



Review Article

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Spinal Metastases and the Evolving Role of Molecular Targeted Therapy, Chemotherapy, and Immunotherapy

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Metastatic involvement of the spine is a common complication of systemic cancer progression. Surgery and external beam radiotherapy are palliative treatment modalities aiming to preserve neurological function, control pain and maintain functional status. More recently, with development of image guidance and stereotactic delivery of high doses of conformal radiation, local tumor control has improved; however recurrent or radiation refractory disease remains a significant clinical problem with limited treatment options. This manuscript represents a narrative overview of novel targeted molecular therapies, chemotherapies, and immunotherapy treatments for patients with breast, lung, melanoma, renal cell, prostate, and thyroid cancers, which resulted in improved responses compared to standard chemotherapy. We present clinical examples of excellent responses in spinal metastatic disease which have not been specifically documented in the literature, as most clinical trials evaluate treatment response based on visceral disease. This review is useful for the spine surgeons treating patients with metastatic disease as knowledge of these responses could help with timing and planning of surgical interventions, as well as promote multidisciplinary discussions, allowing development of an individualized treatment strategy to patients presenting with widespread multifocal progressive disease, where surgery could lead to suboptimal results.

Keywords: Spine metastases, Metastatic cancer, Targeted therapy, Mutation, Chemotherapy, Immunotherapy

INTRODUCTION

Metastatic cancer to spine remains a debilitating consequence of uncontrolled cancer progression with a poor prognosis, that historically portended an overall survival (OS) of less than 6 months from the time of diagnosis.¹ The incidence of spinal metastases is increasing due to a variety of factors including early detection due to improvements in imaging modalities, enhanced response to first-line cancer therapies allowing longer survival and development of distant metastases as a late-stage manifestation of the disease progression, and the inherent poor response of spinal metastases to existing therapies as compared to visceral disease. The incidence of spinal metastases averages

approximately 40% depending on the primary cancer and is estimated to exceed 100,000 new patients annually.²⁻⁴ Left unchecked, continued metastatic tumor growth within the spinal column ultimately leads to neurologic compromise, intractable pain, spinal deformity, instability, and significant limitation in the quality of life. The incidence of spine metastatic disease has been estimated to be 16%–74% in patients with lung cancer, 65%–75% in patients with breast cancer, and 65%–90% in prostate cancer patients.⁵ Conversely while looking at all spine metastases diagnosed in the United States yearly, 14% are derived from breast, 16.3% from lung, 4.1% from melanoma, 13.1% from renal cell, 6.8% from prostate, and 2.3% from thyroid primary cancer.⁶ Mechanistically, metastatic spread to the spine

may occur via direct local invasion from neighboring tissues, migration along neural structures, or hematogenous spread of cancer cells from the site of origin into the bone of the spinal column.^{7,8}

Several frameworks and scoring systems are available to aid with decision making while treating patients with spinal metastatic disease, including the NOMS (neurologic, oncologic, mechanical stability and systemic disease) framework, Tomita score, SINS (spinal instability neoplastic score) score, and Tokuhashi score.⁹⁻¹³ These various algorithms were created to integrate multidisciplinary assessment, evidence-based medicine, and new technology to optimize patient care. At our institution, the overall philosophy for treating patients with metastatic spine disease includes in depth evaluation of their functional status, systemic disease burden and failure of prior treatments. Surgical interventions are performed to decompress the spinal cord in cases of neurological compromise, to allow clearance for spinal stereotactic radiosurgery and to perform stabilization of symptomatic spinal fractures, however, the magnitude of surgery needs to be adjusted on a case-by-case basis to be minimally disruptive to oncological management as prolonged post-surgical recovery can negatively impact performance status and survival. With the advent of genomic analysis, the identification of targetable mutations in an increasing percentage of patients across various tumor types has changed their oncologic management and outcomes. Examples include non-small cell lung cancer (NSCLC) with ALK rearrangements identified in 4%–5% of patients and epidermal growth factor receptor (EGFR) mutations present in 10%–15% of lung cancer patients; ERBB2, CD340, and human epidermal growth factor receptor 2 (HER2)/Neu alterations in breast cancer samples, with HER2 overexpression detected in 18%–25% patients; and BRAF V600E mutation detectable in 33%–55% melanoma patients. Systemic cancer therapy is rapidly changing with the introduction of antiangiogenic agents, immunotherapy, targeted therapy, and cell cycle inhibitors, although this may not be directly translatable to patients with spine metastases. This manuscript represents a narrative overview of the results of clinical trials. Our intention is to raise awareness of the effectiveness of modern chemotherapy, targeted therapy, and immunotherapy for the treatment of patients with bulky spinal metastases derived from primary lung, breast, melanoma, renal cell, prostate, and thyroid cancers, where systemic treatment can be extremely effective in achieving local control within the spine in combination with surgery and/or radiation therapy.

BREAST CANCER

Patients with breast cancer are typically treated with an alkylating agent (cyclophosphamide) and antimetabolites (methotrexate, 5-fluorouracil), doxorubicin containing combination of agents, or combinatorial regimens including platinum-based compounds (cisplatin) or taxanes (paclitaxel, docetaxel) as first-line therapies (Table 1). According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, patients with breast cancer have 6% distant metastases at the time of diagnosis, with 29% 5-year relative survival (SEER; Table 1).¹⁴ Up to 5% of patients with breast cancer have identifiable bone metastases at the time of diagnosis, with a median survival of less than 2 years.¹⁵ Amongst these patients, over 20,000 patients annually present with epidural compression.¹⁶ Patients with hormone receptor (HR)-positive breast cancer are treated with endocrine therapies including estrogen receptor antagonist tamoxifen irrespective of their HER2 status, which has led to improved disease-free survival with minimal toxicity as shown in several clinical trials HERA (78.6% 4-year disease-free survival vs. 72.2% in the control group), NSABP trial BP-31 (12% improvement in disease-free survival at 3 years with 33% reduction in risk of death) and NCCTG N9831 (37% improvement in OS, with 10 year survival increase from 75.2% to 84%) (Table 1).¹⁷ Aromatase inhibitors, luteinizing hormone releasing hormone analogs and selective estrogen degraders are other classes of endocrine therapies used in HR+ breast cancer patients with improved progression free survival (PFS) (Table 1).^{17,18} In patients with HER2 amplification, use of humanized monoclonal antibodies including trastuzumab and pertuzumab or lapatinib improves patient outcomes; phase III randomized double blind CLEOPATRA trial initially evaluated a combination of these as first-line therapy with improvement in the median OS of 57.1 months (vs. 40.8 months) and 37% patients alive at 8 years (vs. 23%), with somewhat positive results reported in APHINITY trial, with 7.1% disease recurrence in the trial group (vs. 8.7%) and 94.1% patients invasive disease free at 3 years (vs. 93.2%) (Table 1).^{17,19,20} Anti-vascular endothelial growth factor receptor (VEGFR) inhibitor bevacizumab has been trialed for treatment of patients with breast cancer with improvements in PFS but not OS: E2100 trial reported 11.8 month PFS (vs. 5.9) with median OS of 26.7 months (vs. 25.2), while AVADO trial reported 10.1 month PFS (vs. 8.2) with median OS of 30.2 months (vs. 31.9), and RIBBON2 reported 7.2 month PFS (vs. 5.1) with median OS of 18 months (vs. 16.4).²¹ Heat shock protein 90 inhibitors (including 17-allylamino

Table 1. Systemic, targeted and immunotherapy treatments used to treat patients with breast, melanoma, non-small cell lung, renal cell, prostate, and thyroid cancers

Histology	Subtype	Incidence of distant metastases at presentation	Early vs. late manifestation	Radio-sensitivity	Systemic treatment options	Investigational treatment options
Breast cancer	HR+ HER2+ 10% cases	37.9%	3 Months	RS	Endocrine therapy ER antagonist tamoxifen Aromatase inhibitors LHRH analogs Estrogen degraders Taxanes with Humanized MAB: trastuzumab, pertuzumab, lapatinib, tucatinib, neratinib +/- capecitabine Anti-VEGFR bevacizumab HSP90 inhibitors	Palbociclib HDACi entinostat, vorinostat PI3Ki buparlisib, pilaralisib mTORi everolimus, sirolimus Immunotherapy HER2 derived peptide
	HR- HER2+ 4% cases	44.7%	2 Months	-	Endocrine sensitive: Endocrine therapy selective estrogen receptor modulators or downregulators, aromatase inhibitors CDK4/6 inhibitors: Palbociclib, ribociclib, abemaciclib PIK3CA mutant: alpelisib + fulvestrant Endocrine resistant: Capecitabine Platinum Doxorubicin PARPi talazoparib	
	HR+ HER2- 68% cases	30.6%	28 Months	-	Capecitabine Platinum Doxorubicin PARPi talazoparib	
Melanoma	HR- HER2- 10% cases	12.2%	45.5 Months	-	Capecitabine Platinum +/- etoposide Doxorubicin Methotrexate, high dose	PDL1+ pembrolizumab with chemotherapy PDL1- chemotherapy PARPi Olaparib, veliparib, talazoparib EGFRi MAB Sactuzumab govitecan
	BRAFV600E	-	-	RR	Dacarbazine	BRAFi dabrafenib, vemurafenib, encorafenib MEKi trametinib, selumetinib, cobimetinib, MEK162 BRAFi + MEKi Anti-CTLA4 ipilimumab PD-1 nivolumab, pembrolizumab T-VEC + GMCSF
Non-small cell lung cancer	BRAFV600E negative	-	-	-	-	Anti-CTLA4 ipilimumab PD-1 nivolumab, pembrolizumab T-VEC + GMCSF
	EGFRmut	-	-	RR	Paclitaxel kanglaite	EGFRi afatinib, osimertinib, gefitinib, erlotinib Bevacizumab
	EML4-ALK	-	-	-	Fluvestatin RANKL MAB denosumab bisphosphonates i.e. Zoledronic acid Platinum based	Crizotinib PI3Ki buparlisib BRAFi dabrafenib for BRAFV600E, MAP2Ki: HER2i MET/VEGFR2i cabozantinib CTLA4 ipilimumab tremelimumab Anti PDI nivolumab, pembrolizumab

