Radiation Therapy for SCLC

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MATOS 2024

Radiation as a Variable

Memorial Sloan Kettering Cancer Alliance

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ORIGINAL ARTICLE

Twice-Daily Compared with Once-Daily Thoracic Radiotherapy in Limited Small-Cell Lung Cancer Treated Concurrently with Cisplatin and Etoposide

Authors: Andrew T. Turrisi, M.D., Kyungmann Kim, Ph.D., Ronald Blum, M.D., William T. Sause, M.D., Robert B. Livingston, M.D., Ritsuko Komaki, M.D., Henry Wagner, M.D., Seena Aisner, M.D., and David H. Johnson, M.D. Author Info & Affiliations

Published January 28, 1999 | N Engl J Med 1999;340:265-271 | DOI: 10.1056/NEJM199901283400403
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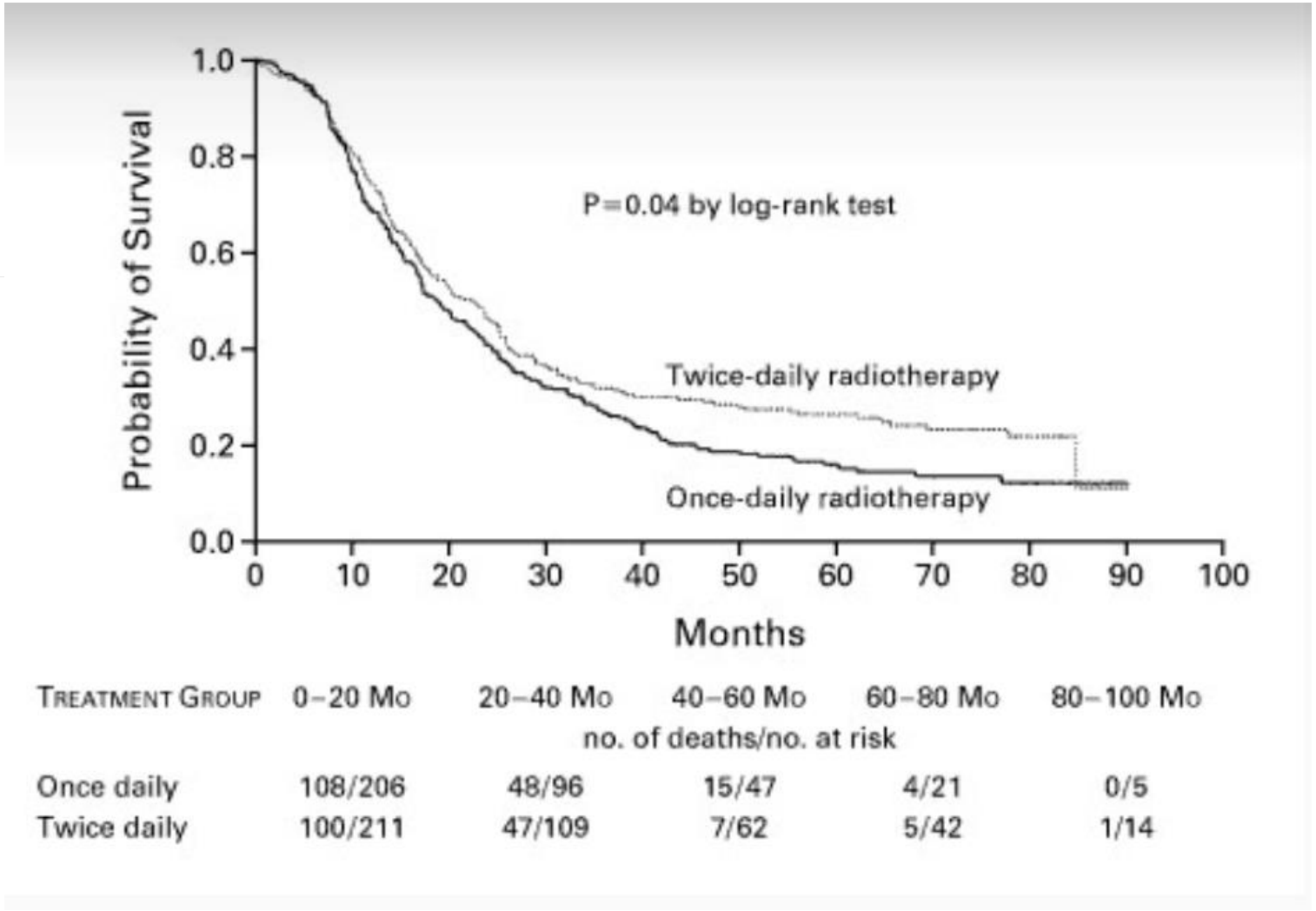

Treatment Group	0–20 Mo	20–40 Mo	40–60 Mo	60–80 Mo	80–100 Mo
	no. of deaths/no. at risk				
Once daily	108/206	48/96	15/47	4/21	0/5
Twice daily	100/211	47/109	7/62	5/42	1/14

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ARTICLES · Volume 18, Issue 8, P1116-1125, August 2017 · *Open Access* Download Full Issue

Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial

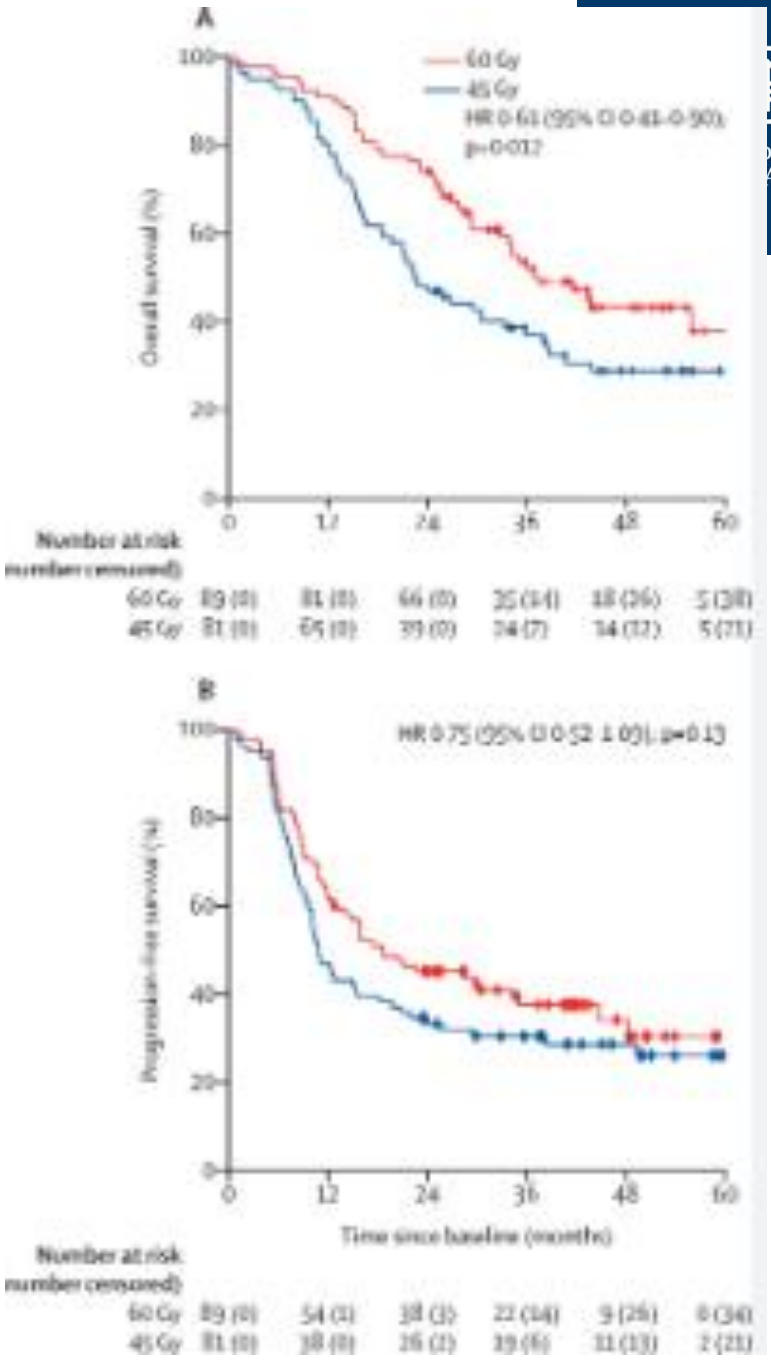
Prof Corinne Faivre-Finn, PhD [a,b] · Michael Snee, DM [c] · Linda Ashcroft, MSc [d] · Wiebke Appel, MD [e] · Prof Fabrice Barlesi, PhD [f] · Adityanarayan Bhatnagar, MD [g] · Andrea Bezjak, MD [h] · Felipe Cardenal, PhD [i] · Prof Pierre Fournel, MD [j] · Susan Harden, DM [Oxon] [k] · Cecile Le Pechoux, MD [l] · Rhona McMenemin, MSc [m] · Nazia Mohammed, FRCR [n] · Mary O'Brien, MD [o] · Jason Pantarotto, MD [p] · Prof Veerle Surmont, PhD [q] · Prof Jan P Van Meerbeeck, PhD [r] · Prof Penella J Woll, FRCP [s] · Prof Paul Lorigan, FRCP [a] · Prof Fiona Blackhall, PhD [a] for the CONVERT Study Team Show less

No difference in arms – was not an equivalence study, so technically we should still be using 45/30 bid regimen

Clinical Trial > Lancet Oncol. 2021 Mar;22(3):321-331. doi: 10.1016/S1470-2045(20)30742-7.

High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial

Bjørn Henning Grønberg [1], Kristin Toftaker Killingberg [2], Øystein Fløtten [3], Odd Terje Brustugun [4], Kjersti Hornslien [5], Tesfaye Madebo [6], Seppo Wang Langer [7], Tine Schytte [8], Jan Nyman [9], Signe Risum [10], Georgios Tsakonas [11], Jens Engleson [12], Tarje Onsøien Halvorsen [2]



60Gy/40Fx > 45Gy/30Fx with respect to OS and PFS

What to do now?

Clinical Trial > JAMA. 1977 Jun 20;237(25):2730-3.

