Supplementary

Table S1 Ethics review board approval dates and locations

Study site number	ERB approval date	Study site center name	Prefecture	Country
651	21-Apr-2015	Shizuoka Cancer Center	Shizuoka	Japan
652	21-Apr-2015	Kindai University Hospital	Osaka	Japan
653	13-May-2015	Japanese Foundation for Cancer Research	Tokyo	Japan
654	14-Oct-2015	National Cancer Center Hospital East	Chiba	Japan
655	14-May-2015	National Hospital Organization Kyushu Cancer Center	Fukuoka	Japan
656	19-May-2015	Okayama University Hospital	Okayama	Japan
657	13-May-2015	National Cancer Center Hospital	Tokyo	Japan
658	25-Dec-2015	Tokyo Met Cancer & Infectious Diseases Center Komagome Hp	Tokyo	Japan
659	25-Nov-2015	Saitama Prefectural Cancer Center	Saitama	Japan
660	02-Nov-2015	Chiba University Hospital	Chiba	Japan
661	18-Nov-2015	Kyoto University Hospital	Kyoto	Japan
662	19-Jan-2016	Kansai Medical University Hospital	Osaka	Japan
663	26-Oct-2015	Nagasaki University Hospital	Nagasaki	Japan
664	20-Nov-2015	Osaka City General Hospital	Osaka	Japan
665	05-Jan-2016	Kyushu University Hospital	Fukuoka	Japan
666	04-Dec-2015	Foundation for Biomedical Research and innovation	Hyogo	Japan
667	10-Dec-2015	Hyogo Cancer Center	Hyogo	Japan
668	10-Nov-2015	Kanagawa Cardiovascular and Respiratory Center	Kanagawa	Japan
669	11-Nov-2015	Kanazawa University Hospital	Ishikawa	Japan
670	18-Jan-2016	National Hospital Organization Kinki-chuo Chest Medical Center	Osaka	Japan
671	18-Nov-2015	Kurume University Hospital	Fukuoka	Japan
672	19-Nov-2015	Osaka International Cancer Institute	Osaka	Japan
673	28-Oct-2015	National Hospital Organization Yamaguchi Ube Medical Center	Yamaguchi	Japan
674	23-Aug-2016	Aichi Cancer Center Hospital	Aichi	Japan
675	25-Feb-2016	Wakayama Medical University Hospital	Wakayama	Japan
676	15-Jan-2016	Niigata Cancer Center Hospital	Niigata	Japan
678	24-Dec-2015	Niigata University Medical & Dental Hospital	Niigata	Japan
679	24-Mar-2016	National Hospital Organization Shikoku Cancer Center	Ehime	Japan
680	22-Dec-2015	Kishiwada City Hospital	Osaka	Japan
681	13-Jan-2016	Juntendo University Hospital	Tokyo	Japan
682	20-Jan-2016	Osaka Habikino Medical Center	Osaka	Japan
683	17-Dec-2015	Osaka City University Hospital	Osaka	Japan
684	15-Dec-2015	Kobe City Medical Center General Hospital	Hyogo	Japan
685	19-Jan-2016	National Hospital Organization Asahikawa Medical Center	Hokkaido	Japan
686	28-Dec-2015	Nippon Medical School Hospital	Tokyo	Japan
688	10-Feb-2016	St. Luke's International Hospital	Tokyo	Japan
689	22-Jan-2016	Kanagawa Cancer Center	Kanagawa	Japan
690	02-Feb-2016	National Hospital Organization Kyushu Medical Center	Fukuoka	Japan
691	25-May-2016	Nagoya Medical Center	Aichi	Japan
692	13-Feb-2017	Hyogo Prefectural Amagasaki General Medical Center	Hyogo	Japan
693	08-Mar-2017	Himeji Medical Center	Hyogo	Japan
694	15-Feb-2017	Sendai Kousei Hospital	Miyagi	Japan

ERB, ethics review board.

