients (III stage)
- 99/126 (79%) had a mutation detected in tumor tissue (BRAF, NRAS, KIT, TP53, TERT)

- ctDNA detected post-op in 13/52 (25%) patients
- **100% relapsed** (compared to 41% undetectable ctDNA)

Prediction and monitoring of relapse in stage III melanoma using circulating tumor DNA

L. Tan[1,2†], S. Sandhu[1,2†], R. J. Lee[3,4†], J. Li[1,2], J. Callahan[1], S. Ftouni[1], N. Dhomen[3], P. Middlehurst[3], A. Wallace[5], J. Raleigh[1], A. Hatzimihalis[1], M. A. Henderson[1,2], M. Shackleton[6], A. Haydon[6], V. Mar[6], D. E. Gyorki[1,7], D. Oudit[4,8], M. A. Dawson[1,2,9], R. J. Hicks[1,2], P. Lorigan[4,8], G. A. McArthur[1,2], R. Marais[3,4†], S. Q. Wong[1‡] & S.-J. Dawson[1,2,9*‡]