Prophylactic cranial irradiation in small cell carcinoma of the lung. A randomized study

D V Jackson Jr, F Richards 2nd, M R Cooper, C Ferree, H B Muss, D R White, C L Spurr

PMID: 577226

Abstract

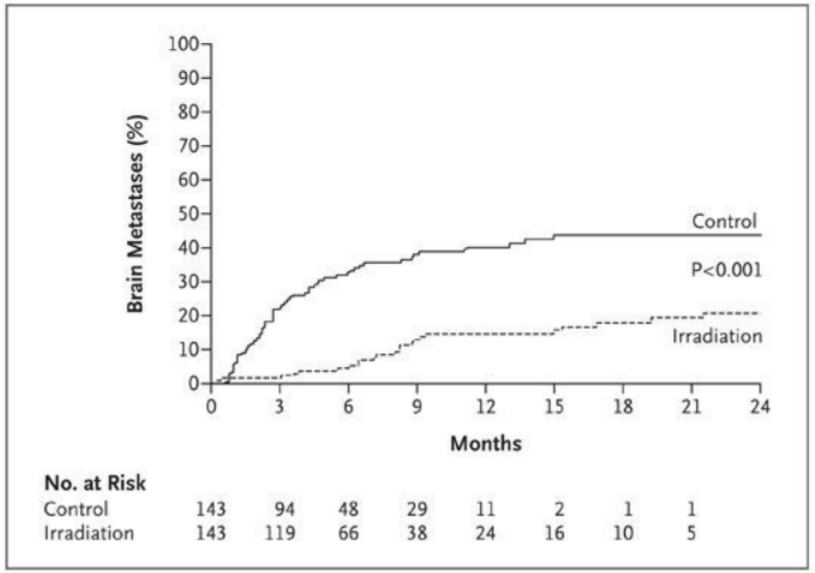
Twenty-nine patients with small cell carcinoma of the lung and without evidence of brain metastasis were randomized into two treatment groups consisting of 14 patients who received prophylactic cranial irradiation (PCI) and 15 who received none (non-PCI). All patients were treated with irradiation of the primary lesion and concomitant chemotherapy. The response rate and median survival of the two groups were not significantly different: 93% and 7.2 months in the non-PCI; 86% and 9.8 months in the PCI; P larger than or equal to .05. Brain metastasis occurred in 0/14 patients in the PCI and 4/15 in the non-PCI (P less than or equal to .05) and was the cause of major neurologic disability in each. Although PCI did not improve response rate or survival, brain metastasis with its attendant neurologic complications was effectively prevented.

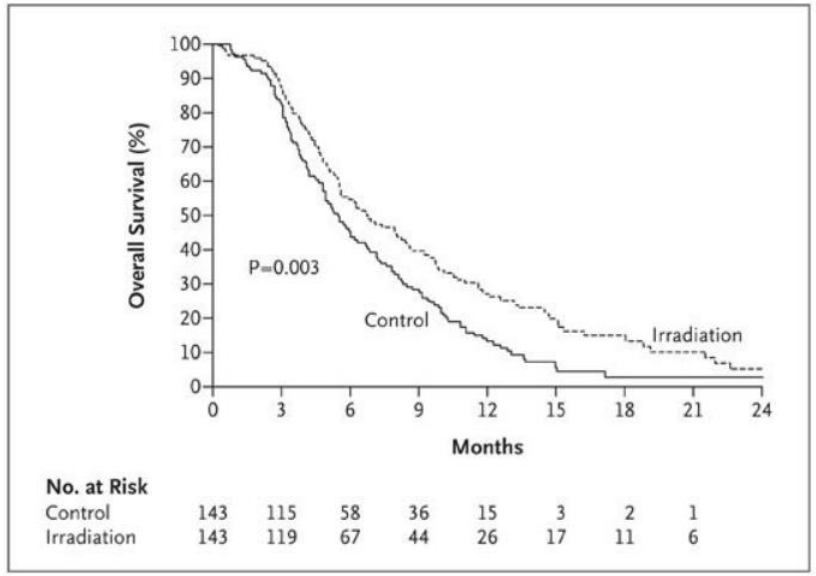
ORIGINAL ARTICLE

Prophylactic Cranial Irradiation in Extensive Small-Cell Lung Cancer

Authors: Ben Slotman, M.D., Ph.D., Corinne Faivre-Finn, M.D., Ph.D., Gijs Kramer, M.D., Elaine Rankin, M.D., Michael Snee, D.M., Matthew Hatton, F.R.C.R., Pieter Postmus, M.D., Ph.D., Laurence Collette, Ph.D., Elena Musat, M.D., and Suresh Senan, Ph.D., F.R.C.R., for the EORTC Radiation Oncology Group and Lung Cancer Group* Author Info & Affiliations

Published August 16, 2007 | N Engl J Med 2007;357:664-672 | DOI: 10.1056/NEJMoa071780 | VOL. 357 NO. 7





Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Ben J Slotman, Harm van Tinteren, John O Praag, Joost L Knegjens, Sherif Y El Sharouni, Matthew Hatton, Astrid Keijser, Corinne Faivre-Finn, Suresh Senan**

www.thelancet.com **Vol 385 January 3, 2015**

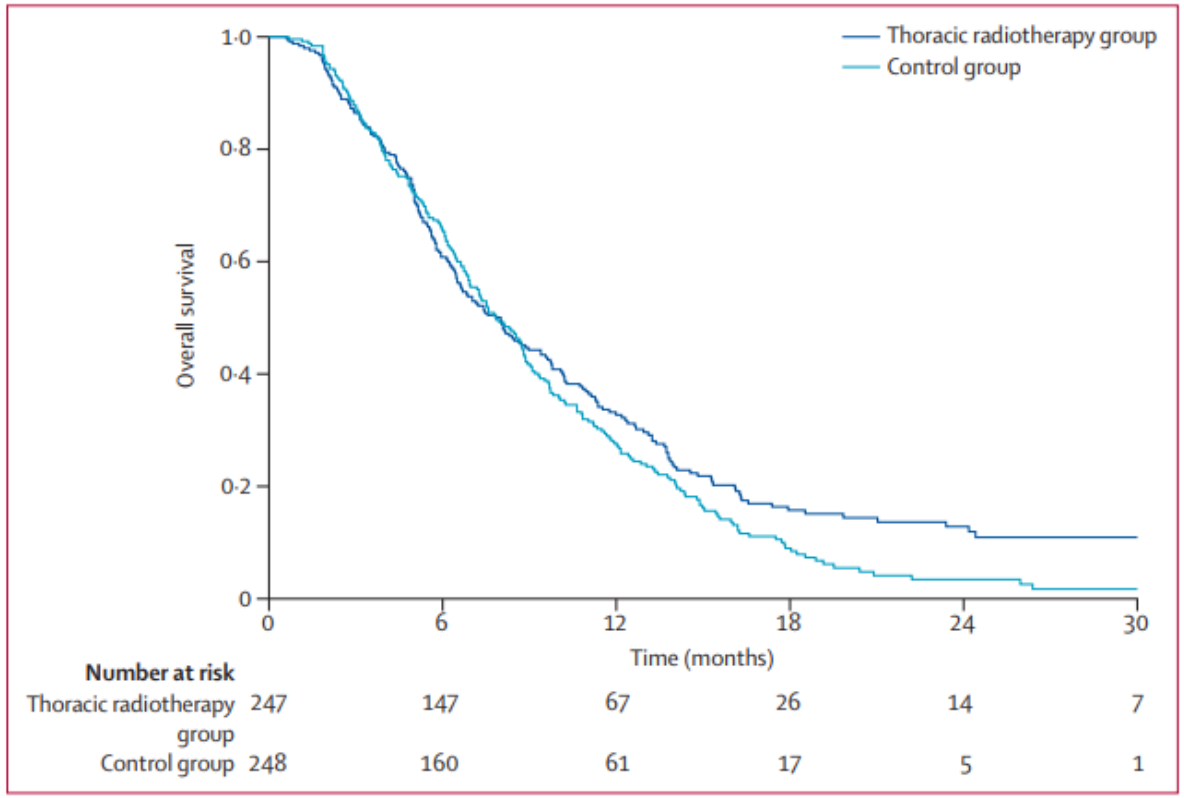
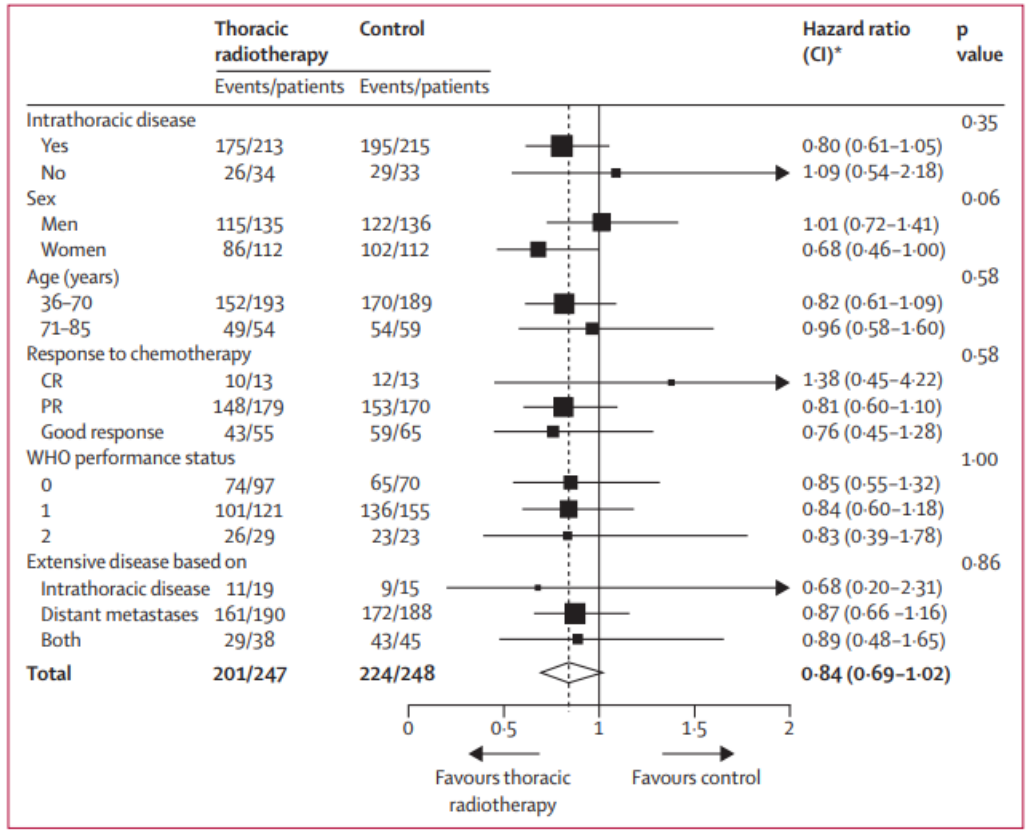


