Small victories add up to paradigm shifts for hard-to-treat tumors

Jane de Lartigue, PhD

Since the "war on cancer" was declared in the 1970s, our view of cancer has evolved to an array of different diseases requiring individual battles. Many have been hard-fought, with even minor improvements in patient survival proving extremely challenging. Here we describe how recent developments are beginning to change the narrative for some of these hard-to-treat tumor types.

Ovarian cancer: the silent killer

Ovarian cancer is known as the silent killer, with vague symptoms that make it hard to detect until advanced stages. Added to this the fact that there is currently no reliable screening test and that resistance to treatment is common makes ovarian cancer an extremely challenging form of cancer to treat. Epithelial ovarian cancer, which accounts for the majority of cases, is the leading cause of death from gynecologic cancer in the United States and the fifth most common cause of cancer-related death.[1] Standard first-line treatment involves surgery and chemotherapy that is often effective, but not durable. Despite advances in these treatments in the past several decades, only modest improvements in survival have been achieved.[2]

Urgent need for new treatment strategies sparked fierce research efforts that have led to several promising developments (Table 1). Most significant are poly(ADP)ribose polymerase (PARP) inhibitors, designed to exploit the sensitivity of cells containing defects in homologous recombination (HR) repair pathways, to DNA damaging therapies. PARP inhibition prevents repair of single-stranded breaks in DNA (Figure 1), which in itself is not lethal, but in combination with defects in HR pathways, that repair the resultant double-stranded breaks, leads to cell death.[3]

It's thought that up to half of high-grade serous ovarian cancers could be deficient in HR repair because of inherited and acquired mutations, most commonly in the Breast Cancer Susceptibility (*BRCA1/2*) genes, or epigenetic alterations.[4,5] Thus PARP inhibition holds significant promise for the treatment of ovarian cancer. Most advanced in clinical development is olaparib, currently being evaluated in phase 3 trials as maintenance therapy for women with platinum-sensitive, relapsed ovarian cancer. In a pivotal phase 2 trial, olaparib led to a significant improvement in progression-free survival (PFS). Although this didn't translate into an overall survival (OS) benefit, a subgroup analysis showed a clear advantage in patients with *BRCA1/2* mutations, thus phase 3 trials in patients with confirmed germline *BRCA1/2* mutations have been initiated.[6,7]

The SOLO trials will involve women with newly diagnosed disease (SOLO-1) and with relapsed/recurrent disease (SOLO-2). In June 2014, the US Food and Drug Administration's Oncologic Drug Advisory Committee voted against accelerated approval of olaparib and recommended waiting for the results of these trials.[8]

A novel clinical trial design has been applied to the evaluation of another PARP inhibitor, rucaparib. Phase 2 and phase 3 trials are being conducted in parallel using a unique HRD (homologous repair deficiency) algorithm that incorporates *BRCA1/2* mutations and loss of heterozygosity. The phase 2 trial (ARIEL-2) will evaluate rucaparib treatment efficacy in molecularly defined subgroups and optimize the HRD test, whereas the phase 3 trial (ARIEL-3) will prospectively validate the HRD test in patients randomized to receive rucaparib or placebo.[9]

Angiogenesis is the formation of new blood vessels from the existing vasculature and is a hallmark of malignant transformation. An angiogenic switch is thought to occur in cancer development that shifts this normally tightly regulated process toward a pro-angiogenic state. The vascular endothelial growth factor (VEGF) pathway is central to pro-angiogenic signaling and thus has been a target for anti-angiogenic therapies, a number of which are being evaluated in late-stage trials.[10]

The most extensively studied is bevacizumab, which is being evaluated as both monotherapy and in combination with other drugs. In July, the FDA granted priority review to bevacizumab and chemotherapy for patients with platinum-resistant dis-

JCSO 2014;12:454-460. ©2014 Frontline Medical Communications. DOI 10.12788/jcso.0097.