(Continued)

Table 1. Systemic, targeted and immunotherapy treatments used to treat patients with breast, melanoma, non-small cell lung, renal cell, prostate, and thyroid cancers (Continued)

Histology	Subtype	Incidence of distant metastases at presentation	Early vs. late manifestation	Radio-sensitivity	Systemic treatment options	Investigational treatment options
Renal cell	Clear cell VHL/VEGFR, PBRM1, SETD2, BAP1, mTOR	-	-	RR	Bevacizumab/IFN alpha IL2 Pazopanib, sunitinib or temsirolimus	VEGFR/PDGFRi Axitinib, pazopanib, sorafenib, sunitinib Cabozantinib VEGFR/AXL/cMet Lenvatinib FGFR/VEGFR/everolimus PD-1/PD-L1 Nivolumab, ipilimumab Everolimus/sorafenib mTORi everolimus, temsirolimus
Prostate cancer	Papillary MET NRF2	-	-	-	-	-
	TP53, PTEN, CDKN2A loss, SMARCB1 loss, TFE3-TFEB fusion	-	-	-	-	-
Thyroid cancer	Differentiated thyroid carcinoma	-	-	RR	Androgen receptor antagonist flutamide, bicalutamide, abiraterone, ketoconazole LHRH agonist/antagonist leuproline, goserelin, degarelix Doxorubicin Docetaxel Cabazitaxel mitoxantrone	EGFRi gefitinib, erlotinib EGFR/HER2i lapatinib EGFR MAB cetuximab MET/VEGFR2 cabozantinib PARPi Olaparib RANKL denosumab antiCTLA4 ipilimumab antiPD1/PD-L1 nivolumab, pembrolizumab, atezolizumab Sipuleucel-T vaccine VEGFR/Flt3/RET/cKIT/BRAFi Sorafenib VEGFR/FGFR/PDGFR/KIT/RETi Lenvatinib
	Anaplastic carcinoma Medullary thyroid carcinoma	-	-	-	-	VEGFR/EGFR/RETi Vandetanib VEGFR2/cMet/AXL/RETi Cabozantinib PI3Ki HER2/3-ALK translocations antiCTLA4 anti-PDI

HR, hormone receptor; HER2, human epidermal growth factor receptor 2; RR, radiation resistant; RS, radiation sensitive; ER, estrogen receptor; LHRH, luteinizing hormone releasing hormone; MAB, monoclonal antibody; HDACi, histone deacetylase inhibitor; PI3Ki, phosphatidylinositol-3-kinase inhibitor; mTORi, mammalian target of rapamycin inhibitor; CDK4/6, cyclin dependent kinases 4/6; PARPi, poly-ADP-ribose polymerase inhibitor; PDL1, programmed death ligand 1; EGFRi, epidermal growth factor receptor inhibitor; BRAFi, v-Raf murine sarcoma viral oncogene homolog B1 inhibitor; MEKi, mitogen activated protein kinase inhibitor; MEK162, mitogen activated protein kinase 162; CTLA4i, cytotoxic T lymphocyte associated protein 4 inhibitor; PD-1, programmed cell death protein 1; T-VEC, talimogene; GMCSF, granulocyte macrophage colony stimulating factor; RANKL, receptor activator of nuclear factor kappa-B ligand; VHL, von Hippel Lindau; VEGFR, vascular endothelial growth factor receptor; PBRM1, polybromo 1; SETD2, su(var), enhancer of zeste, trithorax - domain containing 2; BAP1, ubiquitin carboxyl-terminal hydrolase 1; FGFR, fibroblast growth factor receptor; VEGFRi, vascular endothelial growth factor inhibitor; TP53, tumor protein p53; PTEN, phosphatase and TENsin homolog deleted on chromosome 10; CDKN2A, cyclin dependent kinase inhibitor 2A; SMARCB1, SWI/SNF related, matrix associated, actin dependent regulator of chromatin; TFE3, transcription factor enhancer 3; TFEB, transcription factor EB; RET, rearranged during transfection; PDGFR, platelet derived growth factor receptor; RETi, rearranged during transfection inhibitor; ALK, anaplastic lymphoma kinase.

17-demethoxygel danamycin) have been trialed in breast carcinoma spine metastases with some success in phase I trials.²²

Several CDK4/6 inhibitors, including palbociclib, ribociclib and abemaciclib, have been used for treatment of metastatic HR+ HER2- breast cancer patients that develop hormone resistant disease; PALOMA3 trial reported median PFS of 9.5 months (vs. 4.6) with palbociclib use, while MONARCH2 trial reported 16.4 month PFS (vs. 9.3) with abemaciclib.^{17,23} Palbociclib has been FDA approved in 2015.^{17,23} Histone deacetylase inhibitors (entinostat, vorinostat), phosphatidylinositol 3 kinase (PI3K) inhibitors (buparlisib, pilaralisib) and mammalian target of rapamycin (mTOR) inhibitors (everolimus, sirolimus) have also shown promising results in patients with hormone resistant and HER2+ metastatic breast as a part of combination therapy (Table 1).^{23,24} NCT00676663 reported 4.3 month PFS (vs. 2.3) with median OS of 28.1 months (vs. 19.8) with entinostat use.²³

Systematic categorization in The Cancer Genome Atlas (TCGA) helped identify other mutations that could be targeted in the future, including fibroblast growth factor receptor (FGFR), PTEN, TP53, AKT1/2, KRAS, and SRC (TCGA). Although breast cancer had historically been considered less immunogenic, several clinical trials of anti-PD1 and anti-PDL1 in patients have been conducted with some success, including vaccinating patient with HER2-derived peptide; phase I/II trial reported 89.7% 5 year PFS (vs 80.2%), with PFS as high as 94.6% 5 year PFS in optimally boosted patients (Tables 2, 3, Supplementary Table 1).^{17,25} Poly-ADP-ribose polymerase (PARP) inhibitors (olaparib, veliparib) with or without immunotherapy, EGFR inhibitors and monoclonal antibodies are being trialed in patients with most difficult to treat triple negative breast cancer; phase II trial reported median PFS of 3.7 months (vs. 1.5 months) and median OS of 12.9 months (vs. 9.4 months) with

Table 2. U.S. Food and Drug Administration approved immunotherapy treatments based on primary cancer

Cancer type	ImmunoTx
Breast	Triple negative breast cancer: Atezolizumab+paclitaxel protein-bound PD-L1 > 1% as first line Pembrolizumab, neoadjuvant and adjuvant, in combination with chemotherapy Sacituzumab HER2+ metastatic breast cancer: Margetuximab Pertuzumab + trastuzumab
Melanoma	Adjuvant ipilimumab, nivolumab, or pembrolizumab First-line therapy - Ipilimumab, nivolumab or pembrolizumab - Combination nivolumab+ipilimumab Tebentafusp Atezolizumab
NSCLC	Unresectable stage III: chemoRT, then durvalumab First-line therapies - Pembrolizumab TPS > 50% - Squamous NSCLC: pembrolizumab + carboplatin and nab- paclitaxel - Nonsquamous NSCLC: pembrolizumab + pemetrexed/platinum vs atezolizumab + bevacizumab, paclitaxel and carboplatin Second line therapies - Pembrolizumab TPS > 1% - Atezolizumab or nivolumab Amivantamab Cemiplimab Ramucirumab + erlotinib Nivolumab + ipilimumab, combined with platinum doublet
RCC	Advanced RCC: First-line therapy nivolumab + ipilimumab Second line therapy anti-angiogenic therapy followed by nivolumab Pembrolizumab Nivolumab +cabozantinib

PD-L1, programmed death-ligand 1; HER2, human epidermal growth factor receptor 2; TPS, tumor proportion score; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma.

