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- In the subgroup of PD-L1 ≥1 patients, OS events for OPDIVO + YERVOY + platinum-doublet chemotherapy were 105/203 vs. 139/204 for platinum-doublet alone (HR 0.64‡ [95% CI: 0.50, 0.82]); median OS was 15.8 months vs. 10.9 months

OPDIVO Safety Information[1]

Clinical use:

Efficacy and safety not established in pediatric patients.

Most serious warnings and precautions:

Severe/fatal immune-mediated adverse reactions (imARs): OPDIVO as monotherapy or in combination with YERVOY (ipilimumab) can cause severe and fatal immune-mediated adverse reactions, including pneumonitis, interstitial lung disease, encephalitis, myocarditis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and autoimmune hemolytic anemia. Immune-mediated adverse reactions may involve any organ system. Onset may occur during treatment or months after the last dose. Early diagnosis and appropriate management are essential to minimize potential life-threatening complications. Monitor patients for signs and symptoms of imARs and appropriately manage with treatment modifications. Permanently discontinue for any severe imARs that recur and for any life-threatening imARs.

Administration: Administer OPDIVO under the supervision of physicians experienced in the treatment of cancer.

Allogeneic hematopoietic stem cell transplantation (HSCT): Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Preliminary results from the follow-up of patients undergoing allogeneic HSCT after previous exposure to nivolumab showed a higher than expected number of cases of acute graft-versus-host disease (GVHD) and transplant-related mortality. Complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grades 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic venoocclusive disease (VOD), and other immune-mediated adverse reactions, and intervene promptly.

Multiple myeloma: Increased mortality in patients with multiple myeloma [not an approved indication] when OPDIVO is added to a thalidomide analogue and dexamethasone. Treatment of patients with multiple myeloma with a PD-1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Other relevant warnings and precautions:

- imARs have occurred at higher frequencies when OPDIVO was administered in combination with YERVOY vs. OPDIVO alone
- Severe cases of these imARs have been observed, including fatal cases. Monitor patients for signs and symptoms of:
  - Cardiac adverse events and pulmonary embolism with combination therapy
  - Endocrinopathies, including hypothyroidism, hyperthyroidism, hypoparathyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis
  - Diarrhea, additional symptoms of colitis, and cytomegalovirus (CMV) infection/reactivation
  - Hepatotoxicity, including hepatitis
  - Pneumonitis or interstitial lung disease
  - Nephrotoxicity, including nephritis and renal failure
  - Rash, Stevens-Johnson syndrome, toxic epidermal necrolysis
  - Encephalitis
  - Aplastic anemia
  - Myelitis (including transverse myelitis)
  - Autoimmune hemolytic anemia
  - Myotoxicity (myositis, myocarditis, and rhabdomyolysis)
  - Other imARs, including solid organ transplant rejection and rapid-onset and severe graft-versus-host disease (GVHD)
- Infusion reaction
- Patients on controlled sodium diet
- Caution when driving or operating a vehicle or potentially dangerous machinery
- Haemophagocytic lymphohistiocytosis (HLH)
- Effective contraception in women of reproductive potential
- Pregnancy and nursing women
- Has not been studied in patients with moderate or severe hepatic or severe renal impairment

For more information:

Please consult the OPDIVO Product Monograph at www.bms.com/assets/bms/ca/documents/productmonograph/OPDIVO_EN_PM.pdf for important information relating to adverse reactions, drug interactions, and dosing, which have not been discussed in this piece.

The Product Monograph is also available by calling us at: 1-866-463-6267.

YERVOY Safety Information[2]

Clinical use:

Efficacy and safety not established in pediatric patients.

Contraindication:

In patients with active, life-threatening autoimmune disease, or with organ transplantation graft where further immune activation is potentially imminently life threatening.

Most serious warnings and precautions:

Severe/fatal immune-mediated adverse reactions (imARs): YERVOY as monotherapy or in combination with OPDIVO (nivolumab) can cause severe/fatal imARs, including enterocolitis, intestinal perforation, hepatitis, dermatitis (incl. toxic epidermal necrolysis), Stevens-Johnson syndrome, neuropathy, endocrinopathy, pneumonitis, interstitial lung disease, myocarditis, encephalitis, myasthenia gravis, autoimmune hemolytic anemia and other organ system toxicities. Most occurred during the induction period; onset months after the last dose has been reported. Early diagnosis and appropriate management are essential to minimize life-threatening complications. Monitor patients for signs and symptoms suggestive of imARs. Permanently discontinue treatment for any severe imAR reaction that recurs and for any life-threatening imAR.

Consult the OPDIVO (nivolumab) Product Monograph prior to initiation of YERVOY in combination with OPDIVO.

Administration: Administer YERVOY under the supervision of physicians experienced in the treatment of cancer.

Other relevant warnings and precautions:

- imARs have occurred at higher frequencies when YERVOY was administered in combination with OPDIVO vs. YERVOY alone
- Patients who have had a severe or life-threatening skin adverse reaction on a prior cancer immune stimulatory therapy
- Severe cases of these imARs have been observed, including fatal cases. Monitor for signs/symptoms of:
  - Gastrointestinal adverse reactions
  - Hepatic adverse reactions
  - Pulmonary adverse reactions
  - Renal adverse reactions
  - Skin adverse reactions
  - Encephalitis
  - Neuropathies
  - Endocrinopathies, including diabetes mellitus (including fulminant type 1 diabetes), and diabetic ketoacidosis
- Other imARs including ocular events
- Haemophagocytic lymphohistiocytosis (HLH)
- Vogt-Koyanagi-Harada syndrome
- Serous retinal detachment
- Graft-versus-host disease (GVHD)
- Solid organ transplant rejection in the post-marketing setting
- Infusion reaction
- Patients on immunosuppressive therapy for life-threatening disease or condition
- Autoimmune hemolytic anemia
- Myotoxicity (myositis, myocarditis, and rhabdomyolysis)
- Patients on controlled sodium diet
- Concurrent administration with vemurafenib
- Caution when driving or operating machinery
- Patient counselling information: imARs and fatigue
- Not studied in patients with hepatic impairment
- Not studied in patients with renal impairment
- Pregnancy and nursing women
- Effective contraception in women of reproductive potential
- Close monitoring required: liver function tests, thyroid function test, electrolytes, any signs of imARs

For more information:

Please consult the YERVOY Product Monograph at www.bms.com/assets/bms/ca/documents/productmonograph/YERVOY_EN_PM.pdf for important information relating to adverse reactions, management of imARs, drug interactions, and dosing information, which have not been discussed in this piece.

The Product Monograph is also available by calling us at: 1-866-463-6267.

CI: confidence interval; HR: hazard ratio; mNSCLC: metastatic non-small-cell lung cancer; OS: overall survival; PD-L1: programmed death-ligand 1.

* CheckMate 9LA: a randomized, multicenter, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK tumour aberrations. Patients (N=719) were randomized (1:1) to OPDIVO 360 mg administered intravenously over 30 minutes every 3 weeks in combination with YERVOY 1 mg/kg administered intravenously over 30 minutes every 6 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles.

† Stratified log-rank *p*-value.

‡ Unstratified hazard ratio.

References: 1. OPDIVO Product Monograph. Bristol-Myers Squibb Canada. **2.** YERVOY Product Monograph. Bristol-Myers Squibb Canada. **3.** Paz-Ares L, Ciuleanu T-E, Cobo M, *et al*. First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy in patient with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncology*. 2021;22:198-211.

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Antibody-Drug Conjugates in Breast Cancer: Current Landscape and Future Targets

Jennifer Leigh, MD
Arif Ali Awan, MD

Antibody-drug conjugates (ADCs) have transformed therapeutic options for patients with breast cancer, delivering targeted cytotoxic agents with enhanced efficacy, albeit with systemic toxicity. Since the approval of trastuzumab emtansine in 2012, the ADC landscape has rapidly expanded to include agents targeting HER2, TROP-2, and other novel targets. Currently, four ADCs are approved in breast cancer, showing clinical benefit across HER2-positive, HER2-low, hormone receptor (HR)-positive and triple-negative subtypes. Trastuzumab deruxtecan has demonstrated superior outcomes compared to earlier HER2-targeted ADCs and is the preferred treatment in multiple settings. Anti-TROP-2 ADCs, such as sacituzumab govitecan and datopotamab deruxtecan, have provided improvements in progression-free survival in both triple-negative and HR-positive/HER2-negative disease. Ongoing research is exploring additional targets, such as HER3, Nectin-4, B7-H4, and CD166, with several promising candidates showing efficacy in early phase trials. As ADCs move into earlier lines of therapy and combination regimens, understanding optimal sequencing, toxicity management, and cost considerations will be essential. This review summarizes the current ADC landscape in breast cancer and highlights future directions for this rapidly evolving therapeutic class.

Introduction

Antibody-drug conjugates (ADCs) first entered the breast cancer (BC) treatment paradigm in 2012. In the last few years, ADCs have dramatically changed the treatment landscape in both the curative and advanced setting, leading to significantly improved clinical outcomes for patients with BC.[1,2] ADCs are composed of a monoclonal antibody (mAb), a linker, and a cytotoxic payload.[2] Ideally, the mAb utilized in the ADC targets an antigen highly expressed on tumour cells, with limited expression on normal tissue. The linkers can be cleavable or non-cleavable, and keep the cytotoxic payload attached to the mAb while the ADC is in circulation, and then release a dose of the cytotoxic payload close to the target cells resulting in direct, bystander, and immune-mediated cell killing.[2] In this review, we conducted a search of OVID Medline® from January 1, 1946, to February 25, 2025, along with abstracts from Embase and Cochrane over the last 3 years which retrieved 1,840 unique citations. Using these, we discuss the current landscape of ADC use in BC and highlight future targets and agents under investigation. Currently, four different ADCs are approved by the Food and Drug Administration (FDA) for use in BC (**Figure 1A**), and many novel agents are under investigation as monotherapies or as combinations (**Figure 1B**).[3-6]

Currently Approved ADCs

HER2-positive BC

HER2-positive (HER2+) BC was the first subtype to be targeted by ADCs. Ado-trastuzumab-emtansine (T-DM1) targets HER2 with a non-cleavable linker and anti-microtubule cytotoxic payload, and was first approved for use in the metastatic setting in patients who had prior treatment with taxane and trastuzumab (**Table 1**). This was based on the EMILIA trial comparing T-DM1 to lapatinib + capecitabine (LC), which found both

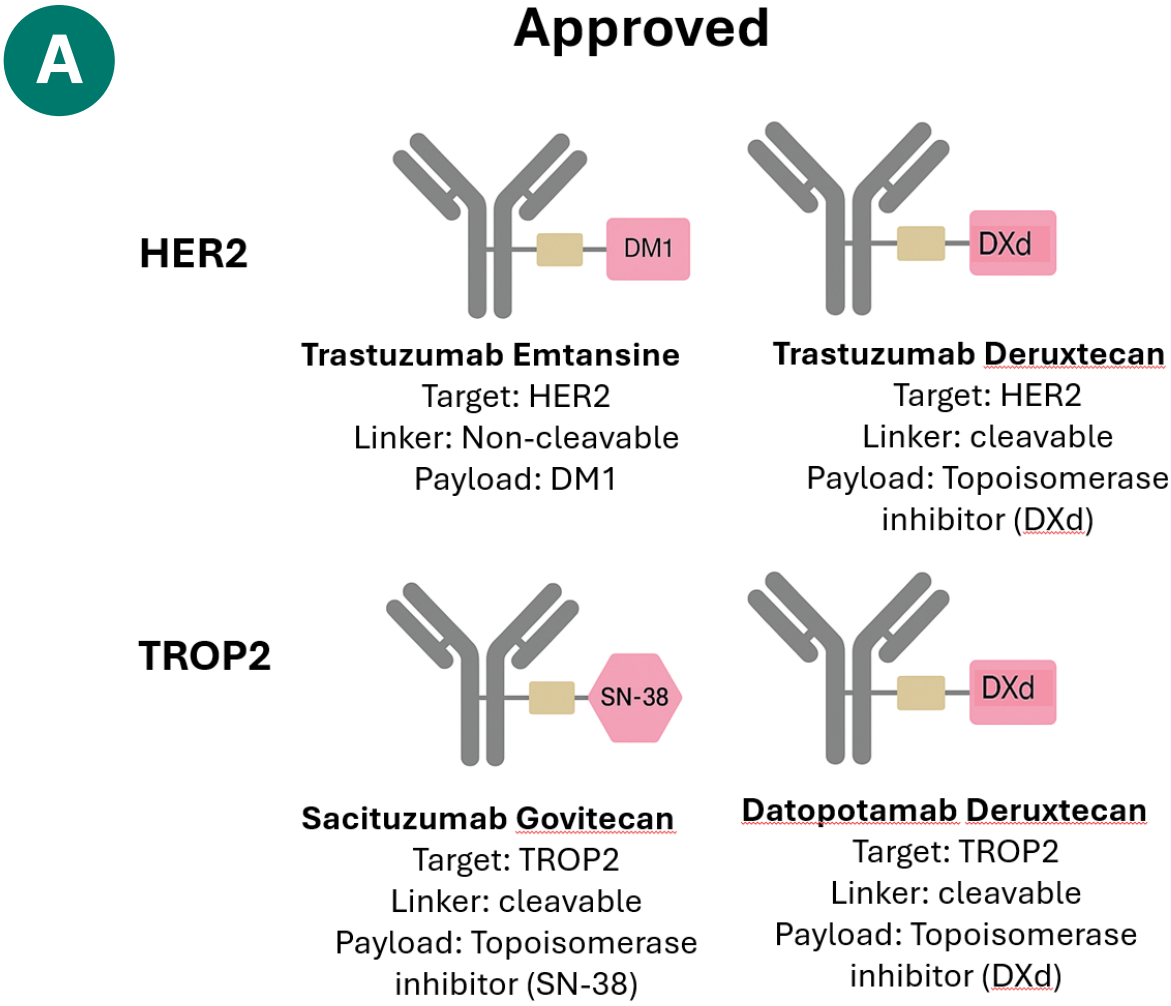

Figure 1A. Approved ADCs for patients with breast cancer; *courtesy of Jennifer Leigh, MD and Arif Ali Awan, MD.*

Abbreviations: ADC: antibody-drug conjugate

improved median progression-free survival (mPFS, 9.6 vs. 6.4 months, HR: 0.65, 95% confidence interval [CI]: 0.55-0.77) and median overall survival (mOS, 29.9 vs. 25.9 months, HR: 0.75, 95% CI: 0.64-0.88).[7] The most common toxicities in this trial were thrombocytopenia and elevated liver enzymes, and rare cardiac dysfunction.[7] The benefit of this therapy was confirmed with the TH3RESA trial, which compared T-DM1 to physician's choice chemotherapy (PCC) in patients who had received prior taxane, trastuzumab, and lapatinib.[8,9] Finally, T-DM1 was shown to be non-inferior to trastuzumab plus a taxane in the first-line setting in the MARIANNE trial; however, the CLEOPATRA regimen of pertuzumab, trastuzumab, and a taxane remains standard of care in this setting.[10,11]

