LUNG CANCER UPDATES

ASCO HIGHLIGHTS

1-5 JUNIO 2018, CHICAGO

Estadíos iniciales e intermedios

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GECP

Grupo Español de Cáncer de Pulmón

Spanish Lung Cancer Group

Phase II Trial of Concurrent Chemoradiation with Consolidation Pembrolizumab in Patients with Unresectable Stage III NSCLC

Hoosier Cancer Research Network LUN 14-179

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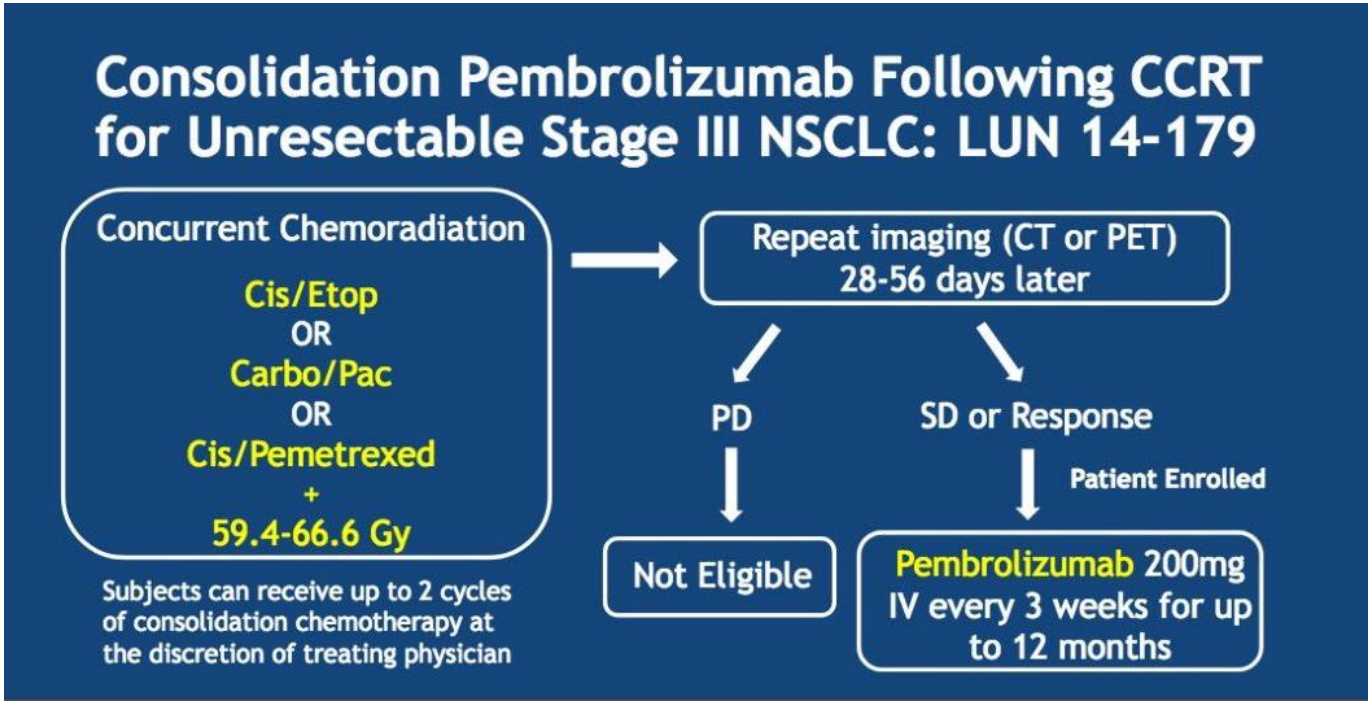
[1] Indiana University Simon Cancer Center, [2] Indiana University Department of Biostatistics, [3] Fort Wayne Medical Oncology and Hematology, [4] Rutgers Cancer Institute of New Jersey, [5] Michiana Hematology/Oncology, [6] University of Louisville James Graham Brown Cancer Center, [7] IU Health Ball Memorial Hospital, [8] City of Hope Comprehensive Cancer Center, [9] Goshen Center for Cancer Care, [10] Nebraska Methodist Hospital, [11] IU Health Arnett Cancer Center, [12] University of Virginia Cancer Health System


Consolidation Pembrolizumab Following CCRT for Unresectable Stage III NSCLC: LUN 14-179
Concurrent Chemoradiation
Cis/Etop
OR
Carbo/Pac
OR
Cis/Pemetrexed
+
59.4-66.6 Gy
Subjects can receive up to 2 cycles of consolidation chemotherapy at the discretion of treating physician
Repeat imaging (CT or PET) 28-56 days later
PD
SD or Response
Patient Enrolled
Not Eligible
Pembrolizumab 200mg IV every 3 weeks for up to 12 months