Figure 2: **Kaplan-Meier curves for overall survival**



Journal of Thoracic Oncology
IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

ORIGINAL ARTICLE | SMALL CELL LUNG CANCER · Volume 12, Issue 10, P1561-1570, October 2017 · *Open Archive*

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Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone to Prophylactic Cranial Irradiation and Consolidative Extracranial Irradiation for Extensive-Disease Small Cell Lung Cancer (ED SCLC): NRG Oncology RTOG 0937

Elizabeth M. Gore, MD [a] · Chen Hu, PhD [b,c] · Alexander Y. Sun, MD [d] · Daniel F. Grimm, MS [e] · Suresh S. Ramalingam, MD [f] · Neal E. Dunlap, MD [g] · Kristin A. Higgins, MD [f] · Maria Werner-Wasik, MD [h] · Aaron M. Allen, MD [i] · Puneeth Iyengar, MD, PhD [j] · Gregory M.M. Videtic, MD [k] · Russell K. Hales, MD [c] · Ronald C. McGarry, MD [l] · James J. Urbanic, MD [m] · Anthony T. Pu, MD [n] · Candice A. Johnstone, MD [a] · Volker W. Stieber, MD [o] · Rebecca Paulus, BS [b] · Jeffrey D. Bradley, MD [p] Show less

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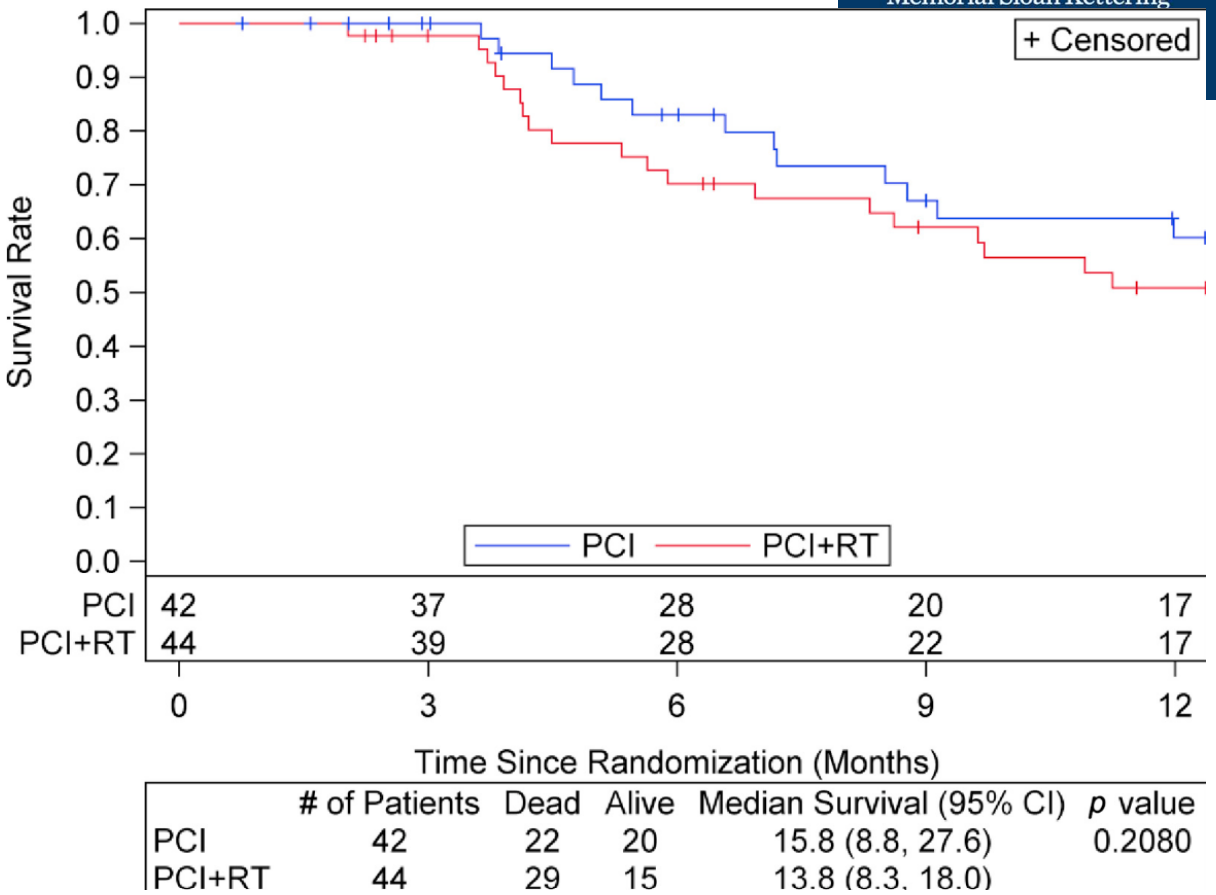

	# of Patients	Dead	Alive	Median Survival (95% CI)	*p* value
PCI	42	22	20	15.8 (8.8, 27.6)	0.2080
PCI+RT	44	29	15	13.8 (8.3, 18.0)	

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ARTICLES · Volume 18, Issue 5, P663-671, May 2017 Download Full Issue

Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial

Toshiaki Takahashi, MD [a] · Prof Takeharu Yamanaka, PhD [c] · Takashi Seto, MD [d] · Hideyuki Harada, MD [b] · Hiroshi Nokihara, MD [e] · Hideo Saka, MD [f] · Makoto Nishio, MD [g] · Hiroyasu Kaneda, MD [h] · Koichi Takayama, MD [i] · Osamu Ishimoto, MD [j] · Koji Takeda, MD [k] · Hiroshige Yoshioka, MD [l] · Motoko Tachihara, MD [m] · Hiroshi Sakai, MD [n] · Koichi Goto, MD [o] · Prof Nobuyuki Yamamoto, MD [p]

Findings

Between April 3, 2009, and July 17, 2013, 224 patients were enrolled and randomly assigned (113 to prophylactic cranial irradiation and 111 to observation). In the planned interim analysis on June 18, 2013, of the first 163 enrolled patients, Bayesian predictive probability of prophylactic cranial irradiation being superior to observation was 0·011%, resulting in early termination of the study because of futility. In the final analysis, median overall survival was 11·6 months (95% CI 9·5–13·3) in the prophylactic cranial irradiation group and 13·7 months (10·2–16·4) in the observation group (hazard ratio 1·27, 95% CI 0·96–1·68; p=0·094). The most frequent grade 3 or worse adverse events at 3 months were anorexia (six [6%] of 106 in the prophylactic cranial irradiation group *vs* two [2%] of 111 in the observation group), malaise (three [3%] *vs* one [<1%]), and muscle weakness in a lower limb (one [<1%] *vs* six [5%]). No treatment-related deaths occurred in either group.

Systemic Therapy as a Variable

ADRIATIC study design

Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study (NCT03703297)

- Stage I–III LS-SCLC (stage I/II inoperable)
- WHO PS 0 or 1
- Had not progressed following cCRT*
- PCI* permitted before randomization

cCRT components

- Four cycles of platinum and etoposide (three permitted†)
- RT: 60–66 Gy QD over 6 weeks or 45 Gy BID over 3 weeks
- RT must commence no later than end of cycle 2 of CT

N=730

R‡

Stratified by: Disease stage (I/II vs III) PCI (yes vs no)

Durvalumab
1500 mg Q4W
N=264

Placebo
Q4W
N=266

Durvalumab + tremelimumab
D 1500 mg Q4W + T 75 mg Q4W for 4 doses, followed by D 1500 mg Q4W
N=200

Treatment until investigator-determined progression or intolerable toxicity, or for a **maximum of 24 months**

Dual primary endpoints:

- Durvalumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Key secondary endpoints:

- Durvalumab + tremelimumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Other secondary endpoints:

- OS/PFS landmarks
- Safety

*cCRT and PCI treatment, if received per local standard of care, must have been completed within 1–42 days prior to randomization.
†If disease control was achieved and no additional benefit was expected with an additional cycle of chemotherapy, in the opinion of the investigator.
‡The first 600 patients were randomized in a 1:1:1 ratio to the 3 treatment arms; subsequent patients were randomized 1:1 to either durvalumab or placebo.

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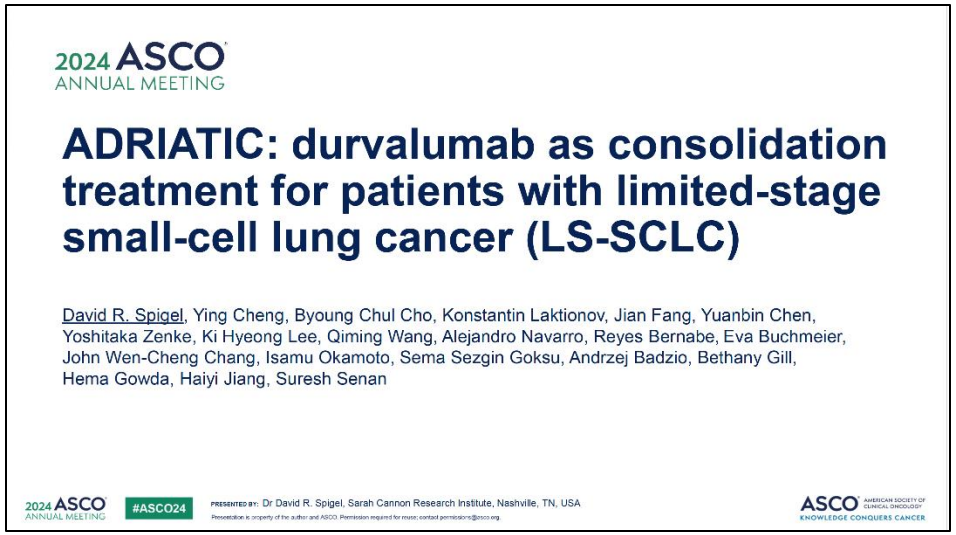
ORIGINAL ARTICLE

Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer

Y. Cheng, D.R. Spigel, B.C. Cho, K.K. Laktionov, J. Fang, Y. Chen, Y. Zenke, K.H. Lee, Q. Wang, A. Navarro, R. Bernabe, E.L. Buchmeier, J.W.-C. Chang, Y. Shiraishi, S.S. Goksu, A. Badzio, A. Shi, D.B. Daniel, N.T.T. Hoa, M. Zemanova, H. Mann, H. Gowda, H. Jiang, and S. Senan, for the ADRIATIC Investigators*



ADRIATIC: Baseline patient characteristics

		Durvalumab (n=264)	Placebo (n=266)
Age, years	Median (range)	62.0 (28–84)	62.0 (28–79)
Sex, %	Male / Female	67.4 / 32.6	70.7 / 29.3
Race, %	White / Asian / Other	49.2 / 49.6 / 1.1	51.5 / 45.5 / 3.0
WHO performance status, %	0 / 1	50.0 / 50.0	47.4 / 52.6
Smoking status, %	Current / Former / Never	23.9 / 67.4 / 8.7	20.7 / 69.5 / 9.8
AJCC disease stage at diagnosis, %	**I / II / III**	**3.0 / 9.5 / 87.5**	**4.1 / 8.6 / 87.2**
Prior chemotherapy regimen, %*	Cisplatin-etoposide / Carboplatin-etoposide	65.5 / 34.5	66.9 / 33.1
Prior radiation schedule, %	Once daily / Twice daily	73.9 / 26.1	70.3 / 29.7
Best response to prior cCRT, %	CR / PR / SD	11.7 / 72.3 / 15.9	12.8 / 75.2 / 12.0
Prior PCI, %	Yes / No	53.8 / 46.2	53.8 / 46.2

*Based on the first cycle of chemotherapy.

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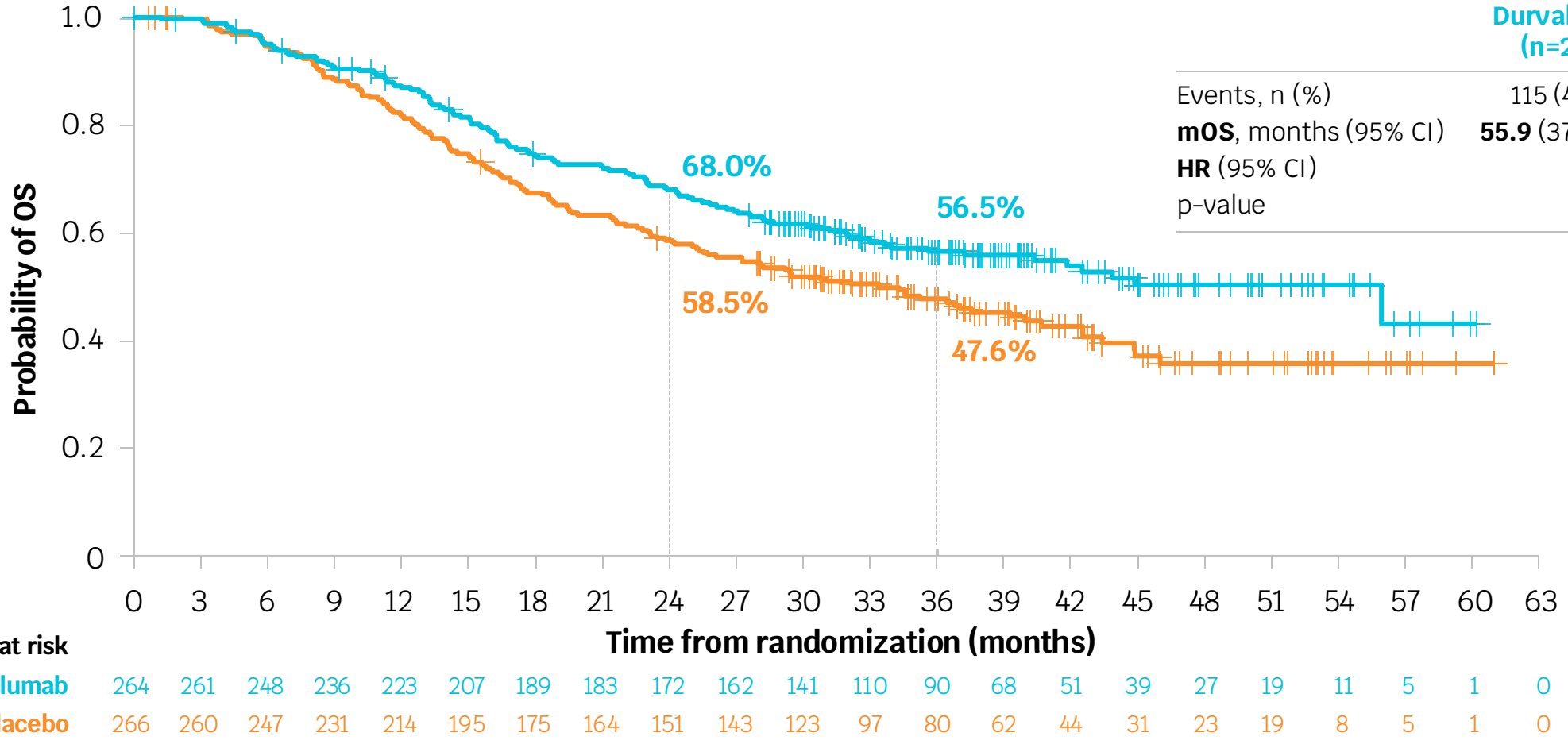
ADRIATIC: Overall survival (dual primary endpoint)

Median duration of follow up in censored patients: 37.2 months (range 0.1–60.9)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	115 (43.6)	146 (54.9)
mOS, months (95% CI)	**55.9** (37.3–NE)	**33.4** (25.5–39.9)
HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	

No. at risk

Durvalumab	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	39	27	19	11	5	1	0
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0

OS was analyzed using a stratified log-rank test adjusted for receipt of PCI (yes vs no). The significance level for testing OS at this interim analysis was 0.01679 (2-sided) at the overall 4.5% level, allowing for strong alpha control across interim and final analysis timepoints.

PRESENTED BY: Dr David R. Spigel

CI, confidence interval; mOS, median OS; NE, not estimable.

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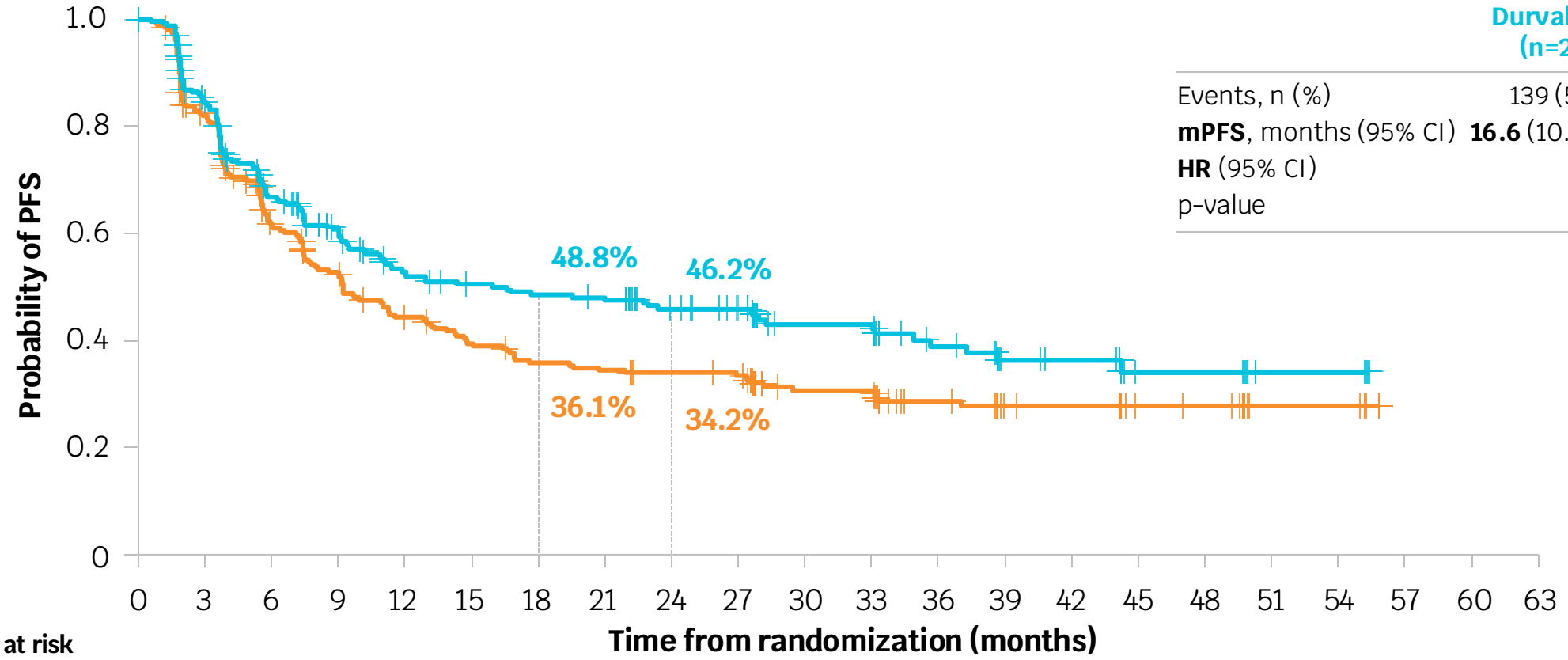
ADRIATIC: Progression-free survival* (dual primary endpoint)

Median duration of follow up in censored patients: 27.6 months (range 0.0–55.8)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	139 (52.7)	169 (63.5)
mPFS, months (95% CI)	**16.6** (10.2–28.2)	**9.2** (7.4–12.9)
HR (95% CI)	**0.76** (0.61–0.95)	
p-value	0.0161	

No. at risk

Durvalumab	264	212	161	135	113	105	101	98	84	78	51	51	33	21	19	10	10	4	4	0	0	0
Placebo	266	208	146	122	100	88	79	76	71	69	47	47	34	23	22	15	14	5	5	0	0	0

*By BICR per RECIST v1.1.

