CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	A multicenter phase II trial of ipilimumab and nivolumab in unresectable or metastatic metaplastic breast cancer: Cohort 36 of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART, SWOG S1609)
Authors	Adams, Sylvia;Othus, Megan;Patel, Sandip Pravin;Miller, Kathy D.;Chugh, Rashmi;Schuetze, Scott M.;Chamberlin, Mary D.;Haley, Barbara J.;Storniolo, Anna Maria V.;Reddy, Mridula P.;Anderson, Scott A.;Zimmerman, Collin T.;O'Dea, Anne P.;Mirshahidi, Hamid R.;Rodon Ahnert, Jordi;Brescia, Frank J.;Hahn, Olwen;Raymond, Jane M.;Biggs, David D.;Connolly, Roisin M.;Sharon, Elad;Korde, Larissa A.;Gray, Robert J.;Mayerson, Edward;Plets, Melissa;Blanke, Charles D.;Chae, Young Kwang;Kurzrock, Razelle
Publication date	2021-10-29
Original Citation	Adams, S., Othus, M., Patel, S. P., Miller, K. D., Chugh, R., Schuetze, S. M., Chamberlin, M. D., Haley, B. J., Storniolo, A. M. V., Reddy, M. P., Anderson, S. A., Zimmerman, C. T., O'Dea, A.P., Mirshahidi, H. R., Rodon Ahnert, J., Brescia, F. J., Hahn, O., Raymond, J. M., Biggs, D. D., Connolly, R. M., Sharon, E., Korde, L. A., Gray, R. J., Mayerson, E., Plets, M., Blanke, C. D., Chae, Y. K., Kurzrock, R. A (2021) 'A multicenter phase II trial of ipilimumab and nivolumab in unresectable or metastatic metaplastic breast cancer: Cohort 36 of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART, SWOG S1609)', Clinical Cancer Research, 28(2), pp.271-278. https://doi.org/10.1158/1078-0432.CCR-21-2182
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1158/1078-0432.CCR-21-2182
Rights	© 2021, American Association for Cancer Research.
Download date	2026-10-09 10:32:55
Item downloaded from	https://hdl.handle.net/10468/12147

University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

A Multicenter Phase II Trial of Ipilimumab and Nivolumab in Unresectable or Metastatic Metaplastic Breast Cancer: Cohort 36 of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART, SWOG S1609)

Sylvia Adams[1], Megan Othus[2,3], Sandip Pravin Patel[4], Kathy D. Miller[5], Rashmi Chugh[6], Scott M. Schuetze[6], Mary D. Chamberlin[7], Barbara J. Haley[8], Anna Maria V. Storniolo[5], Mridula P. Reddy[9], Scott A. Anderson[10], Collin T. Zimmerman[11], Anne P. O'Dea[12], Hamid R. Mirshahidi[13], Jordi Rodon Ahnert[14], Frank J. Brescia[15], Olwen Hahn[16], Jane M. Raymond[17], David D. Biggs[18], Roisin M. Connolly[19,20], Elad Sharon[21], Larissa A. Korde[21], Robert J. Gray[22], Edward Mayerson[2,3], Melissa Plets[2,3], Charles D. Blanke[23], Young Kwang Chae[24], Razelle Kurzrock[4]

[1]New York University Perlmutter Cancer Center, NYU Langone Health, New York, NY; [2]SWOG Statistics and Data Management Center, Seattle, WA; [3]Fred Hutchinson Cancer Research Center, Seattle, WA; [4]University of California San Diego Moores Cancer Center, La Jolla, CA; [5]Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; [6]University of Michigan, Ann Arbor, MI; [7]Dartmouth-Hitchcock Medical Center/Norris Cotton Cancer Center, Lebanon, NH; [8]UT Southwestern/Simmons Cancer Center-Dallas, Dallas, TX; [9]Dayton Physicians LLC-Atrium Hematology Medical Oncology Division (Dayton NCORP), Franklin, OH; [10]Goldschmidt Cancer Center, Capital Region Southwest Campus (Heartland NCORP), Jefferson City, MO; [11]Kaiser Permanente Medical Group (Kaiser Perm NCORP), San Diego, CA; [12]University of Kansas Hospital – Westwood Cancer Center (Kansas MU-NCORP), Westwood, KS ; [13]Loma Linda University Cancer Center, Loma Linda, CA; [14]MD Anderson Cancer Center, Houston, TX; [15]MUSC, Hollings Cancer Center (MUSC MU-NCORP), Charleston, SC; [16]University of Chicago Comprehensive Cancer Center, Chicago, IL; [17]Allegheny General Hospital, Pittsburgh, PA; [18]Centura Health, Frisco, CO; [19]Johns Hopkins University/Sidney Kimmel Cancer Center, Baltimore, MD (during conduct of trial), [20]University College Cork, Ireland (current), [21]National Cancer Institute, Cancer Therapy Evaluation Program, Bethesda, MD; [22]Dana-Farber Cancer Institute-ECOG-ACRIN Biostatistics Center, Boston, MA; [23]SWOG Group Chair's Office, Knight Cancer Institute, Oregon Health and Science University, Portland, OR; [24]Northwestern University, Chicago, IL

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Disclosures:

Nothing to disclose: Dr. Anderson, Dr. Biggs, Brescia, Dr. Blanke, Dr. Chamberlin, Dr. Hahn, Dr. Korde, Dr. Miller, Dr. Raymond, Dr. Reddy, Dr. Sharon, Dr. Storniolo, Dr. Zimmerman; Ms. Plets, Mr. Mayerson,

Dr. Adams has uncompensated consulting or advisory roles with Bristol Meyers Squibb, Genentech, and Merck as well as research funding to her institution from Amgen, Bristol Meyers Squibb, Celgene, Genentech, Merck and Novartis.

Dr. Othus receives compensation for consulting for Merck, Glycomimetics, Daiichi Sankyo, and Biosight; Data safety monitor member for Celgene and Glycomimetics.

Dr. Patel receives scientific advisory income from: Amgen, AstraZeneca, Beigene, Bristol-Myers Squibb, Certis, Eli Lilly, Genentech, Illumina, , Merck, Pfizer, Rakuten, Tempus. Dr. Patel's university receives research funding from: Bristol-Myers Squibb, Eli Lilly, Incyte, AstraZeneca/MedImmune, Merck, Pfizer, Roche/Genentech, Xcovery. Fate Therapeutics, Genocea, Iovance

Dr. Chugh receives research funding from AADi, Novartis, Medivation, Advenchen, Epizyme, Pfizer, Plexxikonn, Springworks, Mundipharma, GSK, Qilu Puget Sound, Janssen, Astra Zeneca;
Member of Advisory Boards for Ipsen, Deciphera.