Table 3. Indications for most common immunotherapy agents

Immunotherapy agent	Indication
CTLA4 inhibitor, ipilimumab, YERVOY	Stage III/IV surgically unresectable malignant melanoma regardless of BRAF status BRAF V600wt unresectable or metastatic Unresectable or metastatic melanoma, BRAF V600wt or BRAF V600mut, in combination with nivolumab Cutaneous melanoma, stage IIIABC post resection including LN, adjuvant First line, metastatic NSCLC PD-L1+, no EGFR/ALK aberrations, with nivolumab First line, metastatic or recurrent NSCLC, no EGFR/ALK aberrations, with nivolumab and 2 cycles of platinum doublet chemotherapy Untreated RCC, relapsed and stage IV intermediate and poor risk RCC regardless of PD-L1, combined with nivolumab Relapsed and stage IV RCC failing TKI, VEGF or mTOR inhibitor use, with nivolumab
PD-1 inhibitor, nivolumab, OPDIVO	First-line failing systemic Tx or metastatic melanoma regardless of BRAF status Unresectable or metastatic melanoma progressive on ipilimumab Unresectable or metastatic BRAF V600Emut melanoma progressive on BRAF inhibitor Unresectable or metastatic melanoma, nivolumab with ipilimumab LN+ or metastatic melanoma post complete resection, adjuvant First line, metastatic NSCLC PD-L1+, no EGFR/ALK aberrations, with ipilimumab First line, metastatic or recurrent NSCLC, no EGFR/ALK aberrations, combined with ipilimumab and 2 cycles of platinum doublet chemotherapy Metastatic NSCLC, progressive on platinum chemotherapy, failed targeted inhibitors for EGFR/ALK aberrations First line, RCC that is untreated, relapsed or stage IV, intermediate or poor risk RCC regardless PD-L1, combined with ipilimumab First line, advanced RCC, combined with cabozantinib RCC progressive on mTOR or VEGFR inhibitors
PD-1 inhibitor, Pembrolizumab, KEYTRUDA	Triple negative breast cancer, early stage, high risk, combined with chemotherapy as neoadjuvant, then single agent adjuvant post resection Triple negative breast cancer, locally recurrent unresectable or metastatic, PD-L1+, in combination with chemotherapy Metastatic melanoma progressive on ipilimumab Metastatic melanoma BRAFmut progressive on BRAF inhibitor Previously untreated melanoma regardless of BRAF status LN+ melanoma post complete resection Metastatic melanoma, limited resectability, no residual, adjuvant Unresectable or metastatic melanoma First line in metastatic NSCLC with high PD-L1 > 50%, no EGFR/ALK mutation First line w/pemetrexed and carboplatin for metastatic nonsquamous NSCLC, no EGFR/ALK mutation, any PD-L1 status First line in metastatic squamous NSCLC in combination with carboplatin, paclitaxel or protein-bound paclitaxel, any PD-L1 status First line in stage III NSCLC patients that are not candidates for surgery, chemo, RT, and metastatic NSCLC patients with PD-L1 > 1%, no EGFR/ALK aberrations Metastatic NSCLC progressive on platinum chemotherapy, having failed targeted inhibitors for EGFR/ALK genomic aberrations, PD-L1+ First-line metastatic RCC, poor, intermediate, favorable, combined with Axitinib
PD-L1 inhibitor, avelumab, BAVENCIO	First-line advanced RCC, together with Axitinib Alternative to pembrolizumab
PD-L1 inhibitor, durvalumab, IMFINZI	Stage III unresectable NSCLC, not progressing on concurrent platinum-based chemotherapy and radiation therapy
PD-L1 inhibitor, atezolizumab, TECENTRIQ	Triple negative breast cancer, unresectable locally advanced or metastatic, PD-L1+ expression, combined with paclitaxel Melanoma, unresectable or metastatic, BRAF V600mut, combined with cobimetinib and vemurafenib First line, metastatic NSCLC, high PD-L1+, no EGFR/ALK genomic aberrations First line, metastatic nonsquamous NSCLC, no EGFR/ALK genomic aberrations, in combination with bevacizumab, paclitaxel, and carboplatin First line, metastatic nonsquamous NSCLC, no EGFR/ALK genomic aberrations, with protein-bound paclitaxel and carboplatin Stage II-III NSCLC, PD-L1+, post resection and platinum chemotherapy, adjuvant Metastatic NSCLC progressive on platinum chemotherapy Metastatic NSCLC, EGFR/ALK genomic aberrations, progressive on targeted therapy

CTLA4, cytotoxic T-lymphocyte antigen 4; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; mTOR, mammalian target of rapamycin; PD-1, programmed-death 1; TX, treatment; LN, lymph node; VEGFR, vascular endothelial growth factor receptor.



Fig. 1. Successful use of CDK4/6 inhibitor palbociclib and letrozole in a patient with advanced breast cancer. Patient is a 61-year-old female who presented with 6/10 neck pain, found to have a non-surgical lytic C2 lesion. Per discussion with medical oncology team, the consensus was for systemic treatment and restaging. Sagittal and axial computed tomography cervical and thoracic spine views prior to initiation of treatment (A, B) and 3 months after treatment with letrozole and Palbociclib (C, D), showing resolution of the lesion.

anti-EGFR inhibitor cetuximab.¹⁷ Combined use of atezolizumab and paclitaxel has been FDA approved for patients with triple negative breast cancer (Tables 1–3; Supplementary Table 1). In our hands, we had notable responses in breast cancer patients treated with CDK4/6 inhibitors in combination with standard systemic treatment. To illustrate bone specific responses, we present in Fig. 1 a case of a 61-year-old patient with a lytic C2 lesion successfully treated using CDK4/6 inhibitor palbociclib in combination with letrozole (Fig. 1). Currently, her OS is 41 months since the time of surgery, and she had been progression free for 31 months while on that regimen.

MELANOMA

Survival in patients with metastatic melanoma has historically been poor, with 16% 5-year survival rates and median OS of

6–9 months.²⁶ Moreover, those patient with spinal metastases fare even worse with a median survival of 4 months.²⁶ According to SEER, patients with skin melanoma have 4% distant metastases at the time of presentation, with 29.8% 5-year relative survival.¹⁴ BRAF inhibitors, including dabrafenib and vemurafenib, are used in up to 50%–65% of metastatic melanoma patients who carry targetable BRAF mutation. The emergence of these agents had resulted in an improved OS of 13.6 months as compared to systemic dacarbazine, with median PFS of 5.1 months (vs. 2.7 months) when treated with dabrafenib (Table 1, Supplementary Table 1).²⁷ In patients with BRAF V600E mutations, the use of MEK inhibitors including trametinib, selumetinib, cobimetinib, and MEK162 have similarly resulted in improved PFS and OS; COLUMBUS trial reported median PFS of 14.9 months versus 7.3 months comparing encorafenib plus binimetinib versus vemurafenib, with the corresponding median OS of 33.6 versus 16.9 months.²⁸

In patients with advanced metastatic disease, the use of immune checkpoint inhibitors has changed the treatment approach for these patients. These novel agents target immune regulatory molecules including ipilimumab targeting cytotoxic T-lymphocyte antigen 4 (CTLA4), nivolumab and pembrolizumab targeting PD-1 and the combined inhibition of CTLA-4 and PD-1 (Tables 2, 3). With this approach, significant clinical improvements have been achieved in patients with advanced melanoma, with 5 year OS of 18.2% (vs. 8.8%) reported by the NCT00-324155 trial.²⁹ Moreover, recent studies showed 82% 1-year survival and 75% 2-year survival in patients receiving a combination of nivolumab and ipilimumab; CheckMate067 reported median OS of 72.1 months versus 36.9 with nivolumab alone versus 19.9 with ipilimumab alone, with 6.5 year OS rates of 57% versus 43% versus 25% with BRAF mutant tumors, and 46% versus 42% versus 22% with BRAF wild type tumors, respectively.³⁰ Despite these impressive results, immune checkpoint inhibitors can be associated with a significant toxicity profile related to autoimmune manifestations and must be monitored closely.^{31,32} In patients without BRAF V600E mutations, immune checkpoint inhibition is considered first-line therapy (Tables 2, 3). Amongst patients with the targetable BRAF V600E mutation, targeted inhibitors are typically given up-front, followed by immune checkpoint inhibition.^{31,32}

Additional focus has been directed on modulating the immune system towards an antitumor state. For example, recent studies have focused on applications of HSV-1 based oncolytic viruses (e.g., talimogene laherparepvec [T-VEC]) to induce lysis of melanoma cells in patients, with resulting antigen release

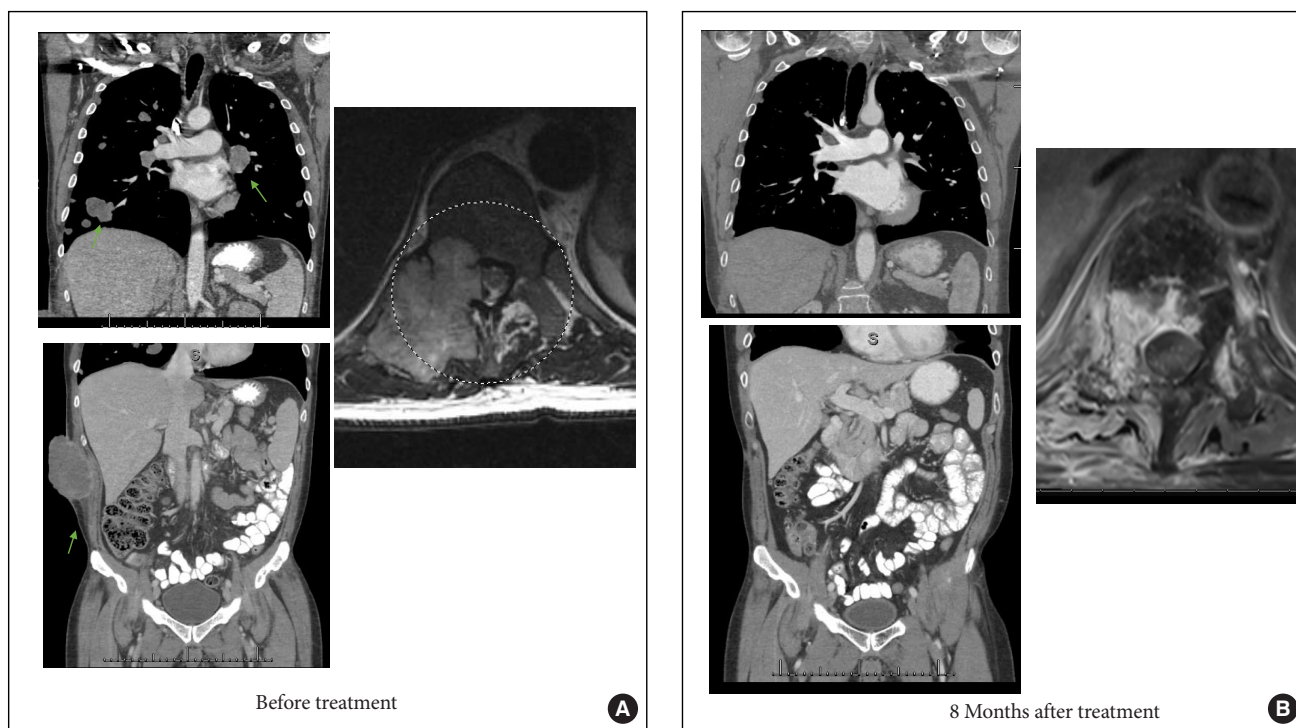


Fig. 2. Successful use of pembrolizumab in a patient with widely metastatic melanoma. Patient is 61-year-old with widely metastatic melanoma refractory to several lines of systemic treatment. Per discussion with medical oncology team, the consensus was for systemic treatment. Panel A demonstrates several sites of bulky metastatic disease (arrows) and a large spinal metastasis at T11 (circle) treated with spinal stereotactic radiosurgery 3 months prior to starting anti-programmed-death 1 therapy. Panel B demonstrates complete resolution of the bulky metastatic disease including the epidural spinal cord compression 8 months after treatment with pembrolizumab. The patient currently remains disease free with a follow-up of 90 months.

and immune response when combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) and immunotherapy and median OS of 23.3 months with T-VEC and 18.9 months with GM-CSF, with the corresponding durable response rates of 16.3% versus 2.1%.³³ T-VEC is the first FDA approved oncolytic virus and is additionally being studied in combination with immune checkpoint inhibitors. Other oncolytic viruses and dendritic cell vaccines are being investigated for treating melanoma patients. Several studies are focused on understanding the mechanisms of immune resistance in melanoma patients, exploring prognostic features of response to immunotherapy, and explore ways to reverse immune evasion.^{34,35} Fig. 2 demonstrate an example of successful use of immunotherapy in a 61-year-old patient with widely metastatic melanoma refractory to several lines of treatment, who presented complete resolution of bulky metastatic disease and remains disease free for more than 90 months after starting treatment anti-PD-1 inhibitor pembrolizumab.