Efficacy of Consolidation Pembrolizumab

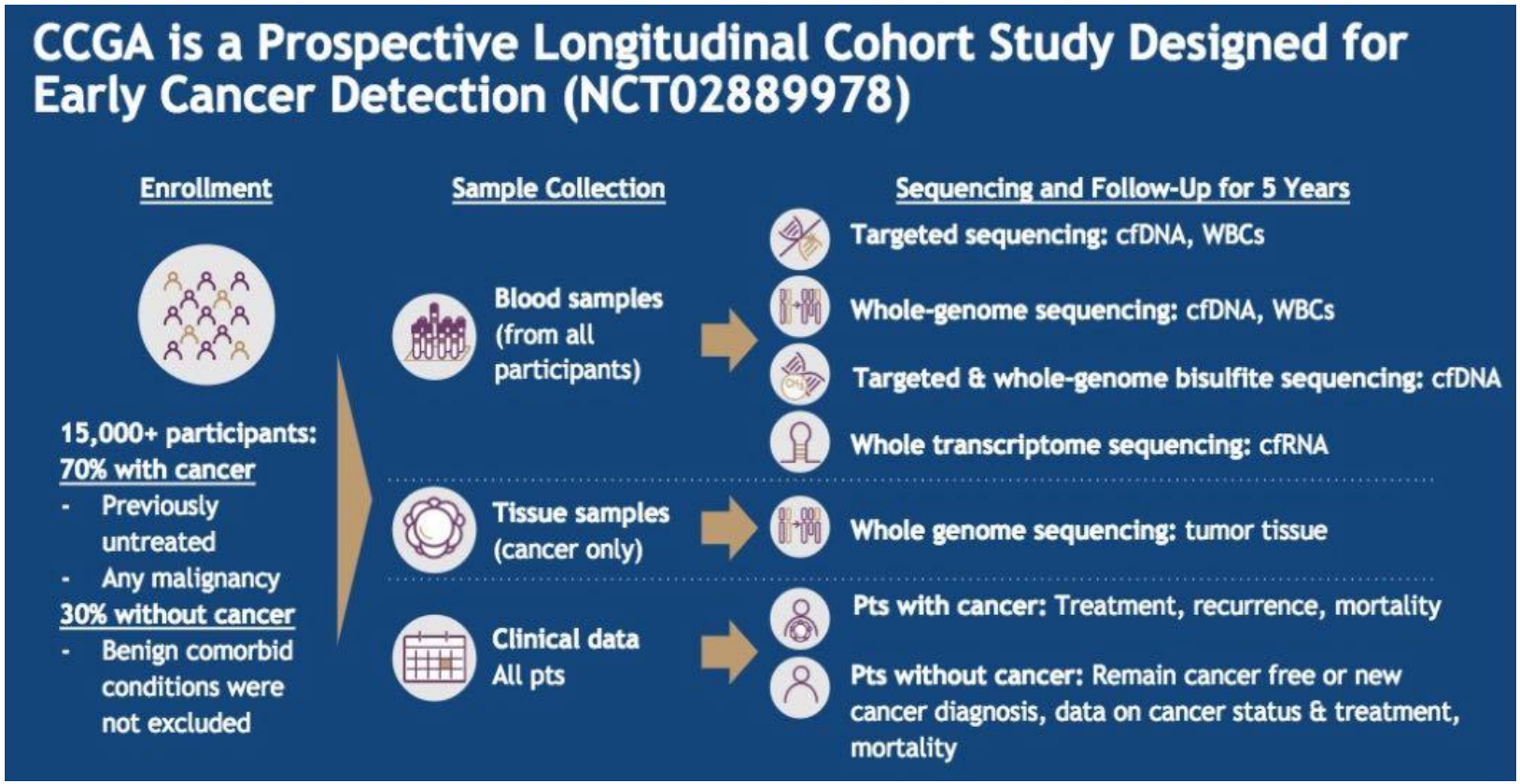
Endpoint	LUN 14-179 (Pembrolizumab)	PACIFIC[1] (Durvalumab)	PACIFIC[1] (Placebo)
Median Follow-up	18.6 months	14.5 months	14.5 months
Time to Metastatic Disease or Death			
Median	22.4 months	23.2 months	14.6 months
12-month	74.7%	-	-
18-month	60.0%	-	-
Progression Free Survival			
Median	17.0 months	16.8 months	5.6 months
12-month	60.2%	55.9%	35.3%
18-month	49.9%	44.2%	27.0%
24-month	44.6%	-	-