PFS was analyzed using a stratified log-rank test adjusted for disease stage (I/II vs III) and receipt of PCI (yes vs no). The significance level for testing PFS at this interim analysis was 0.00184 (2-sided) at the 0.5% level, and 0.02805 (2-sided) at the overall 5% level. Statistical significance for PFS was achieved through the recycling multiple testing procedure framework and testing at the 5% (2-sided) alpha level (adjusted for an interim and final analysis); **PRESENTED BY:** Dr David R. Spigel; mPFS, median PFS.

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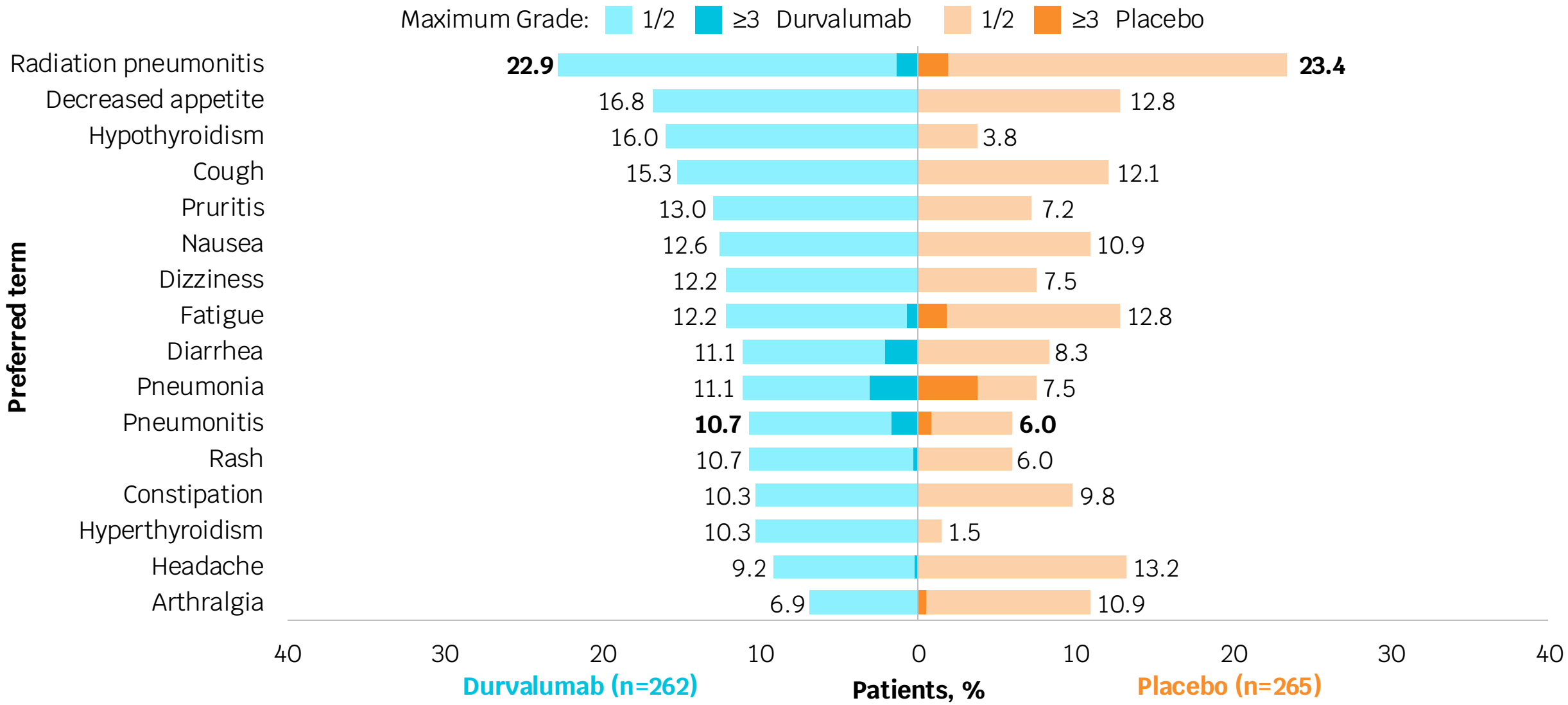
ADRIATIC: Most frequent AEs*



*Occurring in ≥10% of patients in either treatment arm.

PRESENTED BY: Dr David R. Spigel

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ADRIATIC Treatment-related pneumonitis/radiation pneumonitis: Summary

AEs, %		Durvalumab (n=262)	Placebo (n=265)
Pneumonitis/radiation pneumonitis*	**Any grade**	38.2	30.2
	Maximum grade 3/4	3.1	2.6
	Leading to death (grade 5)	0.4	0
	Leading to treatment discontinuation	8.8	3.0
Pneumonitis†	**Any grade**	16.4	6.4
Radiation pneumonitis‡	**Any grade**	23.3	23.8

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ADRIATIC Pneumonitis/radiation pneumonitis: Prior Treatment

	Patients with pneumonitis/ radiation pneumonitis		Patients without pneumonitis/ radiation pneumonitis		ITT population	
	Durvalumab (n=100)	Placebo (n=80)	Durvalumab (n=164)	Placebo (n=186)	Durvalumab (n=264)	Placebo (n=266)
Prior cisplatin / carboplatin etoposide, %*	66 / 34	68 / 33	65 / 35	67 / 33	66 / 34	67 / 33
Prior QD / BID radiotherapy, %	71 / 29	71 / 29	76 / 24	70 / 30	74 / 26	70 / 30
QD total dose: ≥60–≤66 Gy, %	64	68	68	67	66	67
BID total dose: 45 Gy, %	29	28	23	29	25	29
CR / PR / SD to cCRT, %	14 / 76 / 10	16 / 75 / 9	10 / 70 / 20	11 / 75 / 13	12 / 72 / 16	13 / 75 / 12
<14 / 14–<28 / ≥28 days from end of cCRT to R, %	13 / 29 / 58	13 / 30 / 58	12 / 30 / 58	12 / 30 / 58	12 / 30 / 58	12 / 30 / 58
<28 / 28–<56 / 56–<84 / ≥84 days from end RT to R, %	7 / 39 / 35 / 19	11 / 40 / 29 / 20	5 / 40 / 38 / 16	8 / 39 / 28 / 25	6 / 39 / 37 / 17	9 / 39 / 29 / 23
Received prior PCI, %	55	58	53	52	54	54

CR, complete response; PR, partial response; SD, stable disease.
Percentages may not total 100 due to rounding. *Based on the first cycle of chemotherapy.

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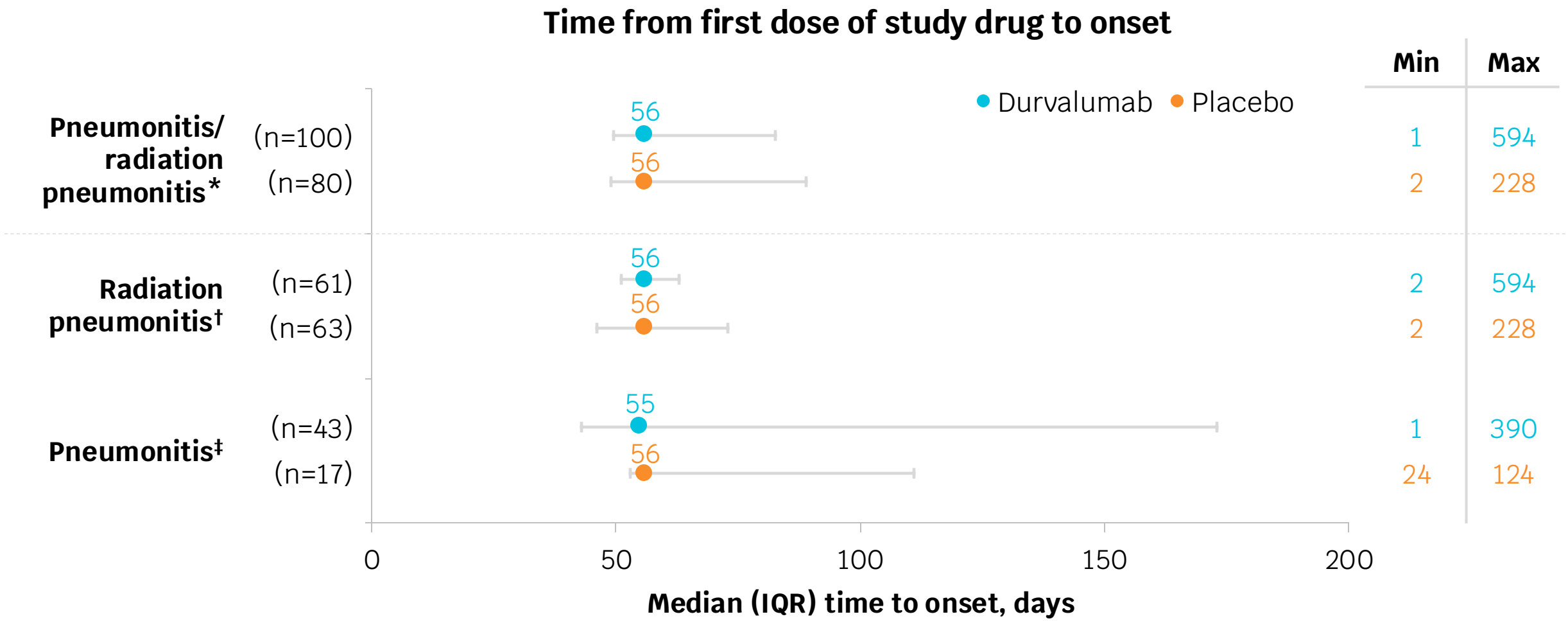
ADRIATIC Pneumonitis/radiation pneumonitis: Time to Onset



IQR, interquartile range.
*Includes the preferred terms of immune-mediated lung disease, interstitial lung disease, pneumonitis, radiation fibrosis – lung, and radiation pneumonitis.
†Includes the preferred terms of radiation fibrosis – lung, and radiation pneumonitis. ‡Includes the preferred terms of immune-mediated lung disease, interstitial lung disease, and pneumonitis.