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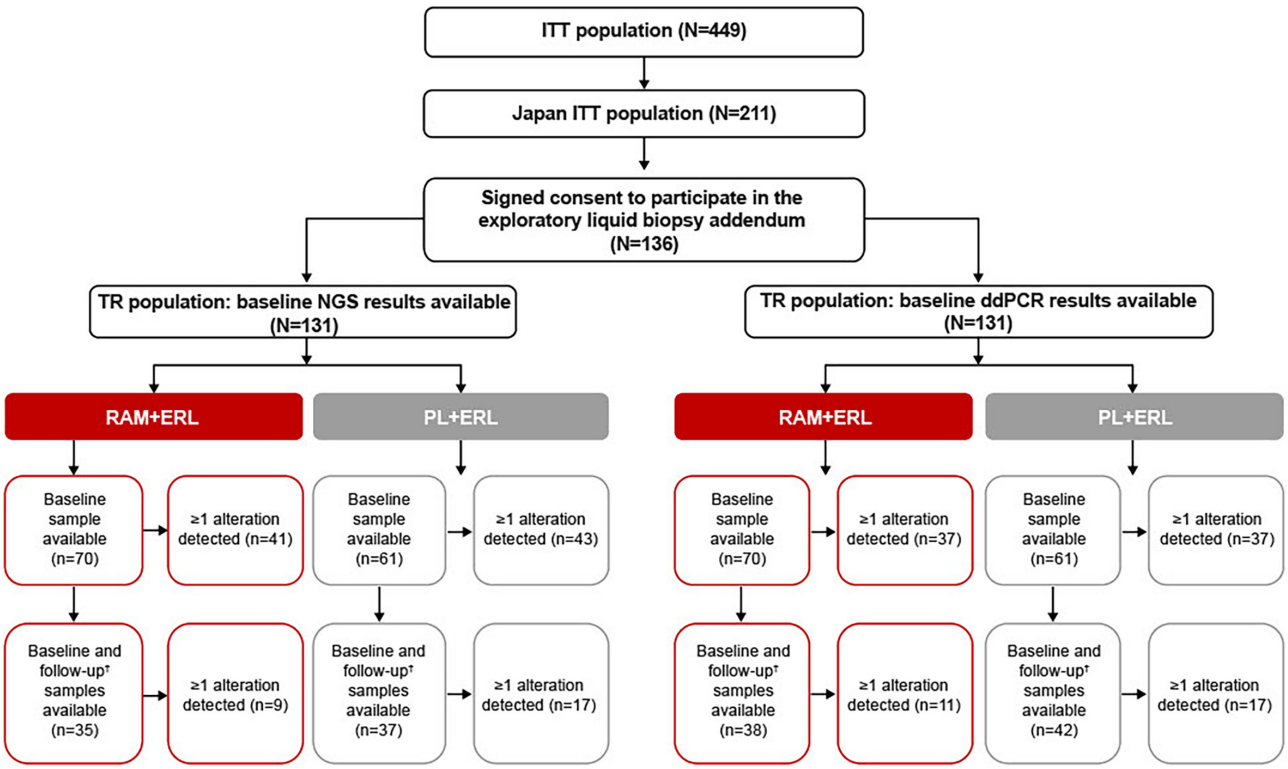

Figure S1 Exploratory liquid biopsy addendum patient flow diagram. †Follow-up was defined as 30-day post-study treatment discontinuation. ddPCR, droplet digital polymerase chain reaction; ERL, erlotinib; ITT, intent-to-treat; NGS, next-generation sequencing; PL, placebo; RAM, ramucirumab; TR, translational research.