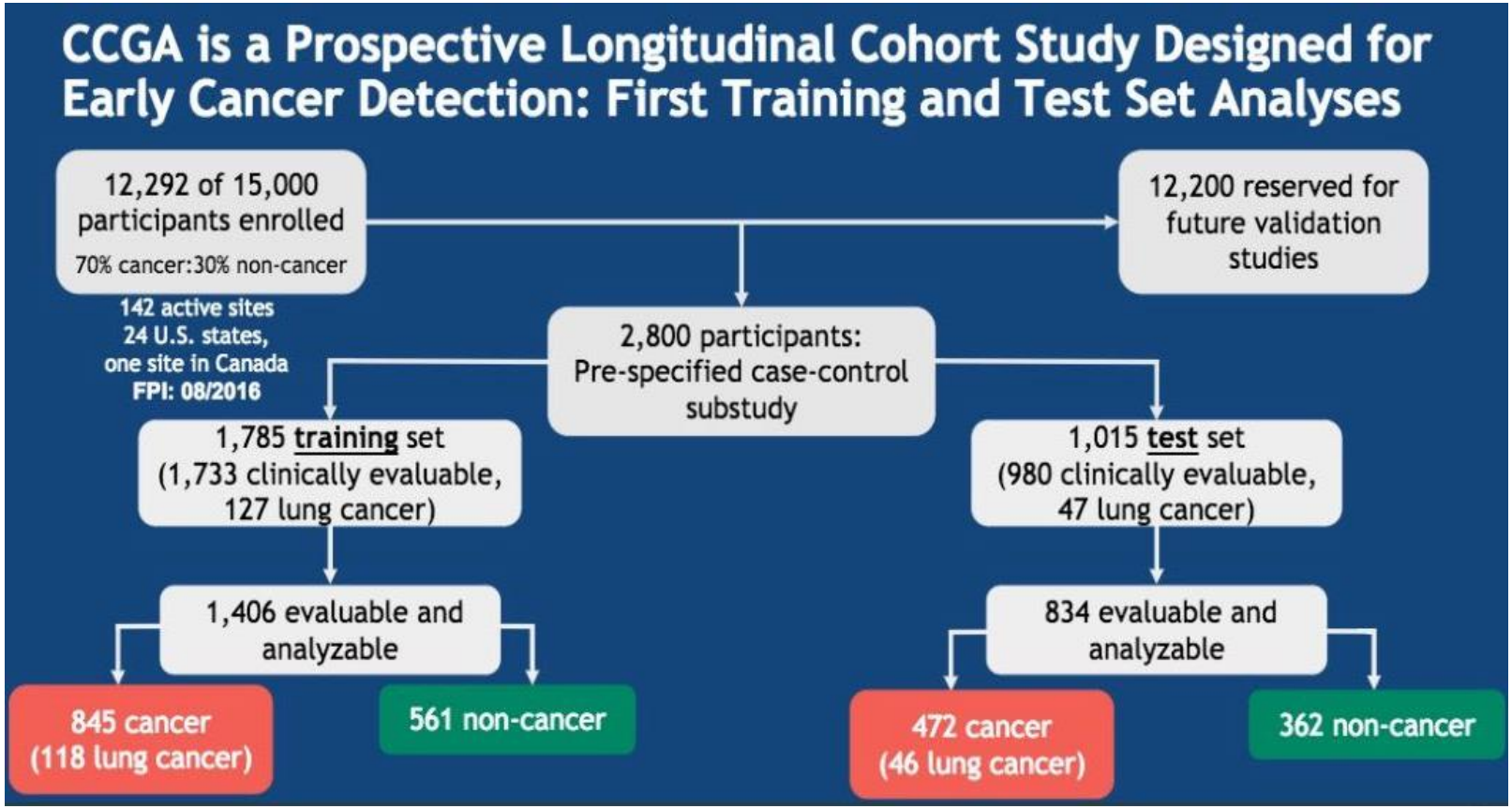
[1]Antonia et al. NEJM. 2017. Nov 16. 1919-1929.

Conclusions

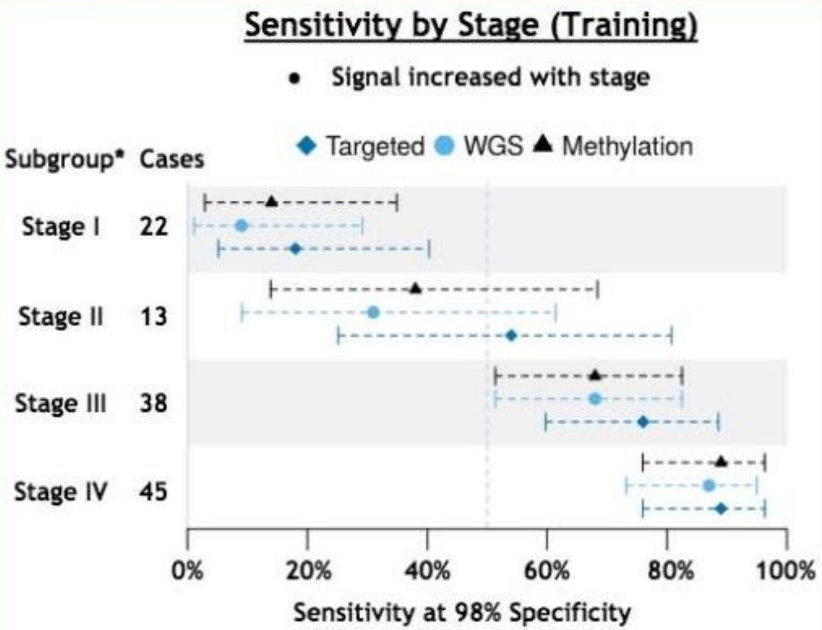
- This trial confirms that consolidation Pembrolizumab following CCRT in stage III NSCLC is feasible and safe in the majority of patients
- Consolidation Pembrolizumab following CCRT substantially improves TMDD and PFS compared to historical control
- Preliminary OS data is promising and suggests a major improvement in survival for this patient population