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ADRIATIC Pneumonitis/radiation pneumonitis: Management and Outcomes

Maximum CTCAE grade of pneumonitis/radiation pneumonitis*		Management/intervention, n				Event outcome,¶ n
		Treatment discontinued	Systemic corticosteroid	High-dose corticosteroid†	Other immunosuppressant	Resolved§
Durvalumab (n=262)	**Total (n=100)**	**23**	**64**	**51**	**1‡**	**38**
	Grade 1 (n=31)	1	2	1	0	6
	Grade 2 (n=60)	14	53	41	0	28
	Grade ≥3 (n=9)	8	9	9	1‡	4
Placebo (n=265)	**Total (n=80)**	**8**	**34**	**28**	**1‡**	**23**
	Grade 1 (n=40)	0	0	0	0	6
	Grade 2 (n=33)	3	28	22	0	13
	Grade ≥3 (n=7)	5	6	6	1‡	4

CTCAE, Common Terminology Criteria for Adverse Events.
*Includes the preferred terms of immune-mediated lung disease, interstitial lung disease, pneumonitis, radiation fibrosis – lung, and radiation pneumonitis.
†A dose that equates to ≥40 mg prednisone daily. ‡Infliximab. ¶If a patient had multiple events within a specific group then the outcome of the event with the highest CTCAE grade, with the worst outcome was counted.
§Resolved includes outcomes of: recovered/resolved, recovered/resolved with sequelae.

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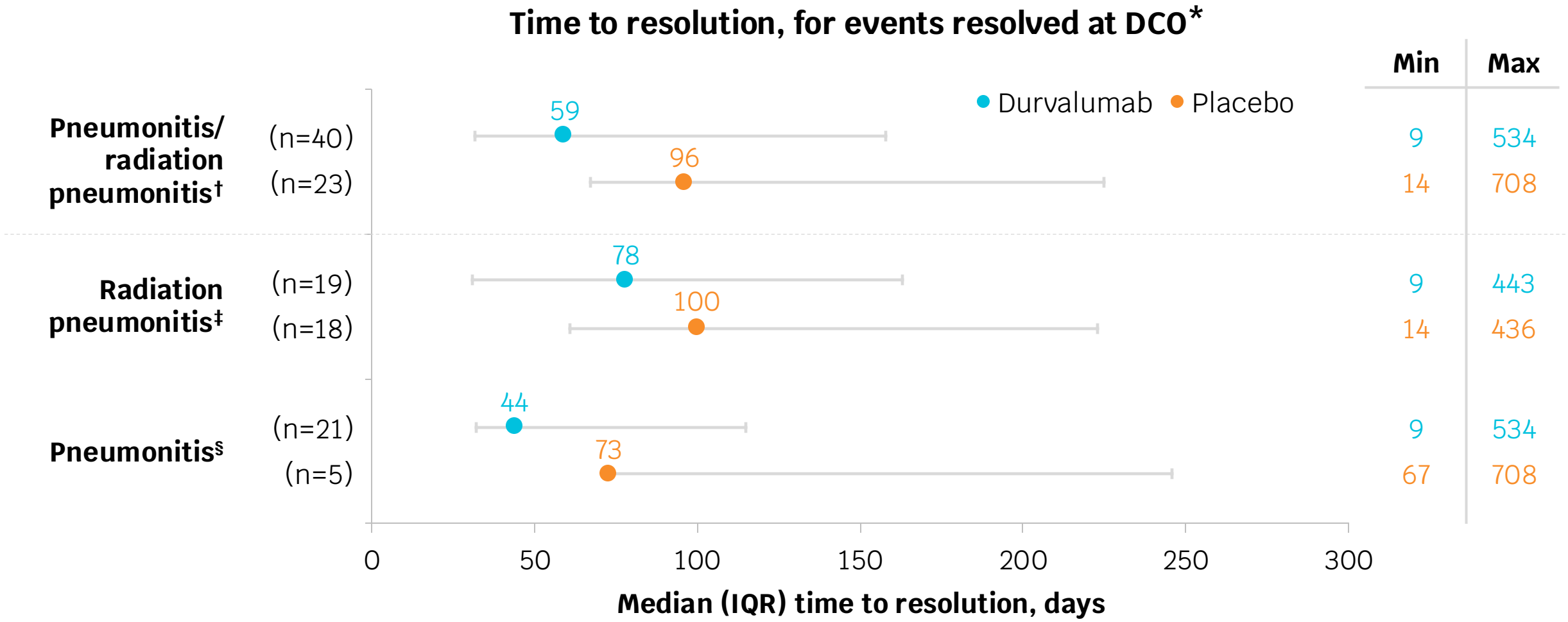
ADRIATIC Pneumonitis/radiation pneumonitis: Time to Resolution



DCO, data cut-off (Jan 15, 2024).
*n = all resolved events; a patient may have had multiple events within a category; resolved includes outcomes of: recovered/resolved, recovered/resolved with sequelae.
†Includes the preferred terms of immune-mediated lung disease, interstitial lung disease, pneumonitis, radiation fibrosis – lung, and radiation pneumonitis.
‡Includes the preferred terms of radiation fibrosis – lung, and radiation pneumonitis. §Includes the preferred terms of immune-mediated lung disease, interstitial lung disease, and pneumonitis.

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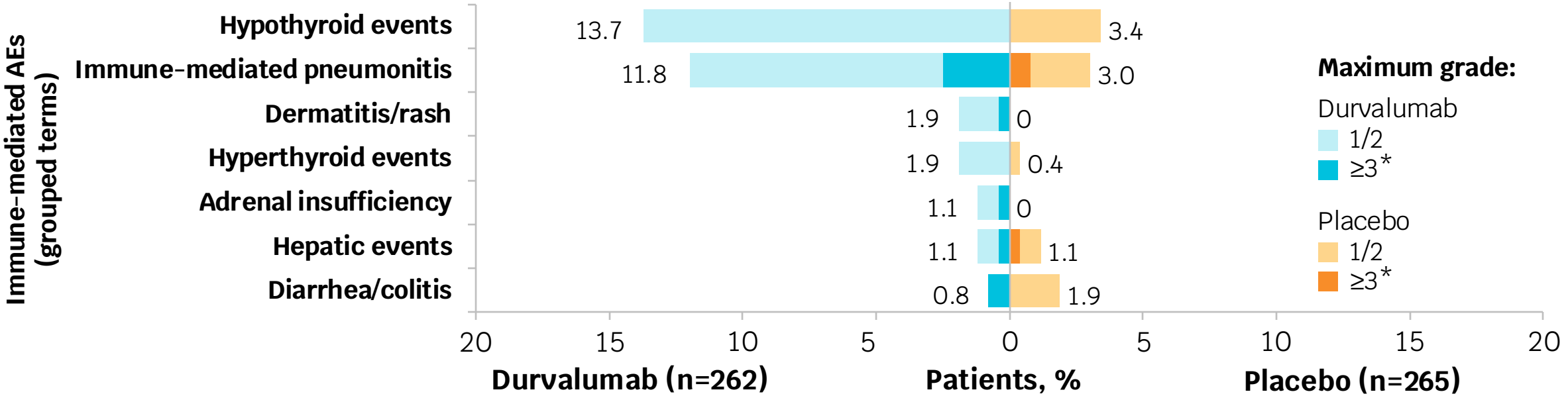
ADRIATIC Immune-mediated AEs: summary

Immune-mediated AEs, %	Durvalumab (n=262)	Placebo (n=265)
Any grade	32.1	10.2
Maximum grade 3/4	5.3	1.5
Serious	9.2	3.0
Leading to death	0.4	0
Leading to treatment discontinuation	7.3	2.6



Events reported in ≥1% of patients in either treatment arm are shown. *All grade ≥3 imAEs were grade 3/4 except one case of grade 5 immune-mediated pneumonitis in the durvalumab arm.

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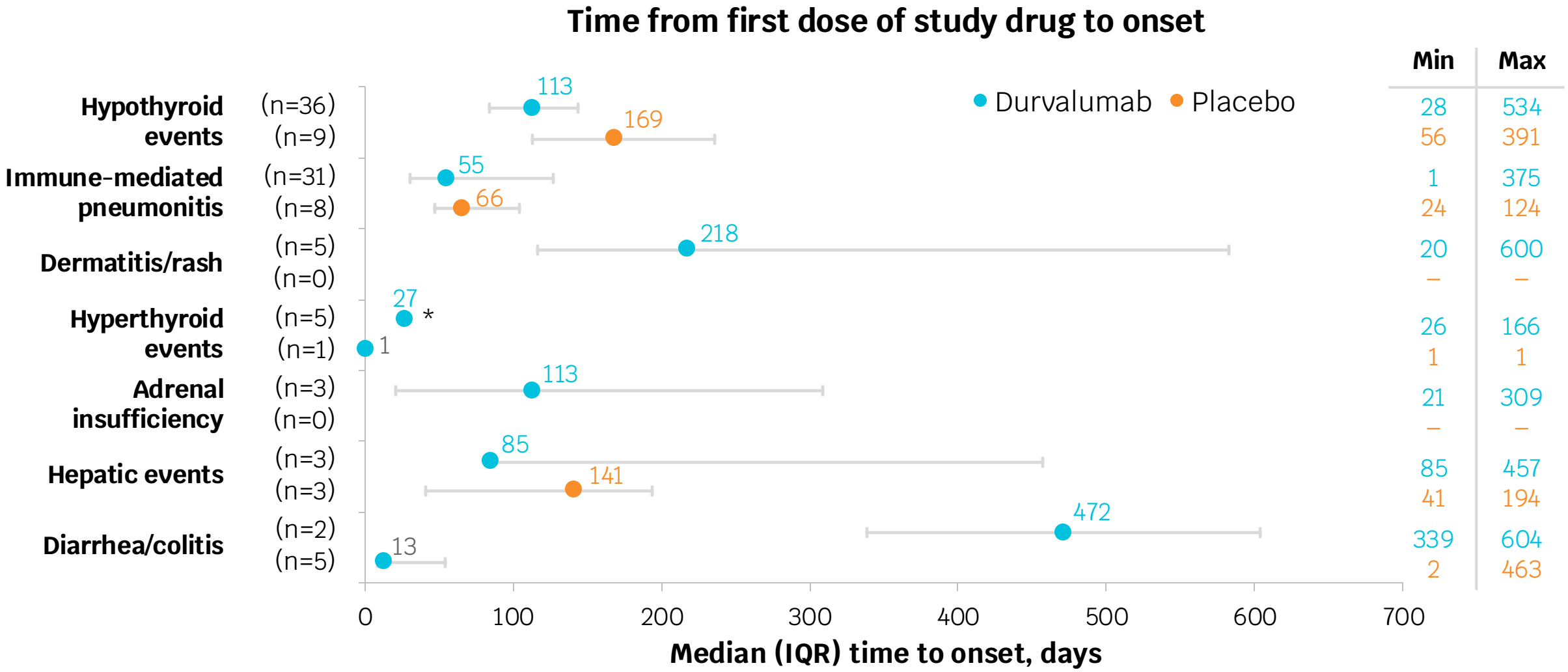
ADRIATIC Immune-mediated AEs: Time to Onset



Events reported in ≥1% of patients in either treatment arm are shown. * IQR 27–29 (not visible due to scale of figure).