T-DM1 has also been incorporated in the curative setting. The KATHERINE trial compared adjuvant use of T-DM1 with trastuzumab in patients with residual disease after neoadjuvant therapy.[12] This demonstrated improved invasive disease-free survival (iDFS) with 13.7% at 7 years (80.8% vs. 67.1%), and a 4.7% improvement in OS at 7 years (89.1% vs. 84.4%, **Table 1**).[12] Based on these positive results, T-DM1 use has become the standard of care in this setting. T-DM1 has also been studied in patients with stage I HER2+ BC and compared to taxane and trastuzumab. While T-DM1 had a 3-year iDFS of 97.8%

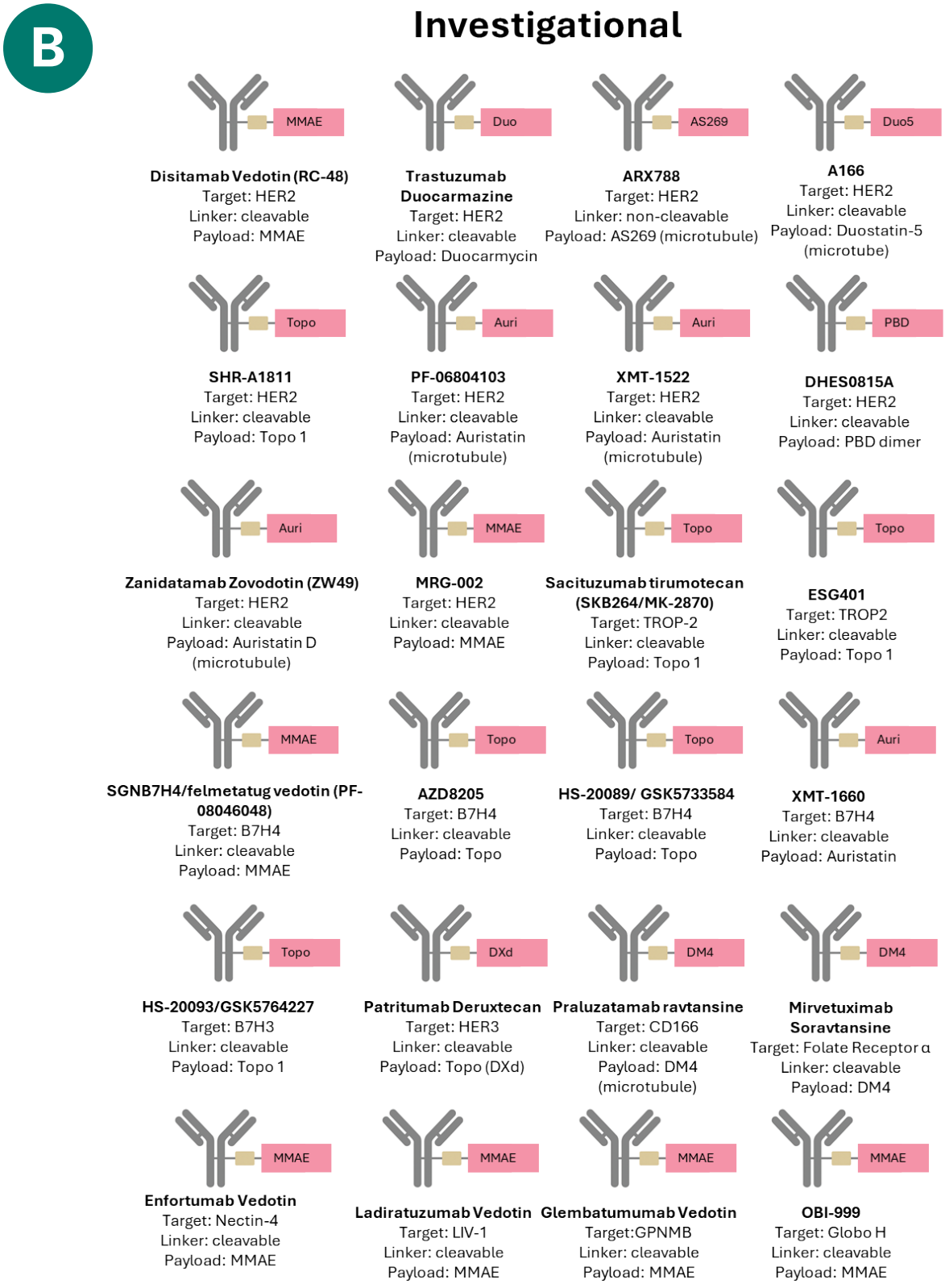

Figure 1B. Investigational ADCs for patients with breast cancer; *courtesy of Jennifer Leigh, MD and Arif Ali Awan, MD.*

Abbreviations: ADC: antibody-drug conjugate

Subtype	ADC	Target	Trial	Setting	Comparator	DFS or PFS	OS	Experimental ADC ORR (%)
HER2+	T-DM1	HER2	KATHERINE	Early BC with residual disease	Trastuzumab	7-year DFS 79.8% (T-DM1) vs 66.2%	7-year 89.1% T-DM1 vs 84.4% Trastuzumab	N/A
			EMILIA	Advanced BC, prior trastuzumab and taxane	Lapatinib + capecitabine	mPFS 9.6 (T-DM1) vs 6.4 months (HR 0.65, 95% CI 0.55-0.77)	mOS 29.9 months (T-DM1) vs 25.9 months (HR 0.75, 95% CI 0.64-0.88)	43.6
			TH3RESA	Advanced BC, prior taxane, trastuzumab and lapatinib	Physician's choice of treatment	mPFS 6.2 (T-DM1) vs. 3.3 months (HR 0.53, 95% 0.42-0.66)	mOS 22.7 months (T-DM1) vs. 15.8 months (HR: 0.68, 95% CI: 0.54-0.85)	31.0
	T-DXd	HER2	DESTINY BREAST 01	Advanced BC, prior TDM1	N/A	mPFS 19.4 months	mOS 29.1 months	62.0
			DESTINY BREAST 02	Advanced BC, prior TDM1	Physician's choice of treatment	mPFS 17.8 (T-DXd) vs. 6.9 months (HR: 0.36, 95% CI: 0.28-0.45)	mOS 39.2 (T-DXd) vs. 26.5 months (HR: 0.66, 95% CI: 0.50-0.86)	70.0
			DESTINY BREAST 03	Advanced BC, prior taxane and trastuzumab	TDM1	mPFS 29.0 (T-DXd) vs. 7.2 months (HR: 0.30, 95% CI: 0.24-0.38)	mOS 52.6 (T-DXd) vs. 42.7 months (HR: 0.73, 95% CI: 0.56-0.94)	78.9
HR+	T-DXd	HER2	DESTINY BREAST 04	Advanced HER2 low BC, one or two prior lines of chemotherapy	Physician's choice of treatment	mPFS 10.1 (T-DXd) vs. 5.4 months (HR: 0.51, 95% CI: 0.4-0.64)*	mOS 23.9 (T-DXd) vs. 17.5 months (HR: 0.64, 95% CI: 0.48-0.86)*	52.6*
			DESTINY-BREAST 06	Advanced HR+, HER2 low BC with progression on endocrine therapy but no chemotherapy	Physician's choice of treatment	mPFS 13.2 (T-DXd) vs. 8.1 months (HR: 0.62, 95% CI: 0.52-0.75)	Data remains immature	56.5
	SG	TROP-2	TROPICS-02	Advanced HR+/HER2- BC, at least one prior ET, taxane, and CDK 4/6 inhibitor, and two to four prior lines of chemotherapy	Physician's choice of treatment	mPFS 5.5 (SG) vs. 4.0 months (HR: 0.66, 95% CI: 0.53-0.83)	mOS 14.4 (SG) vs. 11.2 months (HR: 0.79, 95% CI: 0.65-0.96)	21
	Dato-DXd	TROP-2	TROPION-Breast01	Advanced HR+/HER2-, prior ET, one to two lines of chemotherapy	Physician's choice of treatment	mPFS 6.9 (Dato-DXd) vs. 4.9 months, (HR: 0.63, 95% CI: 0.52-0.76)	Data immature, (HR: 0.84, 95% CI: 0.62-1.14)	36.4
TNBC	SG	TROP-2	ASCENT	Advanced TNBC with ≥2 prior lines of therapy	Physician's choice of treatment	mPFS 4.8 (SG) vs. 1.7 months (HR: 0.41, 95% CI: 0.33-0.63)	mOS 11.8 (SG) vs. 6.9 months (HR: 0.51, 95% CI: 0.33-0.52)	31.0
	T-DXd	HER2	DESTINY BREAST 04	Advanced HER2 low BC, one or two prior lines of chemotherapy	Physician's choice of treatment	mPFS 8.5 (T-DXd) vs. 2.9 months (HR: 0.46, 95% CI: 0.24-0.89)**	mOS 18.2 (T-DXd) vs. 8.3 months (HR: 0.48, 95% CI: 0.24-0.95)**	50.0**

Table 1. Antibody-drug conjugates currently approved for use in breast cancer *courtesy of Jennifer Leigh, MD and Arif Ali Awan, MD.*
* = HR+ group only.
** = TNBC group only.
Abbreviations: ADC: antibody-drug conjugate, **BC:** breast cancer, **CI:** confidence interval, **Dato-Dxd:** datopotamab deruxtecan, **DFS:** disease-free survival, **ET:** endocrine therapy, **HR:** hazard ratio, **HR+:** hormone receptor-positive, **mOS:** median overall survival, **mPFS:** median progression-free survival, **SG:** sacituzumab govitecan, **T-DXd:** trastuzumab deruxtecan, **T-DM1:** ado-trastuzumab-emtansine, **TNBC:** triple-negative breast cancer

(95% CI: 96.3–99.3), it was not associated with fewer clinically relevant toxicities than taxane + trastuzumab.[13]

The second ADC that changed the treatment landscape for HER2+ BC is trastuzumab deruxtecan (T-DXd), which targets HER2 using a cleavable linker and a topoisomerase I cytotoxic payload. The DESTINY-BREAST 01 trial demonstrated activity in patients with advanced HER2+ BC who had previously received T-DM1, with a mPFS of 19.4 months and mOS of 29.1 months, and the most common toxicities were nausea, vomiting, fatigue, myelosuppression, alopecia, and a 2.2% risk of fatal pneumonitis, which is reported as closer to 1% in more recent trials (**Table 1**).[14,15] T-DXd has since been compared to T-DM1 in the Phase III trial DESTINY-BREAST 03, and demonstrated improved mPFS (29.0 vs. 7.2 months, HR: 0.30, 95% CI: 0.24–0.38) and mOS (52.6 vs. 42.7 months, HR: 0.73, 95% CI: 0.56–0.94) as compared to T-DM1, and is now considered the preferred second-line option (**Table 1**).[4] Furthermore, T-DXd has also shown remarkable intracranial activity, challenging the traditional paradigm that these large molecules may not have significant intracranial activity, with 60.7% (95% CI: 50.5–70.8%) of patients with active brain metastases obtaining a confirmed intracranial objective response in the DESTINY-BREAST 12 trial.[16] Several ongoing trials are exploring other indications for T-DXd, including the DESTINY-BREAST 09 trial exploring first-line use (NCT04784715), and the DESTINY-BREAST 05 (NCT04622319) trial exploring adjuvant use in patients with residual disease after neoadjuvant therapy versus T-DM1.

HER2-low/ultralow BC

HER2-low BC is defined as an immunohistochemistry (IHC) score of 1+ or 2+ and negative *in situ* hybridization (ISH), and includes both hormone receptor positive (HR+) and negative (HR-) disease. T-DXd was first approved by the FDA for HER2-low disease following progression on chemotherapy in 2022 (**Table 1**).[2] This was based on results from the DESTINY-BREAST 04 trial, which demonstrated improved mPFS and mOS in comparison to PCC (eribulin, capecitabine, paclitaxel, nab-paclitaxel, and gemcitabine).[17] The trial explored outcomes for patients with HR+ disease and triple-negative BC (TNBC), in addition to the overall cohort. In HR+ patients, mPFS was improved to 10.1 months compared to 5.4 months following PCC treatment (HR: 0.51, 95% CI: 0.4-0.64, **Table 2**). mOS was also improved with T-DXd (23.9 vs. 17.5 months, HR: 0.64, 95% CI: 0.48-0.86). In the subgroup of patients with TNBC, both outcomes demonstrated improvement (mPFS 8.5 vss 2.9 months, HR: 0.46, 95% CI: 0.24-0.89, and mOS 18.2 vs. 8.3 months, HR: 0.48, 95% CI: 0.24-0.95, **Table 1**). Use of T-DXd in HR+/HER2-low and HER2-ultralow (defined as faint HER2 membrane staining in ≤10% of cells, IHC >0 and <1+) patients who have progressed on endocrine therapy (ET) and have not received chemotherapy in the advanced setting, was also recently approved based on improved mPFS in the DESTINY-BREAST 06 trial showing a similar magnitude of mPFS benefit as the DESTINY BREAST 04 trial (**Table 1**).[18]

TNBC

Sacituzumab govitecan (SG) is the first ADC approved for the treatment of metastatic TNBC (mTNBC). It targets TROP-2 and has a cleavable linker and a topoisomerase I cytotoxic payload (**Table 1)**. The Phase III trial ASCENT compared SG to PCC (eribulin, capecitabine, vinorelbine, or gemcitabine) in patients who had received ≥2 lines of treatment.[6] This demonstrated improvement in mPFS (4.8 vs. 1.7 months, HR: 0.41, 95% CI: 0.33–0.63) and mOS (11.8 vs. 6.9 months, HR: 0.51, 95% CI: 0.33–0.52) with neutropenia, diarrhea, nausea, and alopecia being the common side effects. Ongoing trials are exploring the use of SG and datopotomab deruxtecan (Dato-DXd), which also targets TROP-2 and has a cleavable linker and a topoisomerase I cytotoxic payload, in the first-line setting as monotherapy (NCT05382299, NCT05374512) and in addition to pembrolizumab or durvalumab in those with a programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥10 (NCT05382286, NCT06103864). Currently, no ADCs are approved for the curative setting, although their use is being explored in Phase III trials in the neoadjuvant setting and in patients with residual disease after neoadjuvant treatment (NCT06112379, NCT05629585, NCT05633654).[19]

HR+/HER2- BC

SG and Dato-DXd are also used for metastatic HR+/HER2- BC, the most common subtype of BC (**Table 1**). SG is approved in this setting by the US Food and Drug Administration (FDA) and Health Canada in patients who have progressed on endocrine therapy (ET) and two other lines of treatment.[20] Benefit in this setting was demonstrated in the TROPICS-02 trial, which