Dr. Schuetze received research funding to his institution from Adaptimmune, Amgen, GlaxoSmithKline, and Karyopharm

Dr Haley receives research funding fromm Pfizer, Lilly, Daiichi Sankyo, Roche, Puma, Astra Zeneca and Sanofi

Dr. O'Dea has consulting or advisory roles with Pfizer, Puma Biotechnology, Novartis and Daiichi Sankyo/Astra Zeneca.

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Dr. Connolly receives research grants from Novartis, Puma Biotechnology, Merck, Merrimack, Genentech and an unrestricted global education grant from Pfizer

Dr Mirshahidi received honorarium for Advisory board for Takeda, Puma, and Speaker fee for Merck

Dr Haley receives research funding fromm Pfizer, Lilly, Daiichi Sankyo, Roche, Puma, Astra Zeneca and Sanofi

Dr Rodon receives non financial support and reasonable reimbursement for travel from European Journal of Cancer, Vall d'Hebron Institut of Oncology, Chinese University of Hong Kong, SOLTI, Elsevier, GLAXOSMITHKLINE, ; receiving consulting and travel fees from Novartis, Eli Lilly, Orion Pharmaceuticals, Servier Pharmaceuticals, Peptomyc, Merck Sharp & Dohme, Kelun Pharmaceutical/Klus Pharma, Spectrum Pharmaceuticals Inc, Pfizer, Roche Pharmaceuticals, Ellipses Pharma, NovellusDx, Ionctura and Molecular Partners (including serving on the scientific advisory board from 2015-present), receiving research funding from Blueprint Pharmaceuticals, Bayer and Novartis, and serving as investigator in clinical trials with Spectrum Pharmaceuticals, Tocagen, Symphogen, BioAtla, Pfizer, GenMab, CytomX, KELUN-BIOTECH, Takeda-Millenium, GLAXOSMITHKLINE, IPSEN and travel fees from ESMO, US Department of Defense, Louissiana State University, Hunstman Cancer Institute, Cancer Core Europe, Karolinska Cancer Institute and King Abdullah International Medical Research Center (KAIMRC), Molecular Partners

Dr. Gray reports that COI information is up to date in JCO online system

Dr. Chae receives grants or contracts fron BMS, Abbvie, Biodesix, Freenome, Foundation Medicine; Consulting fees from BMS, AsztraZeneca, Pfizer, Genentech, Guardant Health, Foundation Medicine, Tempus, Lunit, Immuneoncia; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, Merck, Genentech, Guardant Health, Biodesix, Lili Oncology

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Dr. Kurzrock receives research funding from Genentech, Merck Serono, Pfizer, Boehringer Ingelheim, TopAlliance, Takeda, Incyte, Debiopharm, Medimmune, Sequenom, Foundation Medicine, Konica Minolta, Grifols, Omniseq, and Guardant, as well as consultant and/or speaker fees and/or advisory board for X-Biotech, Neomed, Pfizer, Actuate Therapeutics, Roche, Turning Point Therapeutics, TD2/Volastra, Bicara Therapeutics, Inc., has an equity interest in IDbyDNA and CureMatch Inc, serves on the Board of CureMatch and CureMetrix, and is a co-founder of CureMatch.

Corresponding Author:

Sylvia Adams, M.D.

NYU Langone Health

Laura and Isaac Perlmutter Cancer Center

160 East 34th Street

New York, NY 10016

Phone: 1-212-731-5705

E-mail: sylvia.adams@nyulangone.org

Running Title: Ipilimumab and Nivolumab in Rare Tumors S1609: Metaplastic Breast Cancer

Funding: Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under grant award numbers U10CA180888, U010CA180819, U10CA180820, U10CA180821; U10180868; U10CA180794, UG1CA233196 and in part by Bristol-Myers Squibb Company. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Bristol-Meyers Squibb Company.

Trial Registration: ClinicalTrials.gov registry: NCT02834013

Prior presentation: The study has been presented in part at the Annual ASCO Meeting in June 2020.

Keywords: Metaplastic breast cancer, rare tumors, S1609, DART, ipilimumab, nivolumab

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

ABSTRACT:

PURPOSE: Metaplastic breast cancer (MpBC) is a rare aggressive subtype that responds poorly to cytotoxics. Median survival is approximately eight months for metastatic disease. We report results for advanced MpBC treated with ipilimumab+nivolumab, a cohort of S1609 for rare cancers (DART: NCT02834013).

METHODS: Prospective, open-label, multicenter phase II (two-stage) trial of ipilimumab (1mg/kg IV q6weeks) plus nivolumab (240mg IV q2weeks) for advanced MpBC. Primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS) and toxicity.

RESULTS: Overall, 17 evaluable patients enrolled. Median age was 60 years (26-85); median number of prior therapy lines, 2 (0-5). ORR was 18%; 3/17 patients achieved objective responses (1 complete, 2 partial responses) (2 spindle cell, 1 chondromyxoid histology), which are ongoing at 28+, 33+ and 34+ months, respectively. Median PFS and OS were 2 and 12 months, respectively. Altogether, 11 patients (65%) experienced adverse events (AEs), including one grade 5 AE. Eight patients (47%) developed an immune-related AE (irAE); with adrenal insufficiency observed in all three responders. Responses occurred in tumors with low tumor mutational burden, low PD-L1 and absent TILs.

CONCLUSION: The ipilimumab and nivolumab combination showed no new safety signals and met its primary endpoint with 18% ORR in advanced, chemotherapy-refractory MpBC. All responses are ongoing at >2 to almost 3 years later. The effect of ipilimumab and nivolumab was associated with exceptional responses in a subset of patients versus no activity. This combination warrants further investigation in MpBC, with special attention to understanding mechanism of action, and carefully designed to weigh against the significant risks of irAEs.

Translational Relevance

SWOG dual anti–CTLA-4 and anti–PD-1 blockade in rare tumors (DART) S1609 is the first study of combination anti–CTLA-4 (ipilimumab) and anti–PD-1 (nivolumab) across rare tumors, with this cohort focusing on metaplastic breast cancer, an aggressive subtype that responds poorly to cytotoxic therapies and in whom immunotherapies have not previously been evaluated. Patients with advanced, chemotherapy-refractory metaplastic breast carcinoma had an 18% objective response rate (3 of 17 patients), which may be driven in part by anti–CTLA-4 as part of the treatment combination since responders all had low tumor mutational

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

burden and included tumors with low tumor-infiltrating lymphocytes and low PD-L1 expression. All responses are ongoing beyond 2+ years.