TABLE 1 Selection of key therapies in advanced ovarian cancer

Drug	Manufacturer	Description	Status of ongoing clinical testing
Olaparib (AZD-2281)	Astra Zeneca	PARP inhibitor	Phase 3
Niraparib	Tesaro	PARP inhibitor	Phase 3
Bevacizumab (Avastin)	Genentech	Anti-angiogenic agent; monoclonal antibody targeting VEGF	Phase 3
Cediranib	Astra Zeneca	Anti-angiogenic agent; VEGFR inhibitor	Phase 3
Trebananib	Amgen	Anti-angiogenic agent; Antiopoietin 1/2 neutralizing peptibody	Phase 3
Pazopanib (Votrient)	GlaxoSmithKline	Anti-angiogenic agent; multi-kinase inhibitor	Phase 3
Aflibercept (Zaltrap)	Regeneron	Anti-angiogenic agent; recombinant fusion protein consisting of VEGF binding portions from the extracellular domain of VEGFR1/2 fused to the Fc portion of IgG1	Phase 2/3
Sunitinib (Sutent)	Pfizer	Anti-angiogenic agent; multi-kinase inhibitor	Phase 2
Rucaparib	Clovis Oncology	PARP inhibitor	Phase 2
Sorafenib (Nexavar)	Bayer/Onyx	Anti-angiogenic agent; multi-kinase inhibitor	Phase 1/2
Veliparib	AbbVie	PARP inhibitor	Phase 1/2
BMN673	BioMarin	PARP inhibitor	Phase 1/2
IMGN853	Immunogen	ADC; monoclonal antibody against folate receptor alpha conjugated to maytansine derivative DM4	Phase 1
BAY 94-9343	Bayer	ADC; monoclonal antibody against mesothelin conjugated to maytansine derivative DM4	Phase 1
DMUC5754A	Roche/Genentech	ADC; monoclonal antibody against MUC-16 conjugated to MMAE	Phase 1

PARP, poly(ADP)Ribose-1; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor

ease based on the findings of AURELIA-3, a phase 3 trial of 361 patients in whom this combination was shown to significantly improve PFS compared with chemotherapy alone.[11]

Cediranib was all but abandoned by its manufacturer after disappointing phase 3 results in other cancer types. However, the recently reported results from the ICON6 trial in ovarian cancer have reignited interest in this agent. A combination of chemotherapy and cediranib followed by cediranib maintenance improved PFS by 3.2 months and OS by 2.7 months.[12] According to a recent press release from AstraZeneca they are in consultation with regulatory agencies in the US and EU with a view to imminent regulatory submissions. Meanwhile, trebananib, which has an alternative angiogenic target, in combination with paclitaxel demonstrated improved PFS in the recently published phase 3 TRINOVA-1 study.[13] Two other studies are ongoing, evaluating trebananib in combination with pegylated liposomal doxorubicin (TRINOVA-2) and trebananib in combination with paclitaxel and carboplatin (TRINOVA-3).

Combining agents that have different modes of action is emerging as a promising strategy to boost the effectiveness of individual drugs. A combination of olaparib and cedira-

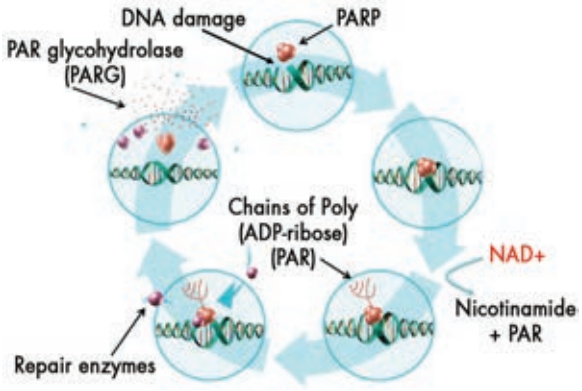

FIGURE 1 PARP1 is a key signaling enzyme involved in triggering the repair of single-strand DNA damage. It binds to DNA adjacent to the damage and then catalyzes the conversion of nicotinamide adenine dinucleotide into nicotinamide and ADP-ribose to produce large, branched chains of poly(ADP-ribose). DNA repair enzymes are then recruited to the site of damage to repair the DNA and the PAR chains are subsequently degraded via PAR glycohydrolase.