Target	Drug	Payload	Breast Cancer Subtype	Phase	Design	Sample Size (*n*)	Efficacy	Safety
CD166	**Praluzatamab ravtansine**	Maytansine	Advanced HR+/HER2 and TNBC	Phase II	Evaluate praluzatamab ravtansine monotherapy in cohort A (HR+/HER2-) and cohort B (TNBC)	60 (HR+/HER2 arm) and 55 (TNBC)	• ORR HR+/HER2- 14.9%, and mPFS 11.4 weeks • ORR TNBC <10%	• Blurred vision (42%), nausea (35%), fatigue (35%), diarrhea (25%), peripheral neuropathy (27%), infusion-related reaction (23%)
HER3	**Patritumab Deruxtecan (HER3-DXd)**	Deruxtecan	HER-3 expressing advanced BC	Phase I/II	Dose escalation followed by dose expansion with both 4.8 mg/kg and 6.4 mg/kg doses	182	• HR+/HER2- : ORR 30.1%, mPFS 7.4 months • HER2+: ORR 42.9%, mPFS 11.0 months • TNBC: ORR 22.6%, mPFS 5.5 months	• Grade ≥3 TEAEs were observed in 71.4% of patients • Most common TEAEs were nausea (79.7%), thrombocytopenia (62.1%), neutropenia (61.0%)
			Advanced HR+/HER2- BC who have progressed on CDK 4/6 inhibitor and one line of chemotherapy	Phase II	All patients received HER3-DXd 5.6 mg/kg IV every 3 weeks	99	• ORR 53.5% • mPFS 9.4 months	• Grade ≥3 AEs occurred in 55.6%. Most frequent AEs were nausea (75%), and diarrhea (53%). Six patients developed ILD.
			HR+/HER2- operable BC, Ki67 ≥20% And/or high genomic risk		Randomized to neoadjuvant HER3-DXd +/- letrozole vs standard of care chemotherapy	122	• ORR 70.0% (HER3-DXd) vs 81.3% (HER3-DXd + letrozole) vs 70.8% (chemotherapy) • pCR rate 4.0% (HER3-DXd) vs 2.1% (HER3-DXd) vs 4.2% (chemotherapy)	• Grade ≥3 TEAEs 18.0% (HER3-DXd) vs. 16.7% (HER3-DXd + letrozole) vs 54.2% (chemotherapy)
HER2	**ARX788**	Amberstatin 269	HER2+ advanced BC post-trastuzumab and taxane	Phase II/III	Randomized to ARX788 vs lapatinib + capecitabine	441	• mPFS: 11.3 (ARX788) vs. 8.25 months	• Grade ≥3 TRAEs 41.4%. Most common blurred vision, dry eye, keratopathy, ILD
	Disitamab vedotin	MMAE	HER2+ and HER2-low metastatic mBC with at least one prior line of chemotherapy, and PAM pathway activation	Phase II	Patients received Disitamab vedotin 2 mg/kg IV every 2 weeks	62	• ORR: 42.9% HER2+ and 33.3% HER2 low • mPFS: 5.7 months HER2+ and 5.1 months HER2 low	• Most common Grade ≥3 TRAEs were neutropenia (17.6%), • GGT increase (13.2%), asthenia (11.0%), peripheral neuropathy (5.9%), and neurotoxicity (0.7%)
	DP303c	MMAE	HER2+ advanced solid tumours	Phase I	Dose escalation followed by dose expansion of DP303c every 3 weeks	94 (68 breast cancer)	• ORR: 51.5% for patients with BC • mPFS: 6.4 months for patients with BC	• Most common TRAEs were corneal disease (87.2%), blurred vision (61.7%), dry eye (57.4%), peripheral neuropathy (46.8%), hypertriglyceridemia (44.7%)

Target	Drug	Payload	Breast Cancer Subtype	Phase	Design	Sample Size (*n*)	Efficacy	Safety
	MRG002	**MMAE**	Advanced HER2-low BC	Phase II	Patients received MRG002 2.6 mg/kg every 3 weeks	56	• ORR: 34.7%	• Most common TRAEs were neutropenia (53.6%), leukopenia (48.2%), AST increase (46.4%), alopecia and ALT increase (39.3%)
	SHR-A1811	**Topoisomerase inhibitor**	HER2+ mBC with brain metastases	Phase II	Patients received SHR-A1811 monotherapy or in combination with pyrotinib (Arm 2) or bevacizumab (Arm 3)	25	• ORR: 76% • Intracranial ORR: 84%	• Grade ≥3 TRAEs occurred in 76%. Most common were neutropenia (64%), leukopenia (48%), thrombocytopenia (28%), anemia (28%), nausea (8%)
			Stage II-III HER2+ BC	Phase II	Randomization to neoadjuvant SHR-A1811, SHR-A1811 + pyrotinib, or nab-paclitaxel + carboplatin + trastuzumab + pertuzumab (PCbHP)	265	• pCR: 63.2% monotherapy, 62.5% SHR-A1811 + pyrotinib, and 64.4% PCbHP	• Grade ≥3 TRAEs were 44.8% with monotherapy, 71.6% SHR-A1811 + pyrotinib, and 38.8% PCbHP
	Trastuzumab duocarmazine (T-Duo)	**Duocarmycin**	HER2+ advanced BC	Phase III	Patients randomized to T-Duo every 3 weeks or physician's choice of chemotherapy	437	• mPFS: 7.0 (T-Duo) vs. 4.9 months (HR: 0.64, 95% CI: 0.49-0.84) • mOS: 20.4 (T-Duo) vs. 16.3 months (HR: 0.83, 95% CI: 0.62-1.09) • ORR: 27.8% (T-Duo) vs. 29.5%	• Grade ≥3 TEAEs 52.8%. Most common AEs conjunctivitis, keratitis, fatigue, dry eye, nausea, alopecia, diarrhea, asthenia, decreased appetite
Nectin-4	**Enfortumab vedotin**	**MMAE**	Advanced TNBC and HR+/HER2 BC	Phase II	Patients received EV 1.25 mg/kg day 1, 8, and 15 of a 28 day cycle	87 (42 TNBC, 45 HR+/ HER2-)	• ORR TNBC: 19.0% • ORR HR+/HER2-: 15.6%	• Special interest TRAEs included skin reactions, peripheral neuropathy, and hyperglycemia
TROP-2	**Datopotomab deruxtecan**	**Deruxtecan**	TNBC with active brain metastases	Phase II	Patients received Dato-DXd 6.0 mg/kg every 3 weeks	8	• Intracranial ORR 37.5%	• Main toxicity: fatigue
	Datopotamab deruxtecan	**Deruxtecan**	Advanced TNBC eligible for first line treatment	Phase I/II	Patients received Dato-DXd plus Durvalumab	62	• ORR: 79% • mPFS: 13.8 months	• Most common AEs nausea (65%) and stomatitis (65%). Grade 3 or 4 AEs occurred in 57%. ILD rate 5%.

Target	Drug	Payload	Breast Cancer Subtype	Phase	Design	Sample Size (*n*)	Efficacy	Safety
	ESG401	**SN-38**	First-line advanced TNBC	Phase IB	Patients received ESG401 1 6 mg/kg IV day 1, 8, and 15 of 28 day cycle	23	• ORR 78.6% • Intracranial disease control rate 73%	• Most common TRAEs were leukopenia (65.2%), neutropenia (69.6%), anemia (43.5%), fatigue (21.7%), nausea (43.5%), and vomiting (34.8%)
	ESG401	**SN-38**	mBC	Phase IA/B	Dose escalation followed by dose expansion of ESG401	141 (74 TNBC, 65 HR+/HER2-, HER2+)	• ORR HR+/HER2-: 34.5% • ORR TNBC: first-line: 85.0%, later line: 35.1% • ORR HER2+: 0% • mPFS HR+/HER2-: 7.6 months • mPFS TNBC: 3.9 months later line patients • mPFS HER2+: 3.8 months	• Most common Grade ≥3 TRAE was neutropenia and leukopenia. No new safety signals
	Sacituzumab tirumotecan (SKB264.MK-2870)	**Belotecan-derivative**	Advanced TNBC, receipt of two or more prior lines of therapy	Phase III	Patients randomized to SKB264 or physician's choice of chemotherapy	263	• mPFS by BICR 5.7 (SKB264) vs 2.3 months (HR 0.31, 95% CI 0.22-0.45) • mOS: NR for SKB264 vs 9.4 months (HR: 0.53, 95% CI: 0.36-0.78) • ORR by BICR 43.8% (SKB264) vs 12.8%	• Most common Grade ≥3 TRAE with SKB264 were neutropenia (32.3%), anemia (27.7%), and leukopenia (25.4%)
B7-H4	**SGNB7H4**	**MMAE**	Metastatic breast cancer, at least 1 cytotoxic prior treatment, including taxane	Phase I	Dose escalation	25 patients with breast cancer	• ORR 28% (7/25)	• Most common TRAE Grade ≥3 Neutropenia (17%), Fatigue (4.9%), No Grade 3 sensory neuropathy
	HS-20089/ GSK5733584	**Topoisomerase inhibitor**	Metastatic breast cancer, at least 1 cytotoxic prior treatment	Phase I	Dose escalation	28 patients with TNBC	• ORR 28.6 % in 28 patients	• Most common TRAE Grade ≥3 WBC decreased (36%), Anemia (24%), nausea/ vomiting (<5)

Table 2. Novel ADC targets being explored for breast cancer; *courtesy of Jennifer Leigh, MD and Arif Ali Awan, MD.*

Abbreviations: ADC: antibody-drug conjugate, **AE:** adverse event, **BC:** breast cancer, **BICR:** blinded independent central reviews, **CI:** confidence interva, **Dato-Dxd:** datopotamab deruxtecan, **ET:** endocrine therapy, **EV:** enfortumab vedotin, **GGT:** gamma -glutamyl transferase, **HR:** hazard ratio, **HR+:** hormone receptor-positive, **ILD:** interstitial lung disease, **IV:** intravenous, **mBC:** metastatic breast cancer, **mOS:** median overall survival, **mPFS:** median progression-free survival, **NR:** not reached, **ORR:** objective response rate, **PAM:** phosphoinositide 3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR), **pCR:** pathological complete response, **TNBC:** triple-negative breast cancer, **TEAE:** treatment-emergent adverse events, **TRAE:** treatment-related adverse events, **WBC:** white blood cell

demonstrated statistically significant improvement in both mPFS (5.5 vs. 4.0 months, HR: 0.66, 95% CI: 0.53-0.83) and mOS (14.4 vs. 11.2 months, HR: 0.79, 95% CI: 0.65-0.96) compared to PCC.[20] Use of Dato-DXd after progression on both ET and chemotherapy was explored in the TROPION-Breast01 study, which compared Dato-DXd to PCC, and demonstrated improved mPFS for Dato-DXd (mPFS 6.9 vs. 4.9 months, HR: 0.63, 95% CI: 0.52–0.76); however, OS data remain immature. Common or pertinent side effects of this therapy are mucositis, nausea/vomiting, fatigue, alopecia, and ocular toxicity. Approval by the FDA for use in metastatic HR+/HER2 BC after progression on ET and chemotherapy was granted in early 2025; however, it is not yet approved by Health Canada.

The Future of ADCs in BC – Novel Drugs and Targets

Human Epidermal Growth Factor Receptor 3 (HER3/Erbb3)

A promising target in BC is HER3, a tyrosine kinase receptor belonging to the HER family. HER3 can form heterodimers with HER2 and/or epidermal growth factor receptor (EGFR), and activate critical pathways including the PI3K/AKT pathway and mitogen-activated protein kinase (MAPK) signaling.[21,22] Patritumab deruxtecan (HER3-DXd) is a first-in-class ADC targeting HER3 with a cleavable linker and a topoisomerase I cytotoxic payload (DXd). HER3-Dxd's activity in HER3-expressing advanced BC was explored in the Phase I/II trial U31402-A-J101 in patients who had received ≥2 lines of prior cytotoxic therapy. The study demonstrated an objective response rate (ORR) of 30.1% in HR+/HER2-, 42.9% in HER2+, and 22.6% in TNBC (**Table 2**).[23] The most common adverse events (AEs) were nausea and cytopenias. ICARUS-BREAST01 is an ongoing Phase II trial exploring the use of HER3-Dxd in advanced HR+/HER2- disease that was previously treated by a CDK 4/6 inhibitor and ≥1 line of chemotherapy, and found an ORR of 53.5% and mPFS 9.4 months.[24] Finally, SOLTI VALENTINE is an ongoing Phase II neoadjuvant study exploring the use of HER3-DXd +/- letrozole compared to standard of care chemotherapy in HR+/HER2- operable BC with Ki67 ≥20% and/or high genomic risk. Preliminary results demonstrate activity (ORR: 70.0% HER3-DXd vs. 81.3% HER3-DXd + letrozole vs. 70.8% chemotherapy, **Table 2**).[25,26]

HER2

Several novel ADCs targeting HER2 are currently under investigation (**Table 2**). Trastuzumab duocarmazine (T-Duo) targets HER2 and has a cleavable linker with a DNA alkylating agent as the cytotoxic payload, and was studied in the Phase III TULIP trial in patients with advanced HER2+ BC after ≥2 HER2-targeted therapies in comparison to PCC (**Table 2**).[27] The mPFS was improved by 2.1 months with T-Duo (7.0 vs. 4.9 months, HR: 0.64, 95% CI: 0.49-0.84), although clinically significant ocular toxicity limits its use.

ARX788 targets HER2 and has a tubulin inhibitor as the cytotoxic payload connected to the mAb with a non-cleavable linker, and has demonstrated activity in advanced HER2+ BC (**Table 2**). The ACE-Breast 02 study evaluated use in patients with HER2+ BC who had been treated with prior trastuzumab and taxane, and demonstrated mPFS of 11.3 months vs. 8.3 months for patients treated with LC (HR: 0.64, 95% CI: 0.49-0.82).[28] The mOS has not yet been reached in this study. Grade 3 or higher treatment-related adverse events (TRAEs) were similar in both groups (41.4% for ARX788 and 40.0% for LC). Multiple ongoing trials explore the use of ARX788 in HER2-low disease and in patients with brain metastases.

Disitamab vedotin (RC48) targets HER2 and has a cleavable linker attached to a microtubule inhibitor as the cytotoxic payload. It has demonstrated efficacy in HER2+/HER2-low pre-treated metastatic BC (mBC). A Phase I/II trial demonstrated ORRs of 42.9% (HER2+) and 33.3% (HER2-low), and mPFS of 5.7 (HER2+) and 5.1 months (HER2-low).[29]

Three other HER2-targeted ADCs in development are DP303c, MRG002, and SHR-A1811. DP303c is an ADC being studied and developed in China, and studies showed an ORR of 51.5% in patients with mBC.[30] MRG002 has demonstrated an ORR of 34.7% in advanced HER2-low BC that has progressed on standard therapies.[31] Finally, SHR-A1811 is being studied in an ongoing Phase II trial of pre-treated HER2+ BC with radiotherapy-naïve brain metastases not requiring immediate treatment. This study showed an intracranial-ORR (IC-ORR) of 84% and ORR of 76%. Grade 3 or 4 TRAEs occurred in 76% of patients, and were predominantly cytopenias and nausea.[32] There is also evidence for the efficacy of SHR-A1811 in the neoadjuvant setting in stage II/III HER2+ BC, with an impressive

63.2% pathological complete response (pCR) rate when used as monotherapy.[33] A summary of novel HER2-targeting ADCs can be found in **Table 2**.