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Introduction:

Metaplastic breast cancers (MpBC) are rare (~1% of breast cancers) and very aggressive tumors, typically composed of both an adenocarcinoma and a metaplastic component (squamous, chondroid, spindle, rhabdoid or osseous, typically of same clonal origin as ductal carconima component) [1-3]. MpBC has a poor response to standard cytotoxic therapies [4], and a median survival of eight months for metastatic disease, which is significantly worse than that of non-metaplastic triple-negative breast cancer (TNBC) [5].

The molecular signature of MpBCs has similarilities to the claudin-low and mesenchymal subtypes of TNBC. There is an enrichment of stem cell-associated genes including genes involved in epithelial-to-mesenchymal transition [6]. Genomic studies have found that MpBC may have amplification of epidermal growth factor receptor, as well as alterations in genes involved in the PI3K/Akt pathway, Wnt/β-catenin signaling, and cell cycle dysregulation [7].

Frequent overexpression of PD-L1 was recently demonstrated in primary MpBC, with PD-L1 positivity in tumor cells [8]. Tumor-infiltrating lymphocytes (TIL) have also been demonstrated in MpBC, including PD-1 expressing TILs [8, 9] suggestive of an immunogenic cancer phenotype in some patients. These findings and preliminary evidence of clinical activity of PD-1 blockade in MpBC [10], led to the inclusion of MpBC into the DART study as cohort 36.

Here, we present the results of the metaplastic breast cancer cohort on DART (DUAL ANTI-CTLA-4 AND ANTI-PD-1 BLOCKADE IN RARE TUMORS, S1609), a prospective phase II study conducted through the National Cancer Institute (NCI)-supported SWOG Cancer Research Network.

Patients and Methods

Patients and Procedures

DART is a multicenter (>800 sites), open label, Phase II basket study (NCT02834013) of ipilimumab and nivolumab for rare malignancies. It is being conducted by the Early Therapeutics and Rare Cancers Committee under the auspices of SWOG and the NCI. The Cancer Therapy Evaluation Program (CTEP) provided study

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

medication under an NCI Cooperative Research and Development Agreement (CRADA) with Bristol-Myers Squibb (BMS). The study was conducted in accordance with the Declaration of Helsinki. The trial design and eligibility criteria for DART were previously reported [11]. All participants provided written informed consent authorized by each enrolling center's internal review board.

Eligible patients for cohort 36 must have had a histologically confirmed diagnosis of MpBC with disease measurable as per RECIST v1.1 [12]. Enrollment was directed into study cohorts (baskets) based on the local pathology report (the DART trial did not mandate central review/verification of the rare histologies). All patients' cancers had progressed following at least one line of standard therapy and there must not have been other approved/standard therapy available that has been shown to prolong overall survival. Patients may have received either prior anti-CTLA4 or other prior anti-PD-1/anti-PD-L1 therapy (but not both) provided that it was completed at least four weeks prior to registration. Patients were required to have an ECOG PS 0-2, be at least 18 years of age and have adequate organ function, within specific hematologic, renal, hepatic, adrenal, and thyroid parameters. Exclusion criteria included certain autoimmune diseases and ongoing Grade 3/4 irAEs. For patients with brain metastases, central nervous system (CNS) directed therapy must have been completed ≥ 28 days prior to registration and patients must have been off steroids for at least seven days with stable disease at time of registration.

Patients received nivolumab 240 mg every two weeks and ipilimumab 1 mg/kg every six weeks (both intravenously, one cycle is 6 weeks). Disease assessments were performed at baseline and thereafter at weeks 8, 16, 24, and then every 12 weeks. Treatment continued until tumor progression, unacceptable toxicity, or withdrawal of consent.

Endpoints and statistical analysis

The primary endpoint of the study was objective response rate (ORR) (confirmed complete and partial response (CR and PR, respectively)) as assessed by RECIST 1.1 criteria [12]. The regimen was considered of interest for further study if the true ORR was 12% or higher (2 responses out of 16 eligible patients). Subset analyses within the cohort were not prespecified.

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

As previously described, all cohorts used a two-stage design [13]. If ≥1 response was observed in the first six eligible and evaluable patients, accrual to the second stage to a total of 16 patients would be opened. Two or more responses out of 16 patients were considered evidence that the treatment regimen merits further investigation, provided other data including adverse events (AEs) also appeared satisfactory. This design has 87% power (under an alternative response rate of 30%) with a one-sided alpha of 13% (null response rate assumed to be 5%) in each stratum.

Secondary endpoints were toxicity (per CTCAE version 4), overall-survival (OS), and progression-free survival (PFS); PFS was equal for RECIST [12] and iRECIST [14] in this cohort. PFS and OS estimates were calculated utilizing the Kaplan-Meier method [15] and compared using log-rank tests. Confidence intervals (CIs) for medians were built using the method of Brookmeyer and Crowley [16]; CI for point estimates were calculated employing the log-log transformation. CIs for the primary ORR analysis accounted for the two-stage design and the observed sample size of 17 patients [17]. All analyses were performed using R version 4.0.1.

Results

Patient Characteristics

Overall, 19 patients from 17 National Clinical Trial Network (NCTN) institutions were registered for cohort 36, with 17 patients meeting eligibility criteria and receiving protocol therapy (CONSORT **Supplemental Figure 1**). Enrollment was rapid, with 8 eligible patients enrolled January to May 2018 (first stage) followed by a temporary study hold to analyze responses to determine proceeding to the second stage, followed by enrollment of an additional 9 eligible patients from October 2018 to April 2019.

Patient demographics and tumor characteristics are listed in **Table 1**. The median age was 60 years (range 26-85 years); all patients were female and the majority Caucasian. As expected for MpBC, the majority of tumors were TNBC, high grade and exhibited high proliferation. Patients had received a median number of two prior lines of systemic therapies, including standard chemotherapies (anthracycline, taxanes, eribulin mesylate,

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

carboplatin, cisplatin, capecitabine), angiogenesis inhibitors, mTOR inhibitors, anti-PD-1 inhibitors, BET inhibitors, HDAC inhibitors, and other investigational agents.

Toxicities

Treatment-related AEs are summarized in **Table 2**. Overall, 11 patients (65%) experienced an AE, with 3 (18%) having a grade 3-4 AE and 1 grade 5 AE (unknown cause, possibly related, further detail in **Table 2**). Altogether, 47% of participants experienced an irAE; the most common were liver function test (LFT) abnormalities, adrenal insufficiency, and rash.