Reproduced with permission. Source: Toss A, Cortesi L. Molecular mechanisms of PARP inhibitors in BRCA-related ovarian cancer. J Cancer Sci Ther. 2013;5:409-416.

nib recently made waves at the 2014 American Society of Clinical Oncology meeting at which investigators reported their findings from a phase 2 study showing that the combination improved PFS by more than 8 months compared with olaparib alone. Although the overall rate of grade 3 and 4 toxicities was higher for the combination, it was generally well tolerated.[14]

A revolution in metastatic melanoma

Although primary melanoma can be treated surgically, around one-fifth of patients will develop metastatic melanoma that has an extremely poor prognosis.[15] Until 2011, only 2 therapies were FDA-approved for the treatment of metastatic melanoma – the chemotherapeutic dacarbazine and high-dose interleukin-2 (IL-2; a cytokine that induces T-cell activation and proliferation). Both therapeutic options have low response rates and when responses do occur they tend to be short-lived.

The therapeutic landscape in metastatic melanoma has been revolutionized in the past several years, more than tripling the number of FDA-approved agents (Table 2), beginning with the approval of ipilimumab, which is an antibody that targets cytotoxic T-lymphocyte antigen-4 (CTLA-4). Melanoma is one of the most immunogenic tumors and it was already proven to respond to immune stimulation in the form of IL-2 although response rates were low. Numerous other immunotherapies were tested in an effort to improve response, but with limited success.[15-17]

CTLA-4 is an immune checkpoint protein and represents a new paradigm for immunotherapies. With a greater

TABLE 2 Selection of key therapies in metastatic melanoma

Drug	Manufacturer	Description	Status of ongoing clinical testing
Ipilimumab (Yervoy)	Bristol-Myers Squibb	Immune checkpoint inhibitor; monoclonal antibody targeting CTLA-4	FDA approved; Phase 3 trials ongoing
Pembrolizumab (Keytruda)	Merck	Immune checkpoint inhibitor; monoclonal antibody targeting PD-1	FDA approved; Phase 3 trials ongoing
Vemurafenib (Zelboraf)	Genentech/ Daiichi Sankyo	BRAF inhibitor	FDA approved; Phase 3 trials ongoing
Dabrafenib (Tafinlar)	GlaxoSmithKline	Selective BRAF inhibitor	FDA approved; Phase 3 trials ongoing
Trametinib (Mekinist)	GlaxoSmithKline	MEK inhibitor	FDA approved; Phase 3 trials ongoing
Nivolumab (MDX-1106)	Bristol-Myers Squibb	Immune checkpoint inhibitor; monoclonal antibody targeting PD-1	Phase 3
LGX818	Novartis	BRAF inhibitor	Phase 3
Selumetinib (AZD6244)	AstraZeneca	MEK inhibitor	Phase 3
MEK162	Novartis	MEK inhibitor	Phase 3
Pimasertib	EMD Serono	MEK inhibitor	Phase 2
Cobimetinib (XL518)	Exelixis	MEK inhibitor	Phase 2
MEDI4736	AstraZeneca	Immune checkpoint inhibitor; monoclonal antibody targeting PD-L1	Phase 1/2
Refametinib	Bayer	MEK inhibitor	Phase 1/2
Tremelimumab	Pfizer	Immune checkpoint inhibitor; monoclonal antibody targeting PD-1	Phase 1
AMP-514	Amplimmune	Immune checkpoint inhibitor; monoclonal antibody targeting PD-1	Phase 1 in advanced malignancies including melanoma
MPDL3280A	Roche	Immune checkpoint inhibitor; monoclonal antibody targeting PD-1	Phase 1
MDX-1105	Bristol-Myers Squibb	Immune checkpoint inhibitor; monoclonal antibody targeting PD-L1	Phase 1 trial in multiple indications including melanoma
RO4987655	Hoffmann La Roche	MEK inhibitor	Phase 1 in advanced solid tumors including melanoma
E6201	Eisai	MEK inhibitor	Phase 1 in advanced solid tumors including melanoma

