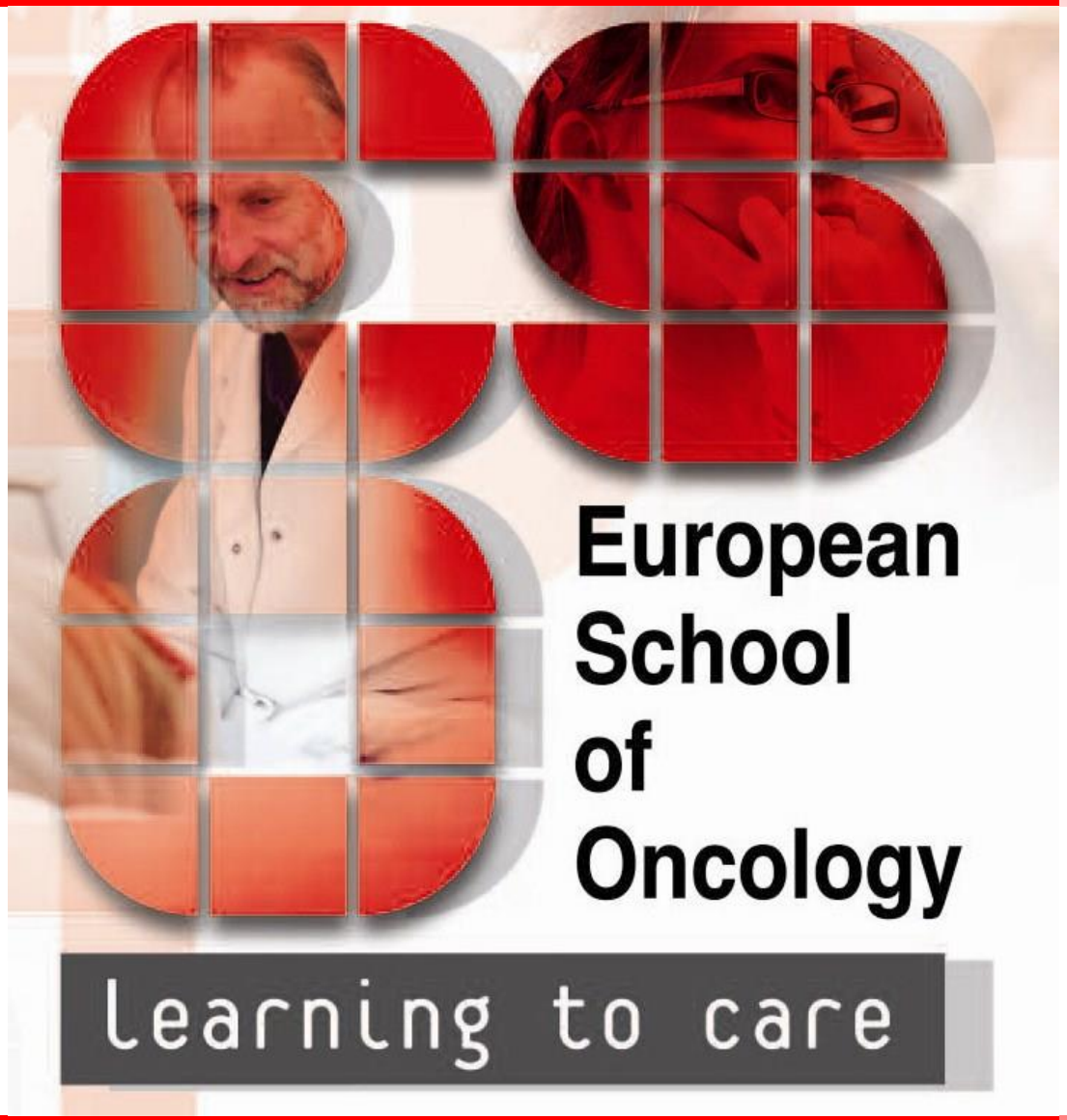

European
School
of
Oncology
learning to care

ESO OBSERVATORY

3RD ESO LUNG CANCER OBSERVATORY:

Innovation and care in the next 12 months

15 April 2016
Geneva, Switzerland

Chairs: M.S. Aapro, CH - E. Felip, ES

The Observatory will be held during the
ELCC 2016 European Lung Cancer Conference

16:45 - 18:15
Palexpo, Room W

For information on other ESO events visit
www.eso.net

European School of Oncology
Learning to care

PANELLISTS

M.S. Aapro
Clinique de Genolier, CH

E. Felip
Vall d'Hebron University Hospital, Barcelona, ES

F. Johansson
Swedish Lung Cancer Association "Stodet", Stockholm, SE

K. Kerr
Aberdeen Royal Infirmary, Foresterhill, Aberdeen, UK

F. Mornex
Centre Hospitalier Lyon Sud, FR

U. Pastorino
Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, IT

Chairs: M.S. Aapro, CH - E. Felip, ES

TOPICS

Screening and surgery advances
U. Pastorino IT

Therapeutic management of unresectable stage III NSCLC: an update
F. Mornex, FR

Anti-PD1 and anti-PDL1 strategies in NSCLC: Their potential role in NSCLC treatment
E. Felip, ES

Predictive markers in NSCLC
K. Kerr, UK

Long-term lung cancer survivors: Patient needs
F. Johansson, SE

Attendance is granted to all participants registered to the ELCC 2016 European Lung Cancer Conference.

The conclusion of the Observatory will be made available on the ESO website www.eso.net

Detailed information available at: www.eso.net

elcc European Lung Cancer Conference

2015-2016 Predictions

- More effective systemic therapies are needed to improve outcomes of patients diagnosed with small cell lung cancer.
- The in 2016 expected results of the NELSON trial will hopefully open the way for low-dose CT lung cancer screening in Europe.
- Immunotherapy is a new standard of care in advanced NCSLC
- The time that you and I live in, is truly the IT-boom of drug development and early diagnostics. The fast, impressive, science gives lots of hope to all people affected. The challenge is for administrators to let efficiently new drugs reach the many in need.

3rd ESO Lung Cancer Observatory: Innovation and care in the next 12 months

Friday 15th April 2016, 16.45 – 18.15

Panellists:

Ugo Pastorino, IT
Françoise Mornex, FR
Enriqueta Felip, ES
Keith Kerr, UK
Fredrik Johansson, SE

Chair: M.S. Aapro, CH – E. Felip, ES

3rd ESO Lung Cancer Observatory: Innovation and care in the next 12 months

Ugo Pastorino

Istituto Nazionale per la Cura e lo Studio del Tumori

Milan, Italy

View of a Surgical Oncologist

EUROPEAN LUNG CANCER
CONFERENCE 2016

3rd ESO Lung Cancer Observatory:
Innovation and Care in the next 12 months

SCREENING AND SURGERY ADVANCES

Ugo Pastorino

Thoracic Surgery, Istituto Nazionale Tumori, Milan

15 YEARS OF LDCT SCREENING:

CONSISTENT DETECTION RATES HIGH FREQUENCY OF STAGE I

		screened	positive CT	LC	stage I
non RCT	16	71,935	21%	1.0%	78%
all RCTs	8	44,629	23%	1.1%	62%
NLST alone		26,309	25%	1%	63%

SIGNIFICANT MORTALITY REDUCTION: - 1% / YEAR

LARGE SCALE SCREENING: WHICH IS THE BEST DESIGN ?

POOLED ANALYSIS OF ALL EUROPEAN RCTs IS ESSENTIAL

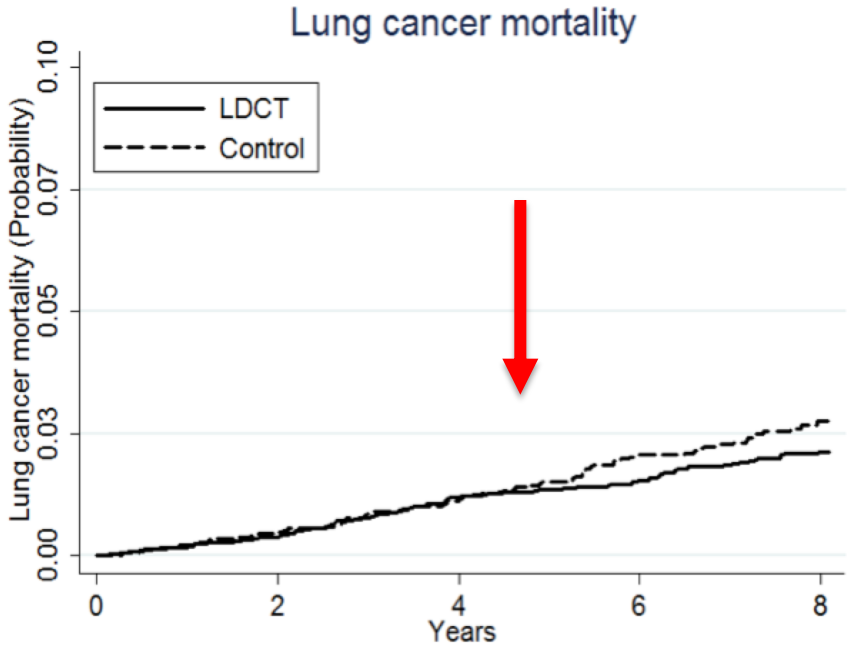
Lung cancer screening: European randomised LDCT trials

Study	Country	Year started	Subjects enrolled	Recruitment	Age	# CT	Years screening
DANTE	IT	2001	2,811	volunteers	60-74	5	5
NELSON	NL–B	2003	15,822	registry	50-74	3	4
ITALUNG	IT	2004	3,206	GPs	55-69	4	4
DLCST	DK	2004	4,104	volunteers	50-70	5	5
MILD	IT	2005	4,099	volunteers	49-75	4-8	8
LUSI	D	2007	4,052	population	50-69	5	5
UKLS	UK	2011	4,055	registry	50-75	1	1
Total			**38,149**				

POOLED ANALYSIS OF DANTE & MILD TRIALS

6,549 PARTICIPANTS, 52,637 PY, 520 DEATHS

non-significant 11% reduction of overall mortality in LDCT arm
as compared to control arm, HR = 0.89 (95% CI: 0.74-1.06)