Outcomes

Efficacy results are shown in **Table 3**. Of 17 enrolled and eligible patients, all of whom had measurable disease, three patients had confirmed objective responses by RECIST 1.1, resulting in an ORR of 18% (95% CI 6%-40%). Notably, all three responses have been durable and have been ongoing at 28+, 33+, 34+ months, respectively and are therefore considered exceptional (**Figure 1**). These responses were observed in spindle cell MpBC (n=2) and chondromyxoid MpBC (n=1). Non-responders had poor outcomes; stable disease (SD) was seen in 18%, none lasting > 6 months. Median PFS and OS were 2 and 12 months, respectively (**Figure 1**). Median follow-up among patients who are alive is 33 months. Cut-off date of data follow-up is 2/4/2021. Three patients had received prior anti PD-1 therapy; none of whom had a tumor response.

Exceptional responders are described in more detail in **Supplemental Table 1.** All three responders had chemotherapy-refractory disease with significant tumor burden. The tumors' baseline target lesion sum ranged from 6.1 to 11.3 cm and cancers had recurred within one year of a taxane and/or anthracycline containing regimen, or progressed on it. None had received prior immunotherapy. Reassuringly, responses persisted despite stopping ipilimumab in one patient and ipilimumab+nivolumab in another patient (**Figure 1**). Of note, all three responders developed significant irAEs with adrenal insufficiency induced in all three.

Genomic Alterations and PD-L1 expression

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Prespecified trial correlative studies have been delayed due to COVID-19 pandemic work restrictions. Molecular and immunohistochemistry (IHC) tumor characterization done as part of routine medical care is shown for all three responding patients in **Supplemental Table 1**. Tumors had low tumor mutational burden (TMB), were microsatellite stable, and two of three had negative or low PD-L1 expression/TILs.

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Discussion

To our knowledge, our study represents the first prospective trial of immunotherapy in MpBC, a rare subset of TNBC. This cohort of the DART trial met its primary endpoint: ipilimumab plus nivolumab was clinically active in advanced MpBC, with responses observed in 3/17 patients (ORR 18%). Importantly, all responses were durable (28+, 33+ and 34+ months), which is rarely observed in MpBC.

Advanced MpBC has a poor prognosis with median OS less than one year despite chemotherapy [18]; therefore, new treatment strategies are urgently needed. MpBCs harbor a wide variety of genomic alterations, the most frequent being in the *TP53* and *PIK3CA* genes [9]. Therapies targeting the PI3K/AKT/mTOR pathway and anti-angiogenesis agents have shown objective responses in a subset of patients [18-21]. The limited treatment options and poor prognosis of MpBC along with the high tumoral PD-L1 expression and TIL presence in some patients [8] provided the rationale to study immunotherapies in this subtype.

Objective responses to dual immunotherapy were seen in three patients, two with spindle cell and one with chondromyxoid histology. All three women had chemotherapy-refractory disease with significant tumor burden (range of baseline target lesion sum 6.1 - 11.3 cm). These responses are remarkable for several reasons. First, they were durable with all responses ongoing beyond 2 years, which is in stark contrast to the short-lived responses observed with chemotherapy [18] as well as with anti-PD-1 blockade in MpBC [10]. Furthermore, three of the patients in our study (all non-responders) who had received *prior* therapy with anti-PD-1 (combined with platinum chemotherapy, targeted agents or a STING agonist) rapidly progressed on that therapy, all within two months. Second, responses were observed in patients with highly chemotherapy-refractory disease, as evidenced by disease recurrence within one year of a taxane and/or anthracycline combination regimen or progression on it, known to be an independent poor prognostic factor for TNBC [22-24]. Third, responses were observed even in tumors with negative or low PD-L1 expression and low TIL. This may suggest a contribution of the anti-CTLA blockade to the efficacy of the regimen studied, as responses to anti-PD-1/anti-PD-L1 therapeutics are enrichedin PD-L1-positive tumors in metastatic TNBC [23, 25]. Fourth, all three responders developed significant irAEs including panhypopituitarism and adrenal insufficiency. While irAE toxicity has been observed across immune checkpoint inhibitor regimens and has been shown to correlate with anti-tumor responses in

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

some studies [26], the duration of treatment is generally longer in responders, which could be a confounder due to longer exposure to therapy. Adrenal insufficiency, for instance, was diagnosed around cycle 3-4 at approximately 4 months in the responders, at which time most of the non-responder patients had come off study for progression. Fifth, our responders had low TMB. TMB can be strongly correlated with responsiveness to checkpoint blockade, with only ~5% of patients responding to anti-PD1/PDL1 agents when TMB is low (≤5 mutations/mb); however, our prior studies suggest that responses to anti-CTL4/anti-PD1/PDL1 combinations, as given in the present study, are independent of TMB [27].

While the contribution of CTLA-4 blockade to the efficacy of the anti-CTLA-4/anti-PD-1 combination and in particular the duration of responses remains unknown in our trial, we would like to reference efficacy data of anti-PD-1/PD-L1 therapy in MpBC as well as TNBC in general. Data from a recently published case series of MpBC, which included 4 patients from an investigator-initiated trial of anti-PD-1 therapy (with capecitabine or paclitaxel) as well as one patient treated off-label with pembrolizumab and bicalutamide) demonstrated objective responses in 3 patients, however, PFS was only 5.3, 5.7 and 8.0 months [28]). In another investigator-initiated trial of anti-PD-1 therapy with nab-paclitaxel one of two patients with MpBC experienced an objective response, however, PFS was only 6.7 months (Adams et al, NCT02752685, unpublished data). In phase 3 trials of chemo-immunotherapy for metastatic (general) TNBC durable responses were observed, however, the percentage of patients with ongoing responses years out is very small. For instance in our final analysis of Impassion130, among patients alive at 3 years, only 16 patients had not experienced progression of disease, representing 1.77% of the 902 patients enrolled and 2.66% of patients treated with the chemo-immunotherapy combination (12/451) [29].

As discussed above, responses to chemo- plus anti-PD-1 therapy observed in MpBC are typically not durable (all ≤ 9 months) and combinatorial immunotherapies may be required to achieve durable responses. However, it is important to note the addition of anti-CTLA-4 to anti-PD-1/PD-L1 regimens has been associated with greater toxicity and higher mortality rates [30, 31]. A meta-analysis of 112 trials involving 19 217 patients showed toxicity-related fatality rates of 0.36% (anti-PD-1), 0.38% (anti-PD-L1), 1.08% (anti-CTLA-4), and 1.23% (anti-PD-1/PD-L1 plus anti-CTLA-4)[30].