TROP-2

Dato-DXd has also been studied in TNBC. The Phase Ib/II BEGONIA trial exploring treatment options for first-line mTNBC includes an arm of durvalumab + Dato-DXd, and has identified an ORR of 79% with mPFS of 13.8 months (**Table 2**).[34] Sacituzumab tirumotecan (SKB264/MK-2870) targets TROP-2 and has a topoisomerase I inhibitor as cytotoxic payload connected using a cleavable linker. In previously treated mTNBC, it demonstrated an ORR of 42.4% and a mOS of 16.8 months in a Phase II trial. In patients with high TROP-2 expression, the ORR was 53.1% and mOS was not reached.[35] A Phase III trial exploring its use in the third-line or later is underway, as well as a Phase II study exploring first-line use with an anti-PD-L1 mAb, and in the curative setting for patients with TNBC with residual disease (NCT06393374). Finally, ESG401 also targets TROP-2 and has a topoisomerase I inhibitor as the cytotoxic payload, and is being explored in advanced BC of all subtypes. In the pre-treated setting, ORRs of 34.5%, 35.1%, and 0% were detected for HR+/HER2-, TNBC, and HER2+ subtypes, respectively.[36] In the first-line treatment of TNBC, the ORR was 78.6% with evidence of central nervous system (CNS) activity (**Table 2**).[37]

Nectin-4

Nectins are important mediators for cell-cell adhesion, and Nectin-4 gene amplification has been observed in BC.[38] Enfortumab vedotin (EV) targets Nectin-4 with a mAb that is connected to a microtubule inhibitor payload with a cleavable linker. Its use is currently being explored in the ongoing Phase II trial EV-202, which has two BC-specific cohorts (HR+/HER2- and TNBC) who have previously received a taxane or anthracycline.[39] Preliminary results demonstrate activity, with an ORR of 19.0% in patients with TNBC and 15.6% in those with HR+/HER2- disease. Toxicities are in line with those previously observed with EV, and include rash, peripheral neuropathy, and hyperglycemia.

B7-H4

B7-H4 is an immune checkpoint ligand upregulated in breast cancer and expressed at low levels in normal tissue. SGNB7H4/felmetatug vedotin (PF-08046048) targets B7-H4 and has a microtubule inhibitor cytotoxic payload.[40] The ORR for patients with BC was 28% (7/25) with common toxicities being fatigue, nausea, and neuropathy. HS-20089/GSK5733584 targets B7-H4 and has a topoisomerase I inhibitor cytotoxic payload, and has demonstrated an ORR of 28.6% in 28 patients with TNBC, with myelosuppression and nausea being the most common toxicities.[41] Other ADCs targeting B7-H4, such as AZD8205 and XMT-1660, and an ADC targeting B7-H3, another checkpoint from the same family (HS-20093/GSK5764227), are being assessed in Phase I trials.

CD166

CD166 is a transmembrane type-1 glycoprotein involved in cell adhesion and migration that is present in healthy and tumour tissue.[42] Praluzatamab ravtansine (CX-2009) is a CD166 targeting probody drug conjugate which uses a cleavable linker to connect a microtubule inhibitor cytotoxic payload, in which the antigen-binding site is masked, thus reducing healthy tissue binding.[43] An ongoing Phase II trial evaluating its use in pre-treated advanced HR+/HER2 and TNBC has demonstrated an ORR of 14.9% in the HR+/HER2- cohort with a mPFS of 11.4 months, and an ORR of <10% for TNBC (**Table 2**).[44] Common toxicities included blurred vision, nausea, fatigue, diarrhea, peripheral neuropathy, and infusion-related reactions.

Conclusions

ADCs have dramatically changed the landscape of BC treatment, and have led to significant gains in clinical outcomes. All four currently approved ADCs are utilized in the metastatic setting, and T-DM1 is also approved for curative intent use. Several novel drugs are under development targeting HER2 and TROP-2, as well as exciting novel targets, including HER3, nectin-4, B7-H4, and CD166. It is anticipated that the indication and use of ADCs in BC will continue to expand in metastatic and curative settings as single-agent and in combinations with increasing need for evidence-based guiding of ADC sequencing, rationale combinations, toxicity management, and cost implications for the healthcare systems.

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Perioperative Treatment Strategies for Lung Cancer in 2025: A Paradigm Shift

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Perioperative management of resectable non-small cell lung cancer (NSCLC) has evolved significantly with the integration of immune checkpoint inhibitors and targeted therapies. This review synthesizes current evidence from key clinical trials, highlighting the improved survival outcomes achieved with neoadjuvant and perioperative chemoimmunotherapy in oncogene-wildtype NSCLC, as well as adjuvant tyrosine kinase inhibitors (TKIs) in epidermal growth factor receptor (EGFR)- and anaplastic lymphoma kinase (ALK)-altered tumours. While neoadjuvant immunotherapy has demonstrated high pathological response rates and long-term survival benefits, perioperative strategies may offer added value in selected subgroups. The ADAURA and ALINA trials have established adjuvant osimertinib and alectinib as new standards of care in oncogene-driven disease. Unresolved questions remain regarding optimal treatment sequencing, duration, and patient selection. Emerging tools such as circulating tumour DNA and artificial intelligence hold promise for refining risk stratification and guiding individualized treatment approaches.

Introduction

Lung cancer remains a leading cause of cancer-related mortality, with surgery offering curative potential for early-stage resectable non-small cell lung cancer (NSCLC).[1] Approximately 25–30% of patients present with resectable disease, yet up to 55% experience recurrence despite surgery. Historically, adjuvant cisplatin-based chemotherapy provided modest survival benefits, with a 5-year absolute survival benefit of 5.4% for stage II–III disease.[2] Perioperative therapy—encompassing neoadjuvant, adjuvant, or combined approaches—aims to eradicate micrometastases and improve long-term outcomes. The integration of immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) into perioperative regimens has redefined standards of care, enabling tailored approaches based on molecular profiling.[3] This review evaluates the latest evidence shaping perioperative strategies for both subgroups.

NSCLC Without Oncogene Addiction

Adjuvant Treatment

Adjuvant immunotherapy has significantly advanced the treatment landscape for resectable NSCLC. Two pivotal studies, the IMpower010 and PEARLS/KEYNOTE-091 trials, have reshaped current clinical practice by demonstrating the efficacy of ICIs following mandatory platinum-doublet chemotherapy. The IMpower010 trial evaluated adjuvant atezolizumab in patients with stage II–IIIA NSCLC following platinum-based chemotherapy, with treatment given for one year. This study revealed substantial benefits in disease-free survival (DFS) and overall survival (OS) among programmed cell death ligand 1 (PD-L1)-positive populations, with a DFS hazard ratio (HR) of 0.70 for patients with PD-L1 expression of ≥1% and an impressive HR of 0.43 for those with PD-L1 expression of ≥50%.[4] Additionally, the OS was significantly improved, with HRs of 0.71 for PD-L1 expression of ≥1% and 0.43 for PD-L1 expression of ≥50%.[5] These

compelling results led to regulatory approvals from the US Food and Drug Administration (FDA) for atezolizumab in patients with PD-L1 expression of ≥1% and from the European Medicines Agency (EMA) for those with PD-L1 expression of ≥50%. In contrast, the PEARLS/KEYNOTE-091 trial assessed pembrolizumab as an adjuvant therapy in stage II-III NSCLC, regardless of PD-L1 expression. Pembrolizumab demonstrated a DFS improvement in the overall population, achieving an HR of 0.76, which resulted in its approval by both the FDA and EMA for stage II-III NSCLC irrespective of PD-L1 status.[6] With discordance to the above studies, the more recent CCTG BR31 trial investigated adjuvant durvalumab in patients with PD-L1 expression of ≥25%; however, it did not show a significant DFS benefit.[7] A potential explanation for this discrepancy lies in the superior performance of the control arm in CCTG BR31, which reported a DFS of 54 months compared to 37 months in the IMpower010 study and 42 months in the PEARLS/KEYNOTE-091 trial, possibly reflecting differences in surgical quality.

Neoadjuvant and Perioperative Treatment

Neoadjuvant and perioperative strategies have significantly advanced the treatment landscape for resectable NSCLC. **Table 1** summarizes the neoadjuvant and perioperative trials with key results.

The CheckMate 816 trial remains the only Phase III trial evaluating an exclusively neoadjuvant approach, combining nivolumab with chemotherapy, which demonstrated a 37% reduction in the risk of disease recurrence or death (HR: 0.63; p=0.0052) and a 24.0% pathologic complete response (pCR) rate versus 2.2% with chemotherapy alone.[8] Four-year follow-up data revealed sustained event-free survival (EFS) benefits, and a recent news release confirmed a statistically significant improvement in OS.[9,10]

Similarly, the CheckMate 77T trial evaluated a perioperative strategy, adding one year of adjuvant nivolumab to neoadjuvant nivolumab-chemotherapy, and achieved a 42% reduction in EFS risk (HR: 0.58; 95% confidence interval [CI]: 0.42–0.81) and a 25.3% pCR rate versus 4.7% with neoadjuvant chemotherapy alone.[11]

In the absence of head-to-head trials comparing neoadjuvant to perioperative nivolumab, a cross-trial analysis suggested EFS improvement of a perioperative over a neoadjuvant-only approach, particularly in patients without pCR and PD-L1 <1% subgroups (HR: 0.38).[12] However, in this study patients were censored from surgery rather than being analyzed using a full intention-to-treat approach. It included only those who received at least one cycle of adjuvant nivolumab, excluding approximately 20% of patients from the CheckMate 77T trial who did not proceed to adjuvant treatment and had a poorer overall prognosis. This selection bias favoured the perioperative strategy by artificially enhancing its outcomes, thereby reducing the reliability of the analysis.

An individual patient data (IPD) meta-analysis of prospective clinical trials evaluating neoadjuvant or perioperative chemoimmunotherapy demonstrated that patients achieving a major pathological response or pCR had significantly improved EFS. However, EFS was similar between patients treated in experimental arms that included adjuvant immunotherapy and those who received neoadjuvant treatment alone.[13]

The KEYNOTE 671 trial, which utilized perioperative pembrolizumab, demonstrated both EFS (HR: 0.59) and OS benefits (HR: 0.63), with 48-month OS rates of 68.0% versus 56.7% compared to placebo.[14]

The AEGEAN trial is a Phase III study investigating perioperative durvalumab with neoadjuvant chemotherapy in resectable stage II-IIIB NSCLC. The combination significantly improved EFS (HR: 0.68) and achieved a higher pCR rate (17.2% vs. 4.3%) compared to chemotherapy alone, with a manageable safety profile.[15]

These studies have had a practice-changing impact on the management of resectable NSCLC. The FDA has approved nivolumab with platinum-doublet chemotherapy as a neoadjuvant option, as well as pembrolizumab and durvalumab for perioperative use. Similarly, Health Canada has approved nivolumab with chemotherapy for neoadjuvant treatment and pembrolizumab in a perioperative regimen. However, the role of neoadjuvant chemoimmunotherapy across different stages of resectable NSCLC remains a topic of debate. While the International Association for the Study of Lung Cancer (IASLC) community reached a consensus on recommending its use for stage IIIA and IIIB resectable lung cancer, regardless

Trial name	Phase	Regimen	Key findings	pCR Rate
CheckMate 816[9]	III	Neoadjuvant nivolumab + chemotherapy	EFS HR: 0.63 (37% risk reduction) OS significant improvement (numbers not yet released)	24% vs. 2.2%
CheckMate 77T[11]	III	Perioperative nivolumab + chemotherapy	EFS HR: 0.58 (42% risk reduction)	25.3% vs. 4.7%
KEYNOTE-671[14]	III	Perioperative pembrolizumab + chemotherapy	EFS HR: 0.58 OS HR: 0.63 (48-month OS: 68% vs. 56.7%)	18.1% vs. 4.0%
AEGEAN[15]	III	Perioperative durvalumab + chemotherapy	EFS HR 0.68; OS trends pending	17.2% vs. 4.3%
IMpower010[5]	III	Adjuvant atezolizumab post-chemo	DFS HR: 0.66 (PD-L1 ≥1%)	N/A
KEYNOTE-091[6]	III	Adjuvant pembrolizumab post-chemotherapy	DFS HR: 0.76 (all comers)	N/A
NADIM II[18]	II	Neoadjuvant nivolumab + chemotherapy → adjuvant nivolumab	3-year OS: 81.9% vs. 55.7%	36.8% vs. 6.9%
Neotorch[19]	III	Perioperative toripalimab + chemotherapy	EFS HR: 0.40	24.8% vs. 1.0%
RATIONALE-315[20]	III	Perioperative tislelizumab + chemotherapy	EFS HR: 0.56	MPR of 56% vs. 15%
SAKK 16/14[21]	II	Neoadjuvant chemotherapy → durvalumab	MPR: 60%	18.2%

Table 1. Key Perioperative Immunotherapy Trials in NSCLC; *courtesy of Ramy Samaha, MD, Jonathan Spicer, MD, and Normand Blais, MD.*

Abbreviations: pCR: pathologic complete response, **EFS:** event-free Survival, **HR:** hazard ratio, **MPR:** major pathologic response, **N/A:** not available, **OS:** overall survival, **DFS:** disease-free survival

of PD-L1 expression, no consensus was achieved for stage II.[16] Support for neoadjuvant chemoimmunotherapy in stage II NSCLC comes from a meta-analysis by Sorin et al., which demonstrated a significant improvement in EFS, with an HR of 0.71 for stage II and 0.54 for stage III. In this analysis, the benefit was observed across all PD-L1 expression groups, with HRs of 0.74 for PD-L1 <1%, 0.56 for PD-L1 1–49%, and 0.40 for PD-L1 >50%.[17]

NSCLC With Oncogene Addiction

Epidermal Growth Factor Receptor (EGFR)-Mutant NSCLC

Before the introduction of targeted therapies for early-stage lung cancer, studies showed no difference in prognosis between patients with an EGFR mutation and those with wild-type EGFR.[22]

The ADAURA trial is a Phase III study that assessed the role of adjuvant osimertinib in EGFR-mutant NSCLC. It included patients with

stage IB (≥3 cm), II, and IIIA disease (7th TNM classification), with 60% receiving adjuvant chemotherapy before randomization to osimertinib or placebo for three years. The trial's primary endpoint, DFS in patients with stage II–III disease, showed that osimertinib significantly reduced recurrence with an HR of 0.23. The benefit extended across all enrolled patients (stage IB–IIIA) with an HR of 0.27. Additionally, OS improved across all stages, both in patients who received adjuvant chemotherapy and those who did not.