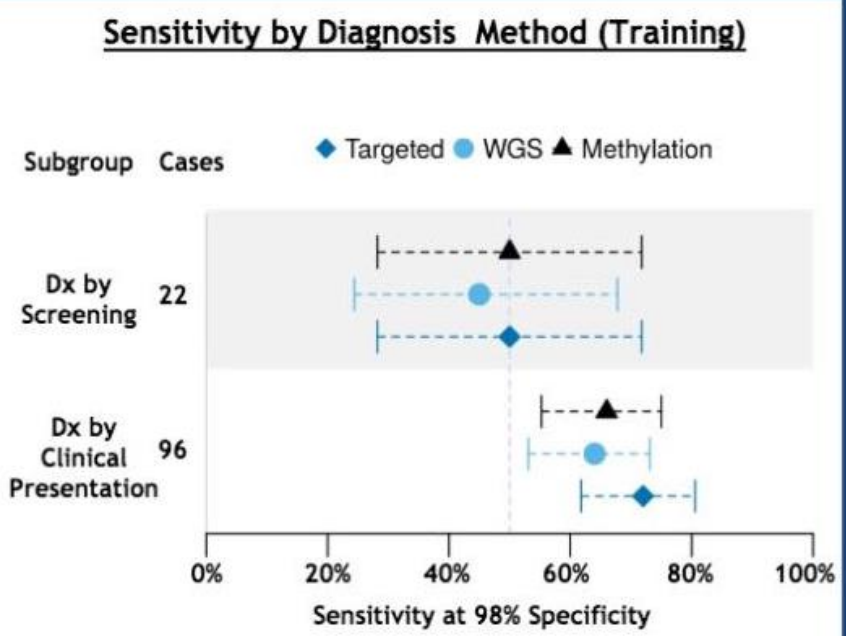
CCGA is a Prospective Longitudinal Cohort Study Designed for Early Cancer Detection (NCT02889978)




CCGA is a Prospective Longitudinal Cohort Study Designed for Early Cancer Detection: First Training and Test Set Analyses
12,292 of 15,000 participants enrolled
70% cancer:30% non-cancer
142 active sites
24 U.S. states,
one site in Canada
FPI: 08/2016
12,200 reserved for future validation studies
2,800 participants: Pre-specified case-control substudy
1,785 training set (1,733 clinically evaluable, 127 lung cancer)
1,015 test set (980 clinically evaluable, 47 lung cancer)
1,406 evaluable and analyzable
834 evaluable and analyzable
845 cancer (118 lung cancer)
561 non-cancer
472 cancer (46 lung cancer)
362 non-cancer

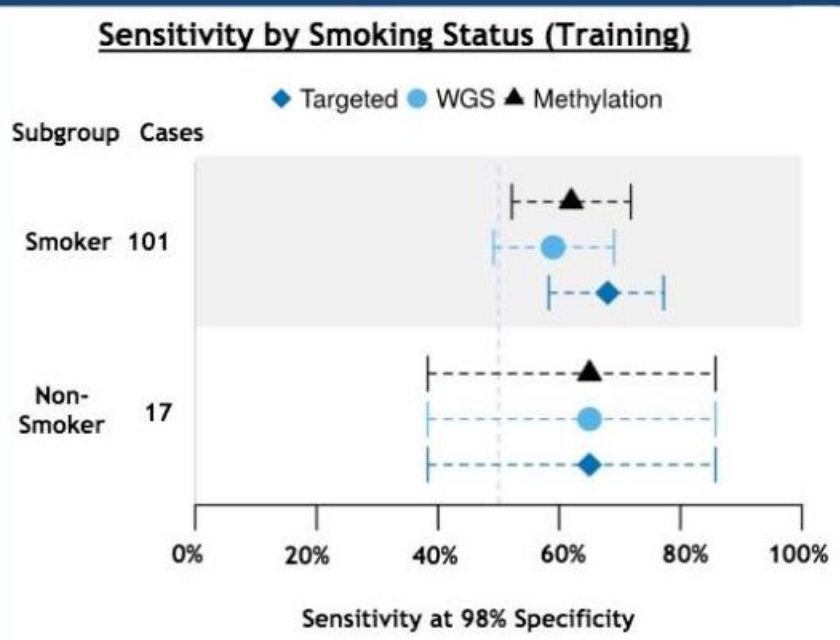
Assays Performed Consistently Within Lung Cancer Stages and by Diagnosis Method

