Abstract LBA8011

Nintedanib (BIBF 1120) + Docetaxel in NSCLC Patients Progressing after One Prior Chemotherapy Regimen: LUME-Lung 1, a Randomized, Double-blind, Phase III trial

Reck M, Kaiser R, Mellemgaard A, Douillard J-Y, Orlov S, Krzakowski M, von Pawel J, Gottfried M, Bondarenko I,Liao M, Barrueco J, Gaschler-Markefski B, Novello S;
for the LUME-Lung 1 Study Group

Disclosures

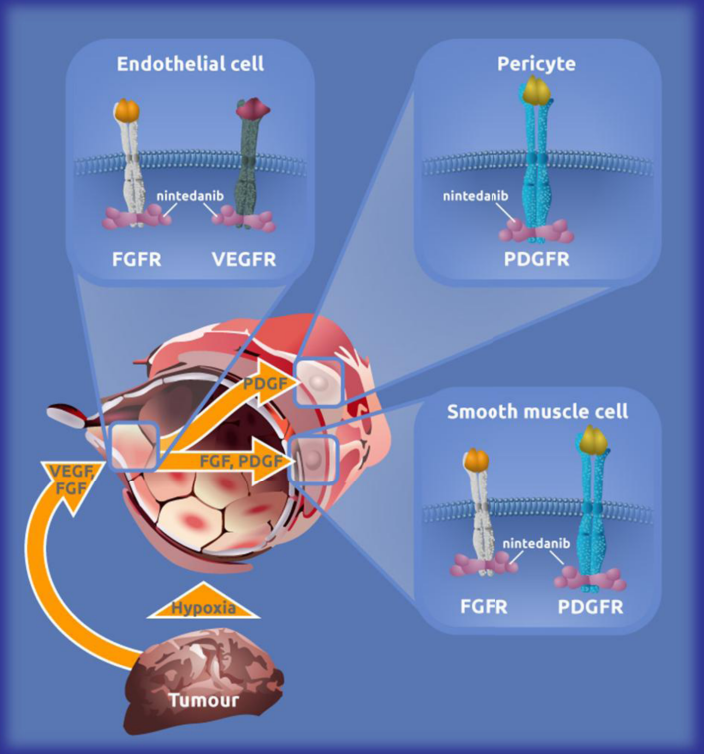
- LUME-Lung 1 trial was funded by Boehringer Ingelheim
- Editorial support was provided by GeoMed, funded by Boehringer Ingelheim

Background

- NSCLC is a heterogeneous disease
  - Different histologies, adenocarcinoma accounts for almost 50%
  - Distinct molecular signatures (EGFR, ALK)
- Available second-line treatments for NSCLC show limited efficacy
  - Long history of failed trials
  - No OS benefit compared with standard of care in phase III trials
- Angiogenesis is implicated in NSCLC growth[1]
  - VEGF, FGF and PDGF signaling contributes toward angiogenesis[2]

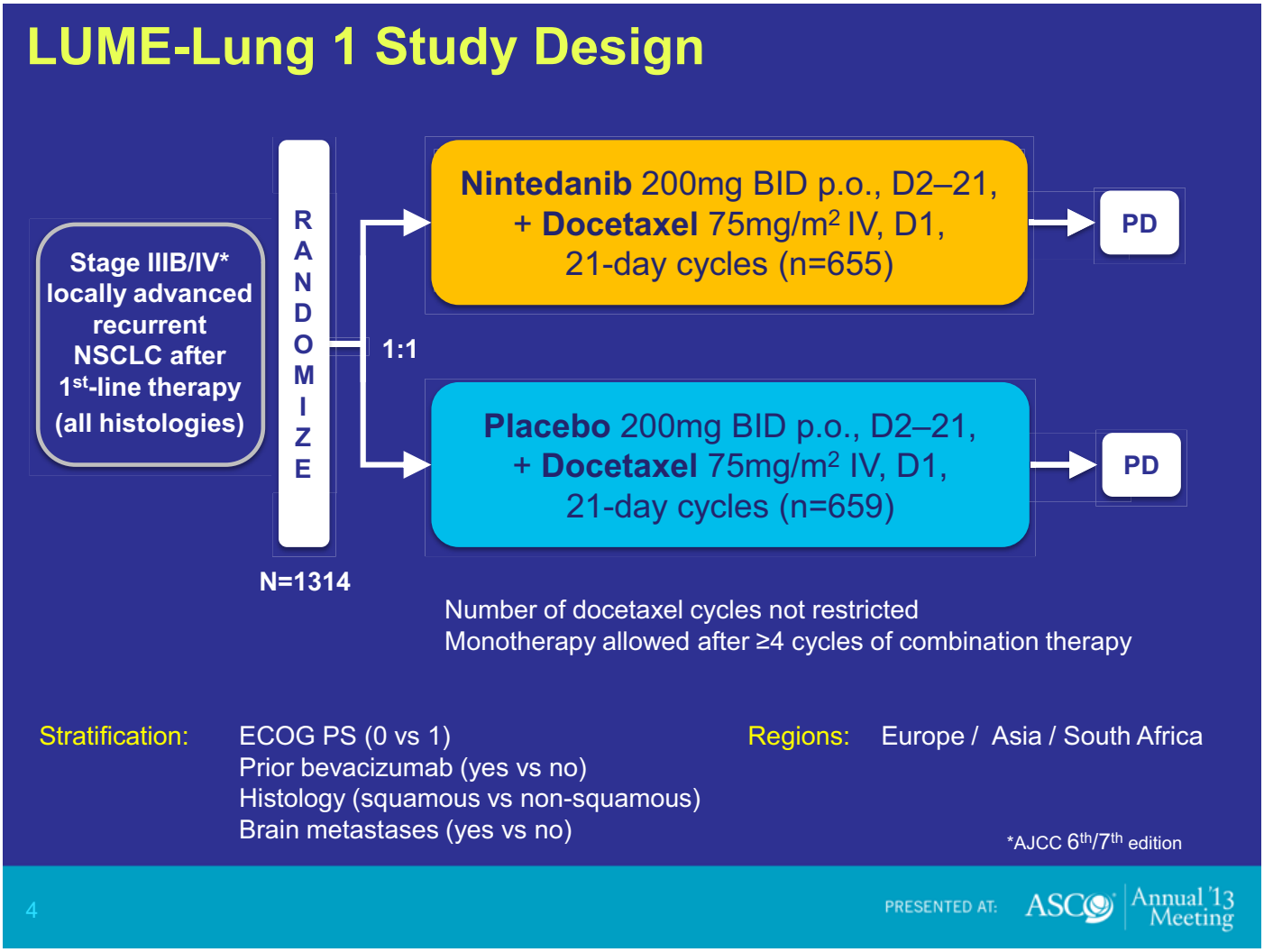
1. Makrilia N, et al. Eur J Intern Med 2009;20:663–7
2. Carmeliet P, Jain RK. Nature 2000;407:249–57

Characteristics of Nintedanib



- Triple angiokinase inhibitor targeting VEGFR 1–3, FGFR 1–3, and PDGFR α/β[1]
- Orally administered
- No drug–drug interaction liability via CYP450[2]
- Combinable with chemotherapy, with manageable safety profile
  - ✓ Docetaxel[2]
  - ✓ Pemetrexed[3]
  - ✓ Paclitaxel/carboplatin[4]
  - ✓ Gemcitabine/cisplatin[5]
- Single-agent nintedanib was active in a phase II trial in recurrent NSCLC[6]

