SINGAPORE 2025 ESMO ASIA

Enozertinib (ORIC-114), a Highly Selective, Brain Penetrant EGFR and HER2 Inhibitor in Previously Treated NSCLC with EGFR Atypical Mutations

Min Hee Hong[1], Konstantinos Levantakos[2], Eun-Kyung Cho[3]; Yu Jung Kim[4], Adnan Khattak[5], Omar Saavedra[6], Sarah Goldberg[7], Nisha Mohindra[8], Danny Nguyen[9], Julia Rotow[10], Sonam Puri[11], Voon Pei Jye[12], Art Weber[13], Karen Velastegui[13], Anneleen Daemen[14], Jian Wang[13], Edna Chow Maneval[13], Pratik S. Multani[13], Byoung Chul Cho[1]

[1]Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Mayo Clinic, Rochester, MN, USA; [3]Gachon University Gil Hospital, Incheon, Republic of Korea; [4]Seoul National University Hospital, Seoul, Republic of Korea; [5]Medical Oncology Clinical Trials Unit, Fiona Stanley Hospital and Edith Cowan University, Murdoch, Australia; [6]NEXT Oncology, Barcelona, Spain; [7]Yale School of Medicine, New Haven, CT, USA; [8]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; [9]City of Hope, Duarte, CA, USA; [10]Dana-Farber Cancer Institute, Boston, MA, USA; [11]Moffitt Cancer Center, Tampa, FL, USA; [12]Sarawak General Hospital, Kuching, Malaysia; [13]ORIC Pharmaceuticals, Inc. San Diego, CA, USA; [14]ORIC Pharmaceuticals, Inc. South San Francisco, CA, USA.

Min Hee Hong, MD
Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

05 December 2025

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

DECLARATION OF INTERESTS

Min Hee Hong, MD

Honoraria

- AstraZeneca, Amgen, Beigene, BMS, Daiichi Sankyo, Janssen, MSD, Ono pharmaceutical, Takeda, Roche, Yuhan

Consulting or advisory role

- AstraZeneca, BeOne Medicines, BMS, Daiichi Sankyo, Janssen, MSD, Ono pharmaceutical, Takeda, Roche, Yuhan

Investigator or co-investigator of trials

- AbbVie, AstraZeneca, Beigene, BMS, Daiichi Sankyo, IMPACT Therapeutics, Ignyta, Janssen, Loxo Oncology, Merck Sereno, MSD, Novartis, ORIC, Roche, Pfizer, Yuhan