One key advantage of adjuvant osimertinib is its ability to lower the incidence of brain metastases, indicating a potential shift in the natural history of the disease. However, discontinuing treatment increases the risk of brain progression, implying that osimertinib may delay rather than eliminate recurrence. Furthermore, at the time of progression, only 43% of patients in the placebo arm received osimertinib, despite it being the standard treatment for metastatic EGFR-mutant NSCLC, reflecting limited crossover in the trial.

In summary, the ADAURA trial established adjuvant osimertinib as an effective strategy for reducing recurrence and improving survival in early-stage EGFR-mutant NSCLC, thus leading to its FDA approval in December 2020 and Health Canada approval in April 2021. However, questions remain regarding the optimal duration of therapy, long-term outcomes, and whether the treatment is truly curative or primarily delays disease progression(23–25).[23-25]

The NeoADAURA trial is an ongoing study evaluating osimertinib alone or in combination with chemotherapy in the neoadjuvant setting.[26]

ALK-Altered NSCLC

The Phase III ALINA trial investigated the use of adjuvant alectinib in patients with ALK-positive NSCLC. The study enrolled individuals with stage IB (≥4 cm), II, and IIIA disease, who were randomized to receive alectinib for two years compared to adjuvant chemotherapy. The primary endpoint, DFS in stage II–III patients, showed statistically significant improvement in the alectinib arm with an HR of 0.24. This benefit extended across all disease stages (IB–IIIA). In this trial, the OS data is not yet mature for analysis. Additionally, 76% of patients in the chemotherapy arm received an ALK-TKI upon progression, which may impact the long-term survival outcomes of this trial.[27]

Therefore, the ALINA trial confirmed the effectiveness of adjuvant alectinib in improving DFS in stage II-III ALK-positive NSCLC, thus leading to its FDA approval on April 18, 2024, and Health Canada approval on June 27, 2024.

The ALNEO trial is a Phase II study investigating the role of alectinib in the perioperative setting, with two neoadjuvant cycles and 24 adjuvant cycles. The primary endpoint is major pathologic response (MPR).[28]

Unmet Needs

The optimal sequencing of systemic therapy in resectable NSCLC remains an open question. Specifically, whether perioperative strategies offer superior outcomes compared to pure neoadjuvant approaches is yet to be determined. The ongoing ETOP 25–23 ADOPT-Lung trial is designed to address this issue by assessing the added value of adjuvant immunotherapy with durvalumab following neoadjuvant chemoimmunotherapy, focusing on its impact on DFS in patients with completely resected stage IIB–IIIB (N2) NSCLC. However, as the trial is still in the recruitment phase, definitive results may emerge at a time when the standard of care has already evolved.[29]

Current treatment decisions are primarily guided by clinical staging, which does not account for the presence of micrometastatic disease—a potential driver of recurrence. This raises the question whether biological markers could enable a more personalized therapeutic approach. Circulating tumour DNA (ctDNA) has emerged as a promising tool for stratifying patients, particularly in identifying those who may be candidates for treatment de-escalation. Nevertheless, the lack of standardized assays and the limited sensitivity—often leading to high false-negative rates—limit its standalone clinical utility. Molecular residual disease (MRD) assessment has shown promise in identifying patients with a high likelihood of cure, especially among those with consistently undetectable ctDNA over time.[30] Yet, as demonstrated in the AEGEAN trial, up to 20% of patients who achieved ctDNA clearance still experienced disease recurrence, underscoring its limitations as a definitive predictor of cure. Importantly, the persistence of detectable ctDNA has been associated with poor outcomes and may help identify patients who could benefit from treatment intensification.[31] Further supporting this approach, a post-hoc analysis of the ADAURA trial

suggested that ctDNA-based MRD monitoring could anticipate disease recurrence, particularly after discontinuation of adjuvant osimertinib. In most cases, MRD detection preceded DFS events, indicating its potential to guide extended adjuvant therapy in selected patients.[32] In summary, while MRD assays offer high specificity, their suboptimal sensitivity limits their current role in guiding treatment de-escalation strategies.

Moreover, artificial intelligence (AI) can play a major role in treatment decisions. Deep learning algorithms have demonstrated high accuracy in predicting post-surgical disease progression, offering potentially valuable insights for clinical decision-making following resection.[33]

Conclusion and Future Directions

The landscape of early-stage non-small cell lung cancer (NSCLC) treatment continues to evolve, presenting several challenges. One key issue is the lack of standardized guidelines and the need for a unified approach to diagnosis and treatment. As diagnostic precision improves, the creation of smaller molecular subgroups complicates clinical trial enrollment and treatment selection. Additionally, overlapping therapeutic strategies may lead to competing options for similar patient populations, raising questions about how best to determine optimal treatment pathways. Additionally, the financial burden associated with longer and more complex treatments should not be overlooked, as it may impact treatment accessibility and patient adherence.

To standardize the management of operable stage II/III NSCLC across Canada, a set of Canadian consensus recommendations has been published to provide evidence-based guidance for clinical practice.[34]

Looking ahead, AI could play a key role in refining treatment selection. Advanced predictive models may help clinicians determine which emerging therapies offer the greatest benefit for individual patients, enabling more precise and effective treatment decisions in an increasingly complex therapeutic landscape.

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Treatment of Neuroendocrine Tumours: Approach of GEP-NETS

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Neuroendocrine tumours (NETs) represent a rare entity, with various anatomic primary tumour sites, three different grades, a functional or non-functional status, and differences in somatostatin receptor expression, making NETs a heterogeneous disease. The management of these tumours is challenging and varies from a simple watch-and-wait strategy to more complex multi-modality treatment combinations. The choice of treatments depends on the previously mentioned factors. NETs most frequently arise from the gastro-entero-pancreatic (GEP) tract. The article reviews the classification, diagnosis, and staging of well-differentiated GEP-NETs, and discusses different therapeutic options.

Introduction

Neuroendocrine tumours (NETs) derive from neuroendocrine cells that are disseminated in the body, and most frequently arise from the gastro-entero-pancreatic (GEP) and bronchopulmonary tracts. It is a rare neoplasm representing 1–2% of all digestive cancers. The majority of NETs are sporadic, and about 20% of cases are part of a hereditary syndrome. GEP-NETs represent about 60% of NET localizations and are most frequently detected in the midgut and, more specifically, in the small intestine (SI). The incidence has increased particularly in the small bowel and rectum, primarily due to incidental diagnosis upon screening endoscopic procedures.[1] The World Health Organization (WHO) classification, updated in 2022, separates neuroendocrine neoplasms (NENs) into well-differentiated NETs and poorly differentiated neuroendocrine carcinoma (NEC).[2] NETs, representing 80 to 90% of NEN, are divided into three grades based on mitotic count and the Ki67 proliferative index (**Table 1**). NETs are often indolent, with a median overall survival (OS) of 9.3 years.[1] Prognosis depends on the grade, primary site, and extent of the disease. Localized and G1 NETs are associated with the longest OS (up to 30 years for localized G1 appendix NETs). Pancreatic NETs (pNETs) have a less favourable prognosis than SI-NETs. In this article, we will review the classification, diagnosis, and staging of well-differentiated GEP-NETs, and discuss the different therapeutic options.

Diagnosis and Staging

Diagnosis of GEP-NETs may be an incidental finding or suspected from clinical symptoms (e.g., bowel obstruction, diarrhea, flushing). NENs produce hormones in about 30–45% of cases[3,4] and symptoms are related to the type of hormone secreted (e.g., insulinoma, gastrinoma, glucagonoma, vasoactive intestinal peptide [VIP]oma, somatostatinoma). Carcinoid syndrome (CS), a result of serotonin and other vasoactive substance secretion (e.g., tachykinins, prostaglandins), is characterized by flushing, diarrhea, and right-sided valvular heart disease. It is particularly associated with liver metastasis since it bypasses the hepatic metabolism that inactivates the hormones.[5] CS has been associated with shorter survival.[4]

Histological diagnosis based on surgical specimen or core biopsy is essential for pathological diagnosis and classification of NENs. It is important to keep in mind that NENs are heterogeneous, even within the same tumour or between different lesions, and this may evolve over time. Intra-tumoural heterogeneity can be detected in up to 30% of NENs, especially in tumours with Ki67 expression >10% and sized ≥2 cm. Inter-tumoural heterogeneity, i.e., between different locations, is the result of molecular alterations–some trials reported a higher Ki67 in metastases than primary tumours— and is related to tumour size >4 cm.[6]

Grade		Mitotic index (*/10 HPF*)	Ki67 index (*%*)
Well-differentiated NEN	G1 - low	<2	<3
	G2 - intermediate	2–20	3–20
	G3 - high	>20	>20
Poorly-differentiated NEN = NEC	G3	>20	>20

Table 1. WHO 2022 classification of neuroendocrine neoplasms of the gastroenteropancreatric system[2]; *courtesy of Nathalie Baudoux, MD and Mustapha Tehfe, MD, MSC.*

Abbreviations: HPF: high-power field, **NEC:** neuroendocrine carcinoma, **NEN:** neuroendocrine neoplasm, **WHO:** World Health Organization

Measurement of 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA), a metabolic product of serotonin, has an excellent 90 percent sensitivity and specificity for carcinoid syndrome. However, the sensitivity is low in the absence of CS.[7] Dosage of chromogranin A (CgA), a hormonally inactive glycoprotein secreted by neuroendocrine cells, is generally not recommended for follow-up, mainly because of a lack of specificity. False positive results were reported due to drugs (proton pump inhibitors), food, non-oncologic comorbidities (e.g., renal failure, atrophic gastritis, pancreatitis), and malignancies (e.g., hepatocellular carcinoma, breast and colon cancers).[8]

Diagnostic imaging should combine anatomical and functional modalities. Regular computed tomography (CT)-scans are essential for staging and follow-up. Well-differentiated NETs express the somatostatin receptor (SSTR) on the cell surface in about 80% of cases. Nuclear medicine modalities have a major role in diagnosis and staging and represent a new therapeutic option. The type of positron emission tomography (PET) to be used depends on the grade of the tumour. ^{68}Ga-DOTATATE-PET, in combination with CT, is the modality of choice for low-grade and differentiated tumours.[9] Considering the previously discussed tumoural heterogeneity, for G2/G3 NETs, both ^{68}Ga-DOTATATE-PET and fluorodeoxyglucose (FDG)-PET may be indicated to separate low-grade lesions from poorly differentiated ones.[10] In case of metachronous metastases or unexpected progression, a new biopsy could be considered.

Treatment

Surgery

Localized Well-differentiated G1&G2 NETs

For well-differentiated G1 and G2 NETs, surgery is the treatment of choice. The modality and extent of surgery depend on the site and size of the tumour, the local invasiveness, and the risk of lymph node metastasis.[11] An endoscopic resection for small size (<1 cm) duodenal, rectal, and type 1 and 2 gastric NETs is a valid option. Non-functional pancreatic NETs sized 2 cm or smaller generally have an indolent course for which an observation strategy may be considered.[12] For young patients, avoiding long-term surveillance with multiple imaging tests and their resulting costs could be an argument for upfront surgery. There is a clear indication of surgery for functional pancreatic NETs, irrespective of tumour size. To prevent carcinoid crisis during surgery, perioperative octreotide treatment has traditionally been recommended. However, its indication is now controversial as a review and meta-analysis showed limited benefit.[13] An intravenous injection of octreotide should be available in case of hemodynamic instability during surgery, in addition to intravenous fluid resuscitation. There is currently no data to support an adjuvant systemic treatment. Surveillance imaging after curative surgery is recommended for up to 10 years.[14]

Advanced and Metastatic Disease

Resection of the primary tumour could lead to prolonged survival in metastatic G1 or G2 GEP-NET cases.[15] Nevertheless, there is a lack of prospective data to conclude a clear strategy. SI-NETs are a particular situation where palliative surgical resection of the primary lesion should be considered because of the frequent association with desmoplasia and fibrosis, which can lead to a bowel obstruction or ischemia. This is particularly true in symptomatic patients with abdominal pain or symptoms of intestinal obstruction.

In cases of GEP-NETs with only liver metastases that can be completely resected, surgery can improve quality of life and survival.[16] When the liver is the predominant site of metastasis but without any surgical possibility, a liver-directed approach like hepatic embolization (e.g., trans-arterial embolization, chemoembolization, or radioembolization) may be a valuable alternative.[17]

Liver transplantation could be considered in selected cases of patients <60 years with unresectable liver metastases without other metastatic sites, with a minimum of 6 months of disease stabilization, as assessed by an experienced multidisciplinary team. A systematic review has reported recurrence rates of 33% to 57%.[18]

Systemic Treatments Options (*Table 2*)

Systemic therapy has the dual aim of controlling symptoms and improving survival outcomes. Whether to watch and wait or to treat depends on the tumour characteristics, grade, ki67 expression, sites, and metastatic burden, as well as the presence of symptoms and the aim of the treatment (curative versus palliative). All available options must be explained and discussed with the patient.

Somatostatin Analogs (SSA)

SSA allow tumour-related symptom relief by 70-80% and are the first-line treatment for NETs. Two long-acting SSA are approved and used in Canada: subcutaneous lanreotide autogel (120 mg) and intramuscular long-acting release octreotide (30 mg), which are both given every 4 weeks. Subcutaneous short-acting somatostatin is reserved for rapid control of functional symptoms and can be given multiple times daily alone or in combination with any of the long-acting SSA. In cases of persistent diarrhea that is refractory to SSA and related to serotonin secretion, telotristat ethyl, an oral tryptophan hydroxylase inhibitor, has shown efficacy in two Phase 3 trials, the TELESTAR and TELECAST trials.[19]

Besides their role in symptom control, SSA have an anti-proliferative effect through the inhibition of growth factors, inhibition of angiogenesis, and modulation of the immune system. They are also indicated for both functional and non-functional advanced GEP-NETs with Ki67 <10%, as first-line treatment, alone or in combination with other systemic treatments. In the PROMID trial, long-acting octreotide showed a delayed tumour progression by 8.3 months compared to placebo in patients with advanced G1 midgut NETs.[20] The CLARINET trial, which included a larger patient population with advanced non-functional G1/G2 (ki67 <10%) GEP-NETs, showed a significant prolonged progression-free survival (PFS) in patients receiving lanreotide, but no OS benefit.[21] In situations where there is progression on standard lanreotide dosing, reducing the interval between injections to 21 or 14 days could be an option. This strategy demonstrated encouraging PFS results in the Phase 2 trial CLARINET FORTE, particularly in patients with Ki-67 <10%.[22]

Peptide Receptor Radionuclide Therapy (PRRT)

PRRT is a type of targeted therapy that uses a radiopeptide somatostatin analog (DOTATATE or DOTATOC) combined with a radioactive compound (generally ^{177}Lutetium [^{177}Lu]) that binds to receptors on tumour cells to deliver radioactivity cytotoxicity. For patients with SSTR-positive GEP-NETs, PRRT is a valid option in the first-line setting, as well as in the second-line after progression on SSA.