1.Hilberg F, et al. Cancer Res 2008;68:4774–8; 2. Stopfer P, et al. Xenobiotica 2011;41:297–311;
3. Bousquet G, et al. Br J Cancer 2011;105:1640–5; 4. Ellis PM, et al. Clin Cancer Res 2010;16:2881–9;
5. Doebele RC, et al. Ann Oncol 2012;23:2094–102; Boehringer Ingelheim, Data on File (clinicaltrials.gov NCT01346540) 6 . Reck M, et al. Ann Oncol 2011;22:1374–81



Major Eligibility Criteria

Key Inclusion Criteria

- Histologically or cytologically confirmed, locally advanced and/or metastatic, stage IIIB–IV NSCLC (according to AJCC*), or recurrent NSCLC (all histologies)
- Relapse or failure after first-line chemotherapy
  - In the case of recurrent disease, one additional prior regimen was allowed for adjuvant and/or neoadjuvant therapy
- ECOG PS 0 or 1

Key Exclusion Criteria

- Previous therapy with docetaxel or VEGF/VEGFR inhibitors (other than bevacizumab)
- Active brain metastases or leptomeningeal disease
- Cavitary or necrotic tumors

*AJCC 6th/7th edition

Statistical Design: Primary Endpoint

- Progression-free survival
  - Assessed by independent central review (modified RECIST v1.0)
  - Imaging performed every 6 weeks
- Statistical assumptions
  - Planned analysis after 713 PFS events had occurred
  - 90% power, two-sided stratified log-rank test, α=5%
  - Hazard ratio: 0.7843

6

PRESENTED AT: ASCO Annual '13 Meeting

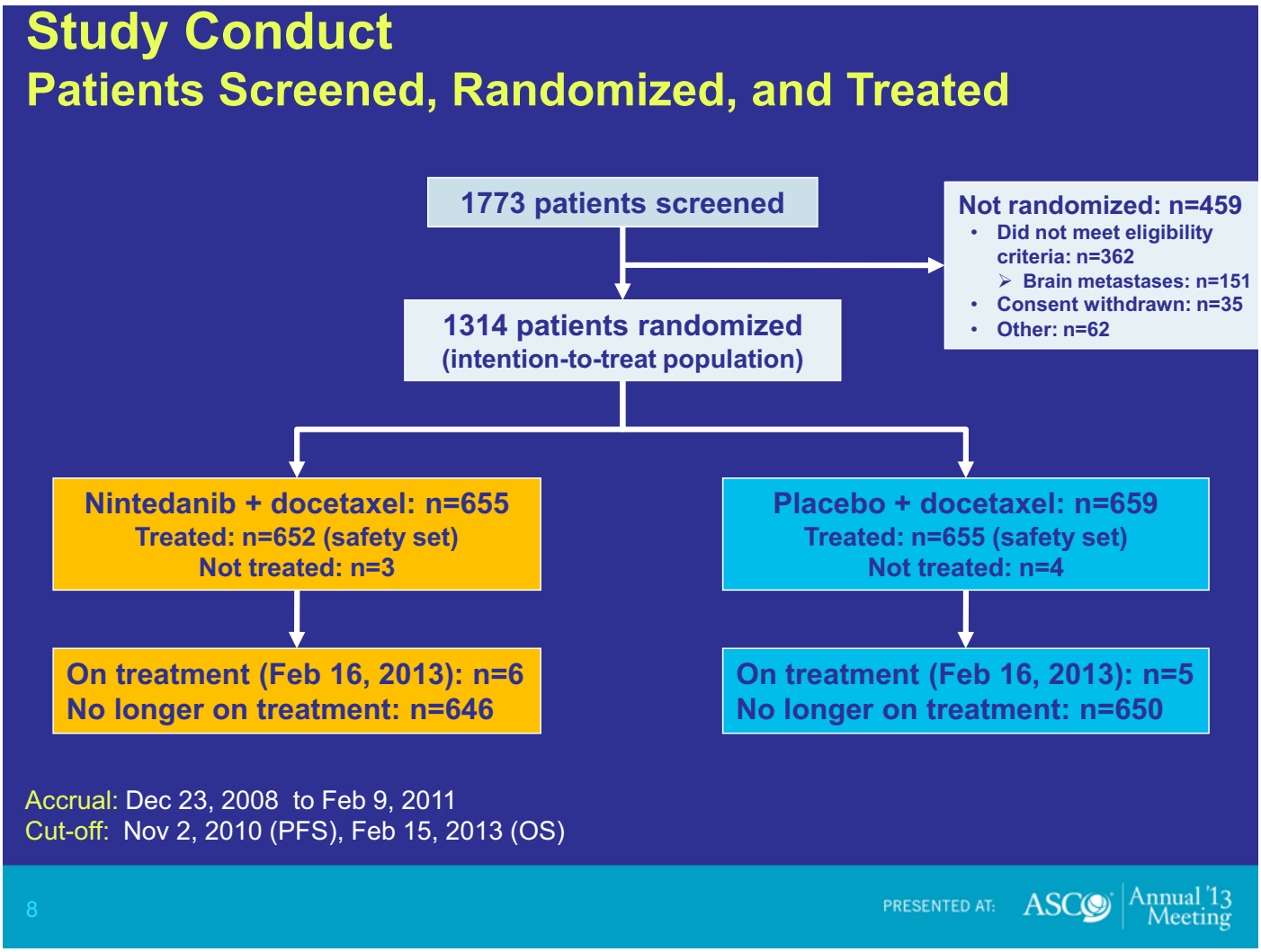
Statistical Design: Key Secondary Endpoint