EUR J CAN PREV, IN PRESS

elcc

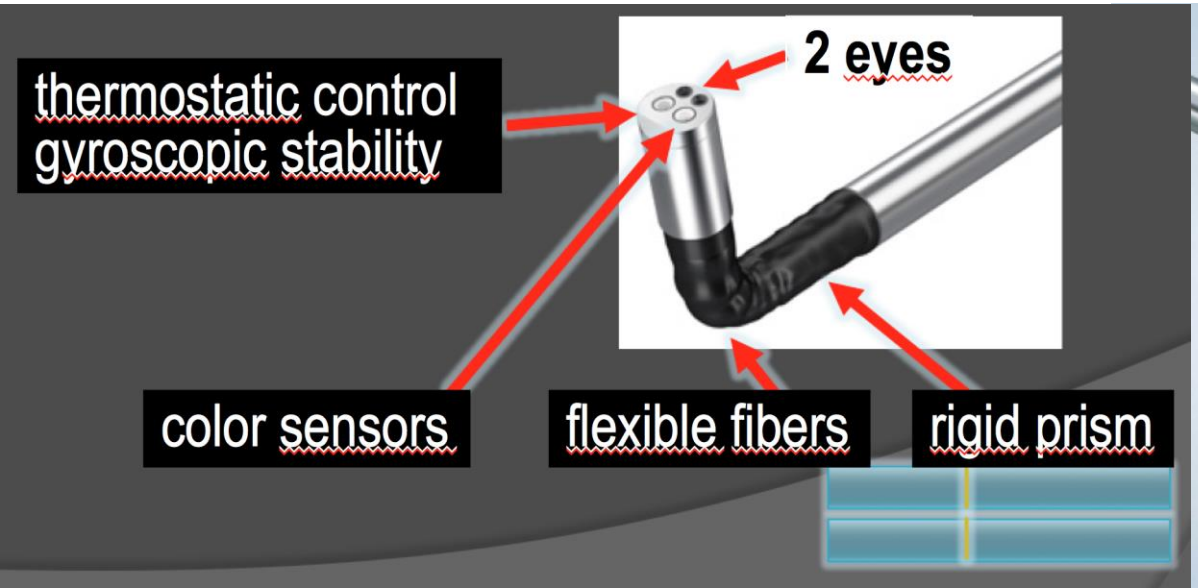
EUROPEAN LUNG CANCER CONFERENCE 2016

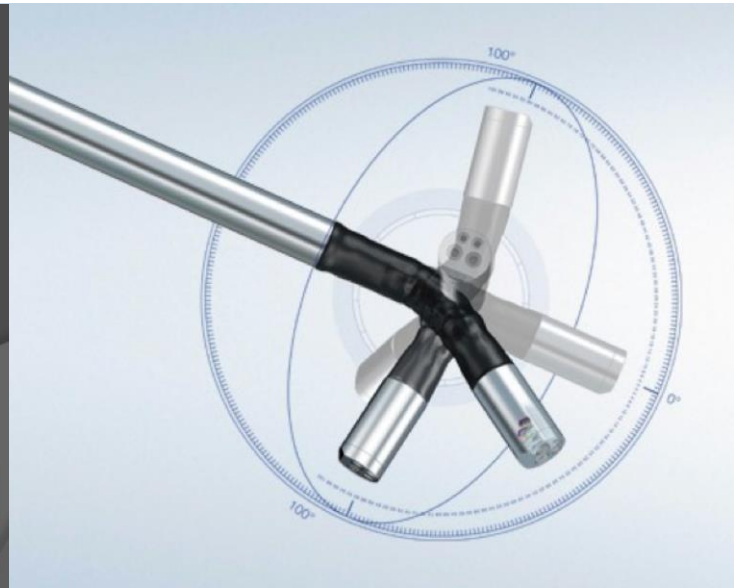
LDCT SCREENING IN 2016: SUMMARY

- good prospects for targeted screening
- pooled analysis of European RCTs essential to improve individual selection (biologic) and define best diagnostic algorithm
- biomarkers validation on-going
- action for quitting can improve outcome

LDCT & LUNG CANCER SURGERY

- minimally invasive approach is the standard
- VATS lobectomy feasible in > 90% of cases
- 3N1 + 3N2 stations must be excised
- new 3D technology has improved performance





2016-2017 Predictions

3rd ESO Lung Cancer Observatory: Innovation and care in the next 12 months

Françoise Mornex, MD, PhD

Université Claude Bernard

Centre Hospitalier Sud

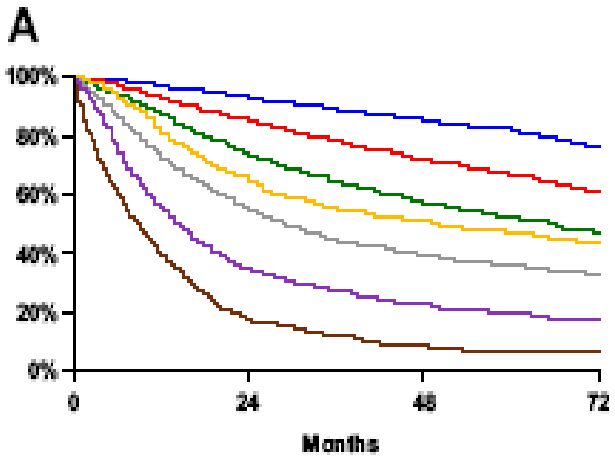
Lyon, France

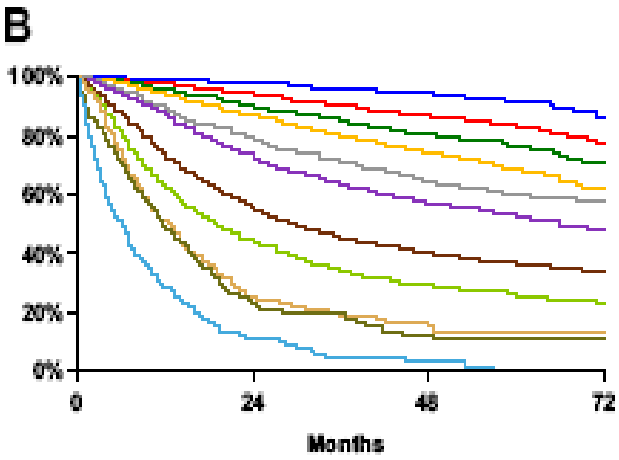
View of a Radiation Oncologist

Therapeutic management of unresectable Stage III NSCLC

Françoise Mornex, MD, PhD
Université Claude Bernard, LYON.
Centre Hospitalier Lyon Sud, LYON, France, EMR 3738.

1-IASLC Staging project: the proposed eighth Edition





7th Ed.	Events / N	MST	24 Month	60 Month
IA	1119 / 6303	NR	93%	82%
IB	768 / 2492	NR	85%	66%
IIA	424 / 1008	66.0	74%	52%
IIB	382 / 824	49.0	64%	47%
IIIA	2139 / 3344	29.0	55%	36%
IIIB	2101 / 2624	14.1	34%	19%
IV	664 / 882	8.8	17%	6%

Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

Figure 2. Overall survival by clinical stage according to the seventh edition (*A*) and the proposed eighth edition (*B*) groupings using the entire database available for the eighth edition. MST, median survival time. Survival is weighted by type of database submission: registry versus other.

2-IMRT as a tool to improve heart tolerance to high dose radiation

RTOG 0617

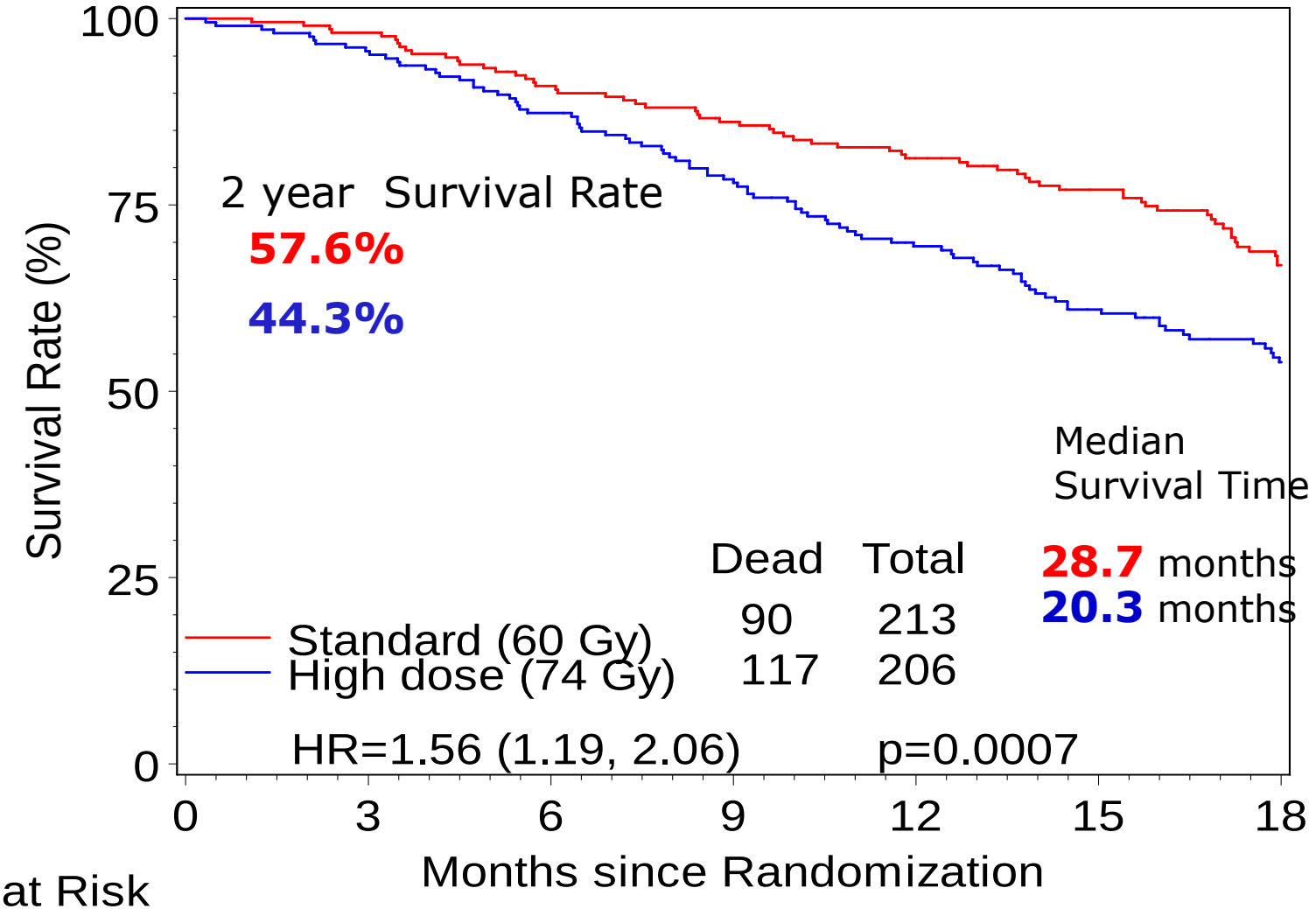
A Randomized Phase III Comparison of Standard-Dose (60 Gy) Versus High-Dose (74 Gy) Conformal Radiotherapy with Concurrent and Consolidation Carboplatin/Paclitaxel +/- Cetuximab In Patients with Stage IIIA/IIIB Non-Small Cell Lung Cancer (NSCLC)

Presenting Author: Jeffrey D. Bradley, MD

NCI Sponsored Cooperative Groups:
RTOG, NCCTG, CALGB

Jeffrey D Bradley, Rebecca Paulus, Ritsuko Komaki, Gregory A. Masters, Kenneth Forster, Steven E. Schild, Jeffrey Bogart, Yolanda I. Garces, Samir Narayan, Vivek Kavadi, Lucien A Nedzi, Jeff M. Michalski, Douglas Johnson, Robert M MacRae, Walter J Curran, and Hak Choy

RTOG 0617 Overall Survival



420 pts

Patients at Risk

Standard	213	207	190	177	161	141	108
High dose	206	197	178	159	135	112	87

RTOG 0617:Multivariate Cox Model Backwards Selection

Covariate	Comparison	HR (95% CI)	p-value
Radiation dose	**60Gy v 74 Gy**	**1.55 (1.07, 2.23)**	**0.020**
Histology	**Non-squam v Squam**	**1.37 (0.94, 1.98)**	**0.097**
Gross Tumor Volume	**Continuous**	**1.002 (1.000, 1.003)**	**0.034**
Heart V5	**Continuous**	**1.010 (1.004, 1.017)**	**0.002**

Exit criteria = p>0.10; radiation dose and histology forced to remain
Covariates dropped from the model were: gender, age, lung V5.