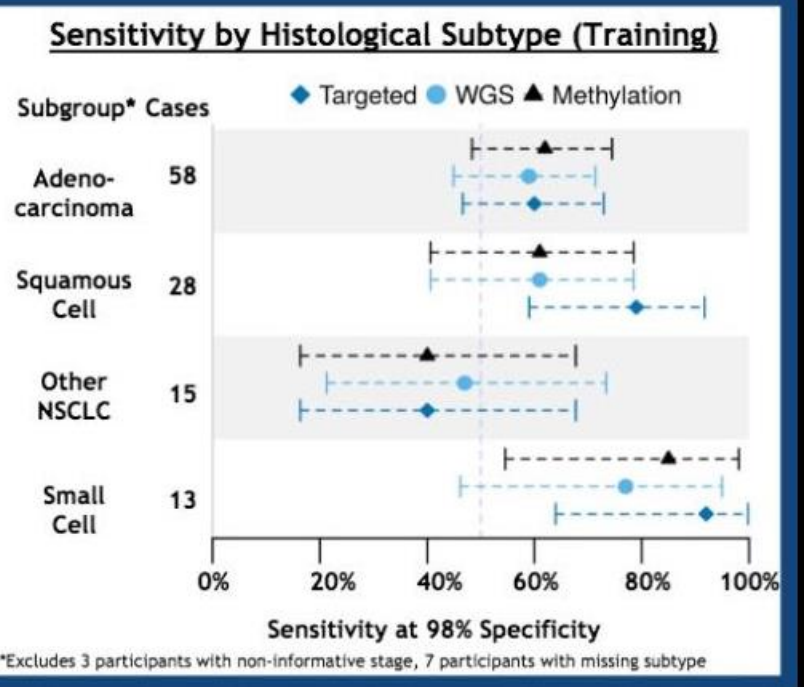




*Excludes 3 participants with non-informative stage

Consistent Biological Signal In Smokers and Non-Smokers and Across Histologies





Surgery a Key Modality for Curative-Intent Treatment of NSCLC

- Annual US resections: 69k (2003) to >86k (2012)[1]
- Projected to keep rising with LDCT screening
- Provides 70-85% of 5-year OS population
- Aggregate 5-year OS only ~50% after resection[2]
- pN stage a powerful prognosticator
  - pN0 49-78%; pN1 35-51%; pN2 28-40% 5-year OS[3]
- Why these ranges?

[1] Pingar, Stocks, Weiss, Steiner. Statistical Brief #186: Most Frequent Operating Room Procedures Performed in U.S. Hospitals, 2003-2012. Accessed March 2, 2018 at: ; [2] Chansky, Detterbeck, Nicholson et al. J Thorac Oncol 2017.12:1109-1121; [3] Osaroglagbon, Lin, Sineshaw, Jemal (manuscript in preparation).

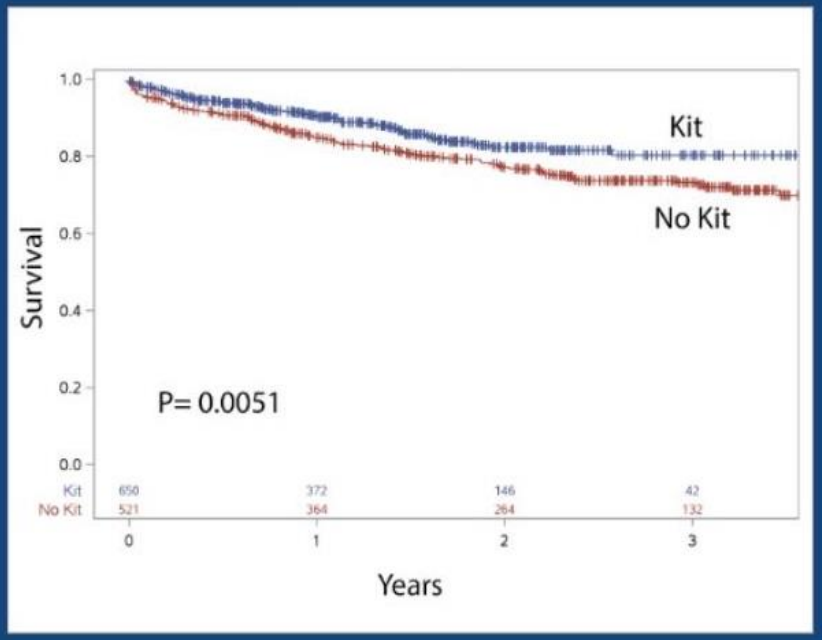
Conceptual Model: The Chain of Responsibility