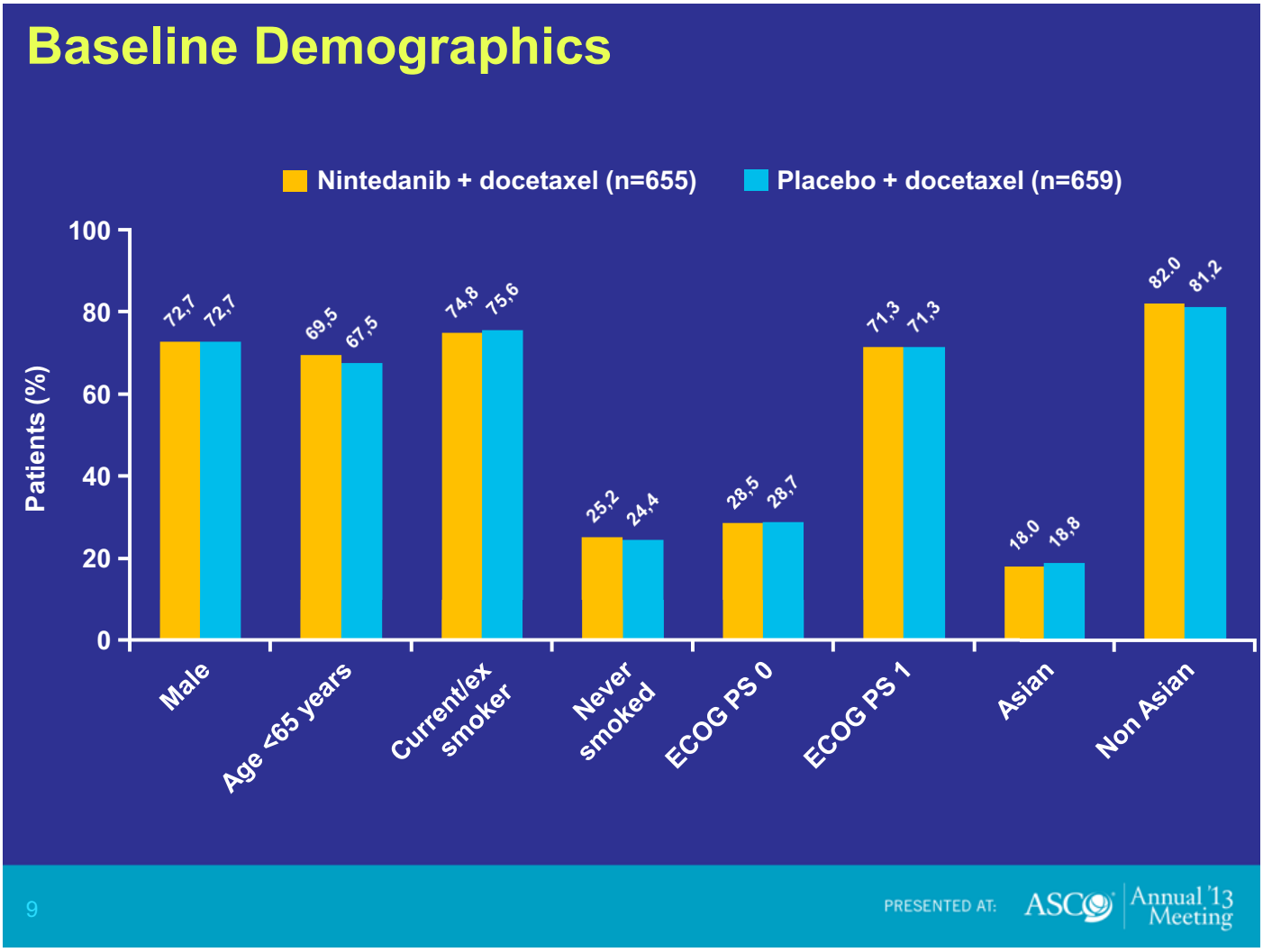
- Overall survival
- Statistical assumptions
  - Planned analysis after 1151 deaths had occurred
  - 80% power, two-sided stratified log-rank test, overall α=5%*
  - Hazard ratio: 0.8475
- Analysis plan extended†
  - Patients with adenocarcinoma histology progressing during first-line treatment or shortly after
  - Patients with adenocarcinoma histology

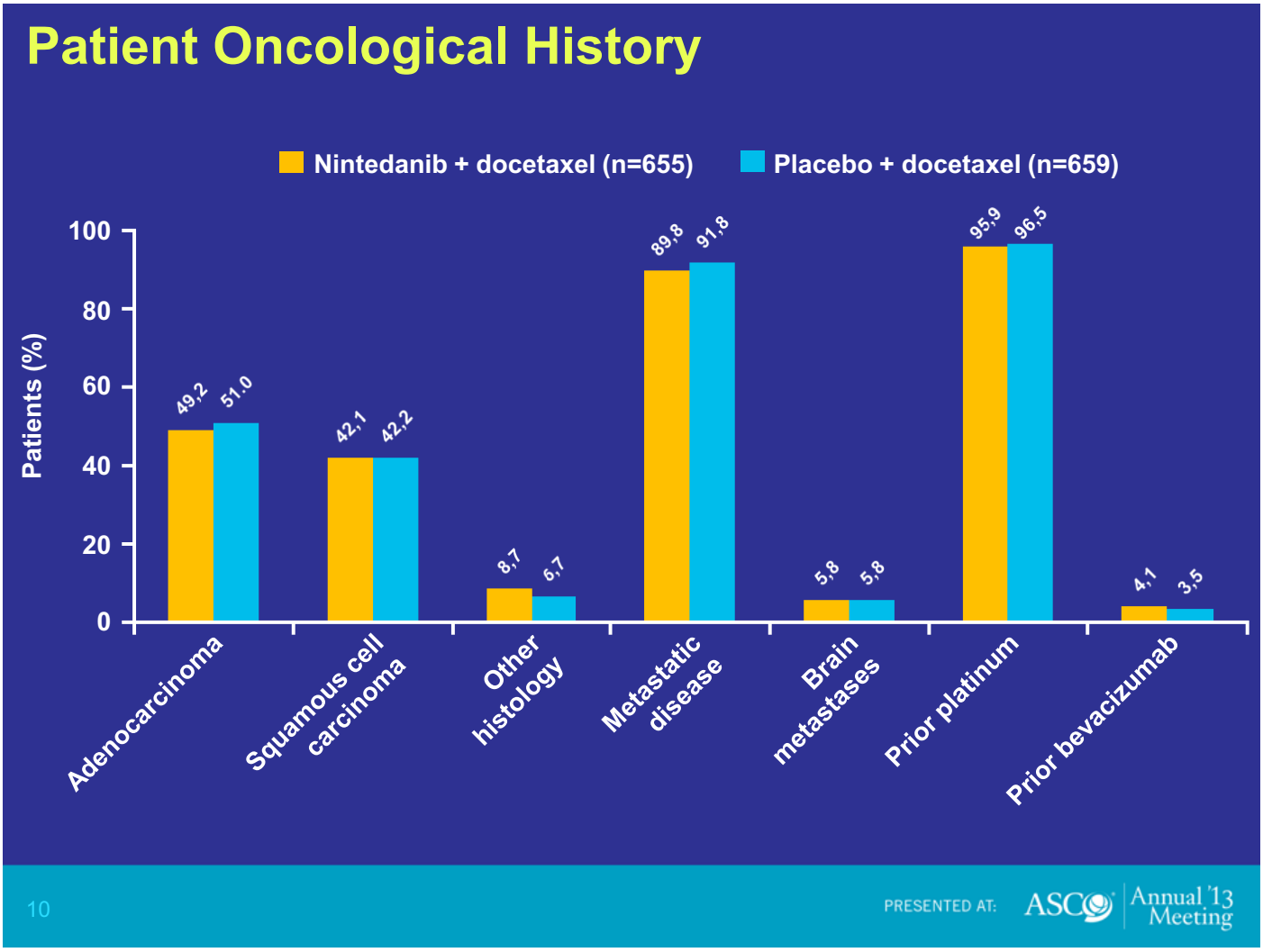
*Adjusted for interim OS data (analyzed at same time as primary PFS), adjusted final α=4.94%
†Fixed sequence order testing implemented prior to database lock to validate findings from independent study (LUME-Lung 2: Hanna N, et al. ASCO 2013. Abstr #8034)