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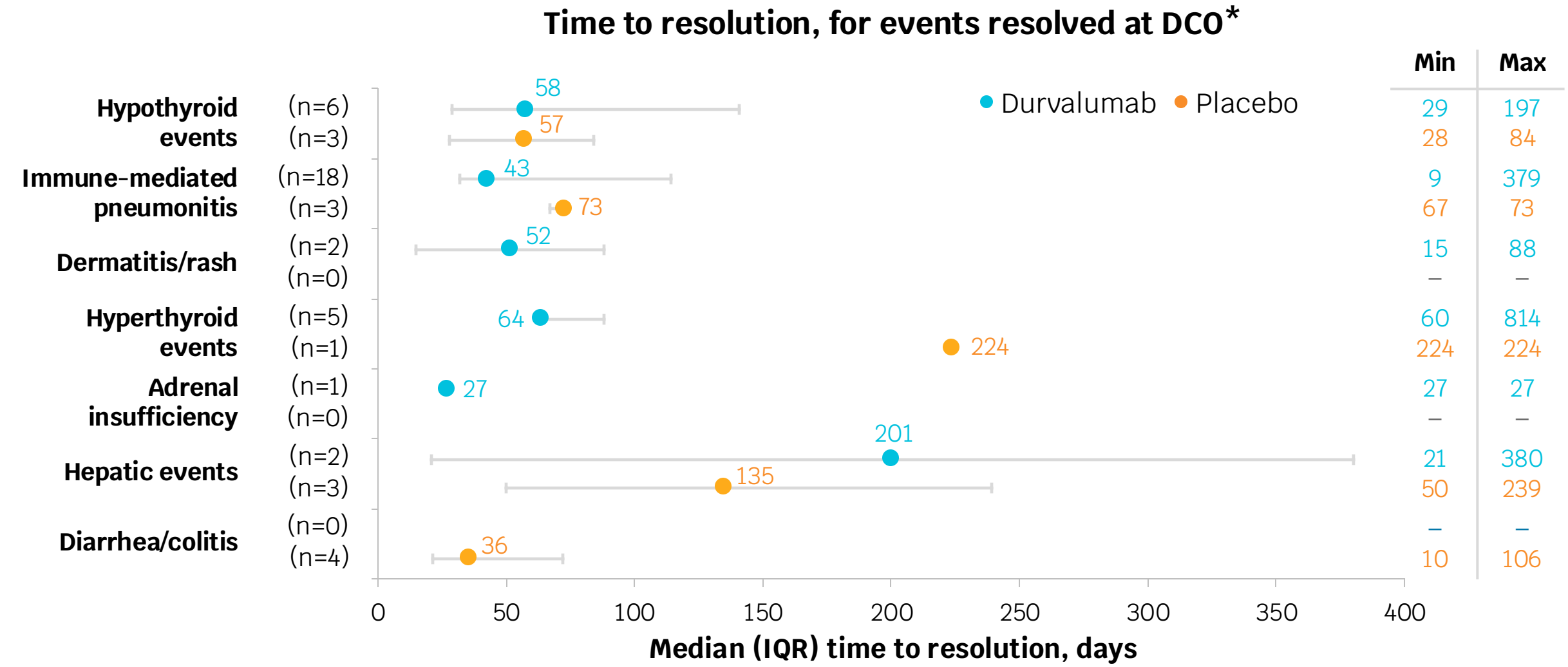
ADRIATIC Immune-mediated AEs: management and outcomes

imAEs (grouped terms)		Management/intervention, n			Event outcome,§ n
		Treatment discontinued	High-dose corticosteroid*	Other immunosuppressant	Resolved¶
Durvalumab (n=262)	Hypothyroid events (n=36)	1	0	0	6
	Immune-mediated pneumonitis (n=31)	13	25	1†	18
	Dermatitis/rash (n=5)	0	1	0	2
	Hyperthyroid events (n=5)	0	1	0	5
	Adrenal insufficiency (n=3)	0	0	0	1
	Hepatic events (n=3)	1	3	1‡	2
	Diarrhea/colitis (n=2)	2	2	1†	0
Placebo (n=265)	Hypothyroid events (n=9)	0	0	0	3
	Immune-mediated pneumonitis (n=8)	3	7	0	3
	Dermatitis/rash (n=0)	-	-	-	-
	Hyperthyroid events (n=1)	0	0	0	1
	Adrenal insufficiency (n=0)	-	-	-	-
	Hepatic events (n=3)	1	3	0	3
	Diarrhea/colitis (n=5)	2	4	1†	4

Events reported in ≥1% of patients in either treatment arm are shown. *A dose that equates to ≥40 mg prednisone daily. †Infliximab. ‡Mycophenolate.
§If a patient had multiple events within a specific group then the outcome of the event with the highest CTCAE grade, with the worst outcome was counted. ¶Resolved includes outcomes of: recovered/resolved, recovered/resolved with sequelae.

Iyengar P, et al. ASTRO 2024

ADRIATIC Immune-mediated AEs: Time to Resolution



Events reported in ≥1% of patients in either treatment arm are included.
*n = all resolved events; a patient may have had multiple events within a category; resolved includes outcomes of: recovered/resolved, recovered/resolved with sequelae.

Iyengar P, et al. ASTRO 2024

NRG-LU005: Phase II/III randomized study of chemoradiation vs. chemoradiation plus atezolizumab

PATIENT POPULATION:
Limited stage SCLC

STRATIFICATION
- Radiation schedule (BID vs daily)
- Chemotherapy (cisplatin vs carboplatin)
- Sex
- ECOG Performance Status (0/1 vs 2)

N = 506

R

Platinum/etoposide x 4 cycles
+
Thoracic RT 45 Gy bid or 66 Gy daily

Platinum/etoposide x 4 cycles
+
Thoracic RT 45 Gy bid or 66 Gy daily
+
Atezolizumab q3 weeks beginning with cycle 2

Atezolizumab q3 weeks for 1 year

Higgins K. TLC 2023

NRG/LU005

Results

- 506 patients accrued from 5/2019 – 6/2022
  - Accrual continued in Japan until 12/23 (n = 544)
  - US accrual: 500
  - Japanese accrual: 44
- 218 institutions
- Median follow up of 21 months

Conclusions

- Concurrent Atezolizumab did not improve survival for patients with LS-SCLC compared with standard chemoradiation.
- Twice daily radiation may be associated with improved survival compared to daily RT and could be considered the optimal choice for RT fractionation. Additional analysis is warranted.

Treatment Compliance

	CRT Only (n = 254)	CRT + Atezo (n = 267)
Any protocol treatment	254 (94%)	267 (97.4%)
Number of atezo doses (median)	NA	8
Reasons for discontinuation		
Adverse event		39 (24.6%)
Physician discretion		16 (10.1%)
Disease progression		71 (44.9%)
Died		13 (8.2%)
Subject withdrawl		13 (8.2%)
Other		6 (3.8%)
Completion of RT	236 (92.9%)	247 (92.5%)
Completion of chemotherapy		
Cisplatin	127 (87%)	128 (88.3%)
Carboplatin	98 (92.5%)	105 (83.3%)

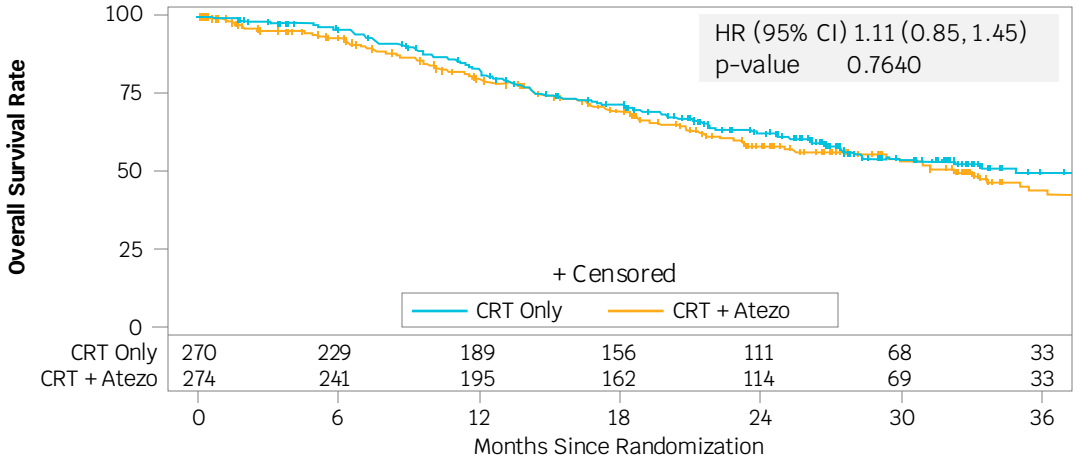
Safety

	CRT Only (n = 254)	CRT + Atezo (n = 267)
Any grade AES	251 (99)	266 (99.6)
Grade 3/4 AEs	235 (92.5)	231 (86.5)
AEs leading to death	4 (1.6)	24 (9)*
Treatment-related AEs leading to death	2 (1)	9 (3)
Grade 3/4 Immune related AEs	16 (6.2)	42 (15.7)
Grade 5 Immune related AEs	0 (0)	4 (1.5)

*Reporting window of 30 days post CRT for control arm and 90 days post end of atezo for experimental arm (11 weeks vs. 15 months)