RTOG undertook a careful re-analysis of all heart contours and doses received by the heart.

IASLC

Heart Dose in RTOG 0617: IMRT vs. 3D RT

- 53% of patients in RTOG 0617 received 3D RT and 47%, IMRT
- The IMRT group had more Stage IIIB patients; larger PTVs (486 mL vs. 427 mL) and larger PTV: lung ratio than the 3D RT group
- In spite of the above, IMRT was associated with:

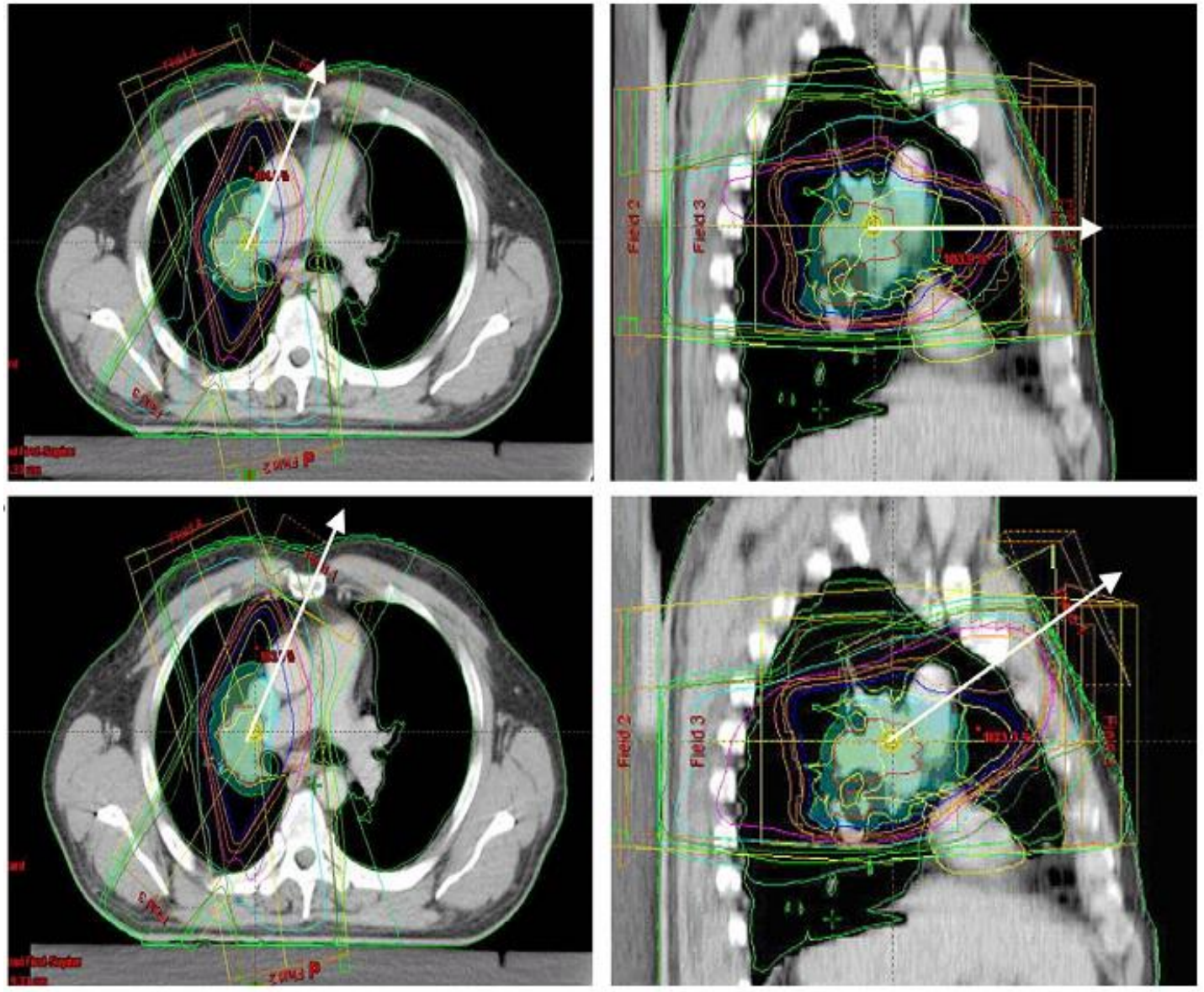
Outcome	3D-CRT	IMRT	P-value
Grade 3+ pneumonitis	8%	3.5%	0.0462
Heart V40	11.4%	6.8%	0.0026

- Conclusion: **"IMRT is able to lower heart dose as compared to 3D RT"** (no difference in OS/PFS between IMRT and 3D RT)

Chun S et al, Oral #20, IASLC 2015

IASLC

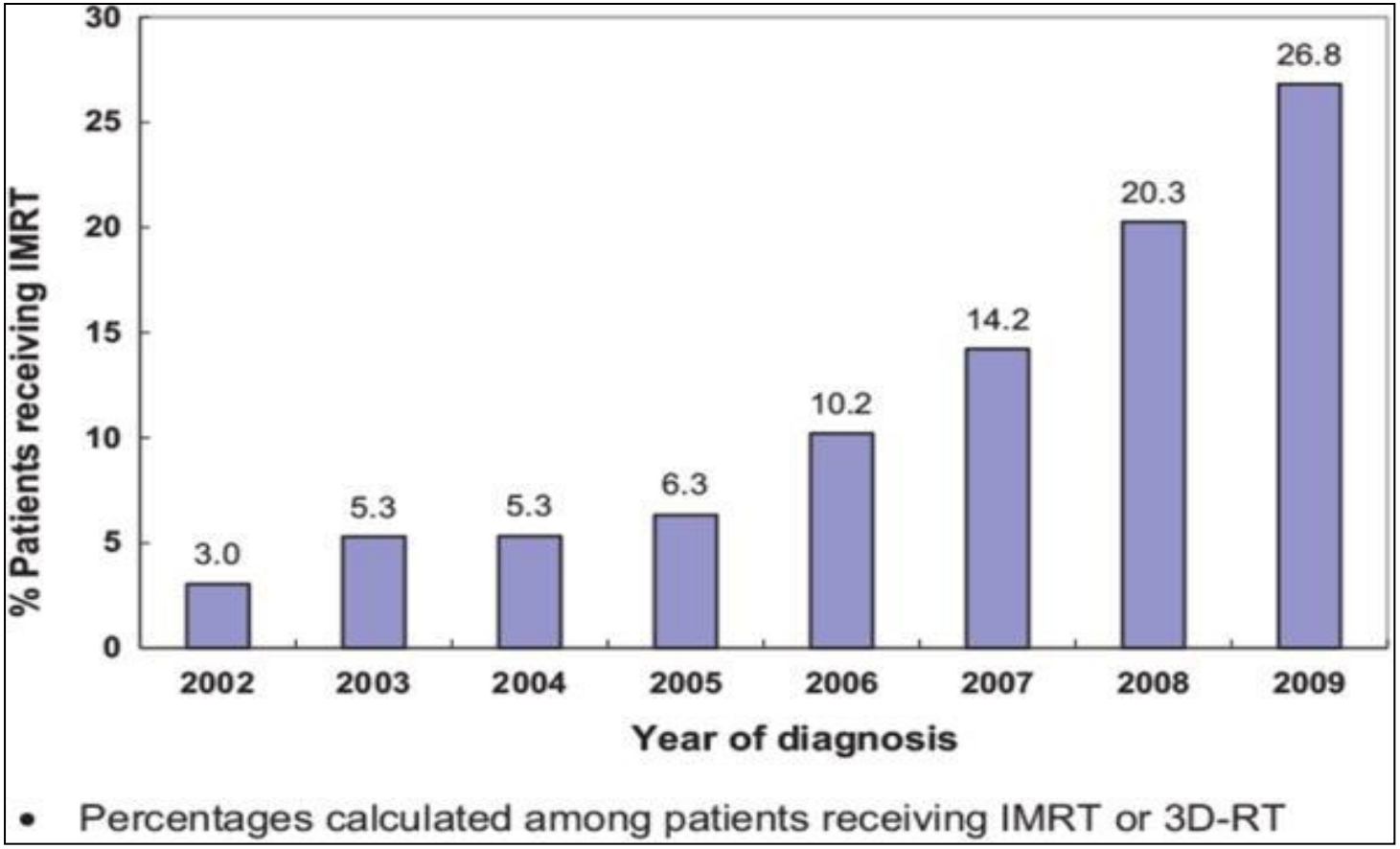
IMRT to reduce the heart dose



Effect of Heart Dose on Survival

Study	Prescription RT Dose	Conclusions	Reference
IDEAL-CRT (Univ. College London)	Mean 67.5 Gy Maximum 73 Gy (30 fractions, isotoxic)	**Strong association between lower OS and heart volumes receiving 65-75 Gy**	Mini33.02: IASLC 2015 (Counsell N)
NKI Amsterdam (retrospective)	66 Gy in 2.75 Gy fractions	**Strong association between lower OS and higher heart doses**	Mini33.03: IASLC 2015 (Belderbos J)

Comparative Effectiveness of Intensity-Modulated Versus 3D Conformal RT Among Patients with Stage III Lung Cancer