The NETTER-1 Phase 3 trial included patients with midgut NET G1 or G2, after progression on SSA, and randomized them to either four injections of ^{177}Lu-dotatate or double-dosing of octreotide long-acting repeatable (LAR) (60 mg; q4w). In this study, treatment improved PFS (28.4 months versus 8.5 months, p<0.001), but not OS.[23]

	Indication	Pan G1-G2	Pan G3	SI G1-G2	SI G3	mPFS (*months*)	mOS (*months*)	ORR (*%*)	References/trials
SSA (vs. placebo) Lanreotide	1st line (84%), GEP-NETs, ki67 <10%, NF	■		■		NR vs. 18, *p<0.001*	84.7 vs 83.7, *p=0.51*	2%	CLARINET[21]
octreotide	1st line, G1, SI-NETs	■		■		TTP: 14.3 vs. 6 months, *p=0.000072*		2%	PROMID[20]
Everolimus (vs. placebo)	1st line or later, GEP-NETs, CS	■		■		16.4 vs. 11.3, SNS*	29.2 vs. 35.2, *NS*		RADIANT-2[27] (SSA + everolimus vs. placebo + SSA)
	1st line or later (40% not pre-treated), pNETs, G1-G2	■		■		11 vs. 4.6, *p<0.001*	44 vs. 37.7, *p=0.3*	<10%	RADIANT-3[28]
	-≥1 line, NF, GEP-NETs	■		■		11 vs. 3.9, *p<0.00001*	27.3 vs. NA, *p=0.037*		RADIANT-4[29]
SSA + EVEROLIMUS (vs. everolimus)	1st line, GEP-NETs, NF	■		■		29.7 vs. 13.6, *p=0.00016*	NE, *HR 0.74 [95% CI: 0.25-2.24]*	23 vs. 8.3	STARTER-NET[30]
SUNITINIB (vs. placebo)	≥1 line (chemotherapy/SSA/local treatment), pNETs, NF&F	■				11.4 vs. 5.5, *p<0.001*	38.6 vs. 29.1, *p=0.02*	9.3 vs. 0	Raymond et al, NEJM 2011[25]
CABOZANTINIB (vs. placebo)	≥1 line (everolimus/PRRT/TMZ), NF, GEP-NETs	■	■	■	■	-Pan: 13.8 vs. 4.4, *p<0.001* -GI: 8.5 vs. 5.6, *p=0.007*	21.9 vs. 19.7**, *HR 0.86, [95% CI: 0.56-1.31]*	19 vs. 0 1 vs. 0	CABINET[26]
PRRT (vs. double dose SSA)	**NF&F:** 1st line, GEP-NETs	■	■	■	■	22.8 vs. 8.5, *p<0.0001*	*pending*	43 vs. 9.3	NETTER-2[24]
	≥1 line, SI-NETs	■	■	■	■	28.4 vs. 8.5, *p<0.0001*	48 vs. 36.3, *p=0.3*	18 vs. 3	NETTER-1[23]
Chemotherapy CAPTEM (vs. TMZ)	≥1 line, G1-G2	■	■	■	■	22.7 vs. 14.4, p=0.022	58.7 vs. 53.8,*p=0.42*	39.7 vs. 33.8	Kunz *et al.*, JCO 2022[33]
FOLFOX (vs. CAPTEM)	≥1 line, G1-G3	■	■		■	6.9 vs. 12, p=0.093		56.4 vs. 27.3	Apostolidis *et al.*, Cancers 2021[35] →retrospective trial

Table 2. Indications and outcomes of systemic treatment for GEP-NET; *courtesy of Nathalie Baudoux, MD and Mustapha Tehfe, MD, MSC.*

■: selected population

***** mPFS significantly longer after adjusting for randomization imbalances such as baseline chromogranin A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA), age, World Health Organization (WHO) performance score (PS), liver involvement, bone metastasis, lung as the primary site.
****** pNET +epNET
Abbreviations: CAPTEM: capecitabine – temozolomide, **CI:** confidence interval, **epNET:** extra-pancreatic neuroendocrine tumours, **FOLFOX:** 5-FU-leucovotin-oxaliplatin, **GEP-NETs:** gastro-entero-pancreatic neuroendocrine tumours, **GI:** gastro-intestinal, **HR:** hazard ratio, **mOS:** median overall survival, **mPFS:** median progression-free survival, **NET:** neuroendocrine tumours, **NF:** non-functional, **NF&F:** non-functional and functional, **NR:** not reached, **NS:** non-significant, **ORR:** overall response rate, **pan:** pancreas, **pNETs:** pancreatic NETs, **PRRT:** peptide receptor radionuclide therapy, **CS:** carcinoid syndrome, **SI:** small intestine, **SI-NETs:** small intestine-NETs, **SSA:** somatostatin analogues, **TTP:** time to progression, **TMZ:** temozolomide

The NETTER-2 Phase 3 trial enrolled patients newly diagnosed with advanced GEP-NETs G2–G3 (Ki67 10–55%) and randomized them to either four injections of ^{177}Lu-dotatate plus octreotide LAR (30 mg; q4w), or octreotide LAR (60 mg; q4w).[24] The trial showed a significant gain in PFS (22.5 months versus 8.5 months), and the OS results are pending. NETTER-2 set up PRRT as a new first-line option for G2/G3 (Ki67 10–55%) GEP-NET. It is noteworthy to mention the 2–3% risk of myelodysplasia associated with PRRT. This rate seems even higher in patients who previously received chemotherapy.

Tyrosine Kinase Inhibitor (TKI)

Sunitinib

Sunitinib, an oral multi-targeted TKI, was compared to placebo in a Phase 3 trial that included patients with progressing pancreatic NETs who were previously treated with SSA, chemotherapy, or local therapy. In this study, the median PFS was significantly longer with sunitinib (11.4 months versus 5.5 months)[25] Although the survival benefit favoured sunitinib, the median OS could not be estimated because of the high number of censored events.

Cabozantinib

Cabozantinib, another oral multi-targeted TKI, has been evaluated in a recent Phase 3 trial, CABINET, in which patients with advanced G1-G3 NETs (32% pancreatic) who progressed after one or more prior lines (everolimus, sunitinib, or ^{177}Lu-dotatate). A gain in PFS (8 months versus 4 months) was observed for G1-G2 GEP-NETs, with similar effects found for OS.[26]

Lenvatinib, sorafenib, pazopanib, axitinib

Lenvatinib, sorafenib, and pazopanib have been evaluated in small Phase 2 trials in patients with GI-NETs, and a signal of activity was detected with response rates of about 22% for pazopanib to 44% with lenvatinib. Axitinib was evaluated in the Phase 3 trial AXINET in combination with SSA for patients with G1-G2 extrapancreatic NETs and showed a response rate of 13.2% and a PFS of 16.6 months (versus 9.9 months for placebo).

Mammalian Target of Rapamycin (mTOR) Inhibitors

Everolimus has been evaluated in several Phase 3 trials in G1-G2 advanced GEP-NETs. The first trial, RADIANT-2, included mostly patients with progressing SI-NETs associated with CS, who were randomized to receive everolimus 10 mg daily versus placebo, plus octreotide LAR (30 mg; q4w).[27] A first analysis did not show a statistically significant gain in PFS. In a subsequent analysis with adjustment for prognostic factors, such as performance status and CgA level, everolimus was found to improve PFS with a 38% reduction risk of progression, but did not benefit OS. The second trial, RADIANT-3, included patients with advanced pan-NETs, and showed a PFS benefit in favour of the everolimus arm (11 months versus 4.6 months).[28] Finally, the RADIANT-4 trial included patients with advanced pre-treated non-functional GI-NETs (24%) and lung NETs, randomly assigned to everolimus versus placebo[29] A statistically significant gain in PFS was observed (11 months versus 3.9 months), as well as a trend towards improved OS. The response rate in all these trials was <10%.

Recently, everolimus plus lanreotide versus everolimus alone as a first-line treatment was evaluated in the Phase 3 STARTER-NET trial in G1/G2 GEP-NETs.[30] The combination arm showed a statistically significant benefit in PFS (29.7 versus 13.6 months) and ORR (23% versus 8.3%), but not in OS.

The combination of everolimus/bevacizumab versus everolimus alone was addressed in a randomized Phase 2 trial in pancreatic NETs. The combination arm showed a better ORR (31% versus 12%), a minor gain of PFS (16.7 months versus 14 months), no OS benefit, and significant toxicity.[31] This combination is not approved in Canada.

Chemotherapy

The role and place of chemotherapy in the treatment of NETs have yet to be defined. The primary site, the tumour grade, Ki67 expression, and the burden and aggressiveness of the disease are among the factors determining the indication for cytotoxic drugs. Streptozocin and/or doxorubicin and/or fluorouracil have historically been used and emerged from controversial trials.[32]

The most commonly used chemotherapy regimens are capecitabine plus temozolomide (CAPTEM) and 5-FU, leucovorin, and oxaliplatin (FOLFOX). In a phase 2 trial, CAPTEM versus temozolomide alone in pre-treated but chemotherapy-naïve G1/G2 advanced pancreatic-NETs demonstrated a gain in PFS (22.7 months versus 14.4 months) and ORR (40% versus 34%).[33] A systematic review confirmed these data and suggests that this regimen is more effective in pancreatic than non-pancreatic NETs.[34]

In a retrospective analysis of patients with G3 GEP-NETs who received chemotherapy in the first-line setting, FOLFOX was shown to result in the best ORR (56.4%), and CAPTEM in the longest PFS (12 months).[35]

Among patients with G1/G3 pancreatic-NETs previously treated with CAPTEM, FOLFOX seems to be effective according to a small retrospective trial (ORR: 45.2%, disease control rate: 93.5%).[36]

A platinum-based chemotherapy plus etoposide regimen is indicated for neuroendocrine carcinomas, but showed no efficacy in G1/G2 or G3 differentiated NETs.[37]

Immunotherapy

Trials with immune checkpoint inhibitors have been disappointing, and their role in NETs has yet to be defined.[38] The combination of an immune checkpoint inhibitor and anti-vascular endothelial growth factor (VEGF) therapy has shown objective responses and encouraging PFS in a small single-arm trial.[39]

Sequencing Therapies

The sequence of treatment depends on the localization of the primary tumour site, tumour grade, functional or non-functional status, expression or absence of somatostatin receptor, as well as widespread and growth development of the disease. There is no established consensus on treatment sequencing because trials are lacking. We propose an algorithm of treatment in **Figure 1**. Clinical and radiological surveillance is an acceptable option for asymptomatic disease with a low tumour burden. Choosing between cytotoxic chemotherapy or PPRT for rapidly progressive NETs with high Ki67 should take into consideration the above-mentioned factors and the accessibility to each treatment. The ongoing Phase 3 COMPOSE trial compares these two options, which will inform the best therapeutic strategy.

Conclusion

GEP-NET remains a rare and heterogeneous disease with no clear consensus on the optimal sequencing of therapy. Understanding and predicting the behaviour of the disease depends on multiple above-mentioned disease characteristics. With increasing incidence and prevalence, more patients will be able to enroll in clinical trials, which will help choose the most adequate treatment for patients with NET. Since GEP-NETs are generally indolent and have an expected survival of several years, the indication and effectiveness of treatments with preservation of quality of life must be properly balanced.

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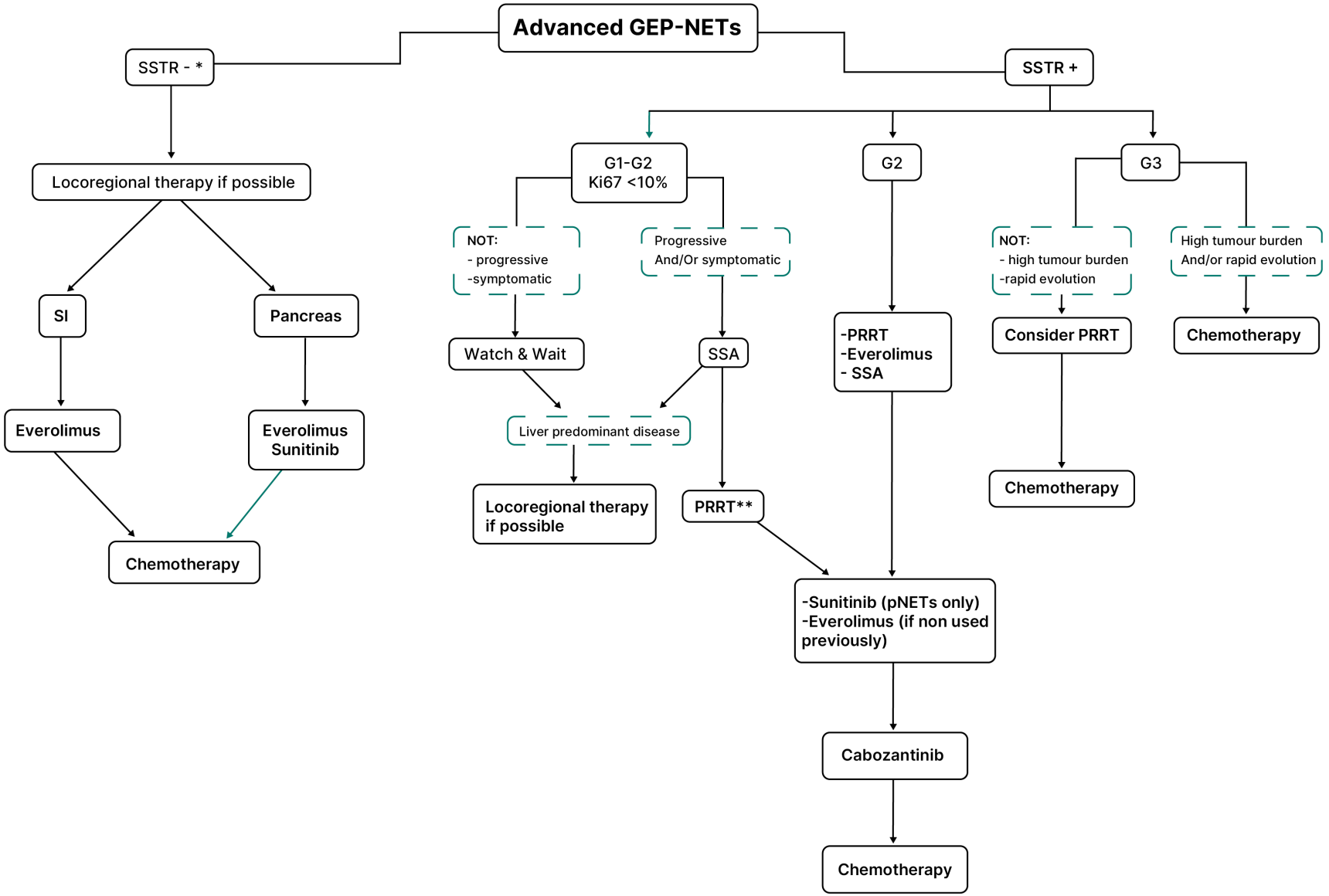

Figure 1. Algorithm for advanced GEP-NETs treatment; *courtesy of Nathalie Baudoux, MD and Mustapha Tehfe, MD, MSC.*

*SSA could be considered. Positive SSTR status is not predictive of response
***only SI-NETs were included in NETTER-1*

Abbreviations: SSTR: somatostatin receptor, **SSA:** somatostatin analog, **PRRT:** peptide receptor radionuclide therapy

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Management of Stage I–II Testicular Germ Cell Tumours: Current Treatment Paradigm and Future Perspectives

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Introduction

Testicular cancer is the most common solid tumour in males aged 15–44 years, with an estimated 1,300 new cases in Canada in 2024.[1] Over 90% are germ cell tumours (GCTs) originating from spermatocyte precursors, with most arising in the testes.[2] Risk factors include cryptorchidism, gonadal dysgenesis, genetic syndromes such as Klinefelter syndrome, family history, and possibly cannabis use.[2]

This review summarizes the evidence-based diagnosis and management strategies of clinical stage I (CSI) and II (CSII) testicular GCTs used at the Princess Margaret Cancer Centre (PM), highlighting potential clinical pitfalls and future directions.[3]

Workup, Diagnosis, and Staging

Most testicular GCTs present as a palpable testicular mass. Radical orchiectomy serves both diagnostic and therapeutic purposes. Pre- and post-orchiectomy tumour markers (TMs) and computed tomography (CT) chest abdomen pelvis should be obtained.[4]

Staging Classification

Testicular GCTs are staged using the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging (**Table 1**), which considers primary tumour extent, lymph node involvement, metastatic sites, and post-orchiectomy serum TM levels (S).[5] A potential pitfall is using pre-orchiectomy TMs for staging, which can lead to over- or under-treatment.