7

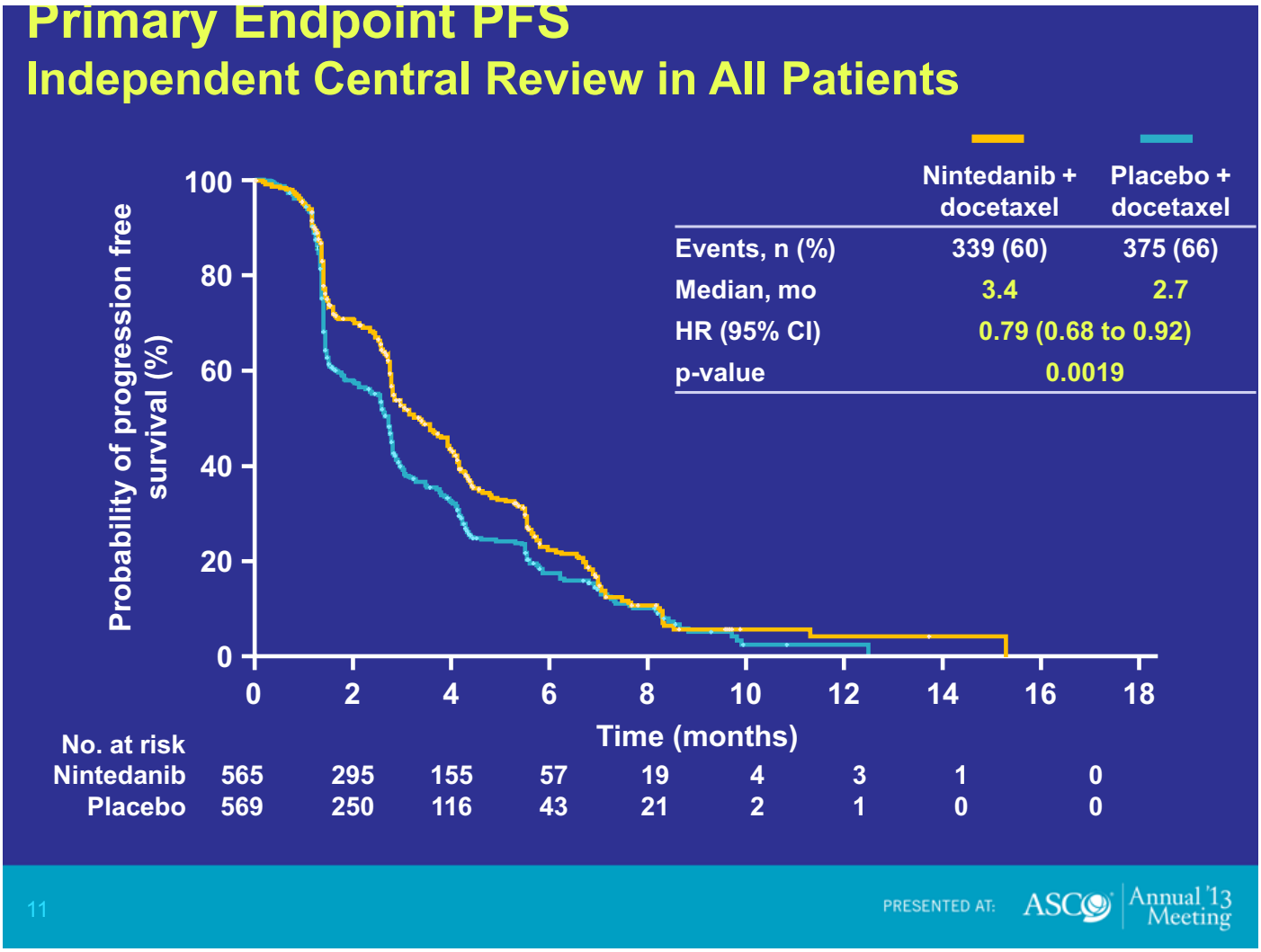
PRESENTED AT: ASCO Annual '13 Meeting







Primary Endpoint PFS
Independent Central Review in All Patients



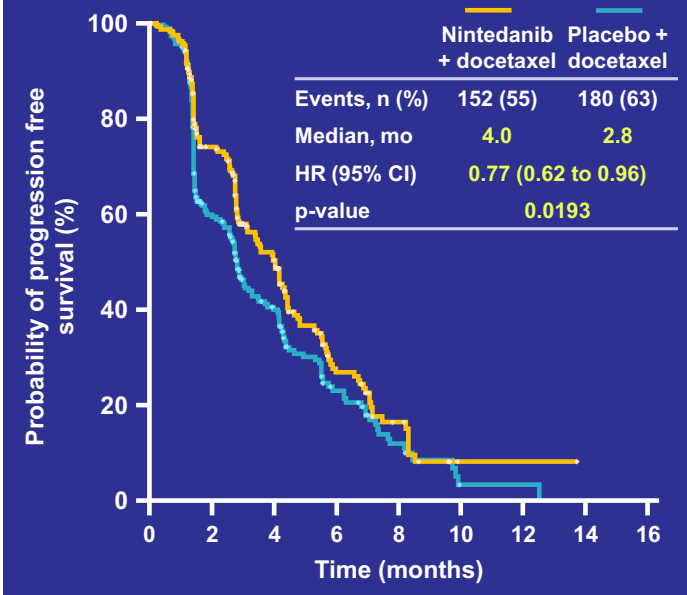
	Nintedanib + docetaxel	Placebo + docetaxel
Events, n (%)	339 (60)	375 (66)
Median, mo	3.4	2.7
HR (95% CI)	0.79 (0.68 to 0.92)	
p-value	0.0019	

11

PRESENTED AT: ASCO Annual '13 Meeting

Primary Endpoint PFS
Independent Central Review in Major Histologies

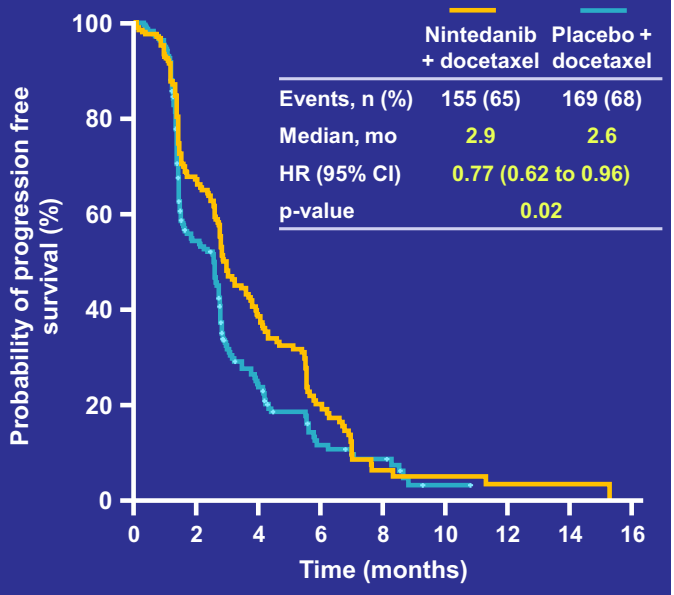
Adenocarcinoma



	Nintedanib + docetaxel	Placebo + docetaxel
Events, n (%)	152 (55)	180 (63)
Median, mo	4.0	2.8
HR (95% CI)	0.77 (0.62 to 0.96)	
p-value	0.0193	

No. at risk								
Nintedanib	277	150	86	32	13	1	1	0
Placebo	285	129	70	28	12	1	1	0