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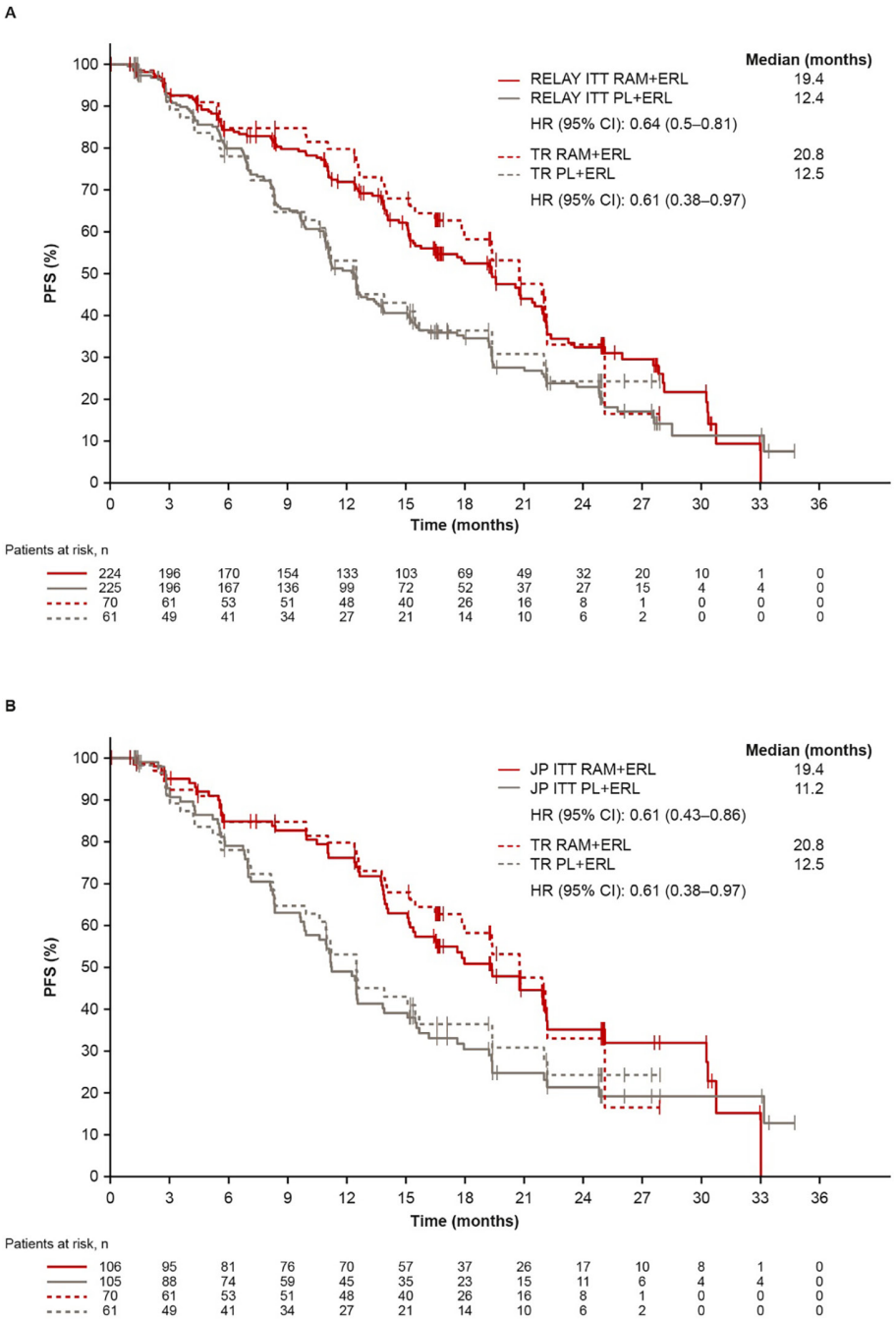

Figure S2 Kaplan-Meier plot of PFS for the TR population and comparison with the (A) RELAY ITT and (B) JP ITT populations. CI, confidence interval; ERL, erlotinib; HR, unstratified hazard ratio; ITT, intent-to-treat; JP, Japanese; PFS, progression-free survival; PL, placebo; RAM, ramucirumab; TR, translational research.

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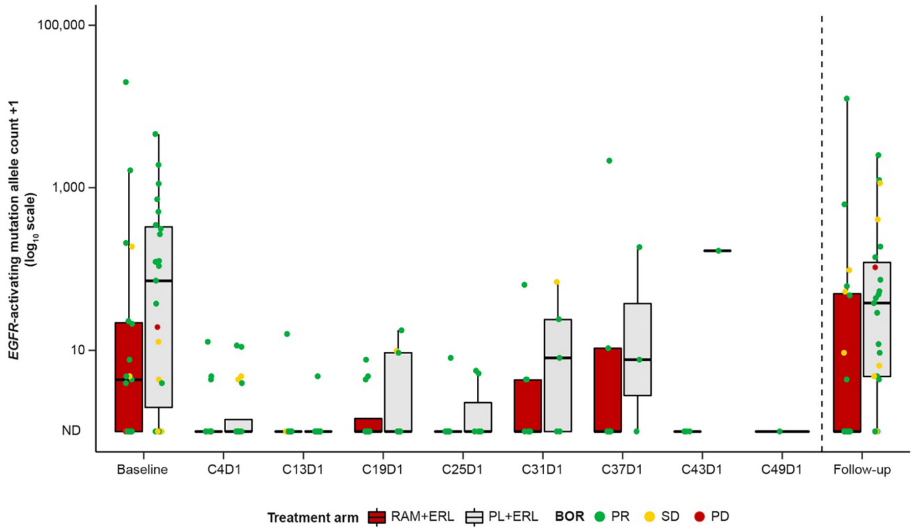