Histologic Classification and Tumour Markers

GCTs are classified as pure seminomas (45%) or non-seminomas (NSGCTs, 55%) based on histology to guide prognosis and management.[4] NSGCTs include embryonal carcinoma (EC), yolk sac tumour, choriocarcinoma, and teratoma.[6]

Pure seminomas do not secrete alpha-fetoprotein (AFP) but can produce some human chorionic gonadotrophin in the blood (B-HCG) with syncytiotrophoblast differentiation. Rising AFP should be treated as NSGCT, even if pathology reports pure seminoma. Choriocarcinomas secrete B-HCG, yolk sac tumours secrete AFP, while EC may result in modest elevations of both. Teratomas are generally marker-negative but may secrete some AFP. Due to its low specificity,[7] LDH alone should not guide treatment decisions for early-stage GCT.[4]

A potential clinical pitfall is basing treatment decisions on persistent low-level TM elevations, without considering false positives. AFP may be elevated in the 10–15 ng/mL range due to heterophile antibodies, liver dysfunction, or hereditary factors.[8,9] B-HCG may show false positives due to hypogonadism, heterophile antibodies, marijuana use, or certain medications.[10] A consistent rise in TMs helps differentiate active GCT from false positives.

Management of Stage I-II Seminoma

With appropriate management, patients with CSI-CSII seminoma have long-term survival rates approaching 100% (**Table 2**), highlighting the need to minimize overtreatment and unnecessary toxicity. At PM, patients are managed in the Multidisciplinary Testes Clinic, which involves experienced uro-oncologists, radiation, and medical oncologists.

CSI Seminoma

Approximately 85% of patients with CSI seminoma are cured with orchiectomy alone.[11] Historically, rete testes invasion (RTI) and a primary tumour size of ≥4 cm were considered risk factors for relapse,[12] although not consistently validated.[11] A recent multicentre study refined risk stratification using lymphovascular invasion (LVI) and three categories of tumour size (<2 cm, >2–5 cm, or >5 cm). Five-year relapse rates were 8% in very low-risk, 20% in low-risk, and 44% in high-risk disease.[13] Only 2.3% of patients had high-risk disease.

Another Danish nationwide study identified elevated preorchiectomy b-HCG, LDH, testicular hilum invasion and LVI as independent risk factors, with five-year relapse rates ranging from 6% (no-risk factors) to 62% (all four risk factors), although only 10% of patients had 3 or 4 risk factors. These contemporary models require further external validation.[14]

Active Surveillance for CSI Seminoma

Active surveillance is preferred for patients with CSI seminoma.[4] Most relapses (95%) occur in retroperitoneal lymph nodes (RPLNs), mainly within the first two years (73%).[15] Virtually all patients who relapse can be cured with subsequent radiation or chemotherapy (**Table 2**).

Our published surveillance protocol includes physical examination, including the contralateral testicle, bloodwork, and low-dose CT scans without intravenous (IV) contrast. CTs of the abdomen and pelvis are obtained every 6 months until year 3, CT abdomen only at years 4, 5, 7, and 9, and chest X-ray at year 9 (see **Table 3**).[16]

Use of magnetic resonance imaging (MRI) versus contrast-enhanced CT and fewer (three total) versus more (seven) scans were explored in the Phase III TRISST trial.[17] MRI was non-inferior, but fewer scans resulted in numerically higher, though not statistically significant, rates of Stage ≥IIC relapse (2.8% versus 0.3%) requiring chemotherapy. At PM, we use non-contrast low-dose CT to minimize radiation exposure, eliminate IV access, and shorten imaging time, with excellent outcomes.[18] Due to the numerically higher advanced relapse rate with three scans, and limited accessibility of MRI, our surveillance protocol remains unchanged.

Adjuvant Radiotherapy for CSI Seminoma

Adjuvant radiotherapy (20 Gy in 10 fractions or 25 Gy in 20 fractions to the para-aortic lymph nodes with or without ipsilateral pelvic lymph nodes) reduces the relapse risk for CSI seminoma from 15-20% to 5%.[19-21] However, most patients are cured with orchiectomy alone. Given the high likelihood of cure upon relapse (with radiotherapy or chemotherapy), adjuvant radiotherapy carries risk of overtreatment for most patients and is therefore not the favoured approach. Toxicities include fatigue, nausea, vomiting, peptic ulcer disease, infertility, cardiovascular disease,[22-24]

TNM Staging	Unit	Value		
Primary Tumour (pT)	pTX	Primary tumour cannot be assessed		
	pT0	No evidence of primary tumour		
	pTis	Germ cell neoplasia *in situ*		
	pT1	Tumour limited to testis (including rete testis invasion) without lymphovascular invasion		
	pT1a*	Tumour <3 cm in size		
	pT1b*	Tumour ≥3 cm in size		
	pT2	Tumour limited to the testis (including rete testis invasion) with lymphovascular invasion OR Tumour invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without lymphovascular invasion		
	pT3	Tumour directly invades spermatic cord soft tissue with or without lymphovascular invasion		
	pT4	Tumour invades scrotum with or without lymphovascular invasion		
	NX	Regional lymph node cannot be assessed		
Regional Lymph Nodes (pN and cN)	pN0	No regional lymph node metastasis	cN0	No regional lymph node metastasis
	pN1	Metastasis with a lymph node mass ≤2 cm in greatest dimension and ≤5 positive nodes, none >2 cm in greatest dimension	cN1	Metastasis with a lymph node mass ≤2 cm in greatest dimension OR multiple lymph nodes, none >2 cm in greatest dimension
	pN2	Metastasis with a lymph node mass >2 cm but not >5 cm in greatest dimension; or >5 positive nodes, none >5 cm in size; or evidence of extranodal extension of tumour	cN2	Metastasis with a lymph node mass >2 cm but ≤5 cm in greatest dimension OR multiple lymph nodes, any one mass >2 cm but ≤5 cm in greatest dimension
	pN3	Metastasis with a lymph node mass >5 cm in greatest dimension	cN3	Metastasis with a lymph node mass >5 cm in greatest dimension
Distant Metastasis (M)	M1	Distant metastases present		
	M1a	Non-retroperitoneal nodal or pulmonary metastases		
	M1b	Non-pulmonary visceral metastases		
	SX	Serum marker studies not available or performed		
Serum tumour markers (S)	S0	Marker study levels within normal limits		
	S1	LDH <1.5 × normal and HCG (IU/L) <5,000 and AFP (ug/L) <1,000		
	S2	LDH 1.5–10 × normal or HCG (IU/L) 5,000–50,000 or AFP (ug/L) 1,000–10,000		
	S3	LDH >10 × normal or HCG (IU/L) >50,000 or AFP (ug/L) >10,000		

Stage Grouping				
Stage	**Tumour**	**Node**	**Metastasis**	**Serum Factor**
0	pTis	N0	M0	S0
I	pT1-4	N0	M0	SX
IA	pT1	N0	M0	S0
IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
IS	Any T	N0	M0	S1-3
II	Any T	N1-3	M0	SX
IIA	Any T	N1	M0	S0
	Any T	N1	M0	S1
IIB	Any T	N2	M0	S0
	Any T	N2	M0	S1
IIC	Any T	N3	M0	S0
	Any T	N3	M0	S1
III	Any T	Any N	M1	SX
IIIA	Any T	Any N	M1a	S0
	Any T	Any N	M1a	S1
IIIB	Any T	N1-3	M0	S2
	Any T	Any N	M1a	S2
IIIC	Any T	N1-3	M0	S3
	Any T	Any N	M1a	S3
	Any T	Any N	M1b	Any S

Table 1. TNM Staging of Testicular GCTs; *adapted from Hamilton et al., CUAJ 2022.*[4]

***** T1a and T1b subclassification applies only to pure seminoma.

Abbreviations: AFP: alpha-fetoprotein, **HCG:** human chorionic gonadotrophin, **LDH:** lactate dehydrogenase.

Histology	Stage	Treatment Modality	RFS	OS
Seminoma	CSI	**Active Surveillance**	**85%**	**100%**
		Adjuvant Radiotherapy	95%	100%
		Adjuvant Chemotherapy (carboplatin)	90.7–97.8%	100%
	CSIIA	**Radiotherapy**	**95%**	**100%**
		Primary RPLND	70-89%	100%[1]
		Chemotherapy	93%	100%
	CSIIB	**Radiotherapy**	**88%**	**100%**
		Primary RPLND	70-89%	100%[1]
		Chemotherapy	**95%**	**100%**
NSGCT	CSI	**Active Surveillance**	**75%**	**100%**
		Adjuvant Radiotherapy	NR	NR
		Adjuvant RPLND	91.60%	100%
		Adjuvant Chemotherapy (BEP)	>95%	100%
	CSIIA	**Primary RPLND**	**80%[2]**	**100%**
		Chemotherapy	>95%	100%
	CSIIB	Primary RPLND	80%[2]	100%
		Chemotherapy	**98%**	**100%**
Seminoma and NSGCT	CSIIC	**Chemotherapy**	**95%**	**96%**

Table 2. Efficacy Outcomes for CSI-CSIIC Testicular GCTs by Treatment Modality; *courtesy of Deepro Chowdhury, MD, FRCPC, Rachel Glicksman, MD, MSC, FRCPC, Robert J. Hamilton, MD, MPH, FRCSC, and Maria Jiang, MD, MSc, FRCPC.*

Preferred treatment approaches at PM are bolded.

[1] Median follow-up 22–32 months only
[2] >90% of patients with S0 disease

Abbreviations: BEP: bleomycin, etoposide, and cisplatin, **CS:** clinical stage, **GCT:** germ cell tumour, **NR:** Not recommended, **NSGCT:** nonseminomatous germ cell tumour, **OS:** overall survival, **RFS:** relapse-free survival, **RPLND:** retroperitoneal lymph node dissection

Time Post Orchiectomy	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Year 1						**CT A&P***						**CT A&P** **CXR**** serum LH, FSH, free & total testosterone
Year 2						**CT A&P**						**CT A&P** **CXR** serum LH, FSH, free & total testosterone
Year 3						**CT A&P**						**CT A&P** **CXR** serum LH, FSH, free & total testosterone
Year 4												**CT Abdo*** ONLY** serum LH, FSH, free & total testosterone
Year 5												**CT Abdo ONLY** serum LH, FSH, free & total testosterone
Year 7												**CT Abdo ONLY** serum LH, FSH, free & total testosterone
Year 9												**CT Abdo ONLY** serum LH, FSH, free & total testosterone

Table 3. Princess Margaret Cancer Centre Surveillance Protocol for CSI Seminoma; *courtesy of Deepro Chowdhury, MD, FRCPC, Rachel Glicksman, MD, MSC, FRCPC, Robert J. Hamilton, MD, MPH, FRCSC, and Maria Jiang, MD, MSc, FRCPC.*

CT A&P* (Abdomen &Pelvis) first 3 years
CXR** (Chest X-Ray)
CT Abdo*** (Abdomen) only after 3 years

and secondary malignancies (standardized incidence ratio [SIR]: 1.62, 95% confidence interval [CI]: 1.43–1.83).[25] Additionally, continued surveillance of the abdomen and pelvis (if not treating ipsilateral pelvis) remains necessary.

Adjuvant Chemotherapy for CSI Seminoma

One cycle of adjuvant carboplatin (AUC 7) reduces relapse risk in CSI seminoma comparably to adjuvant radiotherapy (see **Table 2**). The MRC TE19/EORTC 30982 study showed long-term relapse-free survival (RFS) for both modalities, with a lower risk of contralateral testicular relapse in the carboplatin group (relapse rate in contralateral testicle 0.2% versus 1.2% in favour of adjuvant carboplatin).[26] The SWENOTECA study reported relapse rates of 15.5% with surveillance versus 9.3% with adjuvant carboplatin in patients with one or more risk factors.[27] Despite a risk-adapted strategy, adjuvant carboplatin likely leads to overtreatment and unnecessary toxicity, including fatigue, myelosuppression, infection, nausea, and vomiting. Secondary malignancies (SIR: 0.96, 95% CI: 0.26–2.45) and rarely cardiovascular disease (SIR: 1.44, 95% CI: 0.39–3.69).[28] Therefore it is not the preferred approach at PM. Relapses after adjuvant carboplatin may also have more aggressive tumour biology.[29]

CSII Seminoma

Up to 30% of CSIIA seminomas have benign (pN0) RPLNs, which may regress spontaneously.[30] Short-interval imaging (6–8 weeks) and TM reassessment can help avoid this pitfall.[4,31] Treatment should proceed only if metastatic RPLNs are unequivocal (enlarging, rising TMs or confirmed on biopsy).[6]

Definitive Radiotherapy for CSIIA or CSIIB Seminoma

Radiotherapy delivered to the para-aortic lymph nodes and ipsilateral pelvic lymph nodes known as the “dog-leg” or “modified dog-leg” approach using 3-dimensional conformal radiotherapy (20–25 Gy to the entire volume with a boost to gross disease to a total dose of 30–36 Gy) is preferred for CSIIA/B seminoma due to lower toxicity compared to chemotherapy, and excellent long-term outcomes (**Table 2**).[32] National Comprehensive Cancer Network (NCCN) guidelines suggest a 3 cm cut-off in the trans-axial axis,[33] but recent data suggest low relapse rates with radiation even with RPLNs >5 cm in select patients.[32] Treatment decisions require multidisciplinary input, and consideration of patient preferences.