CTLA-4, cytotoxic T-lymphocyte antigen-4; FDA, US Food and Drug Administration; PD-1, programmed death-1; PD-L1, programmed death ligand-1

understanding of the anti-tumor immune response came the discovery that tumors could circumvent or suppress this response. One of the ways in which they do this is by hijacking a failsafe system, regulated by an inhibitory signaling network of immune checkpoint proteins that ensures cytotoxic T cells are switched off at the appropriate time to minimize collateral damage to healthy tissue. By co-opting this signaling network, cancer cells ensure that T cells are switched off, dampening the anti-tumor immune response (Figure 2).[15-17]

Drugs targeting other immune checkpoint proteins have been developed and pembrolizumab, a monoclonal antibody targeting programmed death receptor-1 (PD1) joined ipilimumab as an FDA-approved treatment option in 2013. It was awarded accelerated approval by the FDA on the basis of a surrogate endpoint; in 173 patients around a quarter of patients showed tumor shrinkage that lasted at least 1.4-8.5 months and beyond. PD1-targeting agents in general have been shown to induce less severe toxicities compared with CTLA-4-targeting agents.[18]

More than a decade ago it was discovered that about 60% of melanomas harbor a mutation in the *BRAF* gene (most commonly a V600E mutation) that encodes a serine/threonine protein kinase. BRAF is an integral part of the mitogen-activated protein kinase (MAPK) pathway that plays a central role in cell growth and proliferation (Figure 3). A number of multikinase inhibitors that included BRAF among their targets were developed, such as sorafenib, but none targeted the V600E mutant form. In 2011, the first selective BRAF inhibitor was approved by the FDA for the treatment of patients with *BRAFV600E* mutant metastatic melanoma. Vemurafenib was approved on the

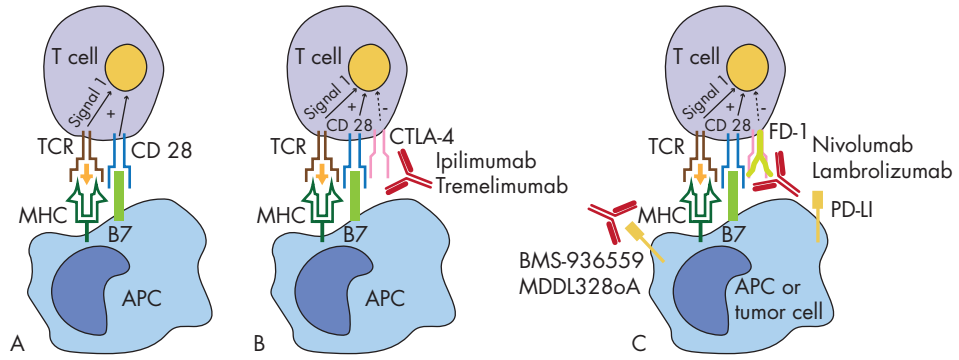

FIGURE 2 Regulation of T-cell activity by immune checkpoint proteins. B, CTLA-4 is a negative regulator of T-cell activation. Inhibitors of CTLA-4 prevent it from binding its ligand, B7, and augment T-cell activation and proliferation. C, Engagement of PD-1 expressed on T cells with PD-L1 expressed on antigen-presenting cells or tumor cells results in T-cell suppression and tumor protection. Blockade of this interaction with either PD-1 or PD-L1 blocking antibodies can 'wake up' exhausted T cells, resulting in an anti-tumor immune response.

CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TCR, T-cell receptor

Reproduced with permission. Source: Shah DJ, Dronca RS. Latest advances in chemotherapeutic, targeted and immune approaches in the treatment of metastatic melanoma. Mayo Clin Proc. 2014;89:504-519.