Squamous Cell Carcinoma

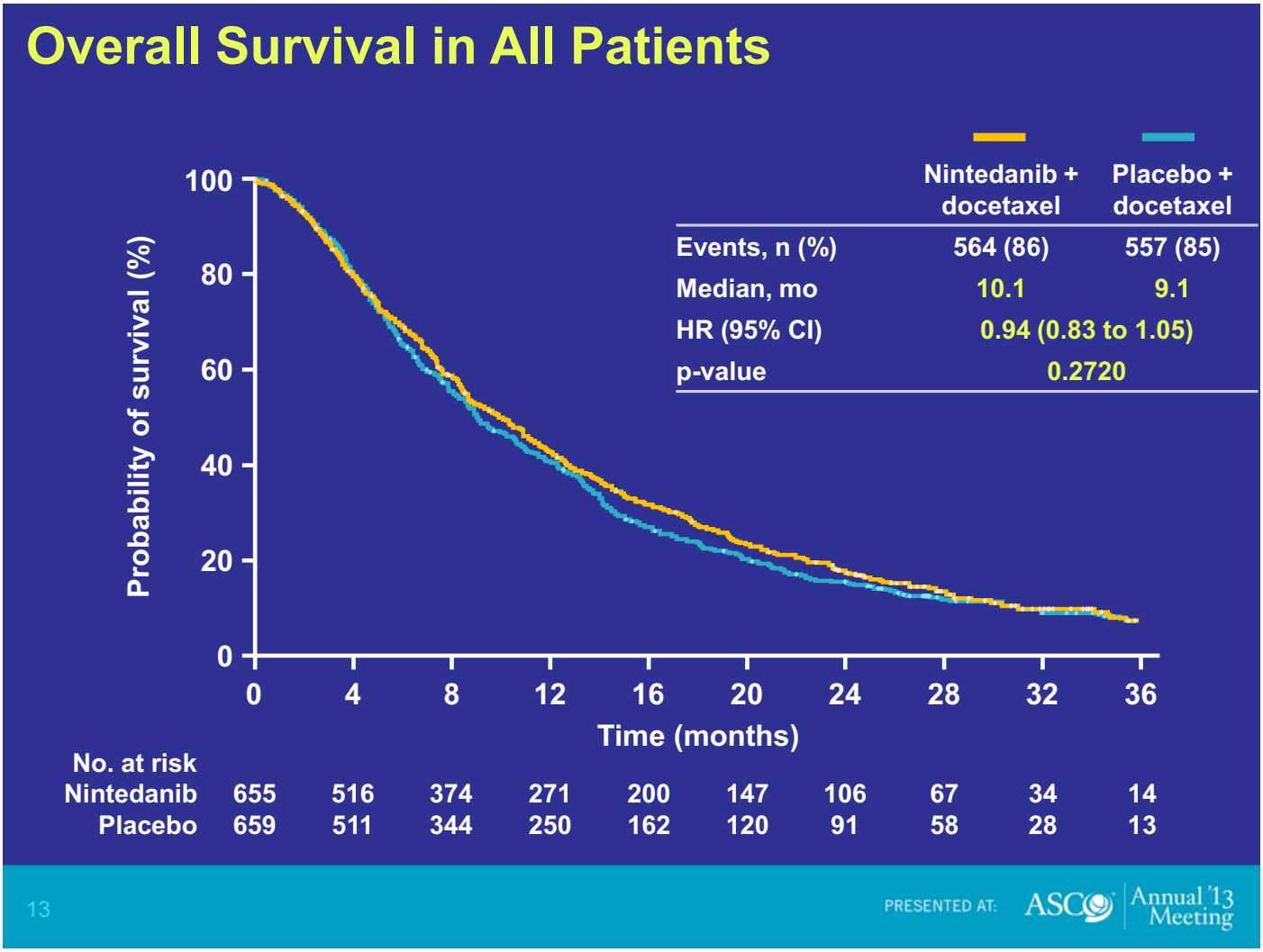


	Nintedanib + docetaxel	Placebo + docetaxel
Events, n (%)	155 (65)	169 (68)
Median, mo	2.9	2.6
HR (95% CI)	0.77 (0.62 to 0.96)	
p-value	0.02	

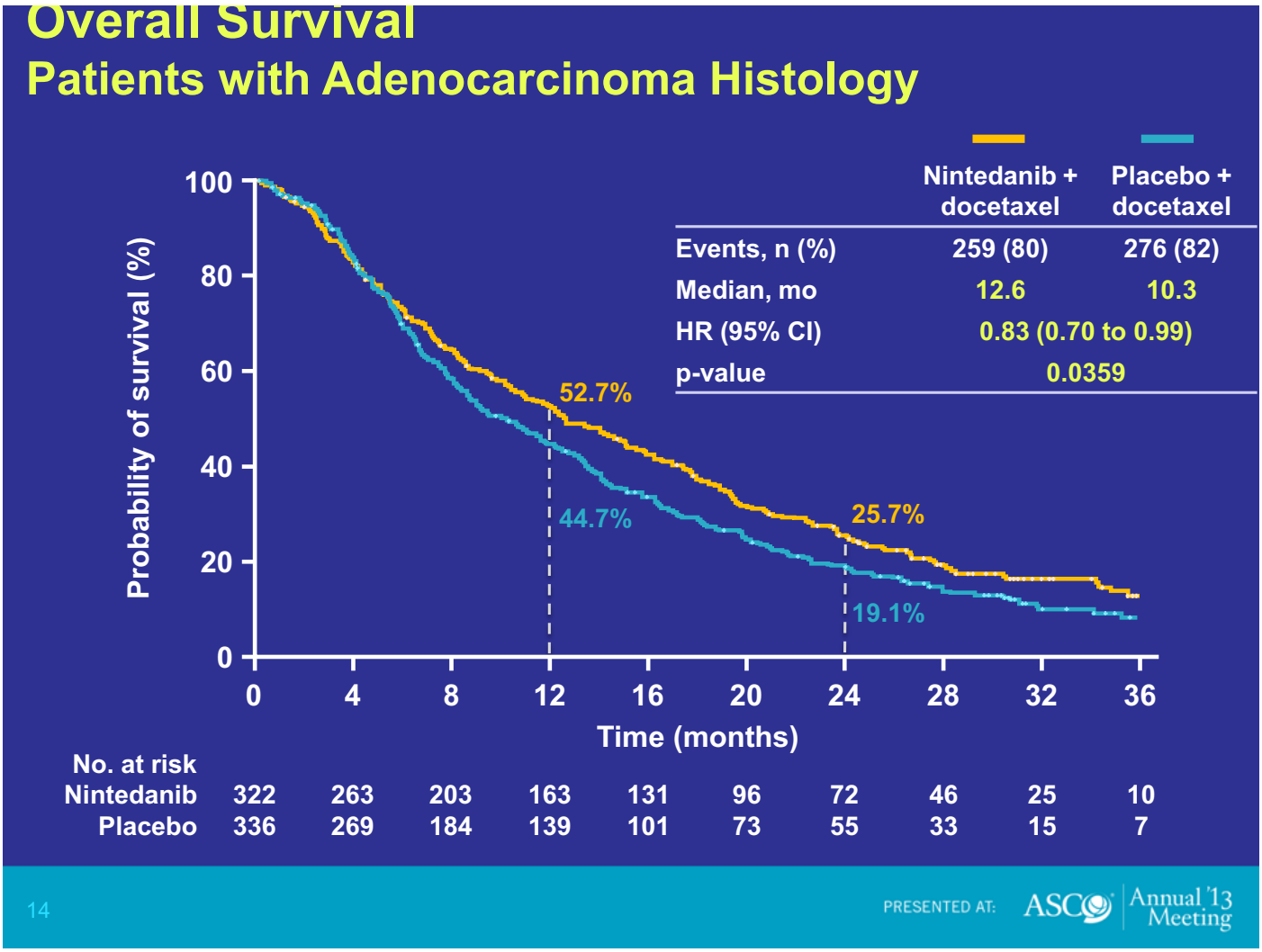
No. at risk								
Nintedanib	240	122	59	22	5	3	2	1	0
Placebo	247	101	36	13	8	1	0	0	0