Self-contained, with lid

Indicates 'mandatory' stations
Checklist
Pre-labelled with anatomic nomenclature

Station-specific containers
Color-coded, named, numbered

Survival: Kit v Non-Kit Resections



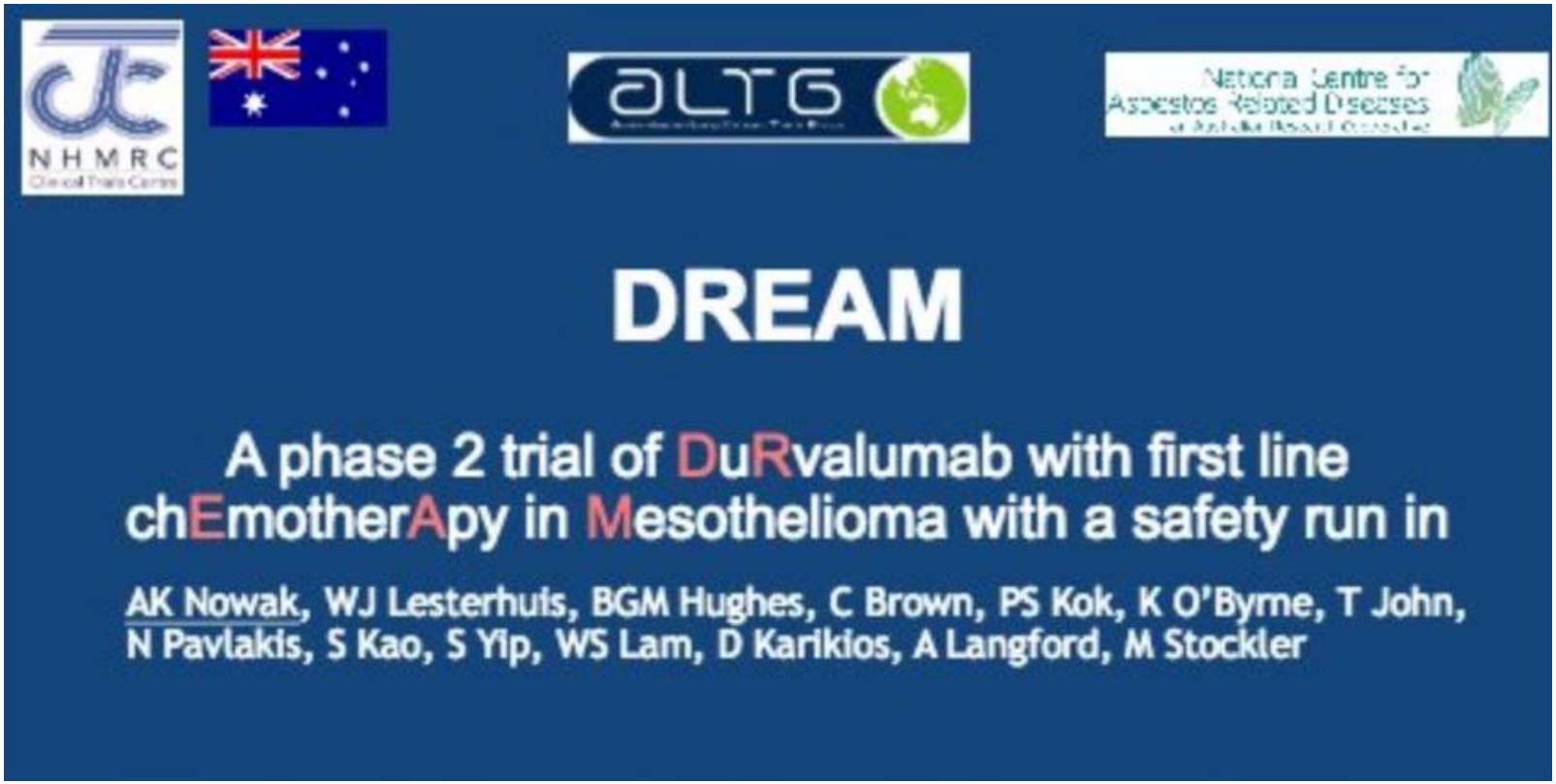
Proportional Hazards Models

Model	Hazard Ratio	P-Value
Crude	0.67 (0.50, 0.89)	.0054
Fully Adjusted* with Surgeon Clustering	0.57 (0.42, 0.77)	0.0003

Sensitivity Analyses

Model	Hazard Ratio	P-Value
Excluding Sub-lobar Resections*	0.61 (0.44, 0.85)	0.0030
Excluding Deaths within 60 days*	0.60 (0.40, 0.90)	0.0123
Only in Adopting Surgeons*	0.54 (0.38, 0.76)	0.0005
Crude- Only in Adopting Surgeons	0.58 (0.43, 0.79)	0.0005

* Fully Adjusted Models (for age, sex, histology, tumor grade, extent of resection, Pathologic t-stage, pathologic m-stage, number of comorbidities, and type of pathologic examination (a subgroup of patients in each group received a pathologic exam with a novel gross dissection method).


NHMRC
ALTG
DREAM
A phase 2 trial of DuRvalumab with first line chEmotherApy in Mesothelioma with a safety run in
AK Nowak, WJ Lesterhuis, BGM Hughes, C Brown, PS Kok, K O'Byrne, T John, N Pavlakis, S Kao, S Yip, WS Lam, D Karikios, A Langford, M Stockler