NON-SMALL CELL LUNG CANCER

NSCLC is likewise associated with poor prognosis with an OS of 8 to 11 months due to rapid lung progression and distant metastatic progression. Skeletal metastasis is common in NSCLC, occurring in 30% of patients and roughly half of skeletal metastases are in the spinal column.³⁶ According to SEER, 56% patients with lung cancer have distant metastases at the time of diagnosis, with 6.3% 5-year relative survival (Table 1).¹⁴ Paclitaxel and kanglaite are commonly used chemotherapeutic agents in patients with lung cancer that has metastasized to bone.³⁷ Additionally, up to 80% of patients with squamous cell lung adenocarcinomas and nearly 60% of patients with lung adenocarcinomas contain targetable mutations in membrane growth factor receptors (EGFR, VEGFR) or protein kinases (RAS, RAF, MEK).³⁸

Immune checkpoint inhibitor use has been trialed in patients with NSCLC as well (Tables 2, 3; Supplementary Table 1). The CTLA4 inhibitor ipilimumab resulted in marginal improvement in patients with advanced NSCLC in a phase II clinical trial, with

no benefit shown in phase III trial, with median OS of 13.4 months (vs. 12.4 months) and median PFS of 5.6 months (vs. 5.6 months) with combined use of chemotherapy with immunotherapy.³⁹ Another CTLA4 inhibitor tremelimumab has been studied in phase II trial as a maintenance therapy; CCTG BR34 trial reported median OS of 16.6 months (vs. 14.1 months) and median PFS of 7.7 months (vs. 3.2 months) in patients with metastatic NSCLC when combined with durvalumab and platinum-based chemotherapy versus immunotherapy, with no significant improvement.⁴⁰ In contrast, anti-PD1 inhibitors nivolumab and pembrolizumab as well as PDL1 inhibitors MEDI4736, MPDL3280A and BMS-936559 show much more promising results; Checkmate017 and Checkmate057 phase III trials show improved survival in NSCLC patients who failed platinum-based chemotherapy of 23% (vs. 8%) 2-year OS in squamous and 29% (vs. 16%) in nonsquamous NSCLC patients when treated with nivolumab vs docetaxel, with pembrolizumab currently approved as first-line treatment in patients with PD-L1 overexpression (Table 3).^{41,42}

EGFR mutations are most common in Asian patients, females and patients with NSCLC.⁴³ EGFR inhibitors including erlotinib and gefitinib have been shown to improve the OS in NSCLC patients with metastatic spine disease for up to 24 to 36 months (Table 1).⁴⁰ Afatinib is another EGFR inhibitor targeting EGFR/HER2/HER4 and has been trialed in lung cancer patients; phase III trial reported with median PFS of 11.1 months (vs. 6.9 months) with afatinib use, with 13.6 month median PFS in patients with exon 19 deletions and L858R EGFR mutations.⁴⁴ Significant improvement in OS and PFS has been noted in patients with NSCLC treated with bevacizumab; phase III BEYOND trial reported median PFS of 12.4 months (vs. 7.9 months) in patients with EGFR mutant tumors, median PFS of 8.3 months (vs. 5.6 months) in wild type tumors and OS of 24.3 months (vs. 17.7 months) when treated with bevacizumab in addition to carboplatin and paclitaxel.^{45,46} In patients with targetable EGFR mutations including T790M, osimertinib has been shown to prolong survival and is first-line therapy, with median PFS of 10.1 months (vs. 4.4 months) as compared to platinum and pemetrexed.⁴⁷ In patients with EML4-ALK fusion commonly present in younger patients and never smokers, a phase II trial with crizotinib has shown promising results; studies report 24.1 month PFS.³⁸ Buparlisib, which is a PI3K inhibitor, is a potential therapy which may result in antitumor activity by inhibiting osteoclast formation.⁴⁸ Other targeted inhibitors including BRAF, MAP2K and HER2 inhibitors are being studied.²³ As an example of effectiveness of targeted therapies, Fig. 3 describes the suc-



Fig. 3. Successful use of epidermal growth factor receptor (EGFR) inhibitor osimertinib in a patient with advanced untreated EGFR mutated non-small cell lung cancer. Patient is a 60-year-old female who presented with thoracic pain, found to have a midthoracic pathologic compression fracture. Per discussion with medical oncology team, the consensus was for systemic treatment after a percutaneous spine fusion. Sagittal and axial magnetic resonance imaging cervical and thoracic spine prior to the initiation of treatment (A, B) and 4 months after treatment with osimertinib (C, D) showing resolution of the lesion.

cessful use of erlotinib in a 60-year-old patient with advanced EGFR mutant NSCLC, she had complete response of all her epidural disease without adjuvant radiotherapy for 16 months. Unfortunately, she progressed with brain, lung and spinal metastasis before could be switched to second generation EGFR inhibitors.

RENAL CELL CARCINOMA

Renal cell carcinoma (RCC) is diagnosed in approximately 75,000 people yearly, with approximately 30% of patients developing bone metastases. According to SEER, 16% patients with RCC present with distant metastatic disease, with 5-year rela-

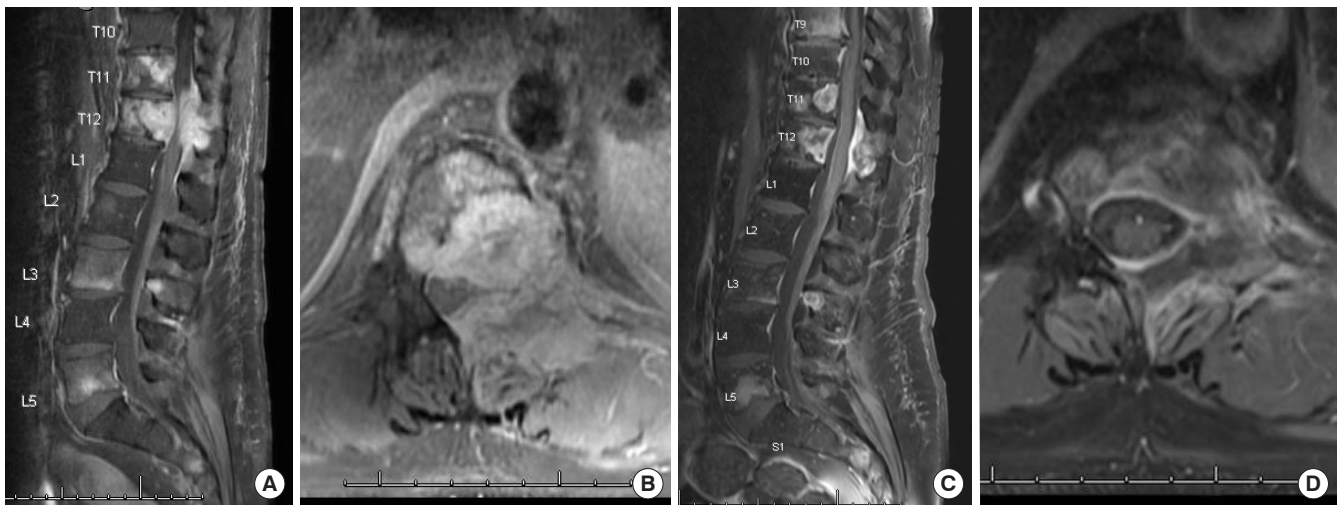


Fig. 4. Successful use of a multitargeted tyrosine kinase inhibitor cabozantinib in a patient with advanced clear cell renal cell cancer. Patient is a 51-year-old male with progressive clear cell renal cell carcinoma. Per discussion with medical oncology team, the consensus was for systemic treatment and restaging, as patient was not a candidate for surgery. Sagittal and axial magnetic resonance imaging of thoracic and lumbar spine prior to initiation of treatment showing significant compression of the thecal sac (A,B) and 3 months after treatment with cabozantinib (C, D) showing resolution of the lesion and significant improvement in cord compression and disease burden.

tive survival of 13.9%.¹⁴ RCC is poorly responsive to hormonal and cytotoxic chemotherapies, with anti-VEGFR tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors, and other TKIs being the mainstay of treatment (Table 1, Supplementary Table 1). Multiple histologic and molecular RCC subtypes have been described with the most frequent subtype being clear cell, a subtype seen in approximately 70% of patients that is associated with VHL mutation and resulting downstream activation of angiogenesis via VEGFR, with additional mutations in PBRM1, SETD2, and BAP1 described by TCGA, as well as alterations of the mTOR pathway components. In contrast, papillary RCC has been associated with alterations in Met and NRF2. Other RCC subtypes harbor mutations in TP53 and PTEN, show loss of CDKN2A and SMARCB1, as well as TFE3-TFEB fusions. Miller et al.⁴⁹ studied 100 advanced RCC patients and reported improved OS with combined stereotactic radiosurgery (SRS)/TKI as compared to SRS alone, reporting lower levels of local failure; at 12 months, local failure occurred in 4% patients treated with first-line TKI, as compared to 19%–27% in therapy naïve patients or patients undergoing SRS w/wo TKI post failing first-line therapy. After nephrectomy with or without resection of metastatic disease, RCC patients usually undergo treatment with first-line systemic therapy including bevacizumab/IFN alpha, high dose IL2, pazopanib, sunitinib or temsirolimus. Second line therapies include axitinib, cabozantinib, lenvatinib/everolimus and nivolumab; other options include everolimus

and sorafenib (Tables 1-3).