12

PRESENTED AT: ASCO Annual '13 Meeting



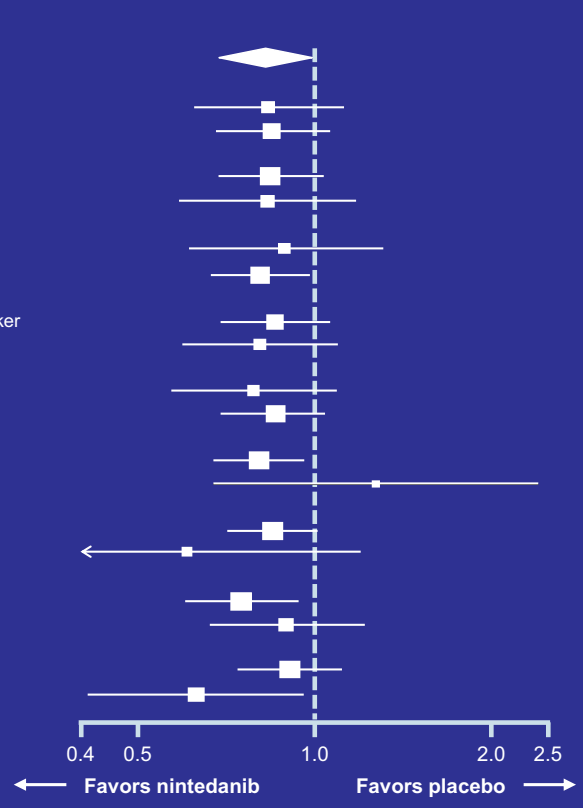
Overall Survival
Patients with Adenocarcinoma Histology



14

PRESENTED AT: ASCO Annual '13 Meeting

Overall Survival
Patients with Adenocarcinoma Histology



15

PRESENTED AT: ASCO Annual '13 Meeting

Best tumor response: Independent Central Review All patients

Best response, n (%)	Nintedanib + docetaxel (n=655)	Placebo + docetaxel (n=659)
Complete response (CR)	0	1 (0.2)
Partial response (PR)	29 (4.4)	21 (3.2)
Stable disease (SD)	325 (49.6)	250 (37.9)
Disease control rate* (CR + PR + SD)	354 (54.0)	272 (41.3)
Progressive disease	200 (30.5)	298 (45.2)

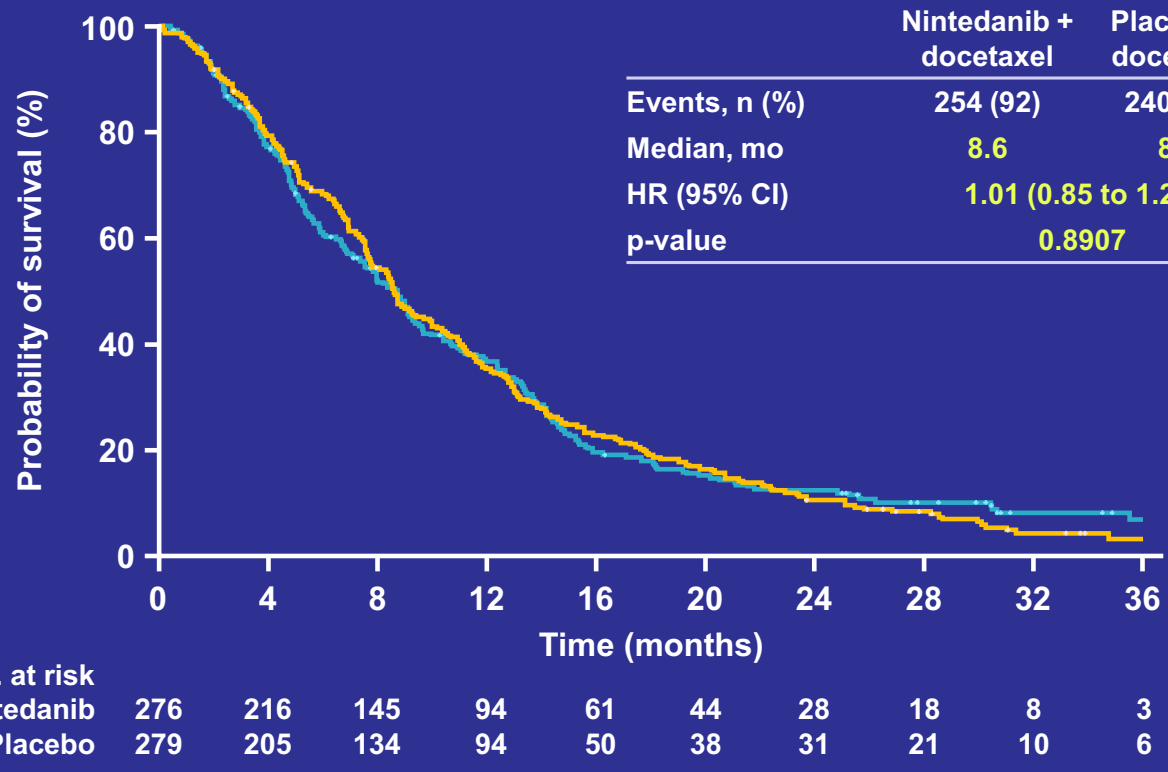
*Statistically significant improvement in disease control rate with nintedanib + docetaxel (odds ratio 1.68; p<0.0001)

Similar results observed across major histological subtypes

16

PRESENTED AT: ASCO Annual '13 Meeting

Overall Survival
Patients with Squamous Cell Carcinoma Histology



	Nintedanib + docetaxel	Placebo + docetaxel
Events, n (%)	254 (92)	240 (86)
Median, mo	8.6	8.7
HR (95% CI)	1.01 (0.85 to 1.21)	
p-value	0.8907	

No. at risk										
Nintedanib	276	216	145	94	61	44	28	18	8	3
Placebo	279	205	134	94	50	38	31	21	10	6

17

PRESENTED AT: ASCO Annual '13 Meeting

Post-study Systemic Anticancer Therapy
All patients

Patients receiving post-study therapy, n (%)	Nintedanib + docetaxel (n=655)	Placebo + docetaxel (n=659)
Any systemic therapy	342 (52.2)	350 (53.1)
Any chemotherapy	203 (31.0)	218 (33.1)
Pemetrexed	54 (8.2)	56 (8.5)
Docetaxel	27 (4.1)	23 (3.5)
Other chemotherapy	136 (20.8)	152 (23.1)
EGFR tyrosine kinase inhibitor	133 (20.3)	131 (19.9)
Anti-angiogenesis agent	3 (0.5)	4 (0.6)
Investigational agent	20 (3.1)	7 (1.1)