Research support

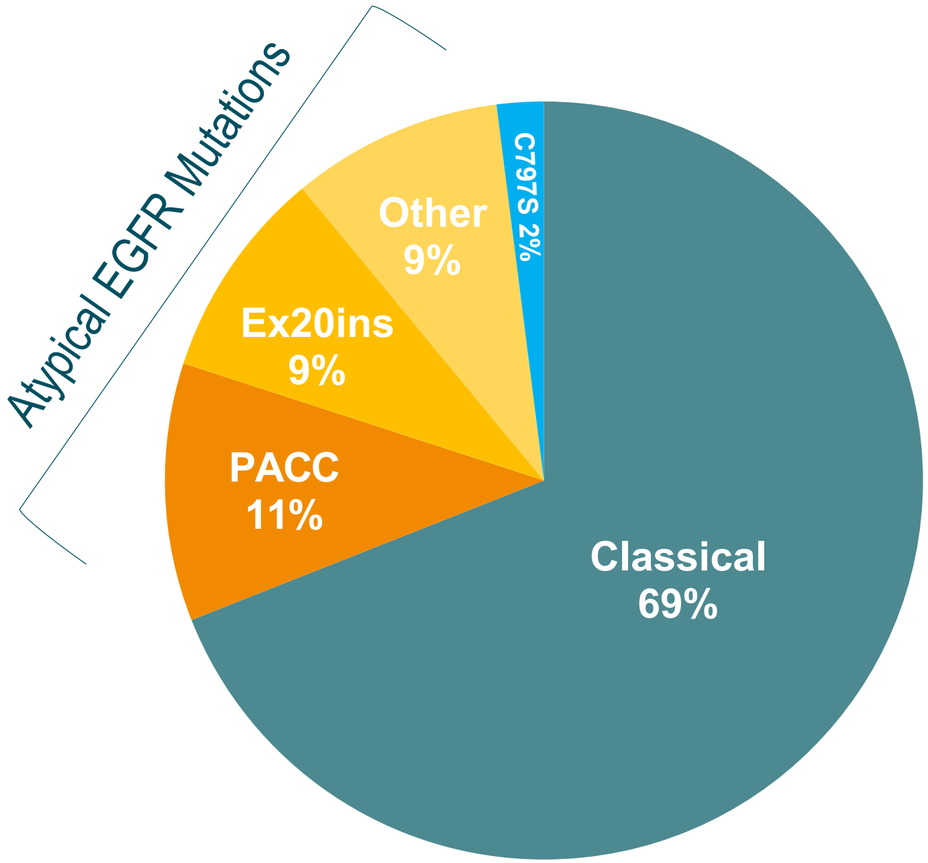
- AstraZeneca, MSD, Novartis, Yuhan

Stock ownership

- GI cell, GI longevity

Epidermal Growth Factor Receptor (EGFR) Atypical Mutations in Non-Small Cell Lung Cancer (NSCLC)

- EGFR atypical mutations are a heterogenous group of non-classical mutations that comprise ~30% of all NSCLC EGFR mutations[1]
    - P-loop and αC-helix compressing (PACC) mutations comprise 11% of all EGFR mutant NSCLC[2]
- ~30% of patients with EGFR mutant NSCLC present with de novo CNS disease highlighting a propensity for CNS spread independent of therapeutic resistance[3]
- ~50% of patients with EGFR-mutant NSCLC develop brain metastases over the course of their disease, which contribute to a worse prognosis and for which effective treatment options are limited[4]



New brain-penetrant therapies are needed to effectively treat NSCLC patients with EGFR atypical mutations

Pie chart: n=3,092 EGFR-mutant NSCLC. Classical = L858R and del19. Other = Non-PACC atypical mutations located in exons 18-21. T790M complexes are distributed over other categories.[2]

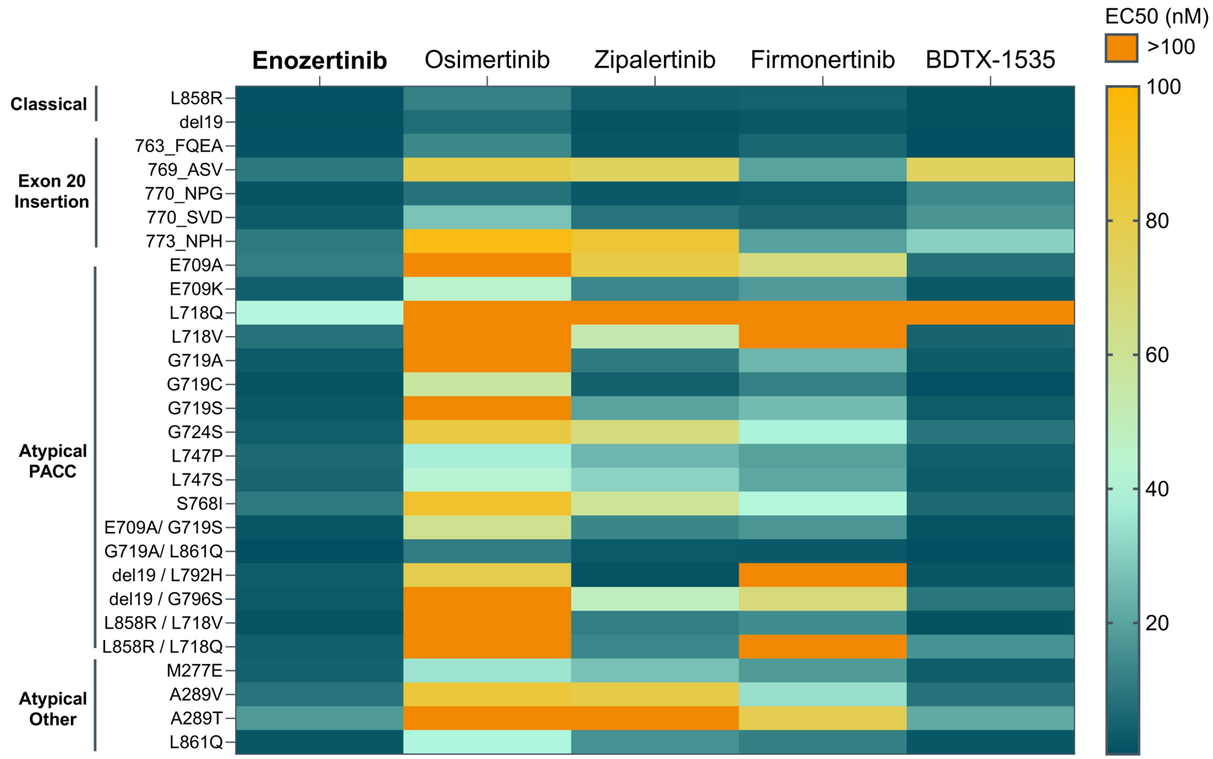
[1]Janning M, et al. *Ann Oncol.* 2022;33(6):602-215; [2]AACR Project GENIE Consortium, *Cancer Discov.* 2017;7(8):813-31; [3]Patil T, et al. *Clin Lung Cancer;2021;21:e191–204*; [4]Wilcox JA, et al. *Ann Oncol.* 2025;36(10):1142-53.