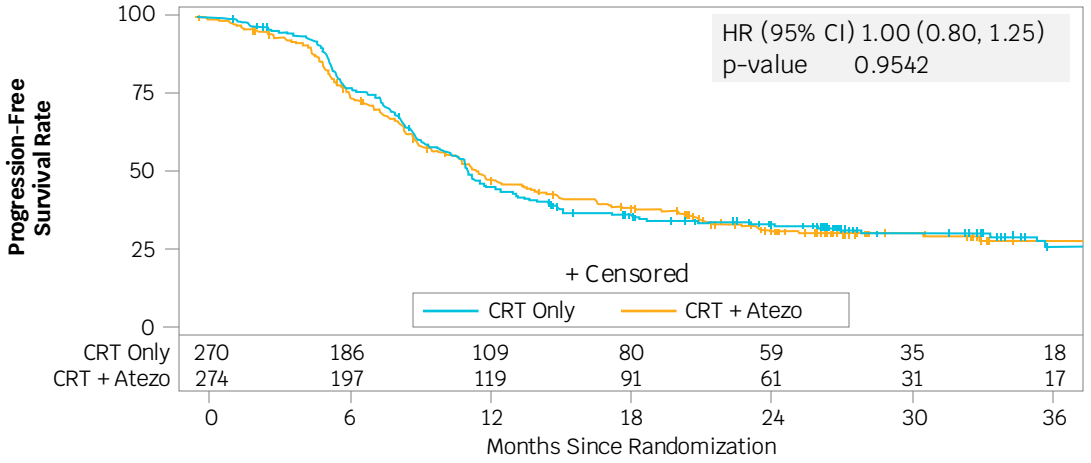
NRG/LU005

Overall Survival



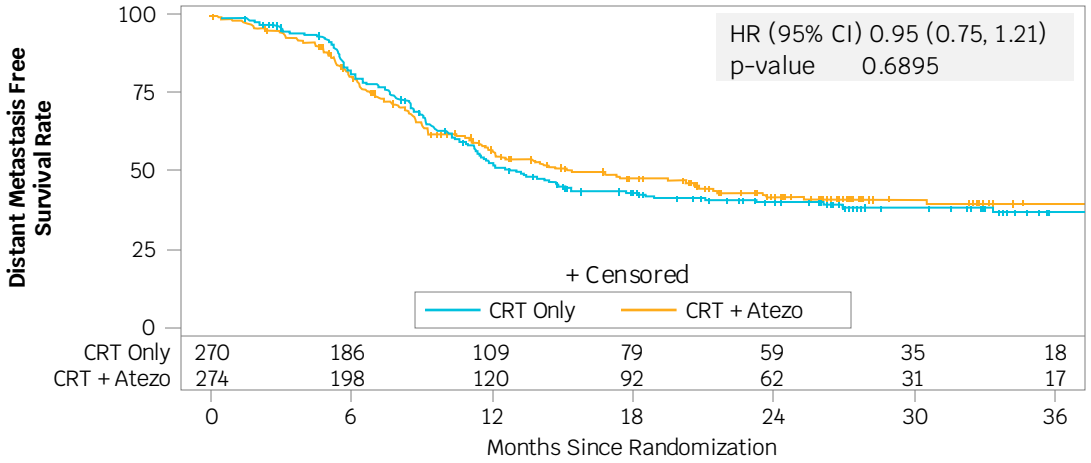
Hazard ratio and one-sided p-value stratified by RT schedule, chemotherapy, and sex

Progression Free Survival



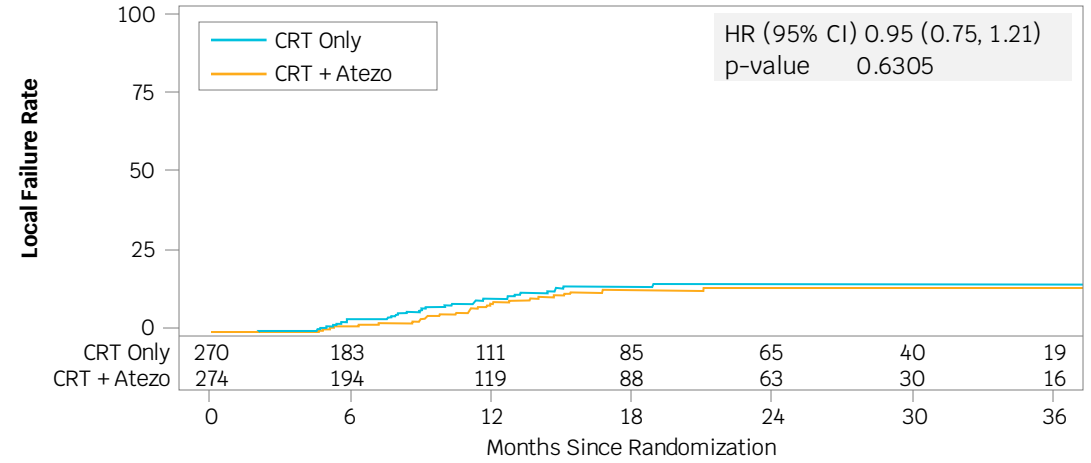
Hazard ratio and p-value stratified by RT schedule, chemotherapy, and sex

Distant Metastasis Free Survival



Hazard ratio and p-value stratified by RT schedule, chemotherapy, and sex

Time to Local Failure



Hazard ratio and p-value stratified by RT schedule, chemotherapy, and sex

Higgins K, et al. ASTRO 2024

Caveats of Cross Trial Comparison Apply

ADRIATIC vs. LU005

- Durvalumab vs Atezolizumab
  - Similar benefit in ES-SCLC studies
- Better outcomes in the control arm of LU005

! Caveats of Cross Trial Comparisons !

	LU005 CRT	LU005 CRT+atezo	ADRIATIC CRT	ADRIATIC CRT +durva	Intergroup	CONVERT	CALGB 30610/ RTOG 0538
Median OS	39.5m	33.1m	33.4m	55.9m	23m	25-30m	28.5-30m
2 Year OS	62.9%	50.3%	58.5%	68%	47%	51-56%	57-58%

- Distinct cohort – ADRIATIC pts had CR/PR/SD after CRT (completed)
- Different populations – N. America/Japan vs. Asia/Europe/S. America
  - Patient immunogenetics
  - Tumor biology/subtypes

Immunotherapy/RT Synergy-Timing is Everything

- Radiation can promote tumor immunogenicity via enhanced antigenicity and adjuvanticity (immunogenic cell death)[1]
- Initiation of IO treatment can result in acute reinvigoration of antitumor T cells in the draining lymph node and periphery[2]
- Radiation to nodal basins (and blood volume) can restrain this acute response

Lesson 3:

- Close interval between RT and IO start can maximize RT-induced immune activation while minimizing RT immune cytotoxicity

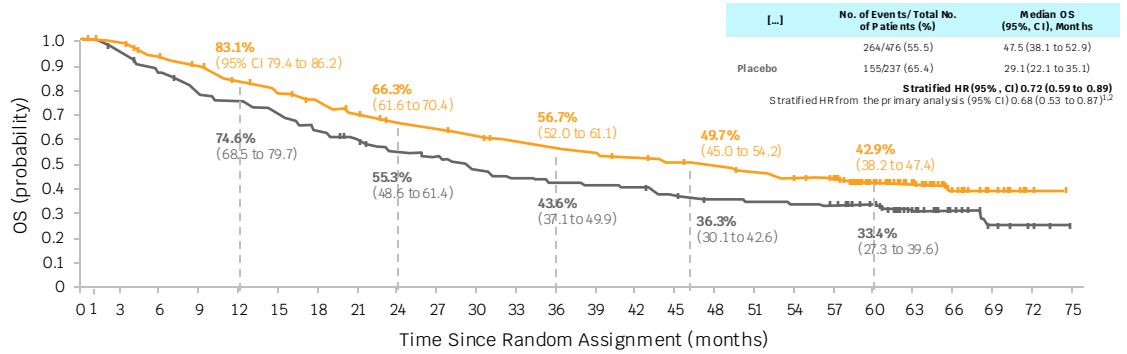
OS

Time from end of concurrent CRT to randomization

<14 days	14/32 (44.0)	24/32 (75.0)	0.47 (0.24-0.91)
14 to <28 days	37/79 (47.0)	51/80 (64.0)	0.59 (0.38-0.90)
≥28 days	64/153 (41.8)	71/154 (46.1)	0.90 (0.64-1.27)

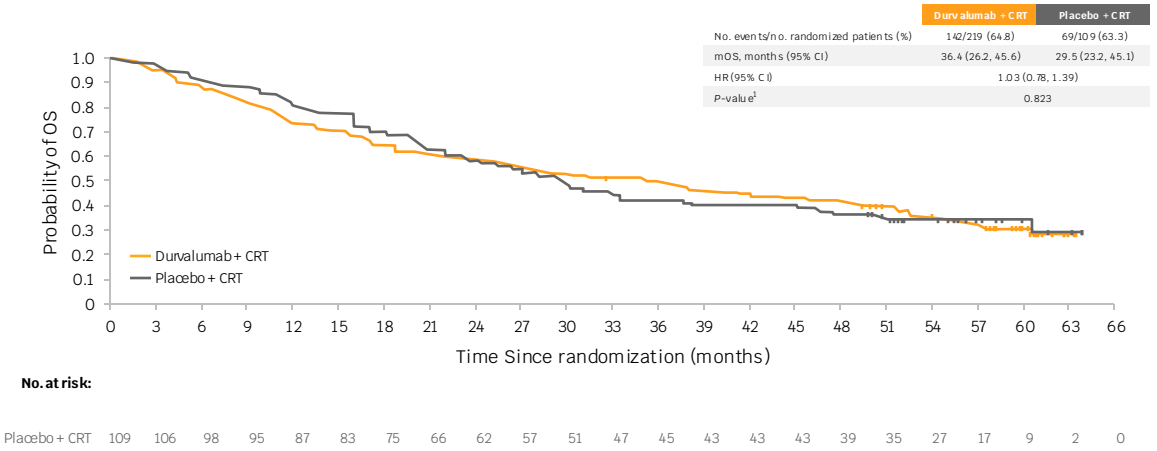
Consolidation vs. Concurrent Immunotherapy

PACIFIC: Consolidative durvalumab



Spigel et al, JCO 2022

PACIFIC-2: Concurrent durvalumab



Bradley et al, ELCC 2024

ADRIATIC, Ching et al, NEJM 2024

[1]Galluzi et al, Nat Rev Clin Onc 2023; Patel and Minn, Immunity 2018. [2]Huang et al, Nature 2017; Huang et al, Nat Med 2019

Samstein R, et al. ASTRO 2024

The Future

1. RAPTOR – consolidation with radiation in ES SCLC with IO?

2. Radiation with novel systemic therapy agents – ADCs, BiTEs, etc.?

3. Targeted therapies with radiation?

4. CAR-T?

5. MRI surveillance and use of SRS for SCLC brain mets?