EGFR, epidermal growth factor receptor

Similar results observed across major histological subtypes

18

PRESENTED AT: ASCO Annual '13 Meeting

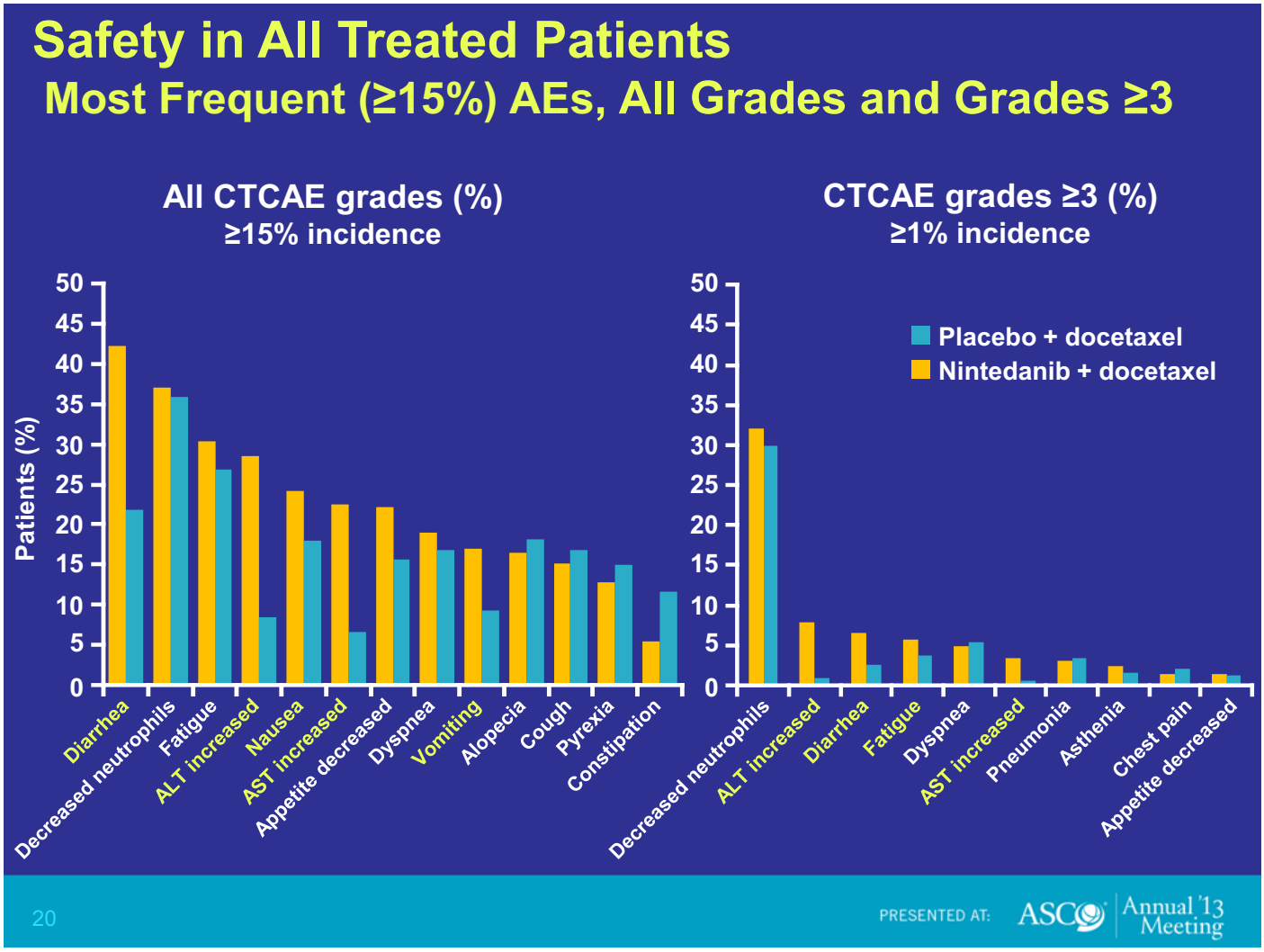
Safety in All Treated Patients
Summary of Adverse Events (AEs)

Patients with AE, n (%)	Nintedanib + docetaxel (n=652)	Placebo + docetaxel (n=655)
Any AE, all grades	610 (93.6)	609 (93.0)
Drug-related AE, all grades	498 (76.4)	446 (68.1)
Any AE, grades ≥3	465 (71.3)	421 (64.3)
Drug-related AE, grades ≥3	331 (50.8)	275 (42.0)
Any AE leading to discontinuation	148 (22.7)	142 (21.7)
Any serious AE	224 (34.4)	206 (31.5)

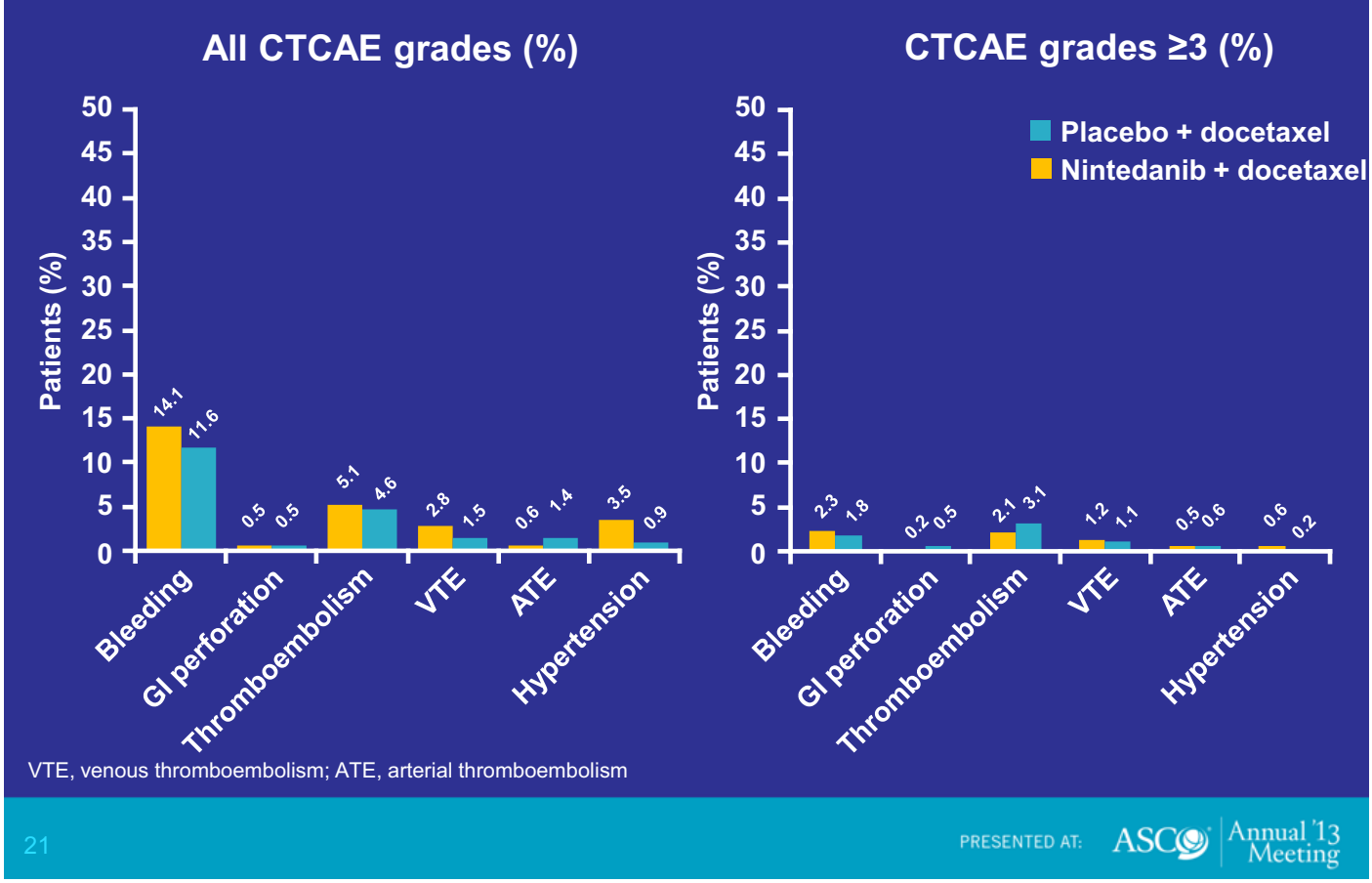
Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was used