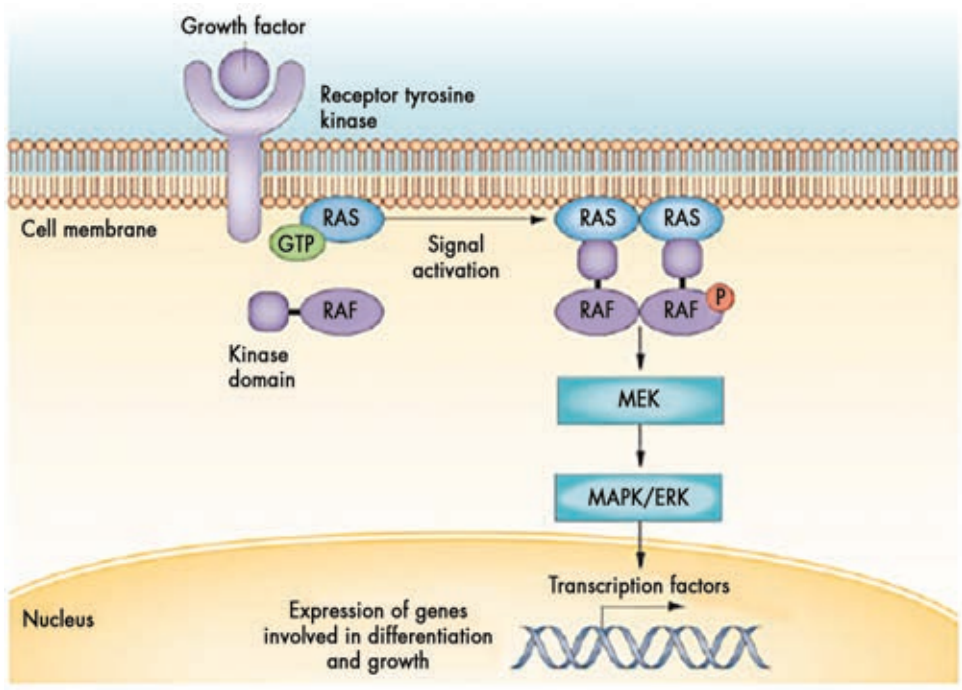

FIGURE 3 MAPK pathway in melanoma. When bound by their growth factor ligands at the cell surface, RTK activate growth signaling cascades via the MAPK pathway. Upon activation of the RTK the GTPase RAS is recruited to the cell membrane and activated. RAS binds and activates the RAF family of protein kinases, which include BRAF. RAF in turn activates MEK and ultimately ERK, which stimulates the activity of transcription factors in the nucleus involved in differentiation and growth. In melanomas with BRAFV600E mutations, the MAPK pathway is constitutively activated from the level of RAF.

GTPase, guanosine triphosphatase; MAPK, mitogen activated protein kinase; RTK, receptor tyrosine kinase

Reproduced with permission. Source: Gibney GT, Messina JL, Fedorenko IV, et al. Paradoxical oncogenesis: the long-term effects of BRAF inhibition in melanoma. Nat Rev Clin Oncol. 2013;7:390-309.

basis of the BRIM-3 study in which overall response rate (ORR), PFS, and OS were all significantly improved compared with dacarbazine. A second selective BRAF inhibitor, dabrafenib, was subsequently approved in 2013 after positive results from the BREAK-3 trial.[15-17]

Despite these promising developments, patients rapidly develop resistance to BRAF inhibitors. As a result, drugs targeting the MEK kinase that sits downstream of BRAF in the MAPK pathway have also been developed. Trametinib was the first MEK inhibitor to receive regulatory approval for metastatic melanoma, on the basis of the METRIC trial demonstrating a 4-month improvement in PFS. Although MEK inhibitors have less severe side effects than do BRAF inhibitors, they are also less effective.[19]