Some of the commonly used targeted inhibitors include VEGFR inhibitors and TKI, including bevacizumab targeting VEGFR, lenvatinib targeting FGFR/VEGFR and Cabozantinib targeting VEGFR/AXL/cMet, with their benefits documented in several phase III clinical trials including CABOSUN, which reported improved PFS of 8.2 months (vs. 5.6 months) as compared to sunitinib with 34% reduction in rate of progression or death.^{50,51} In our hands, cabozantinib has resulted in robust response in bulky spinal involvement as illustrated in Fig. 4 where complete resolution of severe spinal cord compression is demonstrated.

Axitinib, pazopanib, sorafenib, sunitinib targeting VEGFR/PDGFR had likewise shown promising results in patients with metastatic RCC; median PFS was reported as high as 15.7 months with median OS of 29.9 months, with median PFS of 7.4 months and median OS of 13.6 months in sorafenib refractory patients.⁵² PD-1/PD-L1 (nivolumab, ipilimumab) and mTOR inhibitors (everolimus, temsirolimus) have additionally been trialed for treatment of metastatic RCC with promising results (Tables 1-3). Multiple phase 3 clinical trials are ongoing including CLEAR (pembrolizumab-lenvatinib vs. everolimus-lenvatinib vs. sunitinib with PFS of 23.9 months vs. 9.2 months), CheckMate214 (nivolumab-ipilimumab vs. sunitinib with median OS not reached vs. 38.4 months), IMmotion151 (atezolizumab-bevacizumab vs. sunitinib with final OS 36.1 months vs. 38.7 months), JAVE-

LIN Renal 101 (avelumab-axitinib vs. sunitinib with median PFS of 13.3 months and 5.6 months), KEYNOTE-426 (pembrolizumab-axitinib vs. sunitinib with median PFS of 20.6 months vs. 11.3 months), and ADAPT (DC immunotherapy/sunitinib vs. sunitinib with median OS of 27.7 months vs. 32.4 months, and PFS of 6 months vs. 7.83 months) (clinicaltrials.org) for patients with metastatic RCC (Supplementary Table 1).

PROSTATE CANCER

Prostate cancer will commonly metastasize to bone and OS in patients with spine metastases is roughly 2.5 years.⁵³ According to SEER, 7% patients diagnosed with prostate cancer have distant metastases at presentation, with 30.6% 5-year relative survival.¹⁴ Androgen receptor antagonists including flutamide, bicalutamide and abiraterone are commonly used as first-line androgen deprivation agents resulting in improvement in patient outcomes; as reported by STAMPEDE trial median OS was not reached with addition of zoledronic acid, 81 months with addition of docetaxel, 76 months with addition of both, and 71 months with standard of care (Table 1).⁵⁴ Other androgen deprivation therapies include ketoconazole or abiraterone that inhibit CYP17 with resulting androgen synthesis blockade, and use of LHRH agonists/antagonists including leuproline, goserelin, degarelix with resulting downregulation in LHRH receptor signaling, with degarelix inducing and maintaining androgen deprivation for up to 1 year (Table 1).^{55,56}

In patients with androgen resistant prostate cancer, a variety of other therapies have been utilized (Table 1). Small TKIs gefitinib, erlotinib targeting EGFR and lapatinib targeting EGFR/HER2 had shown some success with improvement in prostate-specific antigen (PSA) levels; phase II trial of lapatinib resulted in no radiologic evidence of metastatic disease in 7 of twenty nine patients.^{57,58} Monoclonal EGFR antibody cetuximab has been used alone and in combination with various chemotherapy agents including doxorubicin, docetaxel, and mitoxantrone with some improvement in PSA levels and/or median survival; combination of cetuximab with doxorubicin resulted in stable disease in 65% patients with castration resistant prostate cancer with bone disease (Table 1).^{59,60} MET/VEGFR2 inhibitor cabozantinib has likewise been trialed in patients with metastatic prostate cancer in several phase III trials including COMET-1/2, with no significant improvement in OS, with 15% (vs. 17%) responders and median OS of 11 months (vs. 9.8 months).⁶¹ PARP inhibitors including olaparib have been used in patients with androgen resistant prostate cancer, where phase II TOPARP-A

trial showed an overall 33% response rate, especially in patients with underlying mutations in DNA damage repair pathways or BRCA1/2, while TOPARP-B trial reported 54.3% composite response, with radiographic response in 24.2% and PSA response in 37%.⁶²

In addition, anti-CTLA4 immunotherapy including ipilimumab has been trialed in patients with prostate cancer in phase III trials with improvement in PFS of 5.6 months (vs. 3.8 months) and measured PSA levels (Tables 2, 3).⁶³ Some success was noted with use of PD1/PD-L1 inhibitors, including nivolumab, pembrolizumab, and atezolizumab, especially in patients with mismatch repair impairment, hypermutated prostate cancer lesions and those with microsatellite instability; in CheckMate 9KD trial, combination of nivolumab with docetaxel resulted in 9-month radiographic PFS and OS of 18.2 months (Tables 2, 3).⁶⁴ Several tumor vaccines including an autologous Sipuleucel-T vaccine comprised of antigen presenting cells co-cultured with PA2024 prostatic acid phosphatase linked to GM-CSF have been successfully used to treat prostate cancer, with significant improvement in the reported OS in patients of up to 13 months in several phase III trials including IMPACT trial.⁶⁵ Another area of investigation focuses on the development of chimeric antigen receptor T cells (CAR-T cells) for treating patients with metastatic prostate cancer, which had been previously tested and successfully applied for treatment of patients with hematologic malignancies.^{66,67}

THYROID CANCER

Although the percentage of patients with spine metastases arising from primary thyroid cancer, including differentiated thyroid carcinoma, anaplastic carcinoma and medullary thyroid carcinoma is not high, it is a common endocrine malignancy, and up to 30% patients will develop resistance to standard therapy and progress to metastatic disease (Table 1). According to SEER, 3% patients with thyroid cancer have distant metastases at the time of diagnosis, with 53.3% 5-year relative survival.¹⁴ Targeted inhibitors for the mitogen-activated protein kinase pathway have been trialed in patients with metastatic thyroid cancer. Sorafenib targeting VEGFR/Flt3/RET/cKIT/BRAF and lenvatinib targeting VEGFR/FGFR/PDGFR/KIT/RET have been trialed in patients with differentiated thyroid carcinoma with improvement in PFS and OS, respectively, by several phase II trials, as well as DECISION and SELECT phase III trials, the former of which reported median PFS of 10.8 months (vs. 5.8 months) with sorafenib use in radioactive iodine-refractory lo-



Fig. 5. Successful use of multitargeted tyrosine kinase inhibitor Lenvatinib in a patient with recurrent follicular thyroid carcinoma. Patient is a 70-year-old female who had undergone prior corpectomy with cage placement and posterior spinal fusion, followed by treatment with iodine, external beam radiation therapy and spine stereotactic radiosurgery, with significant progression of her disease shortly thereafter. Sagittal and axial magnetic resonance imaging of cervical and thoracic spine prior to initiation of treatment showing significant anterior cord compression C4–7 (A, B) and 3 months after treatment with Lenvatinib (C, D), showing resolution of the lesion and significant improvement in cord compression.

cally advanced or metastatic differentiated thyroid cancer, while the latter reported median OS of 52.2 months in lenvatinib responders versus 19 months in nonresponders (Table 1; Supplementary Table 1).^{68,69} We have seen robust results using lenvatinib in patients with bulky metastasis of follicular thyroid carcinoma in the spine. We would like to present a 70-year-old patient who had rapid recurrence of multilevel cervical spine metastasis after treatment with radioactive iodine and maximal doses of targeted radiation but had remained progression free for 36 months since starting lenvatinib (Fig. 5). Vandetanib, targeting VEGFR/EGFR/RET, and cabozantinib, targeting VEGFR2/cMet/AXL/RET, have been trialed in patients with medullary thyroid carcinoma with improvement in PFS in phase II and phase III trials, with 30.5 months (vs. 19.3 months) median

OS with vandetanib use, with 26.6 (vs. 21.1) median OS with cabozantinib use, including 44.3 months (vs. 18.9 months) median OS in patients with RET M918T positive disease.^{70,71} More recent studies focus on targeting PI3K pathway, ALK translocations, as well as HER2/3 receptors (Supplementary Table 1).⁷² Panebianco et al reported ELM4-ALK and STRN-ALK fusions in patients with papillary and poorly differentiated thyroid carcinomas.⁷³ Other studies are investigating the effects of immunotherapy including anti-CTLA4 and anti-PD1, and vaccine use (Table 3; Supplementary Table 1).^{74,75}

CONCLUSION

The number of patients with metastatic spine disease continues to rise. Moreover, even the most extensive surgical resection and aggressive radiation therapies are frequently insufficient to control the disease without adjunct medical therapy, which can successfully address residual microscopic disease and prevent recurrence, specifically within the bone environment. Historically, the ultimate demise in patients with metastatic spine disease is due to a combination of their extensive systemic disease burden and aggressive spine disease resulting in neurologic compromise. In the recent years, development of individualized, targeted therapies and novel treatment protocols had heavily depended on the identification of novel mutations and improved understanding of the biology of many cancers, giving hope to patients with spinal metastases to prevent disease progression, avert neurologic deficit and improve their quality of life. However, there remains a large void with developing therapeutic agents that can specifically target cancer within the unique bone milieu. Current literature is lacking in safety, efficacy, and estimates of overall response rates from the use of many of the new treatment agents when administered to patients with spine metastatic disease, however robust response can be achieved in select cases as described in this manuscript. Identification of predictors of favorable response to targeted inhibition, chemotherapy or immunotherapy of spine metastases derived from various primary cancers is a necessary next step.