Min Hee Hong, MD

Enozertinib Was Designed with Best-in-class Drug Properties Including Brain Penetration

- Enozertinib is a selective, orally bioavailable, highly CNS-penetrant, irreversible small molecule inhibitor of mutant EGFR and HER2
  - Exquisite kinome selectivity with no off-target inhibition
  - Strong potency across EGFR atypical mutations
  - Regressions in EGFR atypical PACC mutant mouse models at well-tolerated doses
  - Superior unbound brain to plasma exposure ratio *in vivo* relative to other EGFR atypical-targeted agents
  - Regressions in intracranial EGFR mutant lung tumor model
- Enozertinib at 80 mg and 120 mg once daily (QD) were selected as provisional RP2Ds for dose optimization based on Phase 1 dose escalation safety, efficacy, PK and PD results

Enozertinib Demonstrates Superior *in vitro* Potency Across EGFR Mutants Compared with Other EGFR Inhibitors[1]



Enozertinib is a selective, CNS-penetrant EGFR inhibitor with best-in-class potency against EGFR atypical mutations

Min Hee Hong, MD

HER2, human epidermal growth factor receptor 2; PD, pharmacodynamic; PK, pharmacokinetic; RP2D, recommended phase 2 dose.

[1]Junttila MR, et al. Cancer Research. 2025; In press.

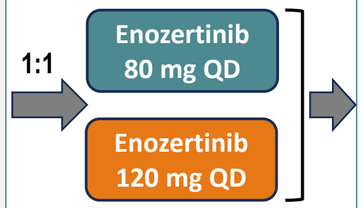
Enozertinib in Advanced NSCLC with or without CNS Involvement

Phase 1/2 Study in patients with NSCLC and EGFR atypical mutations (NCT05315700)

- First-in-human, global study evaluating the safety and preliminary efficacy of enozertinib in patients with advanced NSCLC harboring EGFR or HER2 alterations

Key Eligibility Criteria:

- Locally advanced or metastatic NSCLC with EGFR atypical mutation
  - PACC, Classical-like, del19 non-PACC
  - Single and compound mutations
- Untreated, stable, asymptomatic brain metastases allowed
- Prior therapies allowed, including chemotherapy and prior EGFR TKIs (e.g., afatinib, osimertinib)



Primary endpoint:

- Selection of recommended Ph 2 dose

Secondary endpoints:

- Investigator assessed objective response rate (ORR)
- Safety

Patient Characteristic	80 mg (n=25)	120 mg (n=22)	Total (n=47)
Age, years, median (range)	65 (37-84)	66 (37-76)	65 (37-84)
Female, n (%)	16 (64)	16 (73)	32 (68)
Non-smoker, n (%)	25 (100)	22 (100)	47 (100)
Race: Asian / White / Other, %	64 / 32 / 4	64 / 32 / 5	64 / 32 / 4
ECOG performance status: 0 / 1, %	28 / 72	36 / 64	32 / 68
Brain metastases at baseline*, n (%)	14 (56)	12 (55)	26 (55)
Prior therapies, median	2	2	2
Prior chemotherapy, n (%)	12 (48)	11 (50)	23 (49)
Prior immunotherapy, n (%)	5 (20)	4 (18)	9 (19)
Prior EGFR targeted therapy, n (%)	21 (84)	17 (77)	38 (81)
PACC mutation, n (%)	12 (48)	13 (59)	25 (53)