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

The side effect profile of the anti-CTLA-4/anti-PD-1 combination in our study was consistent with published combination studies [31, 32] and that observed in other cohorts of DART. No unexpected toxicities were observed, however, the fatal event and several potentially life-threatening AEs such as adrenal insufficiency highlight the importance of a thorough risk benefit discussion with patients and their education about possible side effects before treatment start as well as careful monitoring of patients on treatment by oncologists at centers with immunotherapy experience. Furthermore, it is essential to raise awareness among emergency department physicians, critical care providers, and other specialists, especially as serious toxicities can have unusual clinical presentations and grade 5 toxicities can occur very early in the treatment course, as shown for ipilimumab combination therapies with a median 14.5 days[30]. Subsequent studies should therefore carefully consider these risks and possibly modify dosing, as AEs have been shown to occur more often at higher doses of ipilimumab[30], or evaluate newer anti-CTLA-4 formulations such as probodies to widen the therapeutic window[33].

To better understand the molecular basis for responses, correlative samples were collected on study and will be analyzed as per pre-specified plan at Cancer Immune Monitoring and Analysis Centers (CIMAC) sites. Some patients had tumor NGS performed for clinical purposes outside of the DART trial and results were available as part of the medical record. Based on these local data, tumors of responders with NGS available showed low TMB and absence of microsatellite instability (MSI), which is consistent with our published large dataset of 192 MpBC demonstrating a low TMB across these tumors (median 2.7 mutations/Mb) along with microsatellite stability (0/192 MpBC were MSI high)[9].

Strengths of our study include the enrollment of patients at both academic and community centers as well as support from the NCI and SWOG. Furthermore, DART served an unmet need with rare tumors and demonstrated that it was feasible to rapidly accrue even very rare tumors [11], especially since SWOG was able to mobilize >800 sites for the DART study. Limitations of the study include a relatively small sample size within a single arm design per disease cohort, and the lack of a randomized comparison to standard of care therapies. Central pathology review was not mandated, and therefore we relied on local site assessments which may be suboptimal

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

for rare occurring cancers; however, review of all pathology reports was conducted by the study chair confirming the presence of metaplastic components in specimens. Furthermore, for the three responders, digital pathology images were reviewed for assessment of TILs.

In conclusion, amongst 17 patients treated with nivolumab and ipilumumab, three exceptional responses were observed in chemotherapy-refractory, metastatic MpBC, all ongoing at 28+, 33+, 34+ months. Further investigation of this combination is warranted. Of special interest, in this study, responses were dichotomized into the 18% that did remarkably well versus the others that had no significant benefit from ipilimumab and nivolumab. Such a dichotomization may suggest the presence of a unique biomarker for response in these patients and should be taken into consideration in the design of a future trial, possibly with an adaptive design. Interestingly, the exceptional responders included patients whose tumors had low TMB, low TIL and no PD-L1 expression, indicating that the mechanism of response requires further in-depth interrogation, which is planned via collaboration with CIMAC sites .

Acknowledgements

We would like to thank the patients who participated in this trial and their families, as well as the study teams of participating institutions. We also thank Dr. Roberto Salgado for scoring the TILs for the responders.

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

References:

1. Weigelt B, Eberle C, Cowell CF, Ng CK, Reis-Filho JS: **Metaplastic breast carcinoma: more than a special type**. *Nature reviews Cancer* 2014, **14**(3):147-148.
2. Lakhani SR, Ellis. I.O., Schnitt, S.J., Tan, P.H., van de Vijver, M.J.: **Metaplastic carcinoma. WHO classification of tumours of the breast. 4th edition.** *Lyon, France: International Agency for Research on Cancer (IARC); 2012 p 48–52*.
3. Avigdor BE, Beierl K, Gocke CD, Zabransky DJ, Cravero K, Kyker-Snowman K, Button B, Chu D, Croessmann S, Cochran RL *et al*: **Whole-Exome Sequencing of Metaplastic Breast Carcinoma Indicates Monoclonality with Associated Ductal Carcinoma Component**. *Clin Cancer Res* 2017, **23**(16):4875-4884.
4. Wong W, Brogi E, Reis-Filho JS, Plitas G, Robson M, Norton L, Morrow M, Wen HY: **Poor response to neoadjuvant chemotherapy in metaplastic breast carcinoma**. *NPJ Breast Cancer* 2021, **7**(1):96.
5. Aydiner A, Sen F, Tambas M, Ciftci R, Eralp Y, Saip P, Karanlik H, Fayda M, Kucucuk S, Onder S *et al*: **Metaplastic Breast Carcinoma Versus Triple-Negative Breast Cancer: Survival and Response to Treatment**. *Medicine* 2015, **94**(52):e2341.
6. Hennessy BT, Gonzalez-Angulo AM, Stemke-Hale K, Gilcrease MZ, Krishnamurthy S, Lee JS, Fridlyand J, Sahin A, Agarwal R, Joy C *et al*: **Characterization of a naturally occurring breast cancer subset enriched in epithelial-to-mesenchymal transition and stem cell characteristics**. *Cancer Res* 2009, **69**(10):4116-4124.
7. Reddy TP, Rosato RR, Li X, Moulder S, Piwnica-Worms H, Chang JC: **A comprehensive overview of metaplastic breast cancer: clinical features and molecular aberrations**. *Breast Cancer Res* 2020, **22**(1):121.
8. Joneja U, Vranic S, Swensen J, Feldman R, Chen W, Kimbrough J, Xiao N, Reddy S, Palazzo J, Gatalica Z: **Comprehensive profiling of metaplastic breast carcinomas reveals frequent overexpression of programmed death-ligand 1**. *Journal of clinical pathology* 2017, **70**(3):255-259.

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

9. Tray N, Taff J, Singh B, Suh J, Ngo N, Kwa M, Troxel AB, Chae YK, Kurzrock R, Patel SP *et al*: **Metaplastic breast cancers: Genomic profiling, mutational burden and tumor-infiltrating lymphocytes**. *Breast* 2019, **44**:29-32.

10. Adams S: **Dramatic response of metaplastic breast cancer to chemo-immunotherapy**. *NPJ Breast Cancer* 2017, **3**:8.

11. Patel SP, Othus M, Chae YK, Giles FJ, Hansel DE, Singh PP, Fontaine A, Shah MH, Kasi A, Al Baghdadi T *et al*: **A Phase II Basket Trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART SWOG 1609) in Patients with Non-Pancreatic Neuroendocrine Tumors**. *Clin Cancer Res* 2020.

12. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M *et al*: **New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)**. *Eur J Cancer* 2009, **45**(2):228-247.

13. Wagner MJ, Othus M, Patel SP, Ryan C, Sangal A, Powers B, Budd GT, Victor AI, Hsueh CT, Chugh R *et al*: **Multicenter phase II trial (SWOG S1609, cohort 51) of ipilimumab and nivolumab in metastatic or unresectable angiosarcoma: a substudy of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART)**. *J Immunother Cancer* 2021, **9**(8).

14. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litiere S, Dancey J, Chen A *et al*: **iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics**. *Lancet Oncol* 2017, **18**(3):e143-e152.

15. Kaplan EL, Meier P: **Nonparametric Estimation from Incomplete Observations**. *Journal of the American Statistical Association* 1958, **53**(282):457-481.

16. Brookmeyer R, Crowley J: **A Confidence Interval for the Median Survival Time**. *Biometrics* 1982, **38**(1):29-41.

17. Koyama T, Chen H: **Proper inference from Simon's two-stage designs**. *Stat Med* 2008, **27**(16):3145-3154.

18. Tray N, Taff J, Adams S: **Therapeutic landscape of metaplastic breast cancer**. *Cancer Treat Rev* 2019, **79**:101888.

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

19. Moulder S, Helgason T, Janku F, Wheler J, Moroney J, Booser D, Albarracin C, Morrow PK, Atkins J, Koenig K *et al*: **Inhibition of the phosphoinositide 3-kinase pathway for the treatment of patients with metastatic metaplastic breast cancer**. *Annals of oncology : official journal of the European Society for Medical Oncology* 2015, **26**(7):1346-1352.

20. Moulder S, Moroney J, Helgason T, Wheler J, Booser D, Albarracin C, Morrow PK, Koenig K, Kurzrock R: **Responses to liposomal Doxorubicin, bevacizumab, and temsirolimus in metaplastic carcinoma of the breast: biologic rationale and implications for stem-cell research in breast cancer**. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2011, **29**(19):e572-575.

21. Moroney J, Fu S, Moulder S, Falchook G, Helgason T, Levenback C, Hong D, Naing A, Wheler J, Kurzrock R: **Phase I study of the antiangiogenic antibody bevacizumab and the mTOR/hypoxia-inducible factor inhibitor temsirolimus combined with liposomal doxorubicin: tolerance and biological activity**. *Clin Cancer Res* 2012, **18**(20):5796-5805.

22. Adams S, Loi S, Toppmeyer D, Cescon DW, De Laurentiis M, Nanda R, Winer EP, Mukai H, Tamura K, Armstrong A *et al*: **Pembrolizumab monotherapy for previously untreated, PD-L1-positive, metastatic triple-negative breast cancer: cohort B of the phase II KEYNOTE-086 study**. *Ann Oncol* 2019, **30**(3):405-411.

23. Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im SA, Yusof MM, Gallardo C, Lipatov O, Barrios CH, Holgado E *et al*: **Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial**. *Lancet* 2020, **396**(10265):1817-1828.

24. Kassam F, Enright K, Dent R, Dranitsaris G, Myers J, Flynn C, Fralick M, Kumar R, Clemons M: **Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design**. *Clin Breast Cancer* 2009, **9**(1):29-33.

25. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, Dieras V, Hegg R, Im SA, Shaw Wright G *et al*: **Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer**. *N Engl J Med* 2018.

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

26. Xing P, Zhang F, Wang G, Xu Y, Li C, Wang S, Guo Y, Cai S, Wang Y, Li J: **Incidence rates of immune-related adverse events and their correlation with response in advanced solid tumours treated with NIVO or NIVO+IPI: a systematic review and meta-analysis**. *J Immunother Cancer* 2019, **7**(1):341.

27. Goodman AM, Kato S, Bazhenova L, Patel SP, Frampton GM, Miller V, Stephens PJ, Daniels GA, Kurzrock R: **Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers**. *Mol Cancer Ther* 2017, **16**(11):2598-2608.

28. Kim I, Rajamanickam V, Bernard B, Chun B, Wu Y, Martel M, Sun Z, Redmond WL, Sanchez K, Basho R *et al*: **A Case Series of Metastatic Metaplastic Breast Carcinoma Treated With Anti-PD-1 Therapy**. *Front Oncol* 2021, **11**:635237.

29. Emens LA, Adams S, Barrios CH, Dieras V, Iwata H, Loi S, Rugo HS, Schneeweiss A, Winer EP, Patel S *et al*: **First-line atezolizumab plus nab-paclitaxel for unresectable, locally advanced, or metastatic triple-negative breast cancer: IMpassion130 final overall survival analysis**. *Ann Oncol* 2021, **32**(8):983-993.

30. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, Zhao S, Das S, Beckermann KE, Ha L *et al*: **Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis**. *JAMA Oncol* 2018, **4**(12):1721-1728.

31. D'Abreo N, Adams S: **Immune-checkpoint inhibition for metastatic triple-negative breast cancer: safety first?** *Nat Rev Clin Oncol* 2019, **16**(7):399-400.

32. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P *et al*: **Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma**. *N Engl J Med* 2015, **373**(1):23-34.

33. Autio KA, Boni V, Humphrey RW, Naing A: **Probody Therapeutics: An Emerging Class of Therapies Designed to Enhance On-Target Effects with Reduced Off-Tumor Toxicity for Use in Immuno-Oncology**. *Clin Cancer Res* 2020, **26**(5):984-989.

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Figure 1: Outcome of patients with metaplastic breast cancer treated with ipilimumab and nivolumab (RECIST 1.1)

A: Waterfall plot. Horizontal lines mark RECIST progression (+20%) and PR (-30%). Crosshatch indicates patient failed therapy and does not have tumor measurements available due progression (due to new lesions at first assessment (n=3), death before assessment (n=1), or withdrew consent for follow-up when entered hospice before first assessment (n=1)). One patient had 0% change in RECIST measurements and therefore appears as a gap in the waterfall.

B: Swimmer's Plot. By MpBC histology.