Aim

To determine the activity of durvalumab combined with cisplatin and pemetrexed

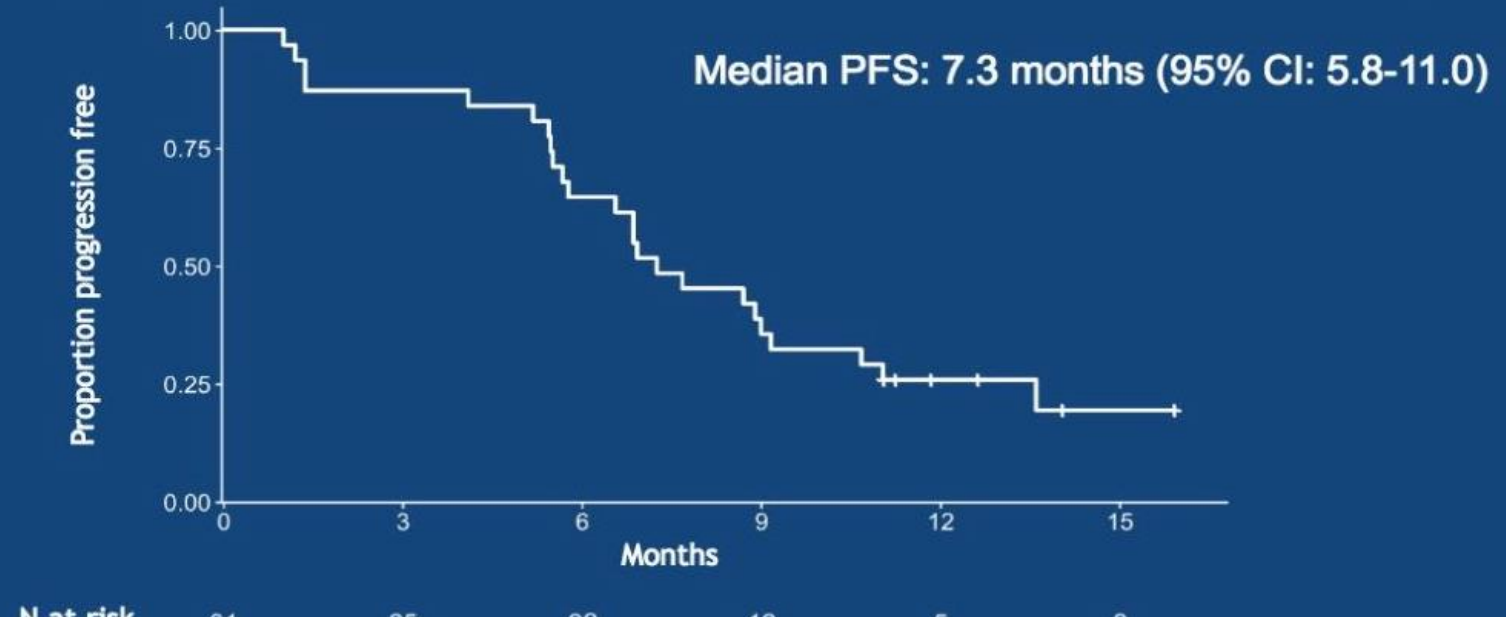
Study Design

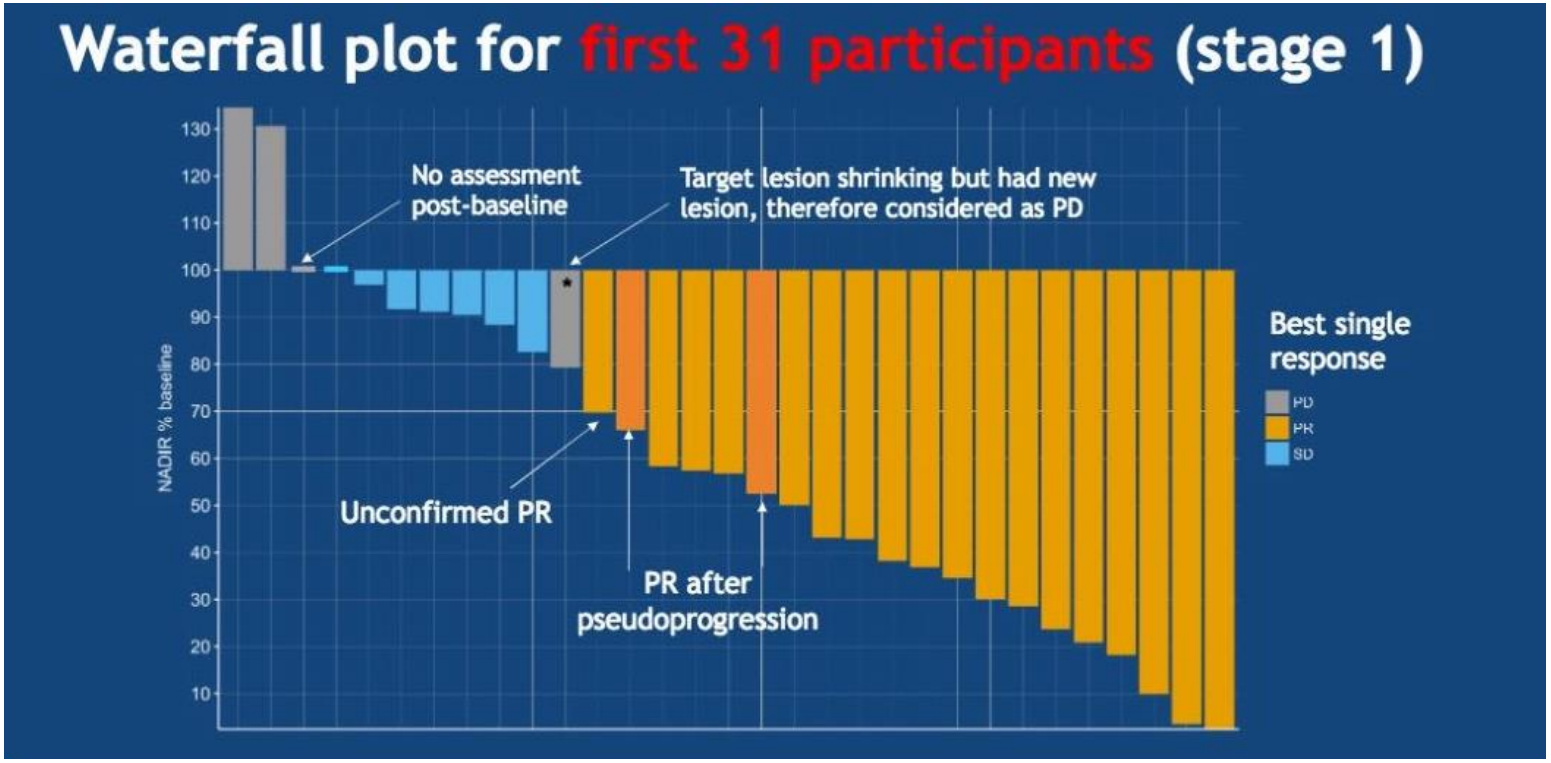
Phase 2, open-label, single arm, multi-centre study with a safety run-in