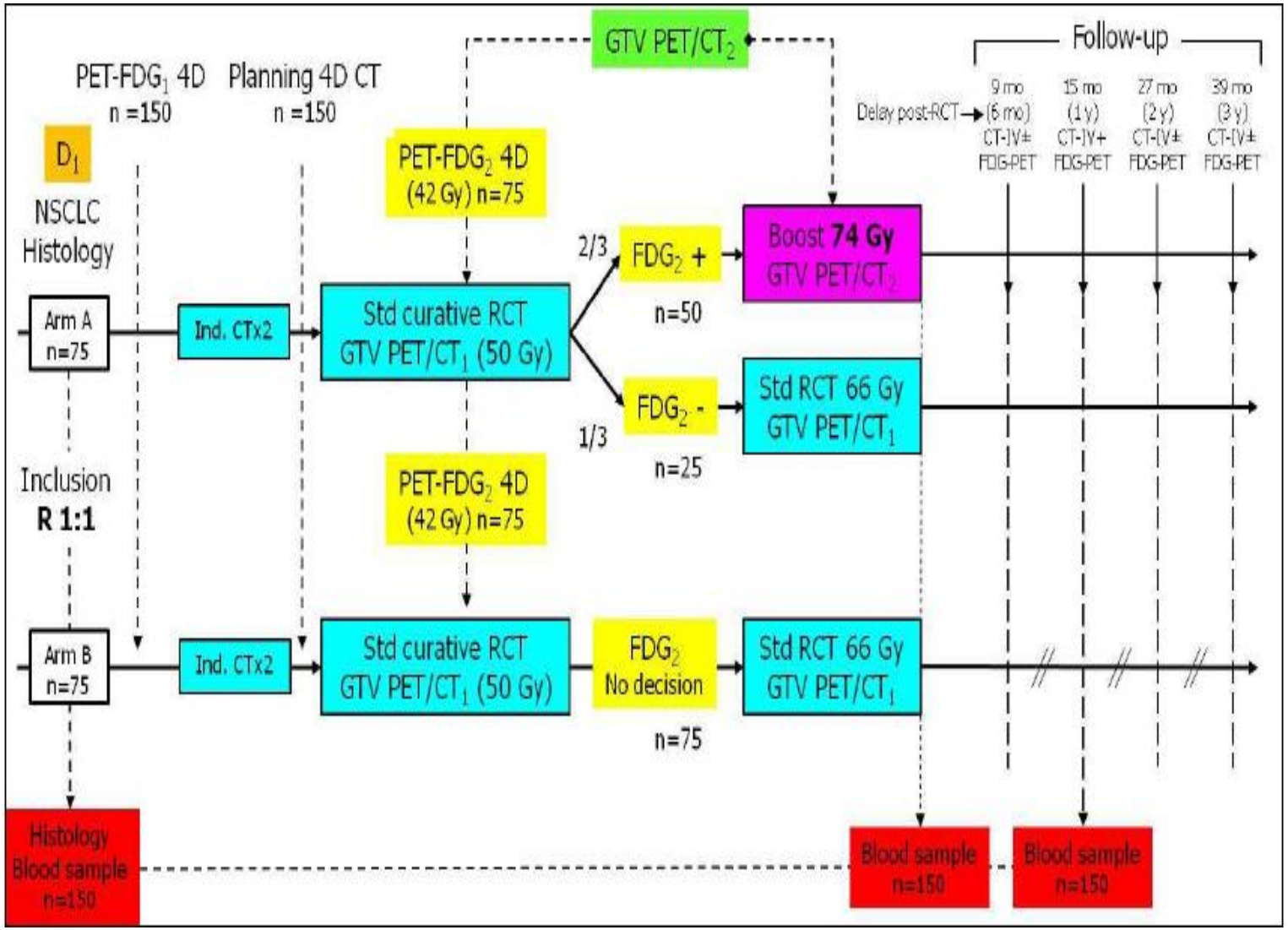


Chen, Aileen, Ling; Cronin, Angel; Schrag, Deborah; JCO. 9(12):1788-1795, 2014

3-"Metabolic irradiation".

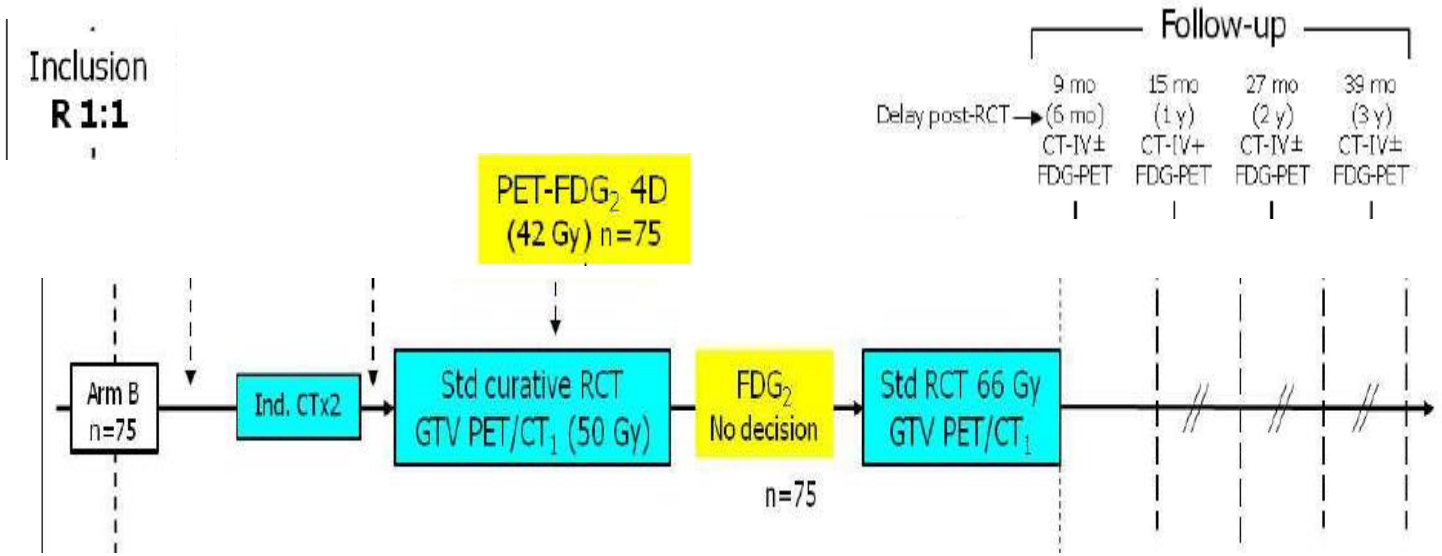
PET-CT contribution:
Response evaluation
and a tool for RT dose escalation?