Data cutoff: August 29, 2025
*CNS disease at baseline includes patients with brain metastases at study entry, including active brain metastases

55% of previously treated patients had brain metastases at study entry, including those with active CNS disease

Min Hee Hong, MD

Treatment-Related Adverse Events (TRAEs) in ≥20% of Patients

Previously treated advanced NSCLC with EGFR atypical mutations

Event, n (%)	80 mg (n=25)	120 mg (n=22)	Total (n=47)
TRAEs Grade ≥3	7 (28)	8 (36)	15 (32)
Dose reduction due to TRAE	5 (20)	15 (68)	20 (43)
Discontinued due to TRAE	0	0	0

- Well tolerated safety profile with TRAEs predominantly Grades 1–2
- No Grade 4 or 5 TRAEs
- No significant off-target toxicities (e.g., myelosuppression, QTc prolongation, hepatotoxicity)
- No discontinuations due to TRAEs
- Higher rate of dose reductions at 120 mg (68%) vs. 80 mg (20%)
  - 80% of dose reductions from 120 mg dose down to 80 mg occurred before ~8 weeks on treatment (2 cycles)

Event	80 mg (n=25)		120 mg (n=22)	
Preferred term, n (%)	Grade 1-2	Grade 3	Grade 1-2	Grade 3
Diarrhea	12 (48)	2 (8)	14 (64)	3 (14)
Paronychia	12 (48)	0	13 (59)	1 (5)
Stomatitis	10 (40)	0	10 (45)	1 (5)
Dermatitis acneiform	8 (32)	0	8 (36)	0
Rash	8 (32)	0	4 (18)	0
Nausea	3 (12)	0	7 (32)	0
Pruritis	5 (20)	1 (4)	5 (23)	0
Mucosal inflammation	4 (16)	0	4 (18)	2 (9)

80 mg dose generally well tolerated;
given high rate of dose reductions at 120 mg dose, most patients received an effective dose of 80 mg QD