Simon's 2-stage design

Reporting primary endpoint for stage 1 patients today

Progression free survival 6 months = 65% (n=31)




Waterfall plot for first 31 participants (stage 1)
NADIR % baseline
130
120
110
100
90
80
70
60
50
40
30
20
10
No assessment post-baseline
Target lesion shrinking but had new lesion, therefore considered as PD
Unconfirmed PR
PR after pseudoprogression
Best single response
PD
PR
SD

NIH National Cancer Institute

Inherited Predisposition to Malignant Mesothelioma due to Mutations in DNA Repair Genes

Raffit Hassan, Betsy Morrow, Tom Walsh, Ming K. Lee, Suleyman Gulsuner, Shaojian Gao, Idrees Mian, Javed Khan, Mark Raffeld, Snehal Patel, Liqiang Xi, Jun S. Wei, Mary Hesdorffer, Jingli Zhang, Kathleen Calzone, Emerson Padiernos, Christine Alewine, David S. Schrump, Seth Steinberg, Anish Thomas, and Mary-Claire King.

Germline mutations by age at diagnosis

Age (years)	Patients with mutation
≤ 40 :	2 / 35
41-60 :	22 / 100
≥61 :	6 / 106

Patients with *BAP1* were more likely to be age 60 yrs. or younger (94% versus 5%; p=0.0003)

Pleural mesothelioma (n = 140)

Germline mutation in 14 patients (10%)

Females: 11 of 42 (26%) pts had germline mutation

Males: 3 of 98 (3%) pts had germline mutation

p=0.0001

Mutations in Females
- 9 with *BAP1*
- 1 with *TP53*
- 1 with *MRE11A*

Mutations in Males
- 3 with *CHEK2*

Peritoneal mesothelioma (n = 92)

Germline mutation in 15 patients (16%)

Females: 5 of 39 (13%) pts had germline mutation

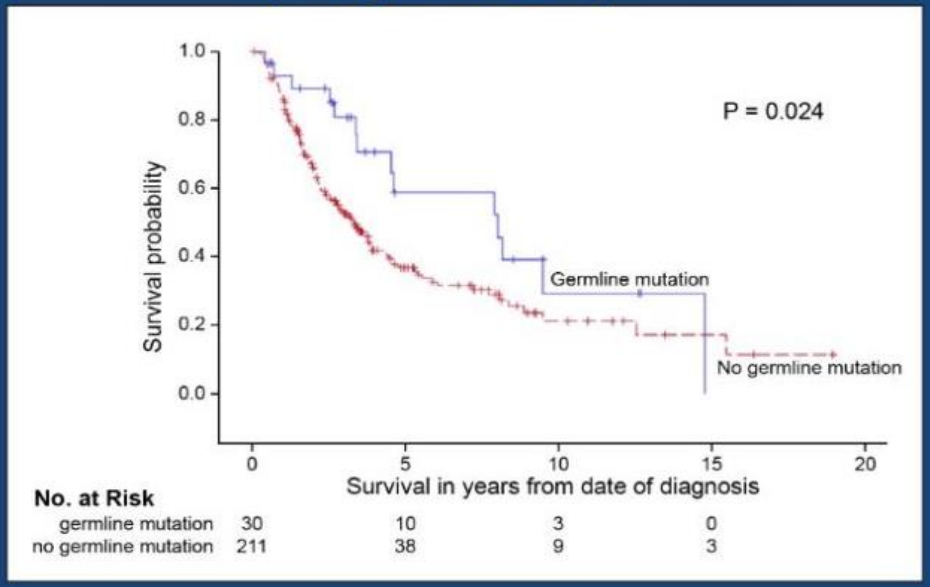
Males: 10 of 53 (19%) pts had germline mutation

Mutations in Females
- 2 with *CHEK2*
- 2 with *PALB2*
- 1 with *BAP1*

Mutations in Males

8 with *BAP1*
- 1 with *MLH1*
- 1 with *POT1*

Germline mutations and overall survival (All patients)



- Abstract 8506: Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158.
- Abstract 8507: Efficacy and safety of rovalpituzumab tesirine in patients with DLL3-expressing, ≥ 3rd line small cell lung cancer: Results from the phase 2 TRINITY study.

Immunotherapy for relapsed SCLC

Agent	RR	PFS (months)	OS (months)
Nivolumab	10%	1.4	4.4
Nivolumab (1 mg/kg) + Ipilimumab (3 mg/kg)	14%	2.6	7.7
Nivolumab (3 mg/kg) + Ipilimumab (1 mg/kg)	10%	1.4	6
Pembrolizumab	18.7% (PD-L1 +ve - 35.7%)	2	9.1 (PD-L1 +ve – 14.9)

Targeted agents for relapsed SCLC

Agent	RR	PFS (months)	OS (months)
Pazopanib	14%	2.5	6
Alisertib	21%	2	NR
Sorafenib	6%	2	6
Sunitinib	9%	1.4	5.6
Rovalpituzumab - tesirine	12.4% (DLL-3 high 24%)	3.9	5.6 (DLL-3 high 5.7)