RTEP 7 – Schéma d'étude



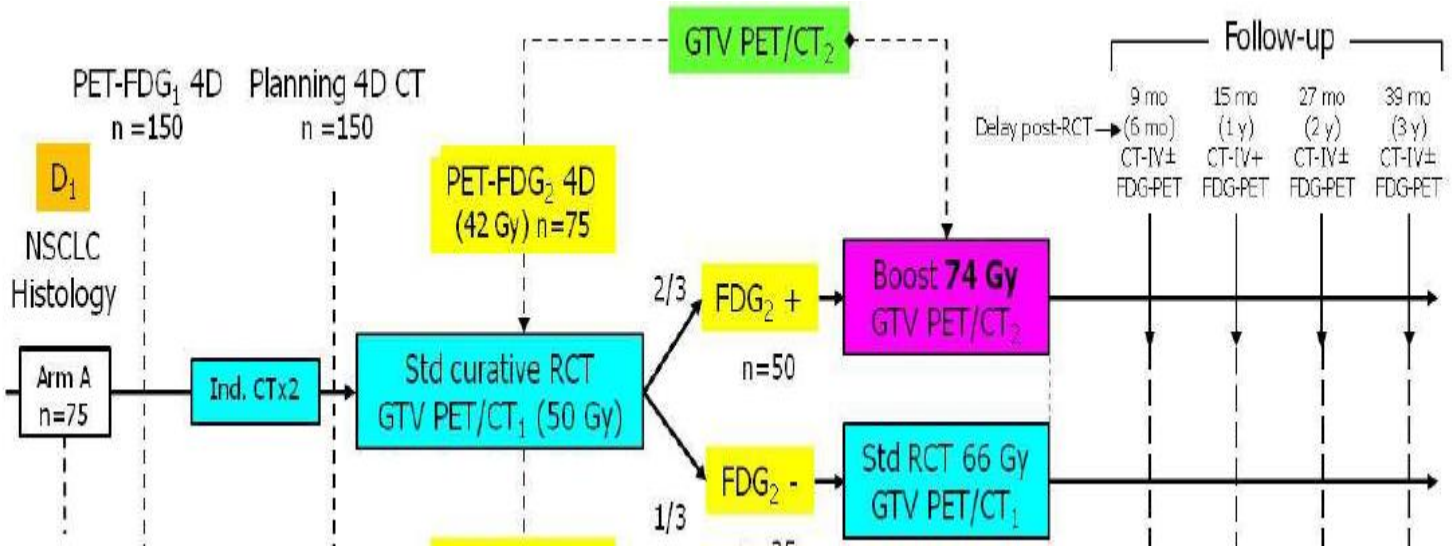
RTEP 7 – Schéma d'étude

BRAS STANDARD = BRAS B
66 Gy en 33 fractions de 2 Gy en 7 semaines

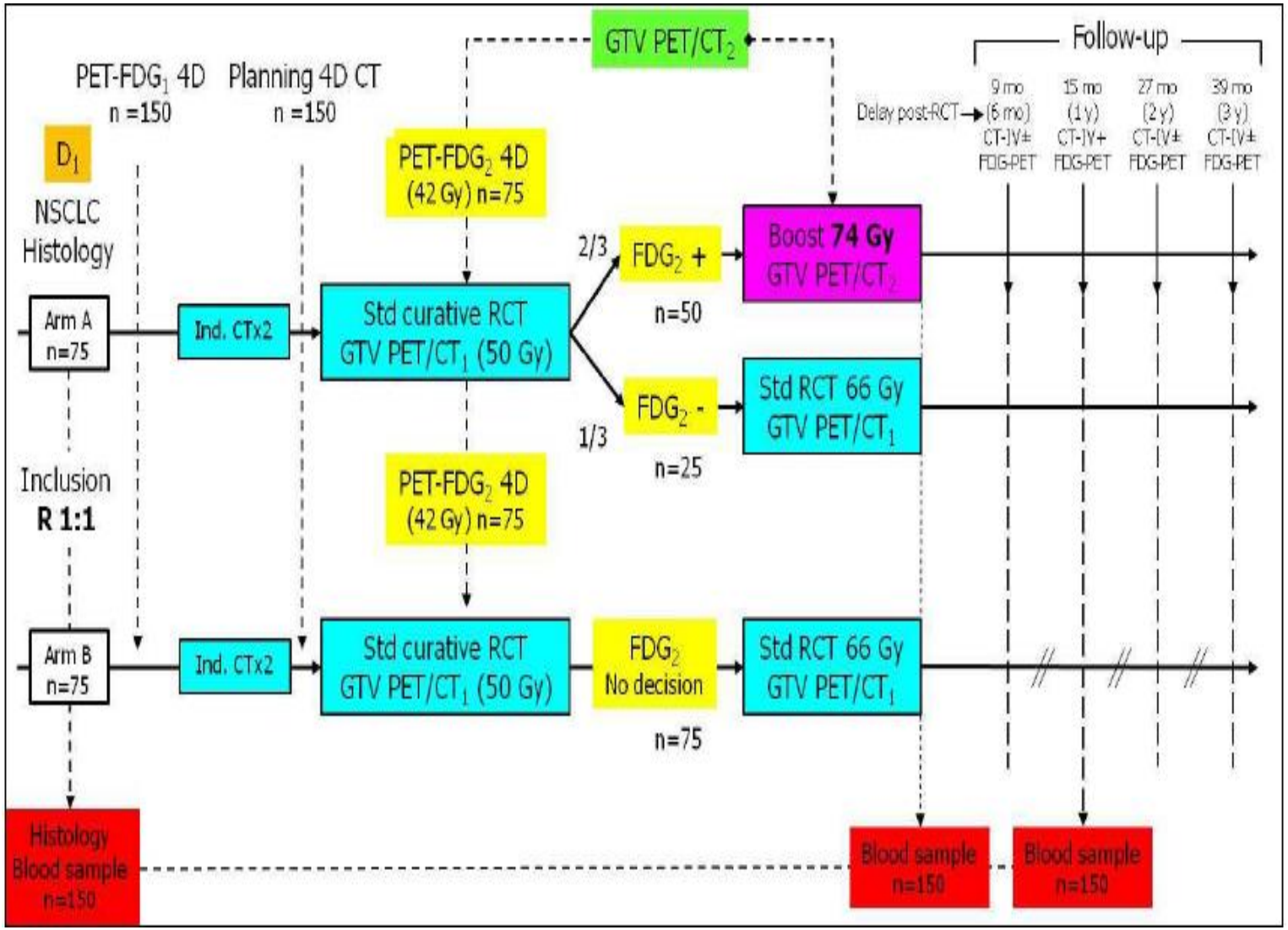


RTEP 7 – Schéma d'étude

BRAS EXPERIMENTAL = BRAS A
Augmentation de dose à 74 Gy si PET–FDG POSITIF à 42 Gy



RTEP 7 – Schéma d'étude

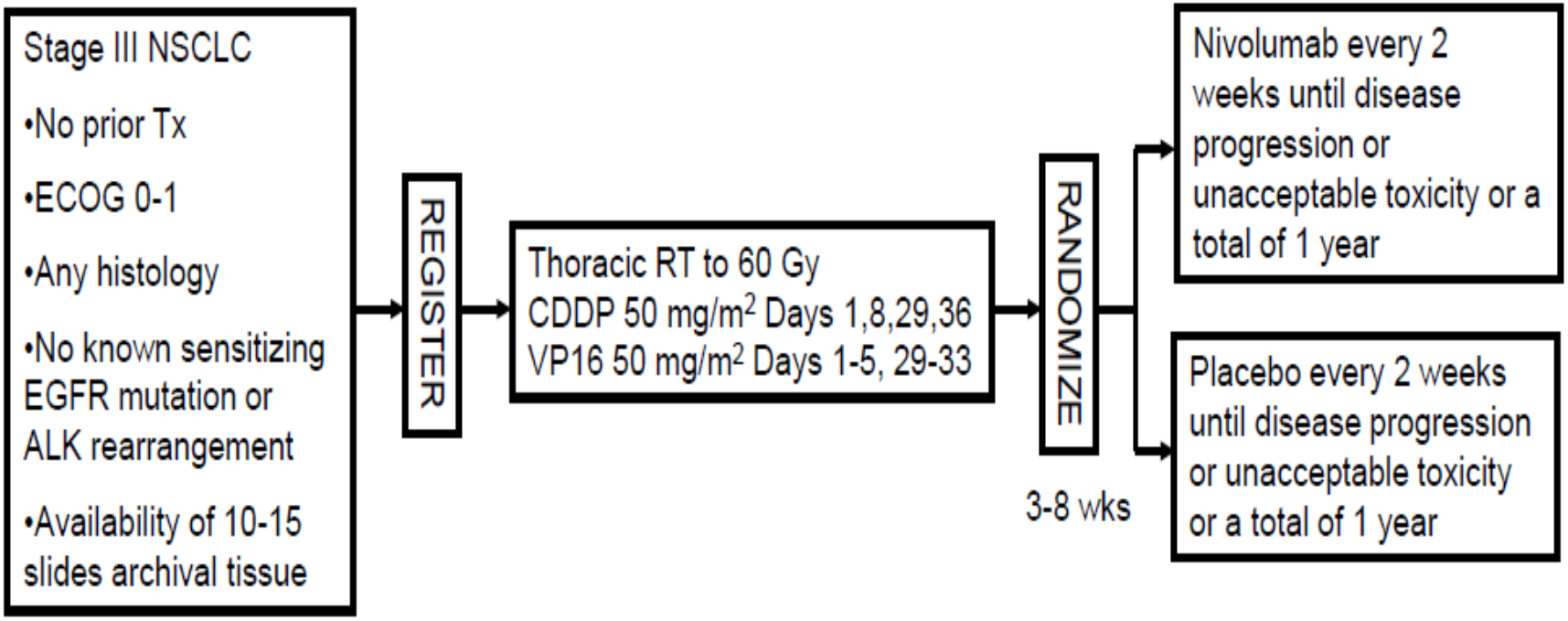


4. Trials with new targeted agents not yet successful, but promising!!

Stage IIIA/B NSCLC trials in progress or planned with rational strategies including targeted agents

- Metformin
- PDL, PDL1 alone (pembrolizumab, MED14736, nivolumab)
- Combinations of immunotherapy agents
- Tecemotide (L-BLP25)+ bevacizumab
- Trametinib (MEK)
- EGFR and ALK positive population only (antibodies, TKIs)

RTOG Foundation



RT ⇨ Nivolumab

IASLC 40 YEARS

2016-2017 Predictions

3rd ESO Lung Cancer Observatory: Innovation and care in the next 12 months

Enriqueta Felip

Vall d'Hebron University Hospital

Barcelona, Spain

View of a Medical Oncologist

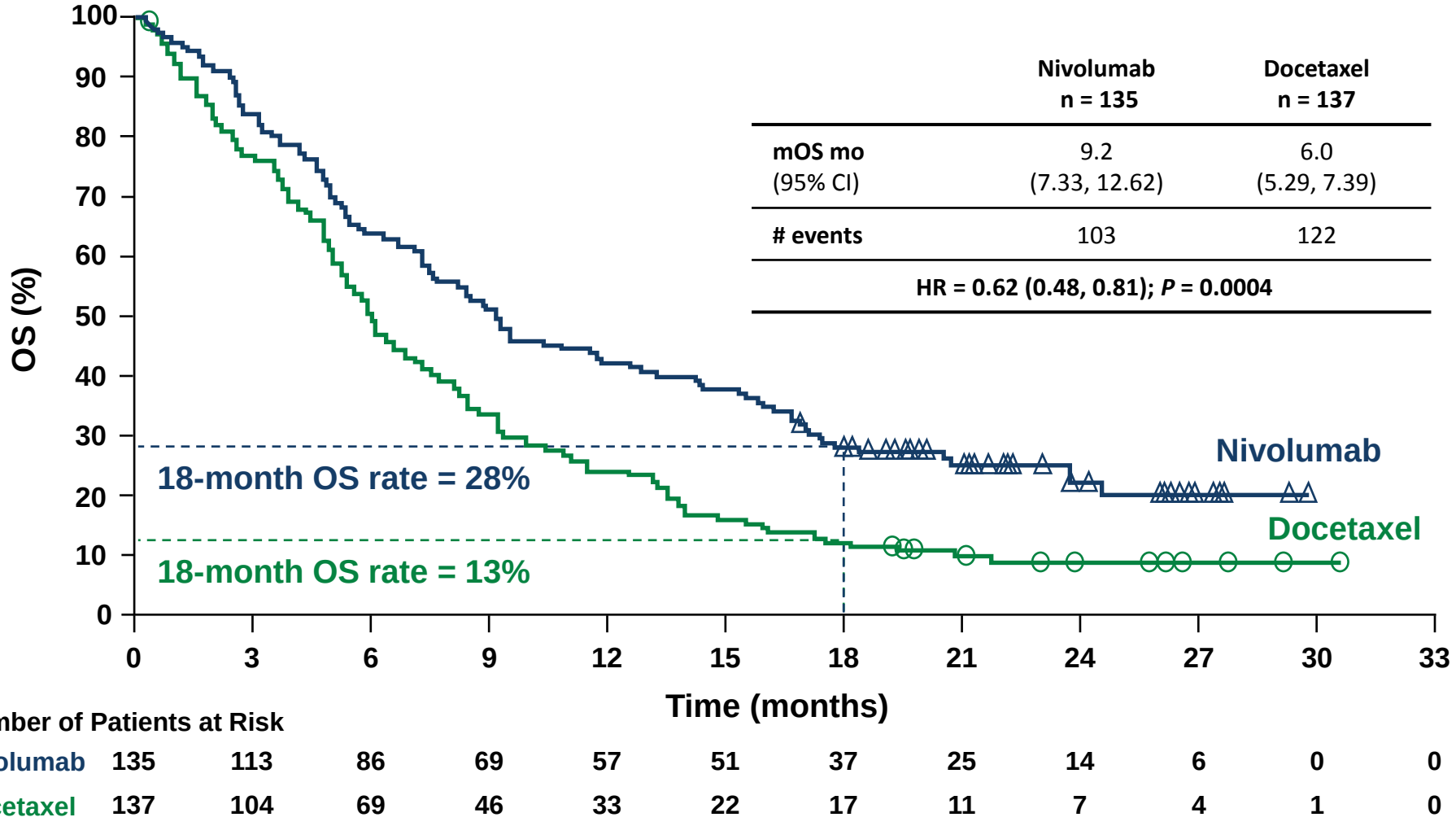
3rd ESO Lung Cancer Observatory: innovation and care in the next 12 months

Anti-PD1 / anti-PDL1 strategies in NSCLC: Their potential role in NSCLC treatment

Enriqueta Felip
Vall d'Hebron University Hospital
Barcelona, Spain

ELCC, Geneva, Switzerland 13-16 April 2016

CheckMate 017: updated overall survival



	Nivolumab n = 135	Docetaxel n = 137
mOS mo (95% CI)	9.2 (7.33, 12.62)	6.0 (5.29, 7.39)
# events	103	122
HR = 0.62 (0.48, 0.81); *P* = 0.0004		

Number of Patients at Risk

Nivolumab	135	113	86	69	57	51	37	25	14	6	0	0
Docetaxel	137	104	69	46	33	22	17	11	7	4	1	0