NOTES

Supplementary Materials: Supplementary Table 1 can be found via <https://doi.org/10.14245/ns.2244290.145>.

Supplementary Table 1. Targeted therapies and immunotherapies approved by the U.S. Food and Drug Administration in the last 2 years

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REFERENCES

- Perrin RG, Laxton AW. Metastatic spine disease: epidemiology, pathophysiology, and evaluation of patients. *Neurosurg Clin N Am* 2004;15:365-73.
- Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. *CA Cancer J Clin* 2022;72:7-33.
- Hernandez RK, Adhia A, Wade SW, et al. Prevalence of bone metastases and bone-targeting agent use among solid tumor patients in the United States. *Clin Epidemiol* 2015;7:335-45.
- North RB, LaRocca VR, Schwartz J, et al. Surgical management of spinal metastases: analysis of prognostic factors during a 10-year experience. *J Neurosurg Spine* 2005;2:564-73.
- D'Oronzo S, Coleman R, Brown J, et al. Metastatic bone disease: pathogenesis and therapeutic options: up-date on bone metastasis management. *J Bone Oncol* 2019;15:004.
- Wright E, Ricciardi F, Arts M, et al. Metastatic spine tumor epidemiology: comparison of trends in surgery across two decades and three continents. *World Neurosurg* 2018;114:e809-17.
- Wu G, Broniscer A, McEachron TA, et al. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nat Genet* 2012;44:251-3.
- Attalla K, Duzgol C, McLaughlin L, et al. The spinal distribution of metastatic renal cell carcinoma: support for locoregional rather than arterial hematogenous mode of early bony dissemination. *Urol Oncol* 2021;39:196.e9-196.e14.
- Laufer I, Rubin DG, Lis E, et al. The NOMS framework: approach to the treatment of spinal metastatic tumors. *Oncologist* 2013;18:744-51.
- Tomita K, Kawahara N, Kobayashi T, et al. Surgical strategy for spinal metastases. *Spine (Phila Pa 1976)* 2001;26:298-306.
- Fourney DR, Frangou EM, Ryken TC, et al. Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. *J Clin Oncol* 2011;29:3072-7.
- Tokuhashi Y, Matsuzaki H, Toriyama S, et al. Scoring system for the preoperative evaluation of metastatic spine tumor prognosis. *Spine (Phila Pa 1976)* 1990;15:1110-3.
- Tokuhashi Y, Matsuzaki H, Oda H, et al. A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis. *Spine (Phila Pa 1976)* 2005;30:2186-91.
- Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2021, based on the November 2020 submission. Accessed February 27, 2022.
- Chan-Seng E, Charissoux M, Larbi A, et al. Spinal metastases in breast cancer: single center experience. *World Neurosurg* 2014;82:1344-50.
- Groenen KHJ, van der Linden YM, Brouwer T, et al. The Dutch national guideline on metastases and hematological malignancies localized within the spine; a multidisciplinary collaboration towards timely and proactive management. *Cancer Treat Rev* 2018;69:29-38.
- Pondé N, Aftimos P, Piccart M. Antibody-drug conjugates in breast cancer: a comprehensive review. *Curr Treat Options Oncol* 2019;20:37.
- Yamamoto Y, Nishimura R, Tanigawa T, et al. Efficacy and safety of TS-1 monotherapy for advanced/metastatic breast cancer - an observational study by the Kumamoto Breast Cancer Cooperative Group (KBCCG). *Gan To Kagaku Ryoho* 2014;41:1221-5.
- Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol* 2020;21:519-30.
- von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med* 2017;377:122-31.
- Kümler I, Christiansen OG, Nielsen DL. A systematic review of bevacizumab efficacy in breast cancer. *Cancer Treat Rev* 2014;40:960-73.
- Yan W, Xiao J, Liu T, et al. The effects of Hsp90 expression

- alteration on spinal metastases of breast carcinoma. *Tumour Biol* 2013;34:1391-7.
23. Cofano F, Monticelli M, Ajello M, et al. The targeted therapies era beyond the surgical point of view: what spine surgeons should know before approaching spinal metastases. *Cancer Control* 2019;26:1073274819870549.
 24. Munster PN, Thurn KT, Thomas S, et al. A phase II study of the histone deacetylase inhibitor vorinostat combined with tamoxifen for the treatment of patients with hormone therapy-resistant breast cancer. *Br J Cancer* 2011;104:1828-35.
 25. Mittendorf EA, Clifton GT, Holmes JP, et al. Final report of the phase I/II clinical trial of the E75 (nelipepimut-S) vaccine with booster inoculations to prevent disease recurrence in high-risk breast cancer patients. *Ann Oncol* 2014;25:1735-42.
 26. Goodwin CR, Sankey EW, Liu A, et al. A systematic review of clinical outcomes for patients diagnosed with skin cancer spinal metastases. *J Neurosurg Spine* 2016;24:837-49.
 27. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2012;380:358-65.
 28. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2018;19:603-15.
 29. Maio M, Grob JJ, Aamdal S, et al. Five-year survival rates for treatment-naïve patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. *J Clin Oncol* 2015;33:1191-6.
 30. Wolchok JD, Rollin L, Larkin J. Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med* 2017;377:2503-4.
 31. Day D, Hansen AR. Immune-related adverse events associated with immune checkpoint inhibitors. *BioDrugs* 2016;30:571-84.
 32. Linardou H, Gogas H. Toxicity management of immunotherapy for patients with metastatic melanoma. *Ann Transl Med* 2016;4:272.
 33. Andtbacka RHI, Kaufman HL, Collichio F, et al. Talimogene Laherparepvec improves durable response rate in patients with advanced melanoma. *J Clin Oncol* 2015;33:2780-8.
 34. Carreno BM, Magrini V, Becker-Hapak M, et al. Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. *Science* 2015;348:803-8.
 35. Uyttenhove C, Pilotte L, Théate I, et al. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. *Nat Med* 2003;9:1269-74.
 36. Goodwin CR, Khattab MH, Sankey EW, et al. Factors associated with life expectancy in patients with metastatic spine disease from adenocarcinoma of the lung. *Global Spine J* 2015;5:417-24.
 37. Cao L, Long L, Hu C. Efficacy of paclitaxel combined with kanglaite injection in treatment of bone metastases of lung cancer. *Iran J Public Health* 2019;48:1445-51.
 38. Shroff GS, de Groot PM, Papadimitrakopoulou VA, et al. Targeted therapy and immunotherapy in the treatment of non-small cell lung cancer. *Radiol Clin North Am* 2018;56:485-95.
 39. Govindan R, Szczesna A, Ahn MJ, et al. Phase III trial of ipilimumab combined with paclitaxel and carboplatin in advanced squamous non-small-cell lung cancer. *J Clin Oncol* 2017;35:3449-57.
 40. Helissey C, Champiat S, Soria JC. Immune checkpoint inhibitors in advanced nonsmall cell lung cancer. *Curr Opin Oncol* 2015;27:108-17.
 41. Horn L, Spigel DR, Vokes EE, et al. Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cancer: two-year outcomes from two randomized, open-label, phase III trials (CheckMate 017 and CheckMate 057). *J Clin Oncol* 2017;35:3924-33.
 42. Reck M, Taylor F, Penrod JR, et al. Impact of nivolumab versus docetaxel on health-related quality of life and symptoms in patients with advanced squamous non-small cell lung cancer: results from the CheckMate 017 Study. *J Thorac Oncol* 2018;13:194-204.
 43. Savas P, Hughes B, Solomon B. Targeted therapy in lung cancer: IPASS and beyond, keeping abreast of the explosion of targeted therapies for lung cancer. *J Thorac Dis* 2013;5 Suppl 5(Suppl 5):S579-92.
 44. Sequist LV, Yang JCH, 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.
 45. Lauro S, Onesti CE, Righini R, et al. The use of bevacizumab in non-small cell lung cancer: an update. *Anticancer Res* 2014;34:1537-45.
 46. Raparia K, Villa C, DeCamp MM, et al. Molecular profiling in non-small cell lung cancer: a step toward personalized medicine. *Arch Pathol Lab Med* 2013;137:481-91.

