

Report on the Third FDA–AACR Oncology Dose-Finding Workshop

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and Amy E. McKee⁵



Abstract

The FDA–AACR Oncology Dose-Finding Workshop, Part 3, was held in Washington, DC, on July 20, 2017, as a continuation of the previous two collaborative dose-finding and optimization workshops presented by the FDA and AACR. This year's workshop focused on combination

therapy with immune-oncology agents and best practices regarding patient and dose selection, predictive biomarkers, and novel clinical endpoints. This summary highlights viewpoints that emerged during the workshop. *Cancer Immunol Res*; 5(12); 1058–61. ©2017 AACR.

Introduction

The meeting was introduced by Elizabeth Jaffee (Johns Hopkins) and Amy McKee (FDA) by noting the overwhelming number of combination immuno-oncology (IO) trials in clinical development. The rapid growth of IO includes FDA approvals of antibodies targeting cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death ligand-1 (PD-L1). The broad scope of clinical trials investigating these agents suggests they may become the backbone to which other cancer therapies are added in the future (1).

The first two dose-finding workshops cosponsored by AACR and FDA focused on small molecule kinase inhibitors (2) and monoclonal antibodies. This third workshop focused on dose finding and optimization for combination IO regimens. Examples of evolving FDA review strategies for dose determination were presented.

IO Overview: Scope of the Problem

This session focused on the evaluation and implementation of IO agents in distinct cancer types. Most speakers noted a clinical development paradigm of PD-1/PD-L1 antibody + X. Robert Vonderheide (University of Pennsylvania) described pancreatic cancer as a "cold" tumor with low mutational burden and scant effector T-cell infiltration that is notoriously resistant to single-

agent immune-checkpoint inhibitors. The critical challenge in pancreatic cancer is to develop IO combinations that strategically release antigens and prime T cells before exposure to PD-1/PD-L1 antagonists. In one strategy, a monoclonal antibody to CD40 combined with gemcitabine and nab-paclitaxel chemotherapies led to T cell–dependent tumor regression and long-term survival in murine models of pancreas cancer (3, 4). A three-arm clinical trial is translating this approach to pancreas cancer patients, randomizing them to receive chemotherapy with gemcitabine and nab-paclitaxel plus CD40 antibody, nivolumab, or the combination of CD40 antibody and nivolumab. The trial is designed both to optimize the dose and schedule of CD40 required to prime pancreatic tumor immunity and to evaluate the potential increased risk of toxicity.

"Current challenges are to identify the patients who require combination therapy to overcome IO resistance, and to identify novel endpoints for rational combinations of IO agents with chemotherapy and targeted therapy."

Renal cell carcinoma (RCC) is a "hot" tumor that can respond to single-agent immune-checkpoint inhibitors. Current challenges are to identify the patients who require combination therapy to overcome IO resistance, and to identify novel endpoints for rational combinations of IO agents with chemotherapy and targeted therapy, noted David F. McDermott (Beth Israel Deaconess Medical Center, Dana-Farber Cancer Institute). Early clinical data suggest that anti-VEGF therapy may prime patients' immune systems for response to immune-checkpoint inhibitors (5). A phase II first-line metastatic RCC trial randomized patients to atezolizumab, atezolizumab and bevacizumab, or sunitinib, and explored the association of progression-free survival (PFS) with prespecified gene expression signatures of the tumor micro-environment. Three candidate-predictive gene expression signatures representing tumor angiogenesis, preexisting immunity, or immunosuppressive myeloid inflammation were identified to be predictive of response to atezolizumab with bevacizumab or sunitinib and advanced for validation in phase III trials (6).

Breast cancer generally tends to be a "cold" tumor, noted Leisha A. Emens (Johns Hopkins). Breast cancer subtypes are

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Note: Supplementary data for this article are available at Cancer Immunology Research Online (<http://cancerimmunolres.aacrjournals.org/>).

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doi: 10.1158/2326-6066.CIR-17-0590

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immunologically heterogeneous: triple-negative breast cancer has no approved targeted therapies and is more likely to be "hot," HER2⁺ breast cancer has targeted therapies that may synergize with immunotherapy and is also more likely to be hot, and ER⁺/PR⁺ breast cancers are most likely to be cold and require priming strategies to induce T cells. Dr. Emens described a chemotherapy dose-ranging trial where a breast cancer vaccine was given in sequence with three low doses of cyclophosphamide prevaccination to mitigate regulatory T cells and doxorubicin postvaccination to promote expansion of effector T cells (7). Tumor-specific antibody responses were mapped on a 3 × 3 dose matrix to identify the chemotherapy dose combination that maximized immunity. "This factorial design determines the optimal combination of multiple interacting variables using as few resources, i.e., patients, as possible," she noted. HER2-targeted agents have significant immune-modulatory activity and may prime the tumor microenvironment for response to vaccines and/or immune-checkpoint modulation in HER-2⁺ breast cancer (8). Additional approaches are required for cold breast cancers. Activating innate immunity with STING agonists can induce T cells in cold tumors, and tumor regression can be augmented by targeting the OX40 and the PD-1 pathways (9). This immunotherapy strategy may be appropriate for cold breast cancers regardless of clinical subtype.

Only 15% to 20% of bladder cancer patients benefit from single-agent immunotherapies, Joaquim Bellmunt (Harvard Medical School, Dana-Farber Cancer Institute) said. Key questions are whether sequential or concomitant immunotherapy is better, and which agents will be synergistic in combination with immune-checkpoint blockade. One key finding is that high fibroblast growth factor receptor-3 (FGFR3) expression is associated with cold bladder tumors (10). Consistent with this, FGFR3 expression is highest in Luminal Cluster I tumors, in which responses to PD-1 blockade have been low (11). The exploration of FGFR3 inhibitors with IO agents in the neoadjuvant setting will facilitate the correlation of immunogenomic biomarkers and radiologic response.

Key Translational Questions for IO Agents

The second session focused on safety considerations for the clinical development of combination IO regimens. Tiffany K. Ricks (FDA) discussed the unique safety concerns of combination IO regimens, including acute cytokine release/immune activation syndromes, other immune-related adverse events, and possible additive or synergistic toxicities with standard cancer drugs (12). The minimally anticipated biologic effect level (MABEL) approach is recommended to guide the starting dose of novel IO agents for clinical trials and should integrate all available data. The toxicology of each agent in the IO combination should be well studied. Dose reduction from the maximum-tolerated dose (MTD) or recommended phase II dose for molecularly targeted agents should be considered for the starting dose, due to the possibility of unexpected toxicities.

Three separate FDA case studies evaluated anti-PD-1 with a kinase inhibitor, anti-PD-1 with a second immune-checkpoint inhibitor, and an antibody specific for a different immune receptor expressed on activated T cells, alone or combined with anti-PD-L1. In the first case, nonclinical studies of the single-agent kinase inhibitor revealed significant cardiac/vascular inflammation in animals without similar findings in humans. Due to

concerns that adding PD-1 blockade could unmask this cardiac toxicity in humans, the FDA recommended a starting dose of the kinase inhibitor equivalent to 20% of the cardiotoxic dose in animals, and adding cardiac monitoring to the clinical trial. In the second case, nonclinical pharmacodynamic (PD) studies showed little to no activity with the second immune-checkpoint inhibitor alone, but adding anti-PD-1 to it resulted in higher T-cell responses and greater antitumor activity than with anti-PD-1 alone. The FDA recommended a MABEL-based starting dose for the second immune-checkpoint inhibitor corresponding to the EC₅₀ for interferon- γ release in T-cell assays. In the third case, monotherapy dose escalation of the different immune receptor agent for two dose cohorts was followed by escalation of this agent at the monotherapy starting dose combined with the recommended dose of anti-PD-L1. This design was based on a concentration-dependent increase in T-cell activation with exposure to this agent *in vitro*, and greater antitumor activity with the combination relative to either single agent in animal models. Thus, pretrial data should describe the toxicology of each drug and the safety and mechanistic rationale of the IO combination based on the totality of the data.

"IO combinations should be based on immunologic mechanisms that both restore and amplify the cancer immunity cycle, culminating in tumor rejection."

Daniel S. Chen (Genentech/Roche) emphasized that, given the over 1200 IO combinations in the pipeline, prioritizing the most promising IO combinations is critical. Because most patients do not respond to immune-checkpoint blockade, the transformative potential of immunotherapy must be expanded to more patients using IO combinations. The cancer immunity cycle can guide the mechanistic development of rational IO combinations (13) in the context of the cancer immune set point, which captures the frequency and avidity of tumor-specific T cells, and host factors such as immunogenetics, the microbiome, viral exposures, age, sunlight exposure, hormonal factors, and drug exposures (14). These models identify four major challenges for the field. First, IO combinations should be based on immunologic mechanisms that both restore and amplify the cancer immunity cycle, culminating in tumor rejection (15). Second, assessment methods should capture classical tumor responses, pseudoprogression as reflected by increasing lesions, and late responses. Modified RECIST, immune-related RECIST, and assessment of tumor growth kinetics all account for these unique response patterns. The kinetics and magnitude of clinical benefit may be different depending on whether preexisting immunity is unleashed (acute endpoints—response rate) or new tumor-specific T cells are generated (late endpoints—survival; refs. 16, 17). Third, biomarkers may be measured in the tumor, the peripheral blood, or draining/distant lymph nodes, and by novel imaging strategies. Fourth, deploying an efficient strategy for prioritizing the best combinations for accelerated clinical development is critical. One approach is to randomize patients across multiple IO combinations relative to a contemporary control arm, rather than relying on historical nonrandomized control data.

Bernard A. Fox (Earle A. Chiles Research Institute) focused on strategies for enhancing existing adaptive immunity. He noted that interrogating T-cell responses to viral antigens and

neoantigens is straightforward, but characterizing T-cell responses to normal proteins is difficult due to immune tolerance. Capitalizing on the coordinated B- and T-cell response by querying the humoral response provides a path forward for identifying T-cell responses to self-antigens (18). In a randomized clinical trial of granulocyte-macrophage colony-stimulating factor (GM-CSF) with anti-CTLA-4 (ipilimumab) in prostate cancer, this strategy identified the protein PAK6 as an immune target (19, 20). The TCR can also be used as a biomarker to study redistribution of tumor-specific T cells from the peripheral blood to the tumor during immunotherapy (21). Highlighting the differences between immune-checkpoint agonists and antagonists, an OX40 agonist effectively delayed tumor growth but a PD-1 antagonist did not. Furthermore, concurrent therapy was not effective, but treating with the OX40 agonist first, followed by the PD-1 antagonist, resulted in a 30% increase in tumor-free survival (22, 23).

Considerations for Dose Selection of IO Combinations

"...the 3 + 3 approach will often result in selection of an incorrect combination dose simply due to chance."

Current dose-finding algorithmic designs (3 + 3) are easy to implement, but do not incorporate existing knowledge as model-based designs do, noted Laura Fernandes (FDA). Chao Liu (FDA) emphasized a preference for model-based designs that capture both early and delayed toxicities, characterize the pharmacokinetic (PK) and PD variability, account for patient heterogeneity, study both a wide range of doses and sequence prior to registration, and collect PK data to explore dose-response and exposure-clearance-response relationships for efficacy and safety (24).

Eric Rubin (Merck Research Laboratories) noted that, for two drug combinations, variables include the dose and schedule for each drug. Two doses and two schedules of two drugs result in 16 cohorts, which would likely require more than 16 months to determine a recommended phase II dose. This complexity can be simplified by "fixing" the dose and schedule of one of the drugs, and focusing dose and schedule finding on the other drug.

The often used 3 + 3 approach is not advised in cases where the recommended phase II dose for at least one of the drugs has a dose-limiting toxicity (DLT) rate near 30%. With an underlying DLT rate of 25% for drug A, the probability of selecting a lower dose for drug A using the 3 + 3 approach in combination is 53% due to chance alone, without considering any additional toxicity from drug B. Thus, the 3 + 3 approach will often result in selection of an incorrect combination dose simply due to chance. Bayesian methods that prespecify a target DLT rate and use larger sample sizes are now preferred for dose finding in combination studies. One popular method is the modified toxicity probability interval design, with a target DLT rate of 25%, where dose finding stops once 14 patients are enrolled at a given dose that meets or is below the targeted DLT rate (25). Combination studies may also exclude severe toxicities from DLT consideration because they are known to be associated with one of the drugs. However, with the exception of an infusion reaction that occurs immediately

after drug A, one can never be sure that an observed DLT originates only from drug A, because toxicities that are well known for drug A may still be enhanced with coadministration of drug B.

Given the number of new products and combinations, creative designs and endpoints are urgently needed. Classical endpoints, such as objective response rate (ORR) or PFS, have known limitations. Model-based tumor growth inhibition (TGI) metrics (26) should be more sensitive than classical endpoints for assessing treatment effect. René Bruno (Staff Scientist, Clinical Pharmacology, Genentech/Roche) presented a drug-disease TGI model based on longitudinal tumor size data that estimates TGI metrics. Those metrics are used as biomarkers to capture treatment effect in multivariate TGI-overall survival (OS) models that relate TGI metrics and baseline prognostic factors to OS (27). He described a TGI-OS model in a phase II study in non-small cell lung cancer (NSCLC) in which on-treatment estimates of tumor growth rate predicted the benefit (hazard ratio, HR) of atezolizumab over docetaxel (28). This model was externally validated in simulating the HR of various subpopulations of patients by baseline biomarkers (PD-L1 expression in tumor/tumor-infiltrating immune cells or T-effector cell and interferon- γ gene signature) in a phase III study (16). On-treatment growth rate is proposed as an alternative endpoint to evaluate dose and scheduling in early IO combination studies.

The multitude of combination IO regimens to test in different disease settings exceeds the patients available to enroll in trials, highlighting the importance of prioritizing the most promising combinations and optimizing the design of every trial.

Amit Roy (Bristol-Myers Squibb) presented the rationale for combining ipilimumab and nivolumab. A phase Ib study (29) and exposure-response data (30, 31) led to the selection of nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg (N113) Q3W in melanoma that proved efficacious in a phase III study (32). In RCC, nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg (N311) Q3W had a better safety profile and will be tested in the pivotal study (33). In NSCLC, the Q3W combination was toxic and nivolumab at 3 mg/kg Q2W plus ipilimumab at 1 mg/kg Q12W was much more tolerable with greater clinical activity (34). Together, these data suggest that optimal dosing for combinations may vary across tumor indications.

Conclusions

Dose and schedule optimization for combination IO trials is a complex endeavor. The multitude of combination IO regimens to test in different disease settings exceeds the patients available to enroll in trials, highlighting the importance of prioritizing the most promising combinations and optimizing the design of every trial. The promise of combination IO therapy is undeniable, and the importance of developing safe and effective combination IO regimens for larger numbers of patients across all cancers is paramount.

Disclosure of Potential Conflicts of Interest

L.A. Emens is on the board of directors of SITC; is an advisory board member for FDA CTGTAC/ODAC; reports receiving commercial research

grants from Genentech/Roche, EMD Serono, Maxcyte, Merck, AstraZeneca, Aduro Biotech, and Corvus; and is a consultant/advisory board member for Gritstone, Molecuvax, eTheRNA, Bayer, Peregrine, Syndax, AstraZeneca, and Amgen. R. Bruno is a staff scientist at Genentech-Roche. E.M. Jaffee reports receiving a commercial research grant from Aduro Biotech, other commercial research support from Bristol-Myers Squibb, and is a consultant/advisory board member for MedImmune. Under a licensing agreement between Aduro Biotech and the Johns Hopkins University, the University and E.M. Jaffee and L.A. Emens are entitled to milestone payments and

royalty on sales of GM-CSF-secreting vaccines. The terms of these arrangements are being managed by the University in accordance with its conflict-of-interest policies. No potential conflicts of interest were disclosed by the other authors.

Acknowledgments

The authors would like to acknowledge Joaquim Bellmunt, Bernard Fox, and Tiffany Ricks for review of the manuscript.

References

- Venneman M, Dranoff G. Combining immunotherapy and targeted therapies in cancer treatment. *Nat Rev Cancer* 2012;12:237–51.
- Janne PA, Kim G, Shaw AT, Sridhara R, Pazdur R, McKee AE. Dose finding of small-molecule oncology drugs: optimization throughout the development life cycle. *Clin Cancer Res* 2016;22:2613–7.
- Byrne KT, Vonderheide RH. CD40 stimulation obviates innate sensors and drive T cell immunity in cancer. *Cell Rep* 2016;15:2719–32.
- Beatty GL, Chiorean EG, Fishman MP, Saboury B, Teitelbaum UR, Sun W, et al. CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. *Science* 2011;331:1612–6.
- Wallin JJ, Bendell JC, Funke R, Sznol M, Korski K, Jones S, et al. Atezolizumab in combination with bevacizumab enhances antigen-specific T cell migration in metastatic renal cell carcinoma. *Nat Commun* 2016;7:12624.
- McDermott D, Huseni M, Rini B, Motzer R, Atkins M, Escudier B, et al. Molecular correlates of differential response to atezolizumab +/- bevacizumab vs. sunitinib in a phase II study in untreated metastatic renal cell carcinoma (RCC) patients. Proceedings of the AACR Annual Meeting 2017, April 1–5, 2017; Washington DC, 2017;17(Suppl 13):CT-081.
- Emens LA, Asquith JM, Leatherman JM, Kobrin BJ, Petrik S, Laiko M, et al. Timed sequential treatment with cyclophosphamide, doxorubicin, and an allogeneic granulocyte-macrophage colony-stimulating factor-secreting breast tumor vaccine: a chemotherapy dose-ranging factorial study of safety and immune activation. *J Clin Oncol* 2009;27:5911–8.
- Chen G, Gupta R, Petrik S, Laiko M, Leatherman JM, Asquith JM, et al. A feasibility study of cyclophosphamide, trastuzumab, and an allogeneic GM-CSF-secreting breast tumor vaccine for HER-2+ metastatic breast cancer. *Cancer Immunol Res* 2014;2:949–61.
- Foote JB, Kok M, Leatherman JM, Armstrong TD, Marcinkowski BC, Ojalvo LS, et al. A STING agonist given with OX40 receptor and PD-L1 modulators primes immunity and reduces tumor growth in tolerized mice. *Cancer Immunol Res* 2017;5:468–79.
- Sweis RF, Spranger S, Bao R, Paner GP, Stadler WM, Steinberg G, et al. Molecular drivers of the non-T-cell inflamed tumor microenvironment in urothelial bladder cancer. *Cancer Immunol Res* 2016;4:562–8.
- Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinomas who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* 2016;387:1909–20.
- ICH. 2010. Guidance for Industry: S9 nonclinical evaluation for anticancer pharmaceuticals.
- Chen DS, Mellman I. Oncology meets immunology: the cancer immunity cycle. *Immunity* 2013;39:1–10.
- Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature* 2017;541:321–30.
- Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014;515:563–7.
- Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017;389:255–65.
- McDermott DF, Atkins MB, Motzer RJ, Rini BI, Escudier BJ, Fong L, et al. A phase II study of atezolizumab with or without bevacizumab vs. sunitinib in untreated metastatic renal cell carcinoma patients. Abstract presented at: 2017 Genitourinary Cancers Symposium; February 16–18, 2017; Orlando FL. Abstract 431.
- Fong L, Kwek SS, O'Brien S, Kavanagh B, McNeel DG, Weinberg V, et al. Potentiating endogenous antitumor immunity to prostate cancer through combination immunotherapy with CTLA4 blockade and GM-CSF. *Cancer Res* 2009;69:609–15.
- Kwek SS, Dao V, Roy R, Hou Y, Alajajian D, Simko JP, et al. Diversity of antigen-specific responses induced in vivo with CTLA-4 blockade in prostate cancer patients. *J Immunol* 2012;189:3759–66.
- Tripathi SC, Peters HL, Taguchi A, Katayama H, Wang H, Momin A, et al. Immunoproteasome deficiency is a feature of non-small cell lung cancer with a mesenchymal phenotype and is associated with a poor outcome. *Proc Natl Acad Sci USA* 2016;113:1555–64.
- Anagnostou V, Smith KN, Forde PM, Niknafs N, Bhattacharya R, White J, et al. Evolution of neoantigen landscape during immune checkpoint blockade in non-small cell lung cancer. *Cancer Discov* 2017;7:264–76.
- Messenheimer DJ, Jensen SM, Afentoulis ME, Wegmann KW, Feng Z, Friedman DJ, et al. Timing of PD-1 blockade is critical to effective combination immunotherapy with anti-OX40. *Clin Cancer Res* 2017;23:6165–77.
- Shrimali RK, Ahmad S, Verma V, Zeng P, Ananth S, Gaur P, et al. Concurrent PD-1 blockade negates the effects of OX40 agonist antibody in combination immunotherapy through inducing T-cell apoptosis. *Cancer Immunol Res* 2017;5:755–66.
- Liu C, Yu J, Li H, Liu J, Xu Y, Song P, et al. Association of time-varying clearance of nivolumab with disease dynamics and its implications on exposure response analysis. *Clin Pharmacol Ther* 2017;101:657–66.
- Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. *Clin Trials* 2010;7:653–63.
- Claret L, Gupta M, Han K, Joshi A, Sarapa N, He J, et al. Evaluation of tumor-size response metrics to predict overall survival in Western and Chinese patients with first-line metastatic colorectal cancer. *J Clin Oncol* 2013;31:2110–4.
- Bruno R, Mercier F, Claret L. Evaluation of tumor size response metrics to predict survival in oncology clinical trials. *Clin Pharmacol Ther* 2014;95:386–93.
- Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016;387:1837–46.
- Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* 2013;369:122–33.
- Feng Y, Roy A, Masson E, Chen TT, Humphrey R, Weber JS. Exposure-response relationships of the efficacy and safety of ipilimumab in patients with advanced melanoma. *Clin Cancer Res* 2013;19:3977–86.
- Agrawal S. Nivolumab dose selection: challenges, opportunities and lessons learned for cancer immunotherapy. FDA–AACR Oncology Dose Finding Workshop, June 13, 2016.
- Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015;373:23–34.
- Hammers HJ, Plimack ER, Infante JR, Rini BI, McDermott DF, Lewis LD, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: the CheckMate 016 study. *J Clin Oncol* 2017. doi: 10.1200/JCO.2016.72.1985. [Epub ahead of print].
- Feltquate D. Challenges in IO-IO combination dose finding: A case study with ipilimumab/nivolumab in NSCLC. FDA–AACR I-O Development Workshop, October 13, 2016.

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Cancer Immunol Res 2017;5:1058-1061.

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