Impressive clinical responses have been observed, however, in patients treated with a combination of MEK and BRAF inhibitors. The results of several trials were recently presented at the European Society for Molecular Oncology (ESMO) meeting. A combination of vemurafenib and cobimetinib improved PFS, with a 49% reduction in the risk of progression, compared with vemurafenib and placebo. In a separate trial, a combination of dabrafenib and trametinib led to a 31% improvement in OS and a 44% reduction in the risk of progression. Significantly, combination therapy reduced the incidence of skin-related side effects, including squamous cell carcinoma.[20,21]

Emptying the arsenal against lethal pancreatic cancer

Pancreatic ductal adenocarcinoma (PDA), which accounts for the majority of pancreatic cancer cases, is among the most lethal of all cancers. It is the only cancer that still has 5-year survival in the single digits, at just 6%. PDA has proven a particularly challenging foe because it is incred-

TABLE 3 Selection of key therapies in advanced pancreatic cancer

Drug	Manufacturer	Description	Status of ongoing clinical testing
Nab-paclitaxel (Abraxane)	Celgene	Albumin-bound, 130 nm particle formulation of paclitaxel administered as a colloidal suspension	FDA approved; phase 3 ongoing
FOLFIRINOX (Erbirinox)	Merck	Combination chemotherapy (folinic acid, fluorouracil, irinotecan, and oxaliplatin)	FDA approved; phase 3 ongoing
Erlotinib (Tarceva)	Genentech/ Astellas Pharma	EGFR inhibitor	FDA approved; phase 3 ongoing
MM-398	Merrimack	Nanoliposomal encapsulation of irinotecan	Phase 3
Algenpantucel-L (HyperAcute Pancreas)	NewLink Genetics	Whole-cell vaccine; uses alpha-gal (a carbohydrate to which humans have pre-existing immunity) modified cancer cells to jump-start the immune system	Phase 3
CRS-207	Aduro Biotech	Vaccine; uses live-attenuated *Listeria monocytogenes* engineered to express the tumor-associated antigen mesothelin	Phase 2
Olaparib (AZD-2281)	AstraZeneca	PARP inhibitor	Phase 3
Veliparib	AbbVie	PARP inhibitor	Phase 2
Ipilimumab (Yervoy)	Bristol-Myers Squibb	Immune checkpoint inhibitor; monoclonal antibody targeting CTLA-4	Phase 2 in combination with other agents; no trials ongoing as monotherapy
Selumetinib (AZD6244)	AstraZeneca	MEK inhibitor	Phase 2
Pimasertib (MSC1936369B)	EMD Serono	MEK inhibitor	Phase 1/2
Vismodegib (Everidge)	Genentech	Hedgehog pathway inhibitor	Phase 1/2
IPI-926	Infinity	Hedgehog pathway inhibitor	Phase 1
MK0752	Merck	Notch pathway inhibitor	Phase 1
R04929097	Roche	Notch pathway inhibitor	Phase 1
GV1001	Pharmexa	Peptide vaccine consisting of a 16 amino acid peptide from human telomerase	Phase 1

EGFR, epidermal growth factor receptor; PARP, poly(ADP)ribose polymerase-1; CTLA-4, cytotoxic T-lymphocyte antigen-4

ibly difficult to diagnose and treat. Most patients are diagnosed at an advanced stage. Furthermore, the location of the tumor makes effective surgical resection difficult, and the dense tumor microenvironment makes it notoriously resistant to chemotherapy.[22,23]

Although researchers seem to have exhausted their entire therapeutic arsenal, very little progress has been made. The *KRAS* gene is a major driver of PDA, and the frustratingly slow progress in treating PDA has been mirrored by the difficulties in developing drugs that target this oncogene. However, the investment has certainly not been wasted (Table 3). The most significant advancement in PDA has been an improved understanding of the biology underlying this disease and the reasons that it is so hard to treat. It has become clear that effective treatment of PDA will require consideration of both the tumor itself and its highly hostile microenvironment. This realization has begun to change the nihilistic narrative for PDA and a number of novel therapeutic strategies are offering significant hope.