47. Wang S, Li J. Second-generation EGFR and ErbB tyrosine kinase inhibitors as first-line treatments for non-small cell lung cancer. *Onco Targets Ther* 2019;12:6535-48.
48. Wang S, Niu X, Bao X, et al. The PI3K inhibitor buparlisib suppresses osteoclast formation and tumour cell growth in bone metastasis of lung cancer, as evidenced by multimodality molecular imaging. *Oncol Rep* 2019;41:2636-46.
49. Miller JA, Balagamwala EH, Angelov L, et al. Spine stereotactic radiosurgery with concurrent tyrosine kinase inhibitors for metastatic renal cell carcinoma. *J Neurosurg Spine* 2016;25:766-74.
50. Bergerot P, Burns K, Prajapati D, et al. Advances in the treatment of metastatic renal cell carcinoma. *Cancer Treat Res* 2018;175:127-37.
51. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the alliance A031203 CABOSUN Trial. *J Clin Oncol* 2017;35:591-7.
52. Escudier B, Gore M. Axitinib for the management of metastatic renal cell carcinoma. *Drugs R D* 2011;11:113-26.
53. Amelot A, Terrier LM, Le Nail LR, et al. Spine metastasis in patients with prostate cancer: survival prognosis assessment. *Prostate* 2021;81:91-101.
54. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016;387:1163-77.
55. Klotz L, Boccon-Gibod L, Shore ND, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int* 2008;102:1531-8.
56. Attard G, Reid AHM, A'Hern R, et al. Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. *J Clin Oncol* 2009;27:3742-8.
57. Goodwin CR, Abu-Bonsrah N, Rhines LD, et al. Molecular markers and targeted therapeutics in metastatic tumors of the spine: changing the treatment paradigms. *Spine (Phila Pa 1976)* 2016;41 Suppl 20:S218-23.
58. Whang YE, Armstrong AJ, Rathmell WK, et al. A phase II study of lapatinib, a dual EGFR and HER-2 tyrosine kinase inhibitor, in patients with castration-resistant prostate cancer. *Urol Oncol* 2013;31:82-6.
59. Slovin SF, Kelly WK, Wilton A, et al. Anti-epidermal growth factor receptor monoclonal antibody cetuximab plus Doxorubicin in the treatment of metastatic castration-resistant prostate cancer. *Clin Genitourin Cancer* 2009;7:E77-82.
60. Fleming MT, Sonpavde G, Kolodziej M, et al. Association of rash with outcomes in a randomized phase II trial evaluating cetuximab in combination with mitoxantrone plus prednisone after docetaxel for metastatic castration-resistant prostate cancer. *Clin Genitourin Cancer* 2012;10:6-14.
61. Sonpavde GP, Pond GR, Fizazi K, et al. Cabozantinib for Progressive metastatic castration-resistant prostate cancer following docetaxel: combined analysis of two phase 3 trials. *Eur Urol Oncol* 2020;3:540-3.
62. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med* 2015;373:1697-708.
63. Beer TM, Kwon ED, Drake CG, et al. Randomized, double-blind, phase III trial of ipilimumab versus placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naive castration-resistant prostate cancer. *J Clin Oncol* 2017;35:40-7.
64. Pritchard CC, Morrissey C, Kumar A, et al. Complex MSH2 and MSH6 mutations in hypermutated microsatellite unstable advanced prostate cancer. *Nat Commun* 2014;5:4988.
65. Schellhammer PF, Chodak G, Whitmore JB, et al. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial. *Urology* 2013;81:1297-302.
66. Priceman SJ, Gerdts EA, Tilakawardane D, et al. Co-stimulatory signaling determines tumor antigen sensitivity and persistence of CAR T cells targeting PSCA+ metastatic prostate cancer. *Oncoimmunology* 2018;7:e1380764.
67. Junghans RP, Ma Q, Rathore R, et al. Phase I trial of anti-PSMA designer CAR-T cells in prostate cancer: possible role for interacting interleukin 2-T cell pharmacodynamics as a determinant of clinical response. *Prostate* 2016;76:1257-70.
68. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 2015;372:621-30.
69. Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* 2014;384:319-28.
70. Wells SA, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin*

- Oncol 2012;30:134-41.
71. Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol* 2013;31:3639-46.
72. Naoum GE, Morkos M, Kim B, et al. Novel targeted therapies and immunotherapy for advanced thyroid cancers. *Mol Cancer* 2018;17:51.
73. Panebianco F, Nikitski AV, Nikiforova MN, et al. Characterization of thyroid cancer driven by known and novel ALK fusions. *Endocr Relat Cancer* 2019;26:803-14.
74. Capdevila J, Wirth LJ, Ernst T, et al. PD-1 blockade in anaplastic thyroid carcinoma. *J Clin Oncol* 2020;38:2620-7.
75. Ma M, Lin B, Wang M, et al. Immunotherapy in anaplastic thyroid cancer. *Am J Transl Res* 2020;12:974-88.

Supplementary Table 1. Targeted therapies and immunotherapies approved by the U.S. Food and Drug Administration in the last 2 years

Date approved	Name/trial/mechanism	Cancer type	Eligibility	Outcomes
1/25/22	Tebentafusp-1ebn, NCT03070392, bispecific GP100 peptide-HLA-directed CD3 T cell engager	Unresectable or metastatic uveal melanoma	HLA-A*02:01 positive adult patients, no prior systemic or liver-directed therapy, no symptomatic untreated brain metastases, no cardiac disease, ok post resection	OS 21.7 months with trial vs. 16 months, PFS 3.3 months with trial vs. 2.9 months
12/3/21	Pembrolizumab	Stage IIB of IIC melanoma post complete resection	Adjuvant Tx, adult and pediatric > 12 years	
11/17/21	Pembrolizumab, KEY-NOTE-564	RCC, intermediate high or high risk of recurrence	Adjuvant Tx, post nephrectomy, with resection of metastatic lesions	Statistically significant improvement in DFS with trial Tx. 109 (22%) in Pembro arm and 151 (30%) in placebo
10/15/21	Atezolizumab	Stage II-IIIa NSCLC	Adjuvant Tx, post resection and platinum based chemoTx, > 1% PD-L1 expression in tumor cells	Median DFS not reached in trial Tx, 35.3 months in BSC arm
10/12/21	Abemaciclib +, first CDK4/6 inhibitor approved for adjuvant Tx, monarchE NCT03155997	HR+ HER2- LN+ early breast ca with high-risk recurrence, Ki67 > 20%	Adjuvant Tx, combined with endocrine Tx (tamoxifen or aromatase inhibitor)	Statistically significant difference in IDFS with trial Tx. 86.1% at 36 months vs. 79% with only tamoxifen or aromatase inhibitor
9/17/21	Cabozantinib, COSMIC-311 NCT03690388	Differentiated thyroid cancer, locally advanced or metastatic	Adult or pediatric > 12 yo, progressive post VEGFR targeted Tx, ineligible of refractory to radioactive iodine	PFS 11 months with trial Tx vs. 1.9 months with placebo
9/15/21	Mobocertinib	Locally advanced or metastatic NSCLC, Study 101 NCT02716116	Adult patients, EGFR exon 20 insertion mutations, progressive on platinum-based chemoTx	ORR 28% with median response duration of 17.5 months
8/17/21	Dostarlimab-gxly, GARNET NCT02715284	Recurrent or advanced solid tumors, dMMR	Adult patients, mismatch repair deficient dMMR	ORR 41.6%, 9.1% complete, 32.5% partial response; DOR 34.7 months, with 95.4% patients with duration of > 6 months
8/13/21	Belzutifan, HIF1 alpha inhibitor, study 004 NCT03401788	RCC, VHL associated	Adult patients, ok for associated CNS hemangioblastoma or pNET not requiring urgent surgery	ORR 49%, median DOR not reached, 56% of responders DOR > 12 months, median TTR of 8 months
8/10/21	Lenvantinib +, CLEAR Study 307 KEYNOTE-581 NCT02811861	Advanced RCC	First line, in combination with pembrolizumab, regardless of PD-L1 status	PFS 23.9 months with trial Tx vs. 9.2 months with sunitinib, ORR 71% vs. 36%, complete response 16% vs 4% respectively
7/26/21	Pembrolizumab +, KEY-NOTE-522 (NCT03036488)	High risk, early-stage triple negative breast cancer TNBC	Neoadjuvant Tx combined with chemoTx, followed by adjuvant single agent post resection, 1-2 cm lesions LN+ or all lesions > 2 cm regardless of PD-L1	CR was 63% with trial Tx vs. 56% with chemoTx only, event-free survival 123 (16%) in trial Tx vs. 93 (24%) in chemoTx alone
11/13/20	Pembrolizumab +, KEY-NOTE-355 NCT02819518	Locally recurrent unresectable or metastatic TNBC	Combined with chemoTx, expressing PD-L1 CPS > 10	Median PFS 9.7 months pembrolizumab + chemoTx vs. 5.6 months placebo
5/28/21	Sotorasib, RAS GTPase family inhibitor, CodeBreak100 NCT03600883	Locally advanced or metastatic NSCLC	Adult patients, KRAS G12C mutation, at least one prior systemic Tx	ORR 36% with median response duration 10 months

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5/21/21	Amivantamab-vmjw, bispecific Ab EGFR/MET, CHRYSALIS NCT02609776	Locally advanced or metastatic NSCLC	Adult patients, EGFR exon 20 insertion mutations, progressive on platinum-based chemoTx	ORR 40% with median response duration 11.1 months
4/7/21	Sacituzumab govitecan, AS-CENT NCT02574455	Unresectable locally advanced or metastatic TNBC	Adult patients, at least 2 systemic therapies, adjuvant or neoadjuvant, at least one systemic therapy for metastatic disease	Median PFS 4.8 months with trial Tx vs. 1.7 months with chemoTx; median OS 11.8 months with trial Tx vs. 6.9 months with chemoTx
3/10/21	Tivozanib, kinase inhibitor, TIVO-3 NCT02627963	Relapsed or refractory advanced RCC	Adult patients, following 2 or more systemic Tx, at least one VEGFR kinase inhibitor other than sorafenib or tivozanib	PFS 5.6 months with trial Tx vs. 3.9 months with sorafenib; median OS 16.4 months with trial Tx vs. 19.2 months with sorafenib; ORR18% trial Tx vs. 8% sorafenib arm
3/3/21	Lorlatinib, Study B7461006 NCT03052608	Metastatic NSCLC	ALK-positive patients as first line, second or third line; no prior systemic Tx for metastatic disease	Improved PFS with trial Tx vs. crizotinib, HR 0.28; median PFS cannot estimate with trial Tx, 9.3 months with crizotinib; in patients with intracranial lesions ORR 82% lorlatinib vs. 23% ORR crizotinib arm
2/22/21	Cemiplimab-rwl, Study 1624 NCT03088540	Locally advanced (not candidate for surgery/chemo), or metastatic NSCLC	High PD-L1 expression TPS > 50%, first line; no EGFR, ALK or ROS1 aberrations	Median OS 22.1 months with trial Tx vs. 14.3 months with platinum chemoTx; median PFS 6.2 months with trial Tx vs. 5.6 months platinum chemoTx; ORR 37% trial Tx vs. 21% platinum chemoTx
2/3/21	Tepotinib, VISION NCT02864992	Metastatic NSCLC	Adult patients, MET exon 14 skipping alterations	ORR 43%, median response duration of 10.8 months
1/22/21	Nivolumab +, CHECK-MATE-9ER NCT03141177	Advanced RCC	Combination with cabozantinib vs sunitinib, first line; previously untreated	Median PFS 16.6 months with trial Tx vs. 8.3 months with nivolumab + sunitinib; HR 0.6; median OS not reached; ORR 55.7% trial Tx vs. 27.1% nivolumab + sunitinib
12/18/20	Osimertinib, ADAURA NCT02511106	Stage IB-IIIa NSCLC, non-squamous histology	Adjuvant Tx, EGFR exon 19 deletions or exon 21 L858R mutations, post resection, with or without prior chemoTx	Median DFS not reached trial arm, 19.6 months in placebo arm
12/18/20	Relugolix, first oral GnRH receptor antagonist, HERO NCT03085095	Advanced prostate cancer	Adult patients, at least 1 year androgen deprivation Tx with recurrence post-surgery and RT, or newly diagnosed castration sensitive	Medical castration rate 96.7% trial Tx by day 29 of 48-week treatment
12/16/20	Margetuximab-cmkb, SOPHIA NCT02492711	Metastatic HER2+ breast cancer	Combined with chemoTx, had 2 or more anti-HER2 regimens, at least one for metastatic disease	PFS 5.8 months trial Tx vs. 4.9 months in trastuzumab plus chemoTx; ORR 22% vs. 16%; median DOR 6.1 months vs. 6.0 months
12/1/20	Pralsetinib, ARROW NCT03037385	Medullary thyroid cancer, advanced or metastatic	Adult and pediatric > 12 yo, RET mutated requiring systemic Tx, or RET fusion + requiring systemic Tx and radioactive iodine refractory	ORR 60% in patients w/prior cabozantinib or vandetanib, with 79% responses lasting over 6 months; ORR 66% with no prior cabozantinib or vandetanib, 84% patients with responses over 6 months