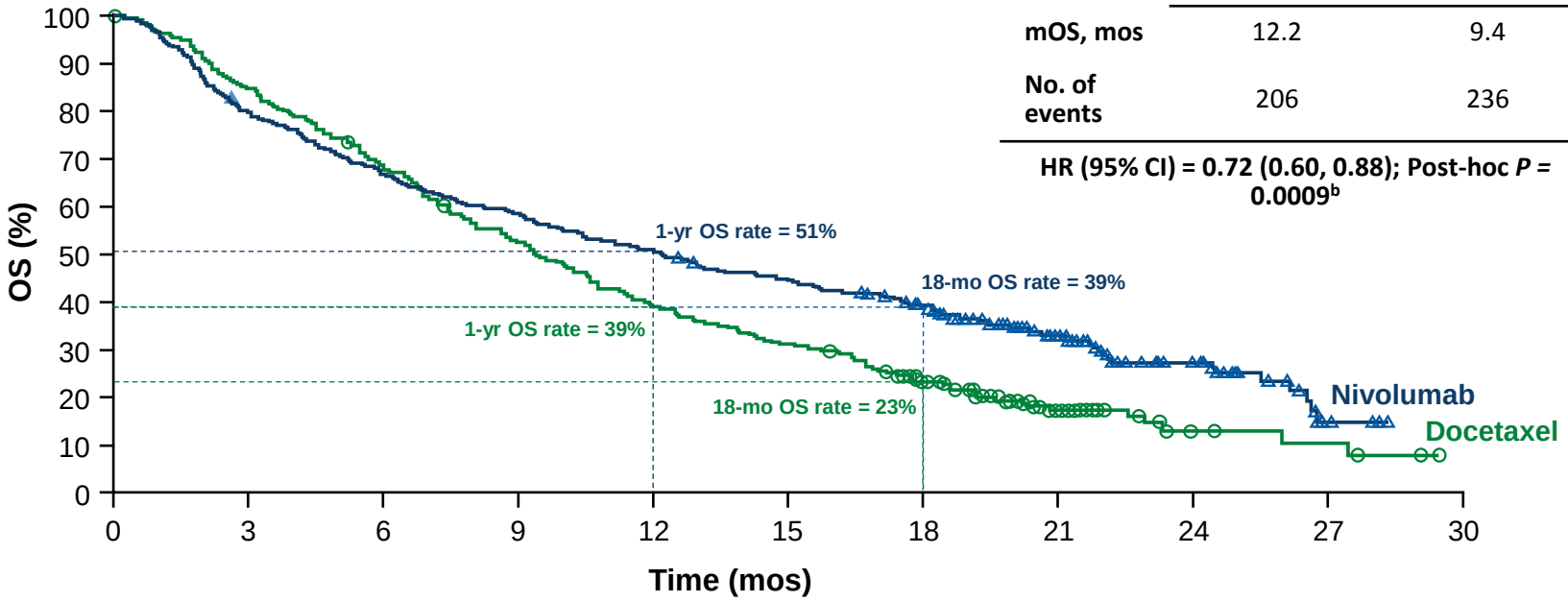
Based on August 2015 DBL.
Symbols refer to censored observations.

Reckamp K, et al. WCLC. 2015. Abstract 736

CheckMate 057: updated overall survival

	Nivo (n = 292)	Doc (n = 290)
mOS, mos	12.2	9.4
No. of events	206	236

HR (95% CI) = 0.72 (0.60, 0.88); Post-hoc *P* = 0.0009[b]



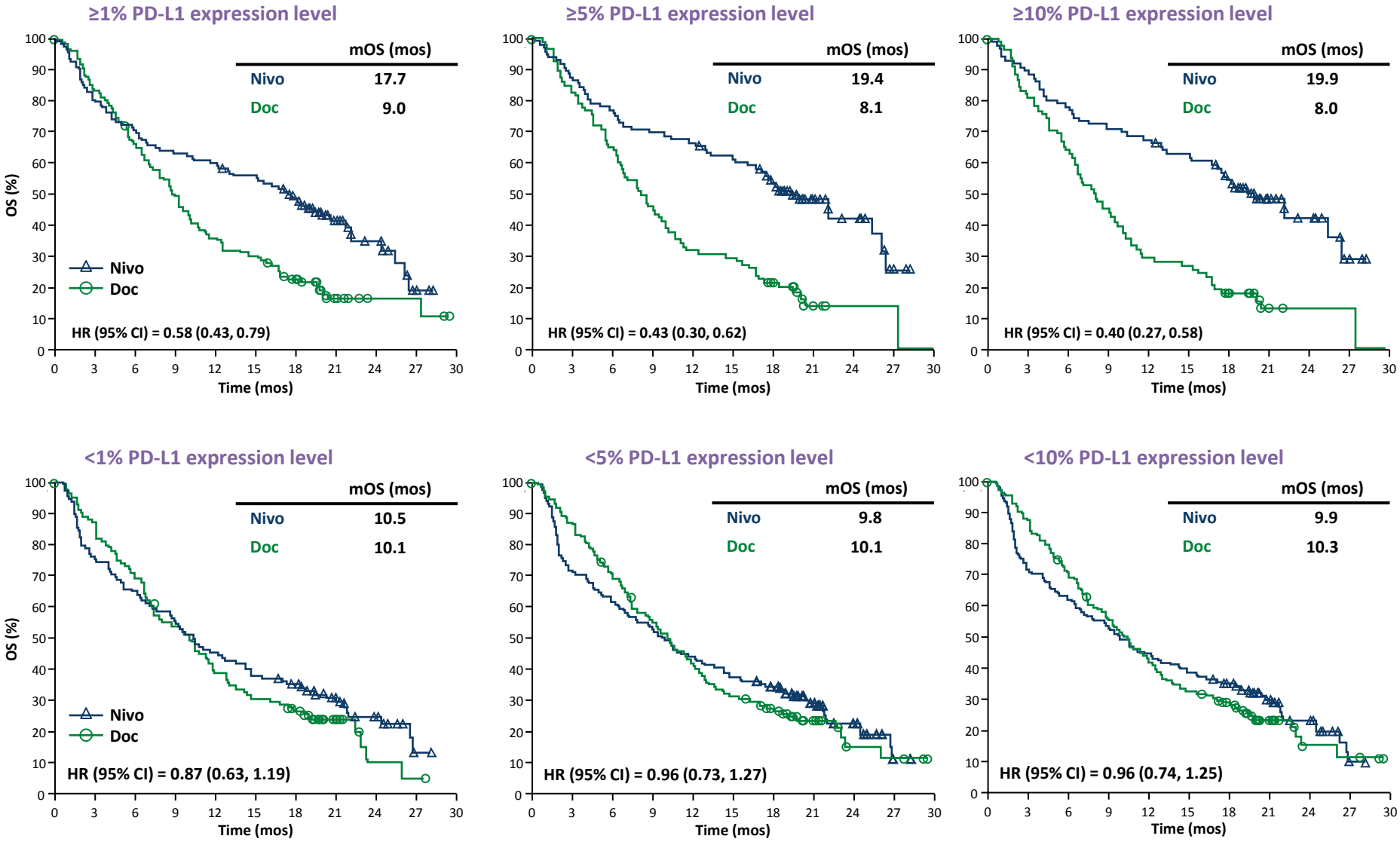
No. of patients at risk (18-mo OS)[b]

Nivolumab	292	233	195	171	148	128	107	55	27	4	0
Docetaxel	290	244	194	150	111	89	61	23	6	4	0

[a]Based on a July 2, 2015, DBL; [b]The formal primary end point testing was based on the interim analysis (March 18, 2015).
HR for 1-yr OS rate: 0.73 (96% CI: 0.59, 0.89), P = 0.0015

Borghaei H, NEJM 15

Overall survival by PDL1 expression

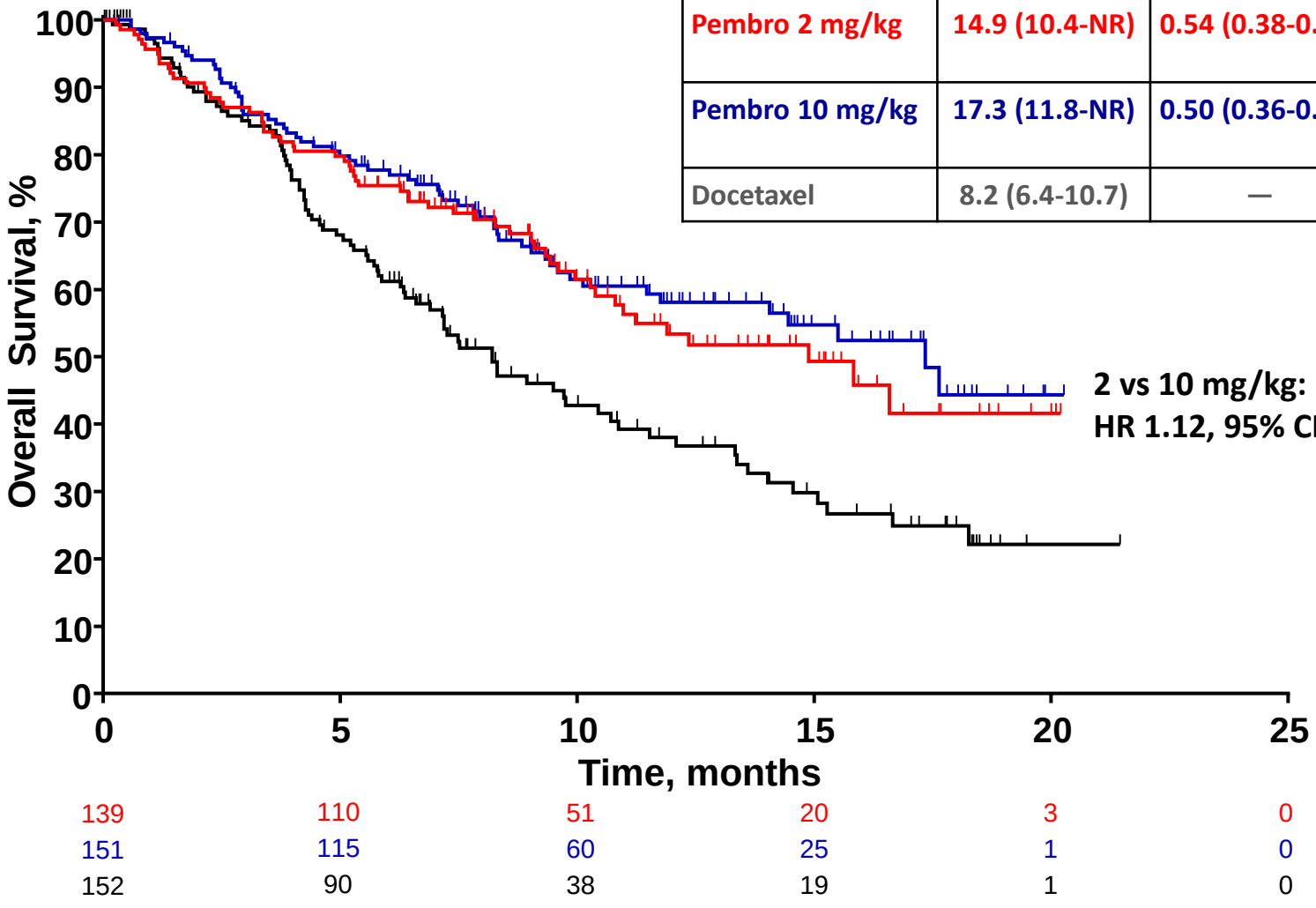


Based on a July 2, 2015 DBL. Symbols represent censored observations.