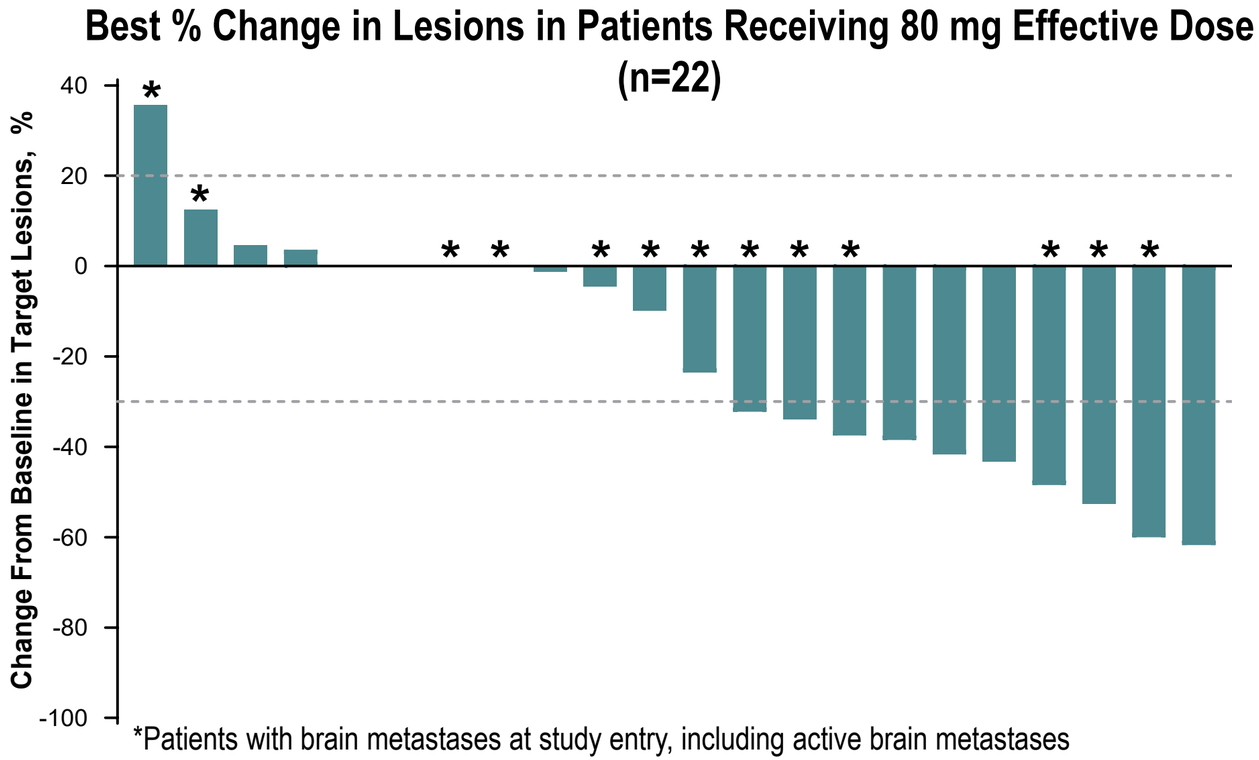
Min Hee Hong, MD

Objective Response Rate (ORR) and Best Tumor Reduction

Previously treated advanced NSCLC with EGFR atypical mutations, PACC cohort

Efficacy Evaluable Population*	Effective Dose 80 mg (n=22)†
Best ORR,‡ % [95% CI]	**36** [17, 59]
Confirmed ORR, % [95% CI]	**36** [17, 59]
Partial response, n (%)	8 (36)
Stable disease, n (%)	12 (55)
Progressive disease, n (%)	2 (9)
Disease control rate (CR + PR + SD), % [95% CI]	**91** [71, 99]
With CNS disease§ at baseline, n	**13**
Best ORR,‡ % [95% CI]	**31** [9, 61]
Confirmed ORR, % [95% CI]	**31** [9, 61]
Partial response, n (%)	4 (31)
Stable disease, n (%)	7 (54)
Progressive disease, n (%)	2 (15)
Disease control rate (CR + PR + SD), % [95% CI]	**85** [55, 98]

CR, complete response; PR, partial response; SD, stable disease
Data cutoff: August 29, 2025
*Reported in the efficacy evaluable population which includes patients who have received ≥1 dose, have ≥1 measurable lesion at baseline, and have had the opportunity for ≥3 post-baseline scans
†22 patients were efficacy evaluable and received an effective dose of 80 mg: in the 80 mg cohort n=12 patients were efficacy evaluable; of the efficacy evaluable patients in the 120 mg cohort, 10 (77%) required an early dose reduction to 80 mg
‡Best objective response rate includes both confirmed and unconfirmed responses
§CNS disease at baseline includes patients with brain metastases at study entry, including active brain metastases