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9/4/20	Pralsetinib, ARROW NCT03037385	Metastatic NSCLC	Adult patients, RET fusion +	ORR 57%, 80% responders with prior platinum Tx with responses over 6 months; ORR 70%, 58% responders with responses over 6 months no prior systemic Tx
7/30/20	Atezolizumab, IMspire150, NCT02908672	Unresectable or metastatic melanoma	BRAF V600E mutated, combination with cobimetinib and vemurafenib	Median PFS 15.1 months trial Tx vs 10.6 months in the placebo arm
6/29/20	Pertuzumab with trastuzumab, vs. hyaluronidase-zzxf; FeDeriCa NCT03493854	HER2+ breast cancer, locally advanced, inflammatory or early stage	Combined with chemoTx as neoadjuvant Tx, >2cm or LN+, part of complete Tx for early breast cancer; or Adjuvant Tx for early breast ca with high risk of recurrence Combined with docetaxel, no prior anti-HER2 therapy or chemotherapy for metastatic disease	Combined trial Tx showed noninferior pertuzumab and trastuzumab serum trough concentrations; pCR was 59.7% trial Tx vs. 59.5% pertuzumab/trastuzumab
6/16/20	Pembrolizumab, KEY-NOTE-158 NCT02628067	Unresectable or metastatic tumors mutation burden high TMB H> 10 mut/MB	Adult and pediatric > 12 years, progressive through prior Tx and no other Tx options, max 10 target lesions, max 5 target lesions per organ	ORR 29%, 4% complete and 25% partial response rate; median DOR not reached, 57% with responses over 12 months, 50% patients with responses over 24 months
5/29/20	Ramucirumab, RELAY NCT02411448	Metastatic NSCLC	Combined with erlotinib, first line, EGFR exon 19 deletions or exon 21 L858R mutations	Median PFS 19.4 months trial Tx vs. 12.4-month placebo plus erlotinib; ORR 76% trial Tx vs. 75%, median DOR 18.0 months vs. 11.1 months
5/26/20	Nivolumab plus ipilimumab +, CHECKMATE-9LA NCT03215706	Metastatic or recurrent NSCLC	Combined with 2 cycles, platinum doublet chemoTx, first line, no EGFR or ALK genomic aberrations	Median OS 14.1 months trial Tx vs. 10.7 months platinum doublet Tx; PFS 6.8 months trial Tx vs. 5 months platinum doublet Tx; ORR 38% vs. 25%; median response duration 10 months trial Tx vs. 5.1 months chemoTx
5/22/20	Brigatinib, ALTAIL NCT02737501	Metastatic NSCLC	Adult patients, ALK mutation +	PFS 24 months trial Tx vs 11 months crizotinib; ORR 74% trial Tx vs 62% crizotinib
5/19/20	Olaparib, PROfound NCT02987543	Metastatic castration resistant prostate cancer	Adult patient, HRR pathway gene mutations (including BRCA1/2 or ATM), progressive on enzalutamide or abiraterone, all had bilateral orchiectomy	rPFS 7.4 months trial Tx vs. 3.6 months with enzalutamide or abiraterone; median OS 19.1 months vs. 14.7 months; ORR 33% trial Tx vs. 2%
5/18/20	Atezolizumab, IMpower110 NCT02409342	Metastatic stage IV NSCLC	High PD-L1 expression > 50% tumor cells, first line, no EGFR or ALK genomic aberrations, no prior chemoTx for metastatic disease	Median OS 20.2 months trial Tx vs. 13.1 months chemoTx platinum; median PFS 8.1 months trial Tx and 5.0 months platinum chemoTx; ORR 38% vs. 29%
5/15/20	Rucaparib, TRITON2 NCT02952534	Metastatic castration resistant prostate cancer	BRCA mutated, prior Tx androgen receptor therapy or taxanes, prior bilateral orchiectomy vs. GhrH analog	ORR 44%, median DOR cannot evaluate, range 1.7-24 months; 56% responders with DOR over 6 months

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Supplementary Table 1. Targeted therapies and immunotherapies approved by the U.S. Food and Drug Administration in the last 2 years (Continued)

Date approved	Name/trial/mechanism	Cancer type	Eligibility	Outcomes
5/15/20	Nivolumab plus ipilimumab, CHECKMATE-227 NCT02477826	Metastatic or recurrent NSCLC	PD-L1 expression > 1%, no EGFR or ALK aberrations, no prior systemic Tx	Statistically significant OS 17.1 months trial Tx vs 14.9 months platinum doublet chemoTx; median PFS 5.1 months vs 5.6; ORR 36% vs 30%; median duration 23.2 months vs 6.2 months
5/8/2020	Selpercatinib, LIBRETTO-001	Metastatic RET fusion + NSCLC; advanced or metastatic RET mutant medullary thyroid cancer requiring systemic Tx; RET fusion positive thyroid ca requiring systemic Tx or radioactive iodine refractory	Adult and pediatric > 12yo; RET fusion +, RET mutation +; NSCLC prior platinum Tx	NSCLC RET fusion+, prior platinum chemo: ORR 64%, 81% responders had responses > 6 months; no systemic Tx ORR 85%, 58% responses > 6 months RET mutant MTC post cabozantinib, vandetanib or both: ORR 69%, 76% responders lasting > 6 months, in previously untreated patients ORR 73%, 61% responses > 6 months RET fusion+ iodine-refractory groups with systemic Tx ORR 79%, 87% responders > 6 months, without systemic Tx ORR 100%, 75% responses > 6 months
5/6/2020	Capmatinib, GEOMETRY mono1, NCT02414139	Metastatic NSCLC, confirmed MET exon 14 skipping	Treatment naïve or previously treated patients	ORR 68%, response duration of 12.6 months in naïve, ORR 41%, response duration 9.7 months in previously treated
4/22/20	Govitecan-hzjy, IMMU-132-01, NCT01631552	Triple negative breast cancer	Adult, at least 2 prior Tx for metastatic disease	ORR 33.3%, median response duration of 7.7 months
4/17/20	Tucatinib+, HER2CLIMB NCT02614794	HER2+ metastatic breast cancer	Adult, advanced unresectable or metastatic including brain, prior Tx trastuzumab, pertuzumab and ado-trastuzumab emtansine	Treatment arm PFS 7.8 months and OS 21.9 months with trastuzumab, capecitabine and tucatinib; control arm PFS 5.6 months, OS 17.4 months; with brain metastases patients PFS 7.6 vs. 5.4 months; ORR 40.6% vs. 22.8%
2/25/20	Neratinib+, NALA NCT01808573	HER2+ breast cancer	Adult, advanced or metastatic cancer, 2 or more prior anti-HER2 based regimens post metastatic diagnoses	Neratinib with capecitabine PFS 5.6 months, PFS at 12 months 29%, OS 21 months, ORR 32.8%, median response duration 8.5 months; lapatinib with capecitabine PFS 5.5 months, PFS at 12 months 15%, OS 18.7 months, ORR 26.7%, median response duration 5.6 months

HLA, human leukocyte antigen; OS, overall survival; PFS, progression free survival; DFS, disease free survival; TX, treatment; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; PD-L1, programmed cell death ligand 1; IDFS, invasive disease free survival; VEGFR, vascular endothelial growth factor receptor; ORR, overall response rate; dMMR, mismatch repair deficient; DOR, duration of response; RCC, renal cell carcinoma; VHL, von Hippel Lindau; CNS, central nervous system; PNET, primitive neuro ectodermal tumor; TTR, time in therapeutic range; TNBC, triple negative breast cancer; LN, lymph node; CR, complete response; CPS, combined positive score; NSCLC, non-small cell lung cancer; KRAS, Kirsten rat sarcoma virus; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; HR, hormone receptor; RT, radiation therapy; RET, rearranged during transfection; pCR, pathological complete response; rPFS, radiographic progression free survival; GhRH, growth hormone releasing hormone; MTC, medullary thyro.