C/D: OS and PFS Kaplan Meier curve

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Table 1: Patient Summary

	N (%) or median (min, max)
Age	60 (26, 85)
Female sex	17 (100)
ECOG PS	
0	5 (29)
1	10 (59)
2	2 (12)
Race/Ethnicity	
White	14 (82)
Black	2 (12)
Asian	1 (6)
Hispanic	1 (6)
Biomarker profile	
ER/PR/HER2 neg (TNBC)	13 (76)
ER or PR low (1-10% pos), HER2 neg	3 (18)
ER/PR >10% pos, HER2 neg	1 (6)
Ki67	87 (20, 100)
Histology	
Spindle	8
Squamous	3
Spindle and squamous	1
Spindle and chondroid	1
Chondroid	2
Chondromyxoid	1
Unknown	1
Prior lines of systemic therapy, includes adjuvant and metastatic setting (median)	2 (0, 5)
Prior anti-PD-1 therapy	
Yes	3 (18)
No	14 (82)

Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; ki67 = ki67 nuclear antigen/proliferation index; min/max = minimum/maximum; N = number; neg = negative; PD-1 = programmed death protein 1; pos = positive; PR = progesterone receptor; PS = performance status; TNBC triple negative breast cancer

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Table 2: Treatment-Related Adverse Events (N = 17 patients)

	N (%) of patients		
	Any Grade	**Grade 3-4**	**Grade 5**
Any	**11 (64.7)**	**4 (23.5)**	**1 (5.9)**
Serious	**4 (23.5)**	**3 (17.6)**	**1 (5.9)**
Led to Discontinuation	**1 (5.9)**	**1 (5.9)***	**0 (0)**
Lead to Death	**1 (5.9)**	**0 (0)**	**1 (5.9)****
AE >10% of Patients			
AST increased	6 (35.3)	1 (5.9)	0 (0)
Fatigue	5 (29.4)	0 (0)	0 (0)
Adrenal insufficiency	4 (23.5)	1 (5.9)	0 (0)
ALT increased	4 (23.5)	0 (0)	0 (0)
Diarrhea	4 (23.5)	0 (0)	0 (0)
Nausea	3 (17.6)	2 (11.8)	0 (0)
Rash maculo-papular	3 (17.6)	1 (5.9)	0 (0)
Abdominal pain	3 (17.6)	0 (0)	0 (0)
Anemia	3 (17.6)	0 (0)	0 (0)
Lymphocyte count decreased	3 (17.6)	0 (0)	0 (0)
Sepsis	2 (11.8)	1 (5.9)	1 (5.9)
Colitis	2 (11.8)	1 (5.9)	0 (0)
Dizziness	2 (11.8)	1 (5.9)	0 (0)
Anorexia	2 (11.8)	0 (0)	0 (0)
Blood bilirubin increased	2 (11.8)	0 (0)	0 (0)
Constipation	2 (11.8)	0 (0)	0 (0)
Headache	2 (11.8)	0 (0)	0 (0)
Hypothyroidism	2 (11.8)	0 (0)	0 (0)
Lipase increased	2 (11.8)	0 (0)	0 (0)
Neck pain	2 (11.8)	0 (0)	0 (0)
Pruritus	2 (11.8)	0 (0)	0 (0)
Vomiting	2 (11.8)	0 (0)	0 (0)
Immune-mediated AE (regardless of frequency)	**8 (47.1)**	**3 (17.6)**	**0 (0.0)**
AST increased	6 (35.3)	1 (5.9)	0 (0)
Adrenal insufficiency	4 (23.5)	1 (5.9)	0 (0)
ALT increased	4 (23.5)	0 (0)	0 (0)
Diarrhea	4 (23.5)	0 (0)	0 (0)
Rash maculo-papular	3 (17.6)	1 (5.9)	0 (0)
Colitis	2 (11.8)	1 (5.9)	0 (0)
Blood bilirubin increased	2 (11.8)	0 (0)	0 (0)
Hypothyroidism	2 (11.8)	0 (0)	0 (0)
Lipase increased	2 (11.8)	0 (0)	0 (0)

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Pruritus	2 (11.8)	0 (0)	0 (0)
Hyperthyroidism	1 (5.9)	0 (0)	0 (0)

*****Study drug discontinuation per investigator discretion, as patient already had achieved a complete response.
******The patient was a 76 year old female with EGOG performance status 2 at enrollment. She had reported urinary frequency around day 14 after first treatment with ipilimumab and nivolumab. She was started on oral antibiotic treatment for urinary tract infection. Presented on day 15 for her next treatment and reported lightheadedness, generalized weakness, poor fluid intake. She developed nausea, emesis and was noted to be short of breath. Treatment was held and she was referred to the emergency room where she developed pulseless electrical activity and required cardiac resuscitation protocols with return of spontaneous circulation. Laboratory tests showed mild anemia, leucocytosis, normal renal function, elevated troponin (4.79 ng/ml) and transaminitis (AST 339 U/L, ALT 114 U/L, normal 4 days prior). Subsequent CT chest with contrast was negative for pulmonary embolism, and demonstrated grossly stable metastatic disease. EKG post arrest showed anterior ST elevation, cardic catheterization however revealed normal coronaries and LVEF at 60-65%. Hence, non-cardiac cause leading to cardiac arrest were suspected, possibly septic shock. She was treated with broad spectrum antibiotic therapy, bicarbonates and vasopressor support. Hemodynamics continued to decline despite multiple vasopressors, and metabolic acidosis worsened despite renal replacement therapy. Due to patient's overall clinical deterioration, her family opted for comfort measures only and patient passed away on day 16 after receiving first dose of both study drugs. Cause of death possibly due to sepsis and possibly related.

Abbreviations: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; N = number

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Table 3: Best response summary by RECIST 1.1 (N = 17 patients)

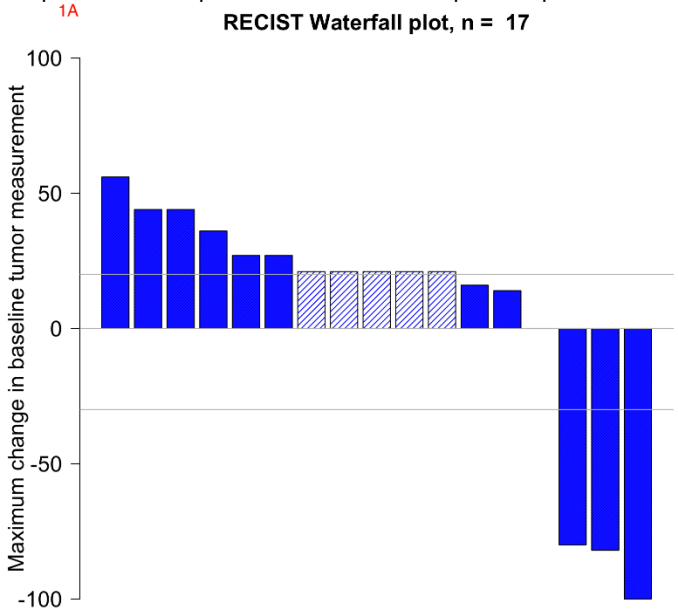
	Patient number (%) or time
CR	1 (6%)
PR	2 (12%)
ORR (CR + PR)	3 (18%)
SD (all <6 months)	3 (18%)
PD*	11 (65%)
Duration of response	28+, 33+, 34+ months, all ongoing
PFS at 6 months	18% (6%, 49%)
Median PFS and OS	2 and 12 months

***includes patients who progressed or died before first on-study assessment
Abbreviations: CR = complete response; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease

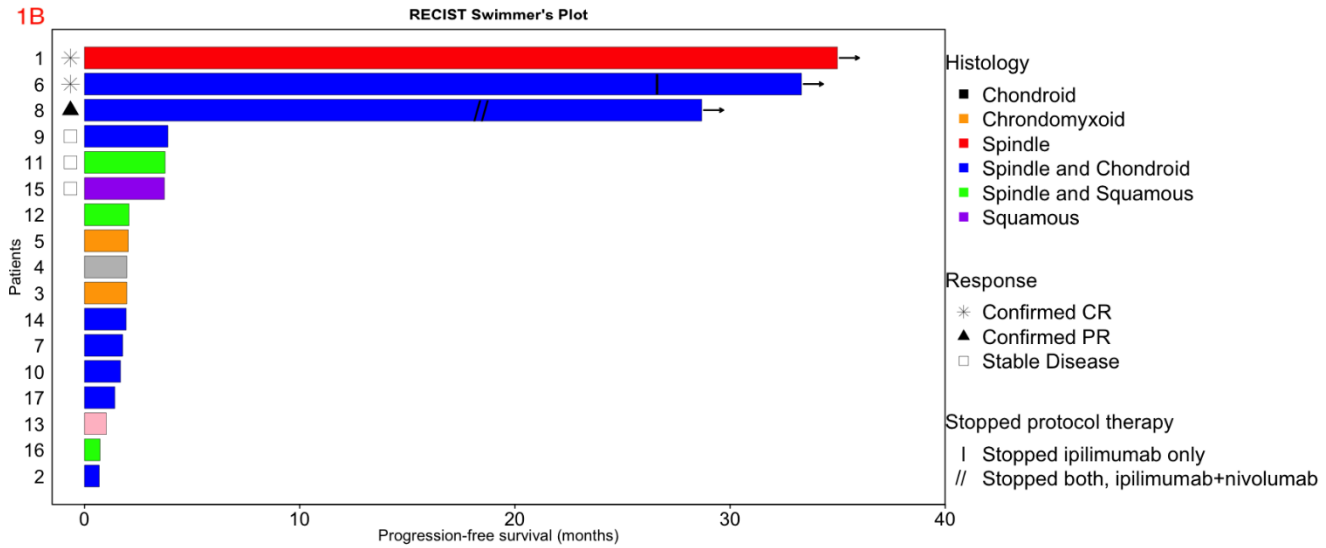
Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

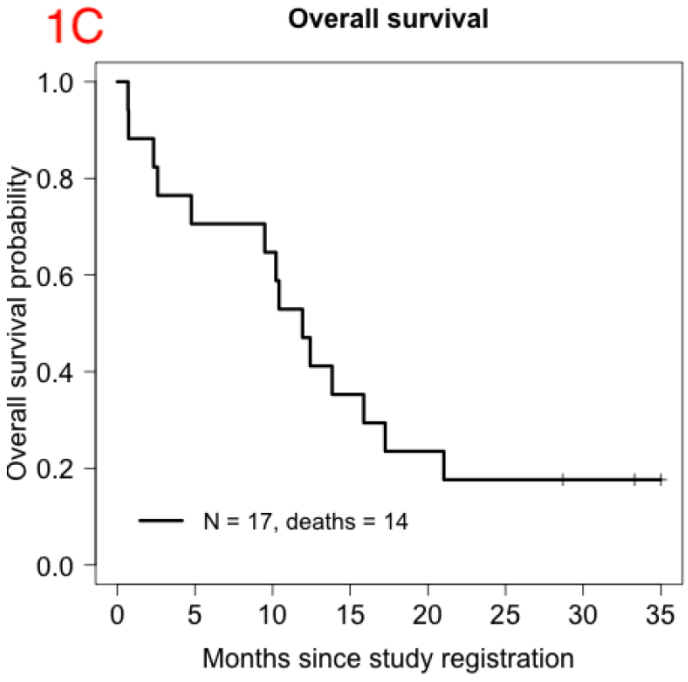
1A



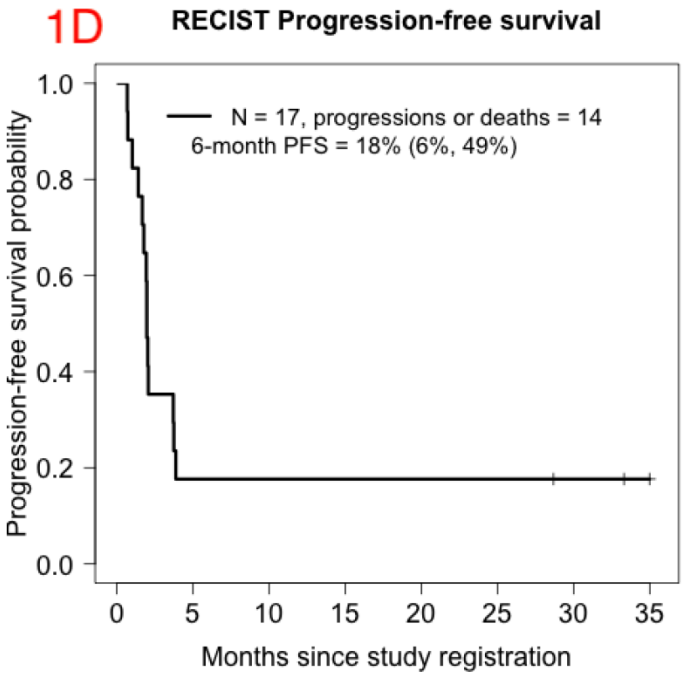
1B



1C



1D



Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.

Author Manuscript Published OnlineFirst on October 29, 2021; DOI: 10.1158/1078-0432.CCR-21-2182
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

AACR American Association for Cancer Research

Clinical Cancer Research

A Multicenter Phase II Trial of Ipilimumab and Nivolumab in Unresectable or Metastatic Metaplastic Breast Cancer: Cohort 36 of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART, SWOG S1609)

Sylvia Adams, Megan Othus, Sandip Pravin Patel, et al.

Clin Cancer Res Published OnlineFirst October 29, 2021.

Updated version	Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-21-2182
Supplementary Material	Access the most recent supplemental material at: http://clincancerres.aacrjournals.org/content/suppl/2021/10/29/1078-0432.CCR-21-2182.DC1
Author Manuscript	Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://clincancerres.aacrjournals.org/content/early/2021/10/28/1078-0432.CCR-21-2182. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.

Downloaded from clincancerres.aacrjournals.org on November 5, 2021. © 2021 American Association for Cancer Research.