Figure S3 *EGFR*-activating mutation allele count (TR population, patients with a valid baseline sample). BOR, best overall response; C, Cycle; D, Day; EGFR, epidermal growth factor receptor; ERL, erlotinib; ND, not detected; PD, progressive disease; PL, placebo; PR, partial response; RAM, ramucirumab; SD, stable disease; TR, translational research.

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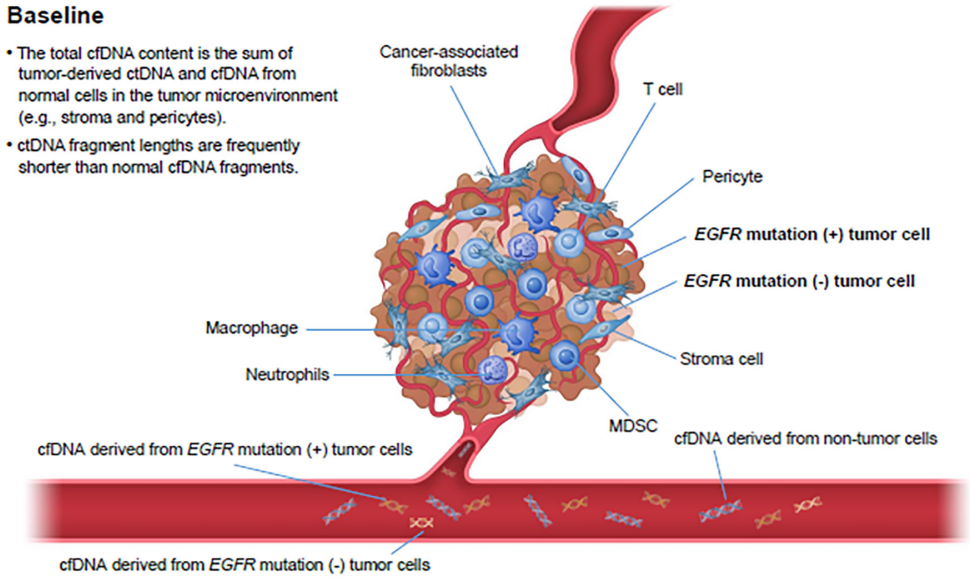