Borghaei H, NEJM 15

KEYNOTE-010, OS, PDL1 TPS ≥50% Stratum

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



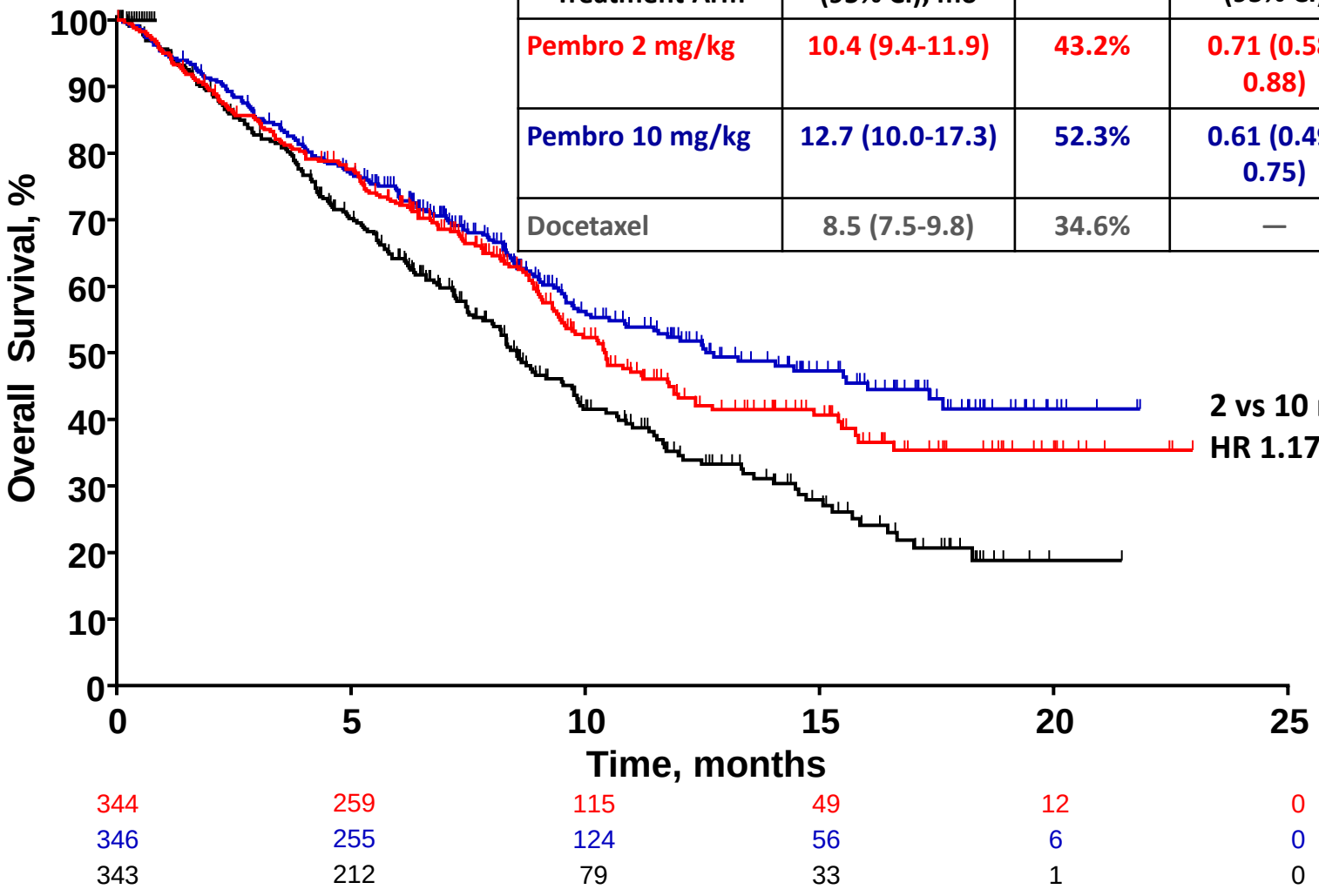
2 vs 10 mg/kg:
HR 1.12, 95% CI 0.77-1.62

Herbst, Lancet 2016

[a]Comparison of pembrolizumab vs docetaxel.

KEYNOTE-010 OS, PD-L1 TPS ≥1% (total population)

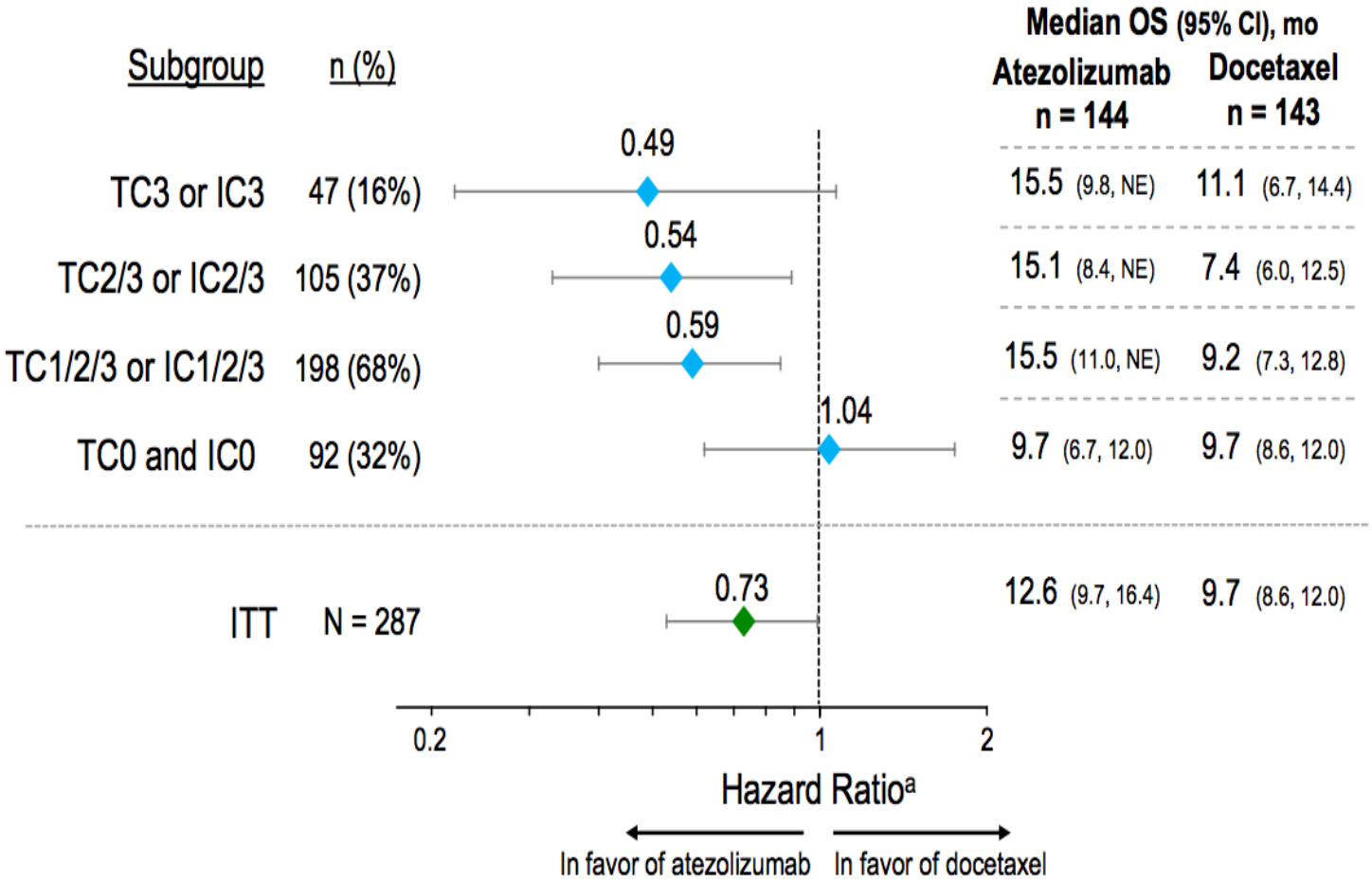
Treatment Arm	Median (95% CI), mo	Rate at 1 y	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	10.4 (9.4-11.9)	43.2%	0.71 (0.58-0.88)	0.0008
Pembro 10 mg/kg	12.7 (10.0-17.3)	52.3%	0.61 (0.49-0.75)	<0.0001
Docetaxel	8.5 (7.5-9.8)	34.6%	—	—



Herbst, Lancet 2016

[a]Comparison of pembrolizumab vs docetaxel.