The development of novel forms of chemotherapy (FOLFIRINOX and nab-paclitaxel) has given us new standard treatments in the frontline setting. MM-398 is another novel chemotherapy formulation that is in late-stage clinical testing. Results from the NAPOLI-1 trial were recently reported, demonstrating improvements in OS, PFS, and ORR for a combination of MM-398, 5-fluorouracil, and leucovorin.[24] The developer has stated its intention to submit a new drug application to the FDA by the end of 2014.

Various targeted therapies have been tested, alone and in combination with standard chemotherapy. Though most were failures, the epidermal growth factor receptor (EGFR) inhibitor erlotinib showed a modest survival benefit and was approved for use in combination with gemcitabine, and several MEK inhibitors are in phase 1 and 2 clinical trials.

Although the standard approaches to anti-angiogenic therapy have not proven successful for PDA, a number of other strategies for targeting the tumor microenvironment are being investigated, including inhibitors of the Notch and Hedgehog pathways, since components of these signaling networks have key roles in the function of stromal cells in the microenvironment.

Around 5% of all newly diagnosed patients show a genetic predisposition for PDA and the identification of germline *BRCA1/2* mutations in these patients has driven investigation of PARP inhibitors. Olaparib and veliparib have both been the subject of recent promising studies.[22,23]

The use of immunotherapy for the treatment of PDA has proven substantially more challenging than for other solid tumors. However, the use of vaccines has proven successful. Two ongoing phase 3 trials of algenpantucel-L (Figure 4) are evaluating the therapy in surgically resected and locally advanced, unresectable patients, respectively. A combination of 2 other vaccines was awarded breakthrough therapy designation by the FDA recently after a planned interim analysis of a phase 2 trial in which OS was significantly improved.[25,26]

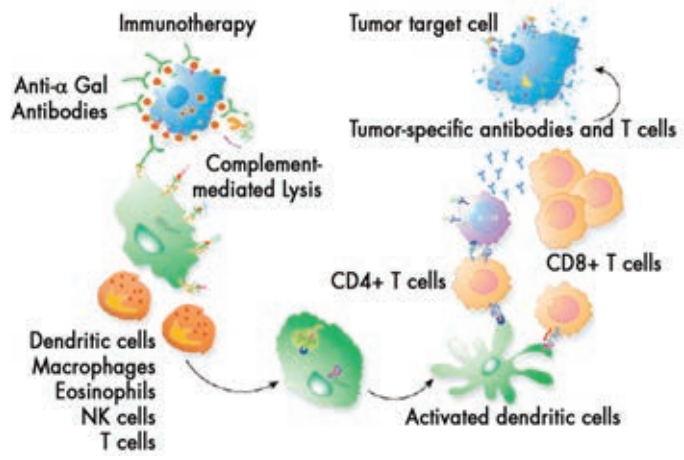

FIGURE 4 Mechanism of action of algenpantucel-L (hyperacute-pancreas) vaccine. The immunotherapy platform consists of novel vaccines designed to stimulate the patient's immune system to recognize and attack cancer cells. Algenpantucel-L is a whole-cell vaccine comprised of tumor-specific cancer cell lines that have been modified to express alpha-gal, a carbohydrate to which humans have preexisting immunity. The aim is to stimulate an antitumor immune response by teaching the immune system to attack the patient's cancer cells.

Reproduced with permission. Source: http://newlinkgenetics.com/hyperacute-immunotherapy.

The wealth of knowledge that has been garnered from both successes and failures in the treatment of these challenging tumor types continues to fuel the rapid development of novel treatment paradigms. Though impressive strides have been taken, there remains substantial room for improvement.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics 2014. CA Cancer J Clin. 2014;64:9.
2. Banerjee S, Gore M. Recent advances in systemic treatments for ovarian cancer. Cancer Imaging. 2012;12:305-309.
3. Eskander RN, Tewari KS. PARP inhibition and synthetic lethality in ovarian cancer. Expert Rev Clin Pharmacol. 2014;7:613-622.
4. Bast RC Jr, Hennessy B, Mills GB. The biology of ovarian cancer: new opportunities for translation. Nat Rev Cancer. 2008;9:415-428.
5. Press JZ, De Luca A, Boyd N, et al. Ovarian carcinomas with genetic and epigenetic BRCA1 loss have distinct molecular abnormalities. BMC Cancer. 2008;8:17.
6. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366:1382-1392.
7. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomized phase 2 trial. Lancet Oncol. 2014;15:852-861.
8. Moore KN, DiSilvestro P, Lowe ES, et al. SOLO1 and SOLO2: Randomized phase III trials of olaparib in patients with ovarian cancer and a BRCA1/2 mutation. J Clin Oncol. 2014;32:5s(suppl; abstr TPS5616).