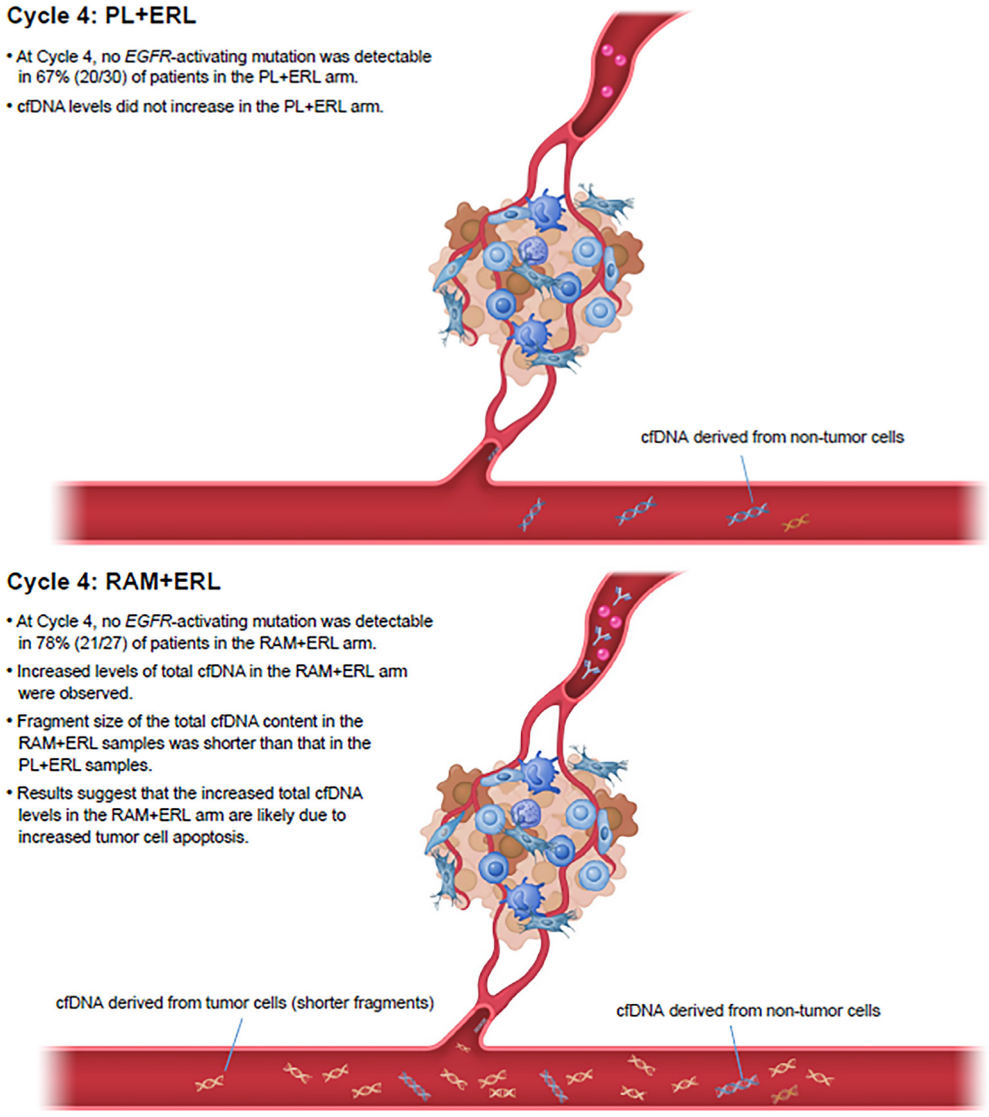

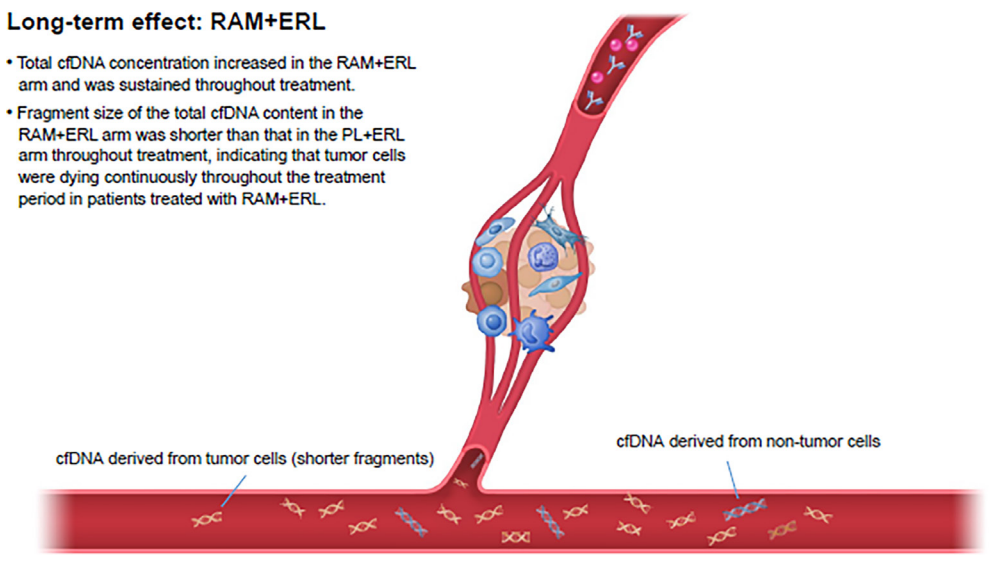

Figure S4 Hypothesized changes in total cfDNA content over time with RAM + ERL or PL + ERL treatment. cfDNA, cell-free DNA; EGFR, epidermal growth factor receptor; ERL, erlotinib; MDSC, myeloid-derived suppressor cell; PL, placebo; RAM, ramucirumab.

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