Poplar: atezolizumab *vs* docetaxel
OS data according to PDL1 level

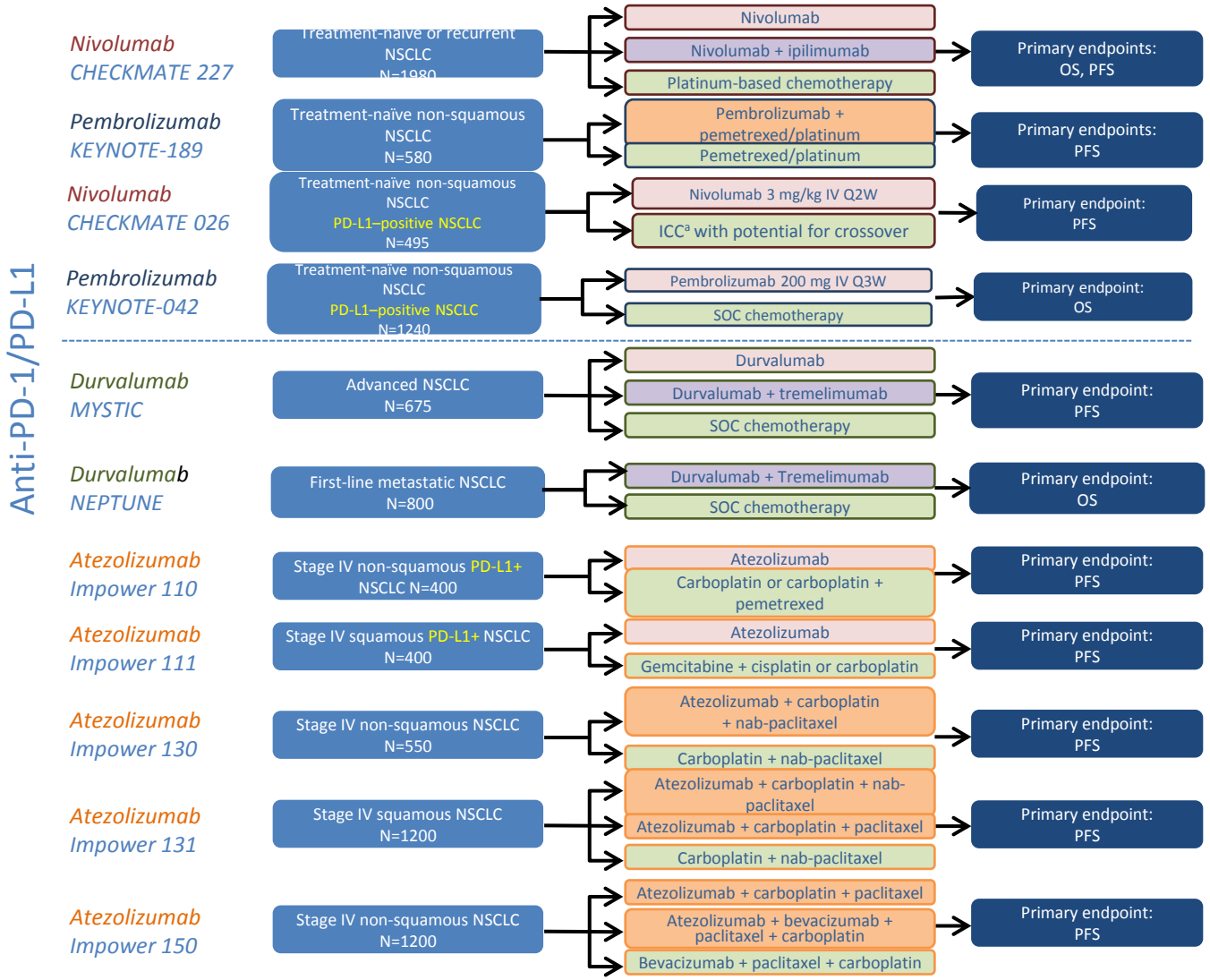


Fehrenbacher L, Lancet 16

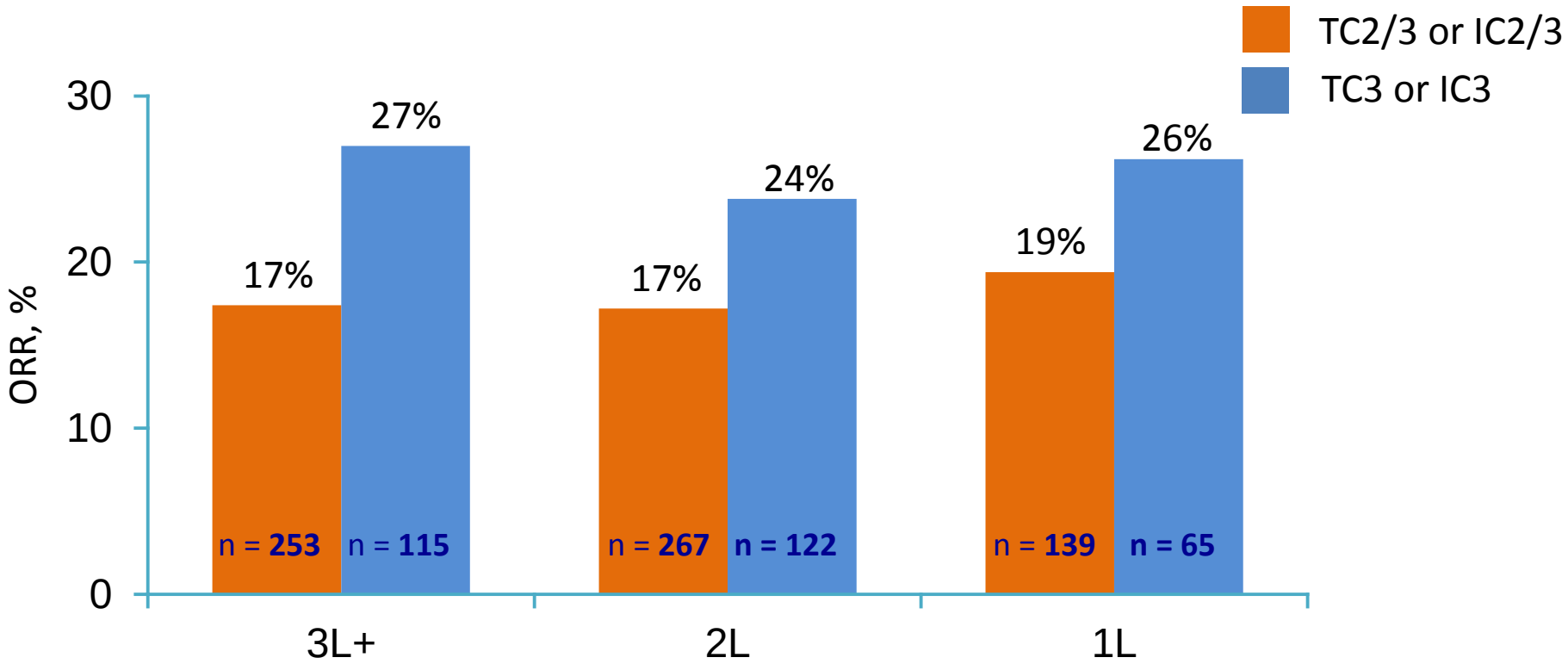
Anti-PD1/-PDL1 toxicity

- Treatment-related AEs less common with anti-PD1/-PDL1 than with docetaxel
- Common side effects are fatigue, pruritus, decreased appetite
- AEs uncommon (<5% of pts) but with special clinical relevance: pulmonary, GI, endocrinophaties

Phase 3 anti-PD1/-PD-L1 combination trials in 1st-line advanced NSCLC (>10,000 patients)



Checkpoints in 1st line
BIRCH: TC3 or IC3 and TC2/3 or IC2/3 subgroups



- BIRCH enrolled patients with tumors that were PDL1 TC2/3 or IC2/3
- 34% of screened pts

Besse, ESMO 2015

Checkpoints in monotherapy *vs* CT in 1st line

- **Phase II trial of nivolumab *vs* investigator's choice CT as 1st-line for stage IV or recurrent PD-L1+ NSCLC (CheckMate 026)**
  - Primary outcome measures: PFS in subjects with strongly PD-L1+ tumor expression

- **Phase III trial of MK-3475 *vs* platinum-based CT in 1L subjects with PD-L1 strong metastatic NSCLC**
  - Primary outcome measures: PFS

PD-1/PD-L1 CDx in development, companions tests

pembrolizumab	nivolumab	Atezolizumab	Durvalumab
22C3	28-8	SP142	SP263
1% or 50% • Tumor only • Only validated cut-off in a prospective clinical study	• Retrospective analysis of 1, 5 and 10%	IHC 3: ≥ 10% tumor immune cells positive for PD-L1 (IC+); IHC 2 and 3: ≥ 5% tumor immune cells positive for PD-L1 (IC+); IHC 1/2/3: ≥ 1% tumor immune cells positive for PD-L1 (IC+); IHC 0/1/2/3: all patients with evaluable PD-L1 tumor IC status	• Cut-off 25% tumor cells in NSCLC
• Developing PD-L1+ IHC CDx with Dako	• Developing PD-L1+ IHC CDx with Dako • No need for PD-L1+ testing in 2L +	• CDx platform (Ventana) for development and to validate commercial PD-L1+ CDx	• Developing CDx for PD-L1+ with Ventana

Anti-PD1/-PDL1 in NSCLC
innovation and care in the next 12 months

- 2nd-line with anti-PD1/-PDL1 for pts with ECOGPS 0-1, RR 20% consistent across studies, less toxicity than docetaxel
  - ✓ Standard in squamous histology irrespective of PDL1 status
  - ✓ Standard in non-squamous histology, determining PDL1 status may help

- Higher RR in pts with PDL1+ tumors, greater benefit in pts with more PDL1 staining
  - ✓ Although different antibodies / different cut-off points, results regarding influence of PDL1 staining, similar across studies
  - ✓ Blueprint project; pathology committee of the IASLC with 6 of the commercial stakeholders to compare the tests for PDL1

- Large number of similar drugs compete in same treatment area
  - ✓ In 2nd-line randomized trials, control arm should include anti-PD1/-PDL1 compounds

Anti-PD1/-PDL1 in NSCLC
innovation and care in the next 12 months

- Recruitment closed for 1st-line trials comparing nivolumab/pembrolizumab *vs* CT in PDL1+ tumors, results expected soon
  - ✓ Knowledge of naïve pts subgroup who will benefit from anti-PD1 strategies according to PDL1 status; will some stage IV NSCLC pts be treated without CT in future?

- Role of anti-PD1/-PDL1 strategies in ECOGPS2 will be defined

- Combination studies ongoing, no treatment change expected for the next 12 mo
  - ✓ With anti-CTL4, encouraging results; toxicity may be an issue
  - ✓ With CT, promising results in small sample size studies

Thanks!!!

efelip@vhebron.net

3rd ESO Lung Cancer Observatory: Innovation and care in the next 12 months

Keith Kerr

Aberdeen University Medical School

Aberdeen Royal Infirmary,

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View of a Pathologist

Predictive markers in NSCLC

Emerging molecular biomarkers as targets

Adenocarcinoma

- ROS1 fusion
- KRAS mutation
- RET fusion
- HER2 mutation
- BRAF mutation
- NTRK fusion

Squamous Cell Carcinoma

- FGFR1 amplification
- CDNK2

EGFR protein IHC
EGFR gene copy number
MET exon14 mutations

Resistance mechanisms
T790M
MET
Phenotype

How will those markers be detected

- Next generation sequencing platforms
  - Multiplex-cost tipping point
  - Different dynamic to requesting
  - Multifactorial data
- Are stand alone tests a thing of the past?
- Role of blood testing

Immunotherapy

- Biological vs Evidential vs Fiscal arguments
- PD-L1 immunohistochemistry
  - It does work
  - Does it work well enough?
  - It is complicated
  - Can it be made less so?
- Other biomarkers
  - Other check points?
  - Mutation burden – however that might be measured

3rd ESO Lung Cancer Observatory: Innovation and care in the next 12 months

Fredrik Johansson

The Swedish Lung Cancer Association www.stodet.se

Stockholm, Sweden

View of an Advocate Representative

2016-2017 Predictions

Long-term lung cancer survivors: patient's needs

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- Swedish Lung Cancer Advocacy
- www.stodet.se

Lung Cancer Europe
www.lungcancereurope.eu

Optimism is the faith that leads to achievement

- Patients want the latest news about new therapies & drugs available; today ePatients have to find & sort this wealth of information themselves.

- Many patients also want to participate in clinical trials and promising drug tests. Unfortunately, trials are not easy to find, and might not be known by the patient's medical team.

2016-2017 Predictions

Contact us

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