19

PRESENTED AT: ASCO Annual '13 Meeting



Safety in All Treated Patients
AEs Frequently Observed with VEGF/VEGFR Inhibitors



VTE, venous thromboembolism; ATE, arterial thromboembolism

21

PRESENTED AT: ASCO Annual '13 Meeting

Summary

- LUME-Lung 1 met its primary endpoint
  - Nintedanib in combination with docetaxel significantly prolonged PFS
  - both in adenocarcinoma and squamous cell carcinoma
- A trend for improved OS was seen in the overall population
- LUME-Lung 1 demonstrated a significant improvement in OS in adenocarcinoma
  - Nintedanib in combination with docetaxel significantly prolonged median OS by 2.3 months with a HR of 0.83 (p=0.0359)
- Nintedanib plus docetaxel was generally well tolerated and no unexpected safety findings occurred

22

PRESENTED AT: ASCO Annual '13 Meeting

Conclusion

- Nintedanib plus docetaxel is the first second line combination to show a significant survival benefit in lung cancer patients with adenocarcinoma compared with an active comparator

Acknowledgements

We would like to thank all patients and their families, the investigators, and all study center staff

Study investigators

Austria— R. Kropfmüller, H. Olschewski, E. Wöll, A. Zabernigg; Belarus— V. Beliakouski, Vasili, V. Bogdan, A. Lysov, A. Prokharau, K. Shelepen, A. Tomchina, E. Zhavrid; Belgium— L. Bosquee, F. Bustin, D. Schallier; Bulgaria— B. Baeva, D. Damyanov, K. Guenova, N. Ivanova, H. Markova, P. Petrov; China— C. Bai, J. Chang, G-Y. Chen, Y. Cheng, J. Fang, J. Feng, C. Huang, W. Li, H. Houjie, M. Liao, J. Liu, X-Q. Liu, Y. Lu, K. Nan, H. Pan, S. Qin, Y. Wu, C-H. Xie, S. Yu, L. Zhang, Y. Zhang, Y. Zhang, C. Zhou; Croatia— I. Gudelj, Z. Kusic, M. Samarzija; Czech Republic— J. Chalupa, Jiri, H. Coupkova, E. Karasova, P. Reiterer, J. Skrickova, J. Vydra; Denmark— A. Mellemgaard, P. Soerensen; France— J. Bennouna, H. Berard, C. Chouaid, P. Fournel, A. Madroszyk, J. Mazieres, J-F. Muir, M. Perol, J-L Pujol, E. Quoix, P-J. Souquet; Georgia— I. Abesadze, R. Gagua, V. Katsarava, D. Tabagari; Germany— A.G. Banat, J. Bargon, H. Bernhard, R. Bonnet, W. Brückl, K. Dalhoff, H.G. Derigs, I. Dittrich, C. Eschbach, J R. Fischer, N. Frickhofen, B. Gahn, S. Gallenberger, C. Geßner, W. Gleiber, F. Griesinger, C. Grohé, S. Gütz, B. Heinrich, H. Höfeler, R.M. Huber, E. Jäger, U. Keilholz, J. Kersten, Y-D Ko, J. Kollmeier, C. Kortsik, J. Lorenz, H-G. Mergenthaler, M. Reck, L. Scheuer, BC. Schmidt, S. Schmitz, F. Schneller, J. Schubert, W. Schütte, M. Sebastian, W. Spengler, M. Thomas, J. von Pawel, C. Waller, H. Wirtz, M. Wolf; Greece— D. Bouros, G. Fountzilas, V. Georgoulias, M. Toumbis, S. Tzannes, K. Zarogoulidis; India— S. Aggarwal, R. Chopra, C.J. Desai, G. Dev Vashishta, D.C. Doval, M. GopiChand, C. Goswami, K.C. Lakshmaiah, H. Malhotra, A. Maru, W. Meenu, H. Menon, P.R. Mohan, R. Mohapatra, S. Nag, K. Pavithran, K. Prasad, D. Raghunadharao, T.C. Raju, T. Sahoo, B. Shailesh, C.D. Sivanandan, N. Somani, PS. Tarini; Israel— J. Brenner, T. Charkovsky, A. Cyjon, M. Gottfried, O. Merimsky, A. Onn, N. Peylan-Ramu; Italy— D. Amadori, E. Bajetta, A. Bearz, C. Boni, S. Bretti, S. Cascinu, L. Ciuffreda, L. Crino, T.M. De Pas, F. Di Costanzo, AA. Martoni, L. Pavesi, G. Scagliotti, S. Siena, A. Zaniboni; Republic of Korea— E.K. Cho, J-H. Kang, B-S. Kim; Lithuania— R. Sakalauskas, R. Zablockis, A. Zlabiene; Poland— E. Chmielowska, A. Fleming, G. Jagiello, A. Kazarnowicz, S. Korzeniowski, M. Krzakowski, R. Kwiatkowski, J. Milanowski, R. Ramlau, I. Ryniewicz-Zander, P. Serwatowski, M. Siemczonek, A. Szczesna; Portugal— T. Almodovar, A. Araujo, F. Barata, J. Cunha, A. Meleiro, B. Parente, H. Queiroga, E. Teixeira; Romania— C. Cebotaru, M. Dediu, D. Filip, D-E. Ganea-Motan, I-C. Iacob, I. Ionas, L. Miron, C. Oprean, E-M. Popescu, L. Vata, C. Volovat; Russia— Z. Akishina, V. Borisov, I. Bulavina, N. Chekha, V. Demchenko, O. Gladkov, R. Khasanov, I. Kiselev, D. Komov, E. Kulikov, M. Leonov, V. Lubennikov, A. Luft, G. Manikhas, V. Moiseyenko, V. Mus, S. Orlov, E. Solovieva, D. Udovitsa, A. Vitsin, V. Vladimirov; Slovakia— L. Jurga, J. Mazal; South Africa— J.E. Bouwer, L.M. Dreosti, L.H. Dupper, G. Landers, R. Mall, J. Raats, B. Rapoport, P. Ruff; Spain— J.E. Alés, I. Fernández, A. Gurpide, S. Hernando, B. Hernández, A. Insa, U. Jiménez, O. Juan, N. Martinez, M. Muñoz, R.M. Pérez, N. Viñolas; Switzerland— C. Caspar, L.V. Rohr; Ukraine— I. Bondarenko, T. Danilova, I. Drobner, O. Dudnichenko, I. Galaychuk, Y. Hotko, V. Komisarenko, N. Lisovska, S. Matviychuk, P. Odarchenko, S. Prokhoda, R. Senyutovich, G. Ursol; United Kingdom— A. Dangoor, N. Davidson, T. Geldart, V. Laurence, G. Middleton, E. Rankin, R. Shah, P. Taylor

24

PRESENTED AT: ASCO Annual '13 Meeting