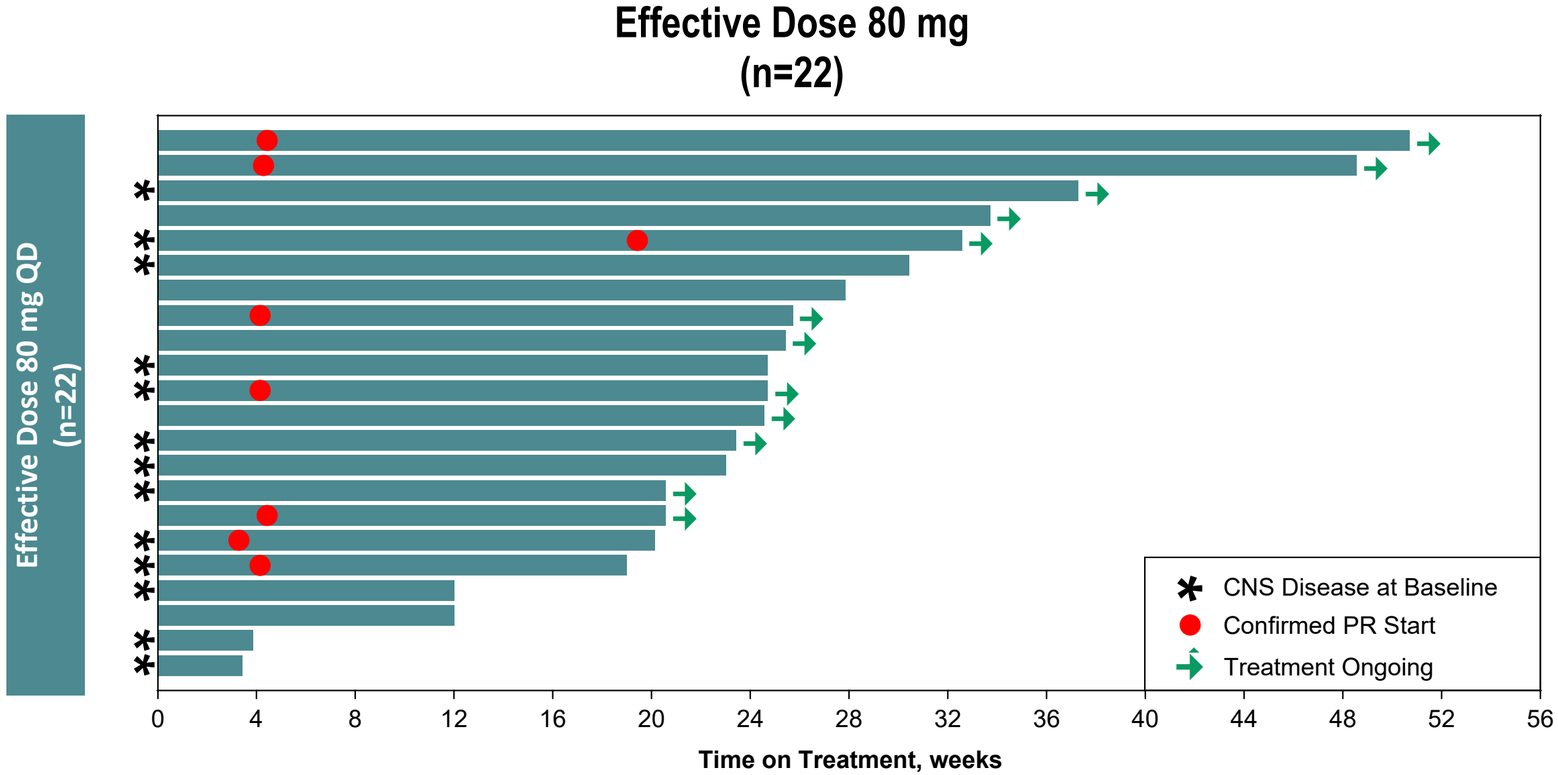


Enozertinib demonstrated strong systemic and CNS antitumor activity in a median 3L+ EGFR PACC mutant NSCLC patient population, 59% (13/22) of whom had brain metastases at study entry

3L, third-line

Treatment Duration and Time of Responses

Previously treated advanced NSCLC with EGFR atypical mutations, PACC cohort



- Median follow-up of 32.6 weeks; 75% (6/8) of responders remain on treatment

Enozertinib demonstrated early and durable responses in a median 3L+ EGFR PACC mutant NSCLC patient population

3L, third-line

Conclusions

- Enozertinib is a selective, CNS-penetrant, orally bioavailable EGFR inhibitor with best-in-class potency against EGFR atypical mutations
- Enozertinib 80 mg dose was generally well tolerated; given high rate of dose reductions at 120 mg dose, most patients received an effective dose of 80 mg QD
- Enozertinib demonstrated strong systemic and CNS antitumor activity in a median 3L+ EGFR PACC mutant NSCLC patient population, 59% of which had brain metastases at study entry
- These findings support 80 mg QD as the recommended enozertinib dose for further development in 1L NSCLC patients with EGFR PACC mutations

SINGAPORE 2025 ESMO ASIA

Acknowledgments

- We thank the patients, families, caregivers, and investigators who participated in this study
- This study was sponsored by ORIC Pharmaceuticals, Inc.
- Editorial assistance was provided by ICON plc (Blue Bell, PA), and was funded by ORIC Pharmaceuticals, Inc.

European Society for Medical Oncology (ESMO)
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE