Review Article on Lung Cancer Diagnostics and Treatments 2015: A Renaissance of Patient Care

New strategies in immunotherapy for non-small cell lung cancer

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Abstract: Treatment for the most common form of cancer (lung cancer) has historically involved use of cytotoxic chemotherapy. With the advent of mutation analysis, more therapies beyond traditional cytotoxics have been discovered. Most recently, the use of immunotherapy has entered the treatment arsenal of non-small cell lung cancer (NSCLC). This review aims to summarize the current and future use of immunotherapy in the treatment of NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); immunotherapy; vaccine

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Introduction

Lung cancer is the leading cause of cancer related death worldwide (1). Cytotoxic chemotherapy can improve survival, but responses are often short-lived (2). Targeted therapies result in high response rates for patients with certain alterations, such as *EGFR* mutations or *EML4-ALK* translocations, but these are found only in a minority of patients and resistance inevitably develops (3,4). Clearly, novel therapeutic approaches are urgently needed.

Utilizing the immune system to fight cancer is an attractive goal, promising the possibility of long term disease control without some of the toxicities of more traditional therapies. In order to grow, cancer must evade immune detection. In lung cancer and many other tumors, T-cell tolerance to tumor antigens is a major barrier to effective immunotherapy, and initial studies of non-specific immune stimulation with interleukin-2 and interferon-alpha showed minimal activity (5,6). Therapeutic checkpoint inhibition or activation of co-stimulatory molecules has the potential to combat this tolerance and allow anti-tumor immune responses. Recent trials with these agents have shown promising results and have renewed excitement in the field of immune therapy for lung cancer. In this article, we will review the results of recently reported clinical trials of immunotherapy agents, and we will discuss ongoing and upcoming research in this field.

Vaccine therapy

Cancers often express antigens not found on normal cells. Many clinical trials have studied the efficacy of vaccines against these antigens. Two large trials of vaccine therapy in non-small cell lung cancer (NSCLC), the Stimulating Targeted Antigenic Response to (START) NSCLC trial and the MAGRIT, a double-blind, randomized, placebo-controlled Phase III study to assess the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small cell lung cancer (MAGRIT) trial, have recently been reported.

The START trial enrolled 1,513 patients with stage III NSCLC who had completed chemoradiation. Patients without progressive disease were then randomized to receive either tecemotide (L-BLP25), a vaccine against

Table 1 Completed NSCLC immunotherapy trials

Immunotherapy	Target	Setting	Patient number	Results
Ipilimumab	CTLA-4	Phase II	204	ir-PFS 5.7 months for phased ipilimumab + chemotherapy *vs*. 4.6 months for placebo + chemotherapy (HR 0.72; P=0.05); ir-PFS 5.5 months for concurrent ipilimumab + chemotherapy *vs*. placebo + chemotherapy (HR 0.81; P=0.13) (9)
Nivolumab	PD-1	Phase III; Checkmate 017	272	OS 9.2 months for nivolumab *vs*. 6 months for docetaxel (P<0.001) (10)
Pembrolizumab	PD-1	Phase I; KEYNOTE-001	495; (Training-182); (Validation-313)	ORR 19.4%; MDR 12.5 months; MDOS 12 months (11)
MPDL3280A	PD-L1	Phase I	53; (37 evaluable)	ORR 24%; 24-week PFS 48% (12)
MEDI4736 (durvalumab)	PD-L1	Phase I	13	3 PR with two additional responses not meeting PR per irRC (13)

NSCLC, non-small cell lung cancer; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HR, hazard ratio; ir-PFS, immune-related progression-free survival; irRC, immune-related response criteria; MDOS, median duration of overall survival; MDR, median duration of response; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand of protein 1; PFS, progression-free survival; PR, partial response.

MUC1, or placebo, and the primary endpoint of the study was overall survival (OS). There was no significant difference in survival between the two arms (median OS 25.6 months with tecemotide *vs*. 22.3 months with placebo), though there was a benefit for the vaccine in patients who received concurrent rather than sequential chemotherapy (30.8 *vs*. 20.6 months, P=0.0175) (7). Unfortunately, these promising results were not confirmed in other studies, and development of this compound has been halted.

In the MAGRIT trial, patients with surgically resected stage IB-IIIA NSCLC were randomized to receive placebo or a vaccine to MAGE-A3. Eligible patients were required to have MAGE-A3 positive tumors. A total of 2,272 patients were randomized and treated. Treatment was well tolerated, but results were disappointing as the trial showed no significant improvement in disease-free survival (60.5 *vs*. 57.9 months, P=0.7379) (8).

With negative results from these two large trials, enthusiasm for vaccine-based therapy for NSCLC has waned, and focus has shifted to treatment with checkpoint inhibitors and other immunotherapy agents.

Checkpoint inhibition

A complex interaction of both inhibition and stimulation of the immune system exists to allow the appropriate destruction of pathogens and abnormal cells while preventing overstimulation that could lead to destruction of healthy cells (autoimmunity). This network of inhibitory and stimulatory signals offers multiple potential targets. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are co-inhibitory factors ("checkpoints") that have been the focus of much research (*Table 1*).

CTLA-4 inhibitors

CTLA-4 is expressed on the surface of T-cells. It inhibits T-cell activation and decreases immune response (14,15). Inhibition of this protein with therapeutic antibodies leads to increased activation of T-cells and anti-tumor responses in some patients. Ipilimumab is an anti-CTLA-4 antibody approved for the treatment of metastatic melanoma (16). Its activity is under investigation for NSCLC.

Preliminary signs of efficacy in NSCLC were seen in a phase II study of ipilimumab in combination with chemotherapy. Patients with previously untreated metastatic NSCLC were randomly assigned to one of three groups: carboplatin/paclitaxel, carboplatin/paclitaxel with concurrent ipilimumab, or carboplatin/paclitaxel with sequential ipilimumab (9). Results were very promising with a statistically significant improvement in progression-free survival (PFS) in the sequential arm (carboplatin and paclitaxel for two cycles followed by addition of ipilimumab with chemotherapy for four more cycles) compared to the chemotherapy alone arm (median PFS 5.1 *vs*. 4.2 months,

P=0.02). Subset analysis showed a greater benefit in patients with squamous histology and thus, a phase III study of ipilimumab in combination with carboplatin and paclitaxel for squamous cell carcinoma of the lung is ongoing (NCT 02279732). Ipilimumab is also being studied in NSCLC in combination with radiation (NCT02239900, NCT02221739) and with other immunotherapy agents (NCT02039674, NCT02174172).

PD-1 inhibitors

PD-1 is expressed on the surface of activated T-cells and has an inhibitory effect on immune response, and multiple therapeutic antibodies against PD-1 are in development. PD-1 inhibitors that have been most extensively studied for lung cancer are nivolumab and pembrolizumab. NSCLC responses to PD-1 inhibition with nivolumab were first reported in a phase I study, with responses seen in 18% of heavily pre-treated NSCLC patients (17). Some of these responses were durable. These results led to two large, phase III trials of nivolumab *vs.* docetaxel in previously treated squamous NSCLC (CheckMate 017, NCT01642004) and non-squamous NSCLC (CheckMate 057, NCT01673867). Results of the CheckMate 017 study were recently reported; patients treated with nivolumab had a statistically significant improvement in OS compared to patients receiving docetaxel (9.2 *vs*. 6.0 months, P<0.001) (10). Nivolumab was FDA approved for previously treated squamous cell carcinoma of the lung based on these data. CheckMate 057 has completed accrual and results are eagerly awaited. A phase III study comparing nivolumab to platinum-doublets for previously untreated NSCLC is currently enrolling patients (NCT02041533).

Pembrolizumab is another PD-1 inhibitor with promising activity in NSCLC. In the recently reported phase I KEYNOTE-001 study, patients with NSCLC were treated with pembrolizumab in different doses and schedules. Most patients (81%) had received prior systemic therapy. Tumor samples from all patients were assessed for programmed cell death ligand of protein 1 (PD-L1) expression prior to treatment. The overall response rate (ORR) in all tumor types was 19.4% with a median duration of response (MDR) of 12.5 months. Median OS was 12 months (11). A phase III trial comparing pembrolizumab to docetaxel for previously treated NSCLC has completed accrual (KEYNOTE-010, NCT01905657); phase III trials in the front-line space are ongoing (KEYNOTE-024, NCT02142738 and KEYNOTE-042, NCT022220894).

PD-L1 inhibitors

An alternate to inhibiting PD-1 is blocking interactions at the ligand level (PD-L1). The two anti-PD-L1 antibodies that are furthest in development for lung cancer are MPDL3280A and MEDI4736. In a phase I study of MPDL3280A, NSCLC patients had a 24% response rate. Some of these responses were long-lasting; a number of patients continued to maintain a response even after the antibody was stopped (12). Larger studies are ongoing: the single arm, phase II BIRCH trial is enrolling patients with PD-L1 positive NSCLC (NCT02031458); the phase III OAK trial randomizes patients with previously treated NSCLC to either MPDL3280A or docetaxel (NCT02008227).

MEDI4736 also has shown promising activity in a phase I study (7), and larger studies are ongoing. The phase III PACIFIC trial is enrolling patients with stage III NSCLC who have completed radiation and randomizing them to either MEDI4736 or placebo (NCT02125461); this is the largest ongoing immunotherapy effort for locally advanced disease. In the phase III ARTIC trial, NSCLC patients who have received multiple prior therapies will be randomized to MEDI4736 *vs.* standard chemotherapy if PD-L1 positive or MEDI4736 in combination with anti-CTLA4 antibody tremelimumab if PD-L1 negative (NCT0235948).

T-cell co-stimulation

"Taking the brakes off" the immune system with checkpoint inhibition has been the major focus of immunotherapy research in NSCLC so far; however, agents that augment co-stimulatory signals are also under study. Ongoing studies are focused on 4-1BB (CD-137), OX40 (CD134), and CD-27 agonists that augment T-cell response, often in combination with checkpoint inhibitors. These three receptors are members of the tumor necrosis factor receptor family and are primarily expressed on T-cells. When activated by interactions with their ligands or with antibodies, these receptors lead to T-cell proliferation and survival, as well as cytokine production (8). Therapeutic antibodies against these receptors are in clinical development.

4-1BB agonists

4-1BB, also known as CD137, is a potent co-stimulatory molecule expressed on activated T-cells, and is not seen

in resting T-cells (13). Interactions between 4-1BB and its ligand lead to T-cell proliferation and activation (18). In pre-clinical models, administration of 4-1BB agonists inhibits tumor growth (19). Urelumab is a fully human anti 4-1BB antibody with agonistic activity. In an initial phase I study, activity was observed in melanoma; no patients with NSCLC enrolled on this trial (20). There is an ongoing phase I/II trial studying the combination of urelumab with nivolumab; this study will enroll patients with NSCLC in an expansion cohort (NCT02253992).

OX40 agonists

Like 4-1BB, OX40 is expressed primarily on activated T-cells and its ligand is expressed on antigen presenting cells (21). When OX40 is activated by either its ligand or therapeutic antibodies, the result is survival and proliferation of T-cells (22). Multiple compounds are in development targeting OX40. MEDI6469 is an anti-OX40 antibody with agonist activity; it is being studied in a phase Ib/II trial as a single agent or in combination with checkpoint inhibition (NCT02205333). An expansion cohort for NSCLC is planned. MEDI6383 is another OX40 agonist currently in phase I studies (NCT02221960).

CD27 agonists

CD27 is another co-stimulatory receptor related to OX40 and 4-1BB. An agonist anti-CD27 antibody, varlilumab, was well tolerated in phase I trials (23). There are ongoing trials enrolling NSCLC patients with varlilumab as a single agent (NCT01460134) and in combination with nivolumab (NCT02335918).

Combination therapy

Striking responses to immunotherapy have been seen; however, with single agent therapy, only a minority of patients will respond. A number of studies are exploring combination therapy in an effort to increase response rates and duration of disease control.

Immunotherapy combinations

As briefly discussed above, ongoing studies are combining multiple immunotherapy agents. Especially promising are combinations of dual checkpoint inhibition with CTLA-4 inhibitors and PD-1 inhibitors. Nivolumab combined with ipilimumab is associated with high response rates in melanoma (24); early phase studies enrolling NSCLC patients are ongoing (NCT01454102). The combination of MEDI4736 and tremilimumab is also under study (NCT02000947). Other studies are ongoing with checkpoint inhibition combined with agents that activate co-stimulatory molecules, such as 4-1BB, CD-27, and OX40.

Immune related toxicity is a concern with these combinations; more than half of all patients treated with a combination of ipilimumab and nivolumab had a grade 3 or 4 treatment-related adverse event (25).

Combinations with chemotherapy

Theoretically, administration of cytotoxic chemotherapy may increase antigen release from tumor cells, potentially increasing efficacy of immunotherapy. A phase II study of ipilimumab combined with carboplatin and paclitaxel suggests improved outcomes (immune-related PFS hazard ratio (HR), 0.72; P=0.05 *vs.* immune-related PFS HR, 0.81; P=0.13) when chemotherapy is administered for several cycles prior to initiation of immunotherapy (9). A number of studies combining checkpoint inhibition with cytotoxic chemotherapy are ongoing (NCT02039674, NCT01454102, and NCT02279732, among others).

Combinations with targeted therapies

EGFR inhibitors have revolutionized the treatment of *EGFR* mutant lung cancer; however, resistance inevitably develops, usually after less than a year (25,26). Studies combining EGFR inhibition with erlotinib or gefitinib with checkpoint inhibitors are ongoing (NCT01454102, NCT0208812).

MEK inhibitors such as trametinib and selumetinib have shown some evidence of activity, especially in *KRAS* mutant NSCLC (27,28). Unfortunately, response rates are low and PFS is short with single agent therapy (28). Trials combining MEK inhibition with immunotherapy in melanoma are ongoing (NCT02224781); trials in NSCLC are likely to follow.

Caution must be exercised when combining targeted agents with immunotherapy. A recent phase I study combining ipilimumab with vemurafenib in metastatic melanoma found the combination to be intolerable, with an unexpectedly high rate of hepatic toxicity (29). This trial shows that unexpected synergistic toxicity may be observed when distinct therapeutics is combined.

Combinations with radiation

Like cytotoxic chemotherapy, radiation can cause tumor antigen release, which may increase efficacy of immune therapy. There have been reports of radiation resulting in response in tumors well outside the radiation field; this is known as the abscopal effect (30), and pre-clinical evidence suggests radiation may increase the efficacy of checkpoint inhibition (31). Ongoing studies are combining checkpoint inhibition with radiation (NCT02239900, NCT02221739, NCT02303990). Toxicity is a concern here as well—pneumonitis is a common and potentially severe toxicity of both immunotherapy and radiation. Patients on these trials will be carefully monitored for pulmonary toxicity.

Biomarker development

Though immunotherapy agents appear to be very active in a subset of NSCLC, many patients will have no response to therapy. Several strategies are being developed to try to select patients most likely to respond to therapy.

PD-L1 staining

Multiple studies have assessed whether expression of PD-L1 can predict for response from checkpoint inhibition. In the phase I study of nivolumab in multiple tumor types including NSCLC, patients whose tumors were positive for PD-L1 (defined as >5% of cells with expression) had a response rate of 36% with nivolumab. None of the patients with PD-L1 negative tumors had a response (17). In the KEYNOTE-001 trial, NSCLC patients with staining for PD-L1 in greater than 50% of cells had longer PFS and OS than those with lower rates of expression when treated with pembrolizumab (11).

The early phase studies with nivolumab and pembrolizumab described above used tumor cell staining for PD-L1 as a marker; Herbst *et al*. examined expression of PD-L1 in both tumor cells and infiltrating lymphocytes in specimens from a phase I study of MPDL3280A (32). Interestingly, they found that expression of PD-L1 on tumor infiltrating immune cells was a significant predictor of response, while PD-L1 expression on tumor cells was not. In patients with NSCLC, the response rate for patients with the highest PD-L1 expression on immune cells (IHC 3) was 83%; the response rate in patients with no staining (IHC 0) was 20%. Of note, a response rate of 20% still compares favorably to response rates seen with cytotoxic chemotherapy for previously treated NSCLC (33).

In summary, studies so far suggest that patients with PD-L1 expression have a higher likelihood of responding to PD-1 or PD-L1 inhibition. These results, however, are all from single-arm trials, and some patients with PD-L1 negative tumors have responded to therapy. The clinical utility of this biomarker has not yet been determined. Ongoing phase III trials randomizing patients to either checkpoint inhibition or standard chemotherapy are incorporating analysis of PD-L1, in addition to other markers. These results should define the role of this marker in selecting patients for therapy. Of note, nivolumab was FDA approved for previously treated squamous cell carcinoma of the lung, without reference to PD-L1 status (10).

Mutational burden

Some of the cancers in which immunotherapy seems particularly active (melanoma, NSCLC, and head and neck squamous cell carcinoma) are cancers with high mutational loads. It has been hypothesized that a high mutation burden correlates with creation of neoantigens, which may be targets for immune cells activated by checkpoint inhibition (34). Several studies have examined the correlation between number of somatic mutations detected by whole exome sequencing and response to immunotherapy agents.

Elegant work by Snyder *et al*. has demonstrated that mutational load in melanoma is associated with clinical benefit to anti-CTLA-4 antibodies tremilimumab and ipilimumab. Specific neoepitopes were identified that predict for benefit—these may resemble epitopes from certain viruses (35).

In the KEYNOTE-001 study in NSCLC, current or former smokers had higher response rates to pembrolizumab than non-smokers (22.5% *vs*. 10.3%) (11). Smokers tend to have far more mutations in their tumors than never smokers; 10 times more in one study (36). Additional studies on tumor samples from this study showed that higher mutation burden was associated with higher rates of durable clinical benefit [partial response (PR) or stable disease lasting longer than 6 months], higher response rates, and longer PFS (34).

Though these results are intriguing, whole genome sequencing has not yet been incorporated into routine clinical care, and mutational burden does not yet have a role in selecting patients for therapy.

Management of immunotherapy related toxicity

The agents described above are generally well tolerated;

however, severe toxicities can occur. Pneumonitis, colitis, and hepatitis have been noted with these agents and can be fatal. Appropriate and timely management of the unique toxicities associated with these agents in critically important; this topic is discussed by Villadolid and Amin in detail in another review in this issue.

Conclusions

It is clear that immunotherapy will play an increasing role in the therapy of lung cancer. Over the next year, the results of several randomized phase III trials comparing checkpoint inhibition with standard chemotherapy will be reported. These studies will help to establish the role of immunotherapy in the treatment of advanced NSCLC. Future research should focus on identification of patients most likely to benefit from therapy, and on rational combination therapy.

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Footnote

Conflicts of Interest: Dr. Carrizosa: Honoraria—Boehringer Ingelheim, Advisory Board—Pfizer. Dr. Gold: Honoriaria—Bristol-Myers Squibb, Advisory Board—Pfizer.

References

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.
2. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-8.
3. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
4. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693-703.
5. Schiller JH, Morgan-Ihrig C, Levitt ML. Concomitant administration of interleukin-2 plus tumor necrosis factor in advanced non-small cell lung cancer. Am J Clin Oncol 1995;18:47-51.
6. Jansen RL, Slingerland R, Goey SH, et al. Interleukin-2 and interferon-alpha in the treatment of patients with advanced non-small-cell lung cancer. J Immunother (1991) 1992;12:70-3.
7. Butts C, Socinski MA, Mitchell PL, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. Lancet Oncol 2014;15:59-68.
8. Vansteenkiste JF, Cho B, Vanakesa T, et al. MAGRIT, a double-blind, randomized, placebo-controlled Phase III study to assess the efficacy of the recMAGE-A3 + A S15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small cell lung cancer. Ann Oncol 2014;25:iv409.
9. Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol 2012;30:2046-54.
10. Spigel DR, Reckamp KL, Rizvi NA, et al. A phase III study (CheckMate 017) of nivolumab (NIVO; anti-programmed death-1 [PD-1]) vs docetaxel (DOC) in previously treated advanced or metastatic squamous (SQ) cell non-small cell lung cancer (NSCLC). J Clin Oncol 2015;33:abstr 8009.
11. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018-28.
12. Spigel DR, Gettinger SN, Horn L, et al. Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). J Clin Oncol 2013;31:abstr 8008.
13. Brahmer JR, Rizvi NA, Lutzky J, et al. Clinical activity and biomarkers of MEDI4736, an anti-PD-L1 antibody, in patients with NSCLC. J Clin Oncol 2014;32:abstr 8021.
14. Brunet JF, Denizot F, Luciani MF, et al. A new member of the immunoglobulin superfamily--CTLA-4. Nature 1987;328:267-70.
15. Krummel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med 1995;182:459-65.
16. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.
17. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.
18. Vinay DS, Kwon BS. Immunotherapy of cancer with

4-1BB. Mol Cancer Ther 2012;11:1062-70.
19. Melero I, Shuford WW, Newby SA, et al. Monoclonal antibodies against the 4-1BB T-cell activation molecule eradicate established tumors. Nat Med 1997;3:682-5.
20. Sznol M, Hodi FS, Margolin K, et al. Phase I study of BMS-663513 a fully human anti-CD137 agonist monoclonal antibody, in patients (pts) with advanced cancer (CA). J Clin Oncol 2008;26:abstr 3007.
21. Croft M. Costimulation of T cells by OX40, 4-1BB, and CD27. Cytokine Growth Factor Rev 2003;14:265-73.
22. Linch SN, McNamara MJ, Redmond WL. OX40 Agonists and Combination Immunotherapy: Putting the Pedal to the Metal. Front Oncol 2015;5:34.
23. Ansell SM, Northfelt DW, Flinn I, et al. Phase I evaluation of an agonist anti-CD27 human antibody (CDX-1127) in patients with advanced hematologic malignancies. J Clin Oncol 2014;32:abstr 3024.
24. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369:122-33.
25. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
26. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
27. Jänne PA, Shaw AT, Pereira JR, et al. Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. Lancet Oncol 2013;14:38-47.
28. Blumenschein GR Jr, Smit EF, Planchard D, et al. A randomized phase II study of the MEK1/MEK2 inhibitor trametinib (GSK1120212) compared with docetaxel in KRAS-mutant advanced non-small-cell lung cancer (NSCLC)†. Ann Oncol 2015;26:894-901.
29. Ribas A, Hodi FS, Callahan M, et al. Hepatotoxicity with combination of vemurafenib and ipilimumab. N Engl J Med 2013;368:1365-6.
30. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med 2012;366:925-31.
31. Tang C, Wang X, Soh H, et al. Combining radiation and immunotherapy: a new systemic therapy for solid tumors? Cancer Immunol Res 2014;2:831-8.
32. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563-7.
33. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-97.
34. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124-8.
35. Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014;371:2189-99.
36. Govindan R, Ding L, Griffith M, et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell 2012;150:1121-34.

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