9. Swisher EM, McNeish IA, Coleman RL, et al. ARIEL 2/3: An integrated clinical trial program to assess activity of rucaparib in ovarian cancer and to identify tumor molecular characteristics predictive of response [ASCO 2014, abstract TPS5619]. J Clin Oncol. 2014;329(suppl):5s.
10. Han ES, Wakabayashi M, Leong L. Angiogenesis Inhibitors in the Treatment of Epithelial Ovarian Cancer. Current Treatment Options Oncol. 2013;14:22-33.
11. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol. 2014;32:1302-1308.
12. Ledermann JA, Perren TJ, Raja FA, at al. Randomised double-blind phase III trial of cediranib (AZD2171) in relapsed platinum sensitive ovarian cancer: Results of the ICON6 trial [European Cancer Congress, abstract 10]. Eur J Cancer. 2013;49.
13. Monk BJ, Poveda A, Vergote I, et al. Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomized, multicenter, double-blind, placebo-controlled phase 3 trial. Lancet Oncol. 2014;15:799-808.
14. Liu JF, Barry WT, Birrer M, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomized phase 2 study. Lancet Oncol. 2014;15:1207-1214.
15. Azijli K, Stelloo E, Peters GJ, et al. New Developments in the treatment of metastatic melanoma: immune checkpoint inhibitors and targeted therapies. Anticancer Res. 2014;34:1493-1506.
16. Tronnier M, Mitteldorf C. Treating advanced melanoma: current insights and opportunities. Cancer Man Res. 2014;6:349-356.
17. Olszanski AJ. Current and future roles of targeted therapy and immunotherapy in advanced melanoma. J Manag Care Pharm. 2014;20:346-356.
18. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomized dose-comparison cohort of a phase 1 trial. Lancet. 2014;384:1109-1117.
19. Grimaldi AM, Simeone E, Ascierto PA. The role of MEK inhibitors in the treatment of metastatic melanoma. Curr Opin Oncol. 2014;26:196-203.
20. Robert C, et al. COMBI-v: A randomized, open-label, Phase III study comparing the combination of dabrafenib and trametinib with vemurafenib as first-line therapy in patients with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma [2014 European Society of Molecular Oncology Meeting, abstract LBA4].
21. Grant McArthur, et al. Phase 3, double-blind, placebo-controlled study of vemurafenib versus vemurafenib and cobimetinib in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma [2014 European Society of Molecular Oncology Meeting, abstract LBA5].
22. Arslan C, Yalcin S. Current and future systemic treatment options in metastatic pancreatic cancer. J Gastrointest Oncol. 2014;5:280-295.
23. Oberstein PE, Olive KP. Pancreatic cancer: why is it so hard to treat? Ther Adv Gastroenterol. 2013;6:321-337.
24. Saif MW. MM-398 achieves primary endpoint of overall survival in phase III study in patients with gemcitabine refractory metastatic pancreatic cancer. J Pancreas. 2014;15:278-279.
25. Uram J, Le DT. Current advances in immunotherapy for pancreatic cancer. Curr Probl Cancer. 2013;37:273-279.
26. Le DT, Wang-Gillam A, Picozzi V, et al. A phase 2, randomized trial of GVAX pancreas and CRS-207 immunotherapy versus GVAX alone in patients with metastatic pancreatic adenomcarcinoma: Updated results. J Clin Oncol. 32, 2014(suppl 3; abstr 177).