Most relapses following radiotherapy (>95%) are out-of-field,[34] and can be successfully treated with 3 cycles of chemotherapy, achieving 10-year overall survival (OS) rates of 91%.[34] However, when both radiotherapy and chemotherapy are used, the risk of long-term toxicities, particularly secondary malignancies, is likely higher.[35]

Chemotherapy for CSIIA or CSIIB Seminoma

Relapse rates after chemotherapy are numerically lower (8-14%) than radiotherapy (11–21%), particularly in CSIIB disease (5% vs. 12%).[36] Given its more unfavourable toxicity profile, chemotherapy is typically reserved for patients with rising TMs or bulky CSIIB disease, the definition of which is not standardized.

The standard chemotherapy regimen is three cycles of bleomycin, etoposide, and cisplatin (BEP) or four cycles of etoposide-cisplatin (EP), if the patient is unable to tolerate bleomycin.[6] Sperm banking should be offered prior to chemotherapy.[37] Acute toxicities include fatigue, alopecia, nausea, vomiting, myelosuppression, neutropenic infections, renal dysfunction, skin toxicity, and venous thromboembolism. Bleomycin-induced lung injury occurs in up to 10% of patients and can rarely be fatal.[38] Risk factors include smoking history, pre-existing lung disease, age >50 years, and renal impairment.[39] Hearing loss and peripheral neuropathy can occur in 20–40% of patients.[39] Other long-term risks include tinnitus, chronic kidney disease, infertility, secondary malignancy, cardiovascular disease, Raynaud’s phenomenon, and avascular necrosis of the hip.

The SAKK 01/10 Phase II trial recently evaluated the combination of one cycle of carboplatin (AUC 7) followed by radiotherapy, and reported 3-year progression-free survival (PFS) of 93.7%, which did not meet the pre-specified 95% target.[40] Given these data, along with concerns for increased long-term toxicity with combination therapy, this approach is not adopted at PM.

Primary RPLND for CSIIA and CSIIB Seminoma

Three Phase II studies, SEMS (n=55), PRIMETEST (n=33), and COTRIMS (n=30), have evaluated retroperitoneal lymph node dissection (RPLND), mainly open surgery, in marker-negative CSIIA and CSIIB seminoma.[41-43] With a median

follow-up of 22–32 months, two-year relapse-free survival (RFS) ranged from 70% to 89%, with most recurrences occurring out-of-field (>90%). The PRIMETEST trial was terminated early due to high relapse rates (30%)[42]; however, all relapses were successfully salvaged with additional surgery or chemotherapy.

Across all three studies, grade >3 short-term complications were observed in 3.6–13% of patients, and included paralytic ileus, chylous ascites, lymphoceles requiring drainage, and pulmonary emboli. Rates of anejaculation were ≤10%, and other long-term surgical complications were rare.[41] The American Urology Association (AUA) now recognizes RPLND as an option for select patients with RPLNs ≤3 cm who wish to avoid chemotherapy or radiotherapy.[43] However, higher relapse rates than standard of care, variations in patient selection, and surgical technique across centres remain concerns. PM has not adopted this approach outside of a clinical trial setting, pending data from larger studies with longer follow-up, consistent with the European Urological Association (EAU) recommendations.[31] The THERATEST trial (NCT06309745) is ongoing and compares RPLND to radiotherapy in seminoma with RPLN <3 cm.

Clinical Stage IIC (CSIIC) Seminoma

CSIIC seminoma is treated with chemotherapy according to the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification.[45] Post-chemotherapy residual masses ≥3 cm may contain viable tumour in up to 30% of cases based on historical data.[46] Fludeoxyglucose positron emission tomography (FDG-PET) has been studied in this setting[47] but is used infrequently due to its low positive predictive value.[4]

Management of Stage I-II NSGCT

CSI NSGCT

Approximately 75% CSI NSGCT are cured with orchiectomy alone.[48] Risk factors include lymphovascular invasion (LVI) (30%) and EC-predominant disease (50%).[49] About 75% of relapses occur in RPLNs.[50] Data from the Danish Testicular Cancer Registry recently showed hilar soft tissue invasion, tumor size (log 2), LVI and EC (absent vs <50% vs ≥50%) were independent risk factors for relapse, with 5-year relapse risk ranging from <5% (no risk factors) to >85% (all 4 risk factors).[51] External validation is warranted.

Active Surveillance for CSI NSGCT

Active surveillance is the preferred approach for CSI NSGCT4 (the PM surveillance protocol is included in **Table 4**).[48] Even in high-risk cases, 50% are cured with orchiectomy alone.[50] Most relapses (90%) occur within the first two years,[15] and are effectively treated with primary RPLND or chemotherapy.[50,52]

Adjuvant Chemotherapy for High-Risk CSI NSGCT

Some centres offer a risk-adapted approach using one cycle of adjuvant BEP for CSI NSGCT with LVI and/or predominant EC histology, reducing relapse risk to <5%.[53] Two cycles of adjuvant chemotherapy yield similar RFS but with increased toxicity and are generally not recommended.[31] Up to 37% of relapses after adjuvant BEP occur beyond 2 years, underscoring the need for long-term surveillance.[54]

The decision to use adjuvant chemotherapy should balance its efficacy in reducing relapse (and risk of requiring 3 cycles of chemotherapy subsequently) against the chance of avoiding chemotherapy and its potential toxicities altogether.[55] There is also some concern that relapses following adjuvant chemotherapy may be more treatment-resistant,[54] although data is limited.

RPLND for High-Risk CSI NSGCT

A German Phase III study compared RPLND with one cycle of adjuvant BEP. Following RPLND, 18% of patients received additional adjuvant BEP. The 12-year relapse rate was higher with RPLND (8.4%) than with adjuvant BEP (1.6%).[56] Only about one-third of patients had pathologic nodal involvement at the time of surgery, highlighting the significant risk of over-treatment.[57] RPLND is rarely used at PM in this context.

CSII NSGCT

Patients with CSIIA disease should undergo short-interval CT scans (6–8 weeks) and serial TMs to differentiate benign lymphadenopathy (20–30%), teratoma, and viable GCT.[30] If TMs remain negative, shrinking lesions are likely benign and can be observed. Persistent, slow-growing cystic lesions may indicate teratoma, warranting RPLND.

Time Post Orchiectomy	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Year 1	Markers*	Markers		Markers CT A&P*** CT Thorax		Markers		Markers CT A&P CT Thorax		Markers		**Markers** **CT A&P** **CT Thorax** Serum LH, FSH, free & total testosterone
Year 2		Markers		Markers		Markers		Markers		Markers		**Markers** **CT A&P** **CT Thorax** Serum LH, FSH, free & total testosterone
Year 3				Markers				Markers				**Markers** Serum LH, FSH, free & total testosterone
Year 4						Markers						**Markers** Serum LH, FSH, free & total testosterone
Year 5												**Markers** **CT A&P** **CT Thorax** Serum LH, FSH, free & total testosterone
Transition to primary care after 5 years. No ongoing imaging/labs required. Physical surveillance of remaining testis.												

Table 4. Princess Margaret Cancer Centre Surveillance Protocol for CSI NSGCT; *courtesy of Deepro Chowdhury, MD, FRCPC, Rachel Glicksman, MD, MSC, FRCPC, Robert J. Hamilton, MD, MPH, FRCSC, and Maria Jiang, MD, MSc, FRCPC.*

Markers* (HCG, AFP, LDH)
CT A&P*** (CT Scan of Abdomen and Pelvis)

Primary RPLND for CSIIA and CSIIB NSGCT

For marker-negative CSIIA NSGCT, primary RPLND is associated with a higher relapse rate (20%) than chemotherapy (<5%); however, it avoids chemotherapy toxicities[58] and is the preferred approach. Relapses post-RPLND are mostly out-of-field when performed at experienced centres,[4] and are highly curable with chemotherapy.

For CSIIB NSGCT, relapse rates after primary RPLND reach 50%,[59] and chemotherapy is often preferred. No standardized criteria exist for selecting primary RPLND versus chemotherapy[60] but TM levels, lymph node (LN) size and distribution may help guide decision making. Patients with an unequivocal rise in TM or rapidly progressing disease should receive chemotherapy.

After RPLND, two cycles of adjuvant chemotherapy can reduce relapse rates (e.g., N2 disease from ≥50% to <5%).[61] However, this undermines the goal of primary RPLND, which is achieving cure without chemotherapy.

Chemotherapy for CSIIA, CSIIB, and CSIIC NSGCT

For CSIIA and CSIIB NSGCT, chemotherapy has lower relapse rates (<5%) than RPLND at the cost of increased short- and long-term toxicity.[58] CSIIC disease, regardless of TM status, should be treated with chemotherapy (see **Table 2**).[62]

Post-chemotherapy, residual masses over 1 cm warrant RPLND to remove any teratoma (to avoid growing teratoma syndrome or somatic transformation) or viable chemo-resistant GCT.[4]

Future Directions

Molecular biomarkers such as micro RNAs (miRNAs), particularly miR371,[63] have shown excellent sensitivity (80–100%) and specificity (90–100%),[64] and may be particularly valuable for detecting marker-negative GCTs.[65]

For metastatic NSGCT treated with chemotherapy, miR371 has shown prognostic value[66-68] and promising ability to assess residual masses (negative predictive value of 100% in NSGCT <3 cm).[66] However, miR371 has limited ability to detect teratoma[69]; with miR375 co-testing this may be improved.[70] Further prospective studies, such as the ongoing SWOG S1823 trial (NCT04435756), are needed. Circulating tumour DNA (ctDNA)[71] also shows potential utility in detecting molecular residual disease post-treatment.[72]

Conclusions

CSI and CSII testicular GCTs are highly curable. Management strategies are tailored to histology, tumour burden, stage, and patient preferences, with an emphasis on minimizing treatment toxicities. Multidisciplinary evaluation is essential, and treatment at experienced centres optimizes outcomes. Ongoing research, including RPLND in CSIIA-CSIIB seminoma and biomarkers, such as miRNA and ctDNA, may enable personalized treatment strategies pending confirmatory data.

For other surveillance protocols including post primary RPLND, radiation or chemotherapy, please refer to page 20–26 **here**.

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Small-Cell Lung Cancer: Integration of Radiation and Immunotherapy for All Stages

Nathalie Daaboul, MD, FRCPC

Small cell lung cancer is an aggressive cancer with a poor prognosis. New treatment paradigms have developed with the incorporation of new therapies in the last few years, aiming to improve patient survival. Some emerging therapies include the addition of immunotherapy to chemotherapy. This article provides a practical review of the current and upcoming treatment options for SCLC in both limited and extensive stages, focusing on integrating radiation and immunotherapy.

Introduction

Epidemiology and Staging of SCLC

Small cell lung cancer (SCLC) is a highly aggressive subtype of neuroendocrine tumours, accounting for approximately 15% of all lung cancer cases.[1] In Canada, an estimated 32,100 Canadians were expected to be diagnosed with lung cancer in 2024.[2] The incidence of SCLC is slowly declining, largely due to reduced tobacco use, as over 95% of patients diagnosed with SCLC have a history of tobacco use.[1,2]

Staging of SCLC is commonly based on the Veterans Administration Lung Group (VALG) classification, which categorizes the disease into two stages. Limited stage is defined as cancer that is confined to one hemithorax and regional lymph nodes, including ipsilateral mediastinal and supraclavicular nodes, and can be encompassed within a single radiation field. Extensive stage, on the other hand, is defined as disease that has spread beyond these regions, including distant metastases or malignant pleural/pericardial effusions. Further, the TNM classification can also be used to stage SCLC.

SCLC is often diagnosed at an advanced stage. Approximately 70% of patients present with extensive-stage disease, for which a curative treatment is no longer possible. Unfortunately, symptoms are usually hard to detect, and the cancer progresses rapidly. Some presenting elements include respiratory symptoms, such as dyspnea, cough, hemoptysis, or systemic symptoms, such as fatigue and weight loss.

Treatment Guidelines for Limited Stage SCLC (LS-SCLC)

Surgical Considerations

Surgery remains controversial in LS-SCLC, but may be considered for very limited stage disease, particularly small tumours without nodal involvement. Often, the diagnosis is made postoperatively when no preoperative biopsy was performed. In such cases, adjuvant chemotherapy, with or without radiotherapy, is required. However, many clinicians would consider chemoradiotherapy (CRT) over surgery. When considering surgery as the main treatment modality, it is advised to present a patient's case in a multidisciplinary tumour board.

Standard of Care: Chemotherapy and Radiotherapy

Chemotherapy

The standard treatment for LS-SCLC involves a combination of chemotherapy and thoracic radiotherapy. The typical regimen includes four cycles of a platinum doublet (cisplatin and etoposide). Cisplatin's main adverse events include myelosuppression, nausea/vomiting, and renal toxicity. Carboplatin can substitute cisplatin in patients with significant comorbidities or advanced age disease.[3,4]

Concurrent administration of chemotherapy and radiotherapy (CRT) is preferred, as it has been shown to be superior to chemotherapy alone in the treatment of LS-SCLC. Chemotherapy monotherapy is not curative and primarily serves a radio-sensitizing role, enhancing the effectiveness of radiotherapy, and it has the potential to decrease micrometastases.

Radiotherapy

Evidence suggests that the earlier radiotherapy is initiated during the treatment course, the better the disease control. Radiotherapy is often started with the second cycle of chemotherapy. Moreover, CRT has also demonstrated superior outcomes compared to a sequential delivery, where radiotherapy follows the completion of chemotherapy.[5,6]

There is significant variability in the administration of thoracic radiotherapy for LS-SCLC across Canada and internationally. Some studies suggest that twice-daily radiotherapy may offer a survival advantage over once-daily regimens.[5] However, no significant differences in overall survival have consistently been demonstrated between these two concurrent modalities in clinical trials. The choice of a radiotherapy schedule often depends on institutional logistics, the capacity of cancer centres, and the ease of access for patients.[3,4] In many jurisdictions, especially in Canada, once-daily radiotherapy remains the preferred approach due to practical considerations and patient convenience.

Prophylactic brain irradiation (PCI) may be considered in patients who have achieved a good response to initial CRT. The rationale for PCI is that it may reduce the incidence of brain metastases. Recommendations for PCI are mainly based on a meta-analysis from the pre-magnetic resonance imaging (MRI) era, which demonstrated a 5.4% improvement in overall survival at 3 years for patients receiving PCI compared to controls.[7] However, a large retrospective study challenged these findings, showing no statistically significant survival benefit for patients receiving PCI vs. those in the observation arm (hazard ratio [HR]: 0.90; $p = 0.29$).[8] Therefore, the practice of using PCI is declining in favour of serial MRI imaging.

ADRIATIC Trial and Durvalumab Consolidation

Despite CRT, LS-SCLC remains associated with a poor prognosis, with a median survival of approximately two years and high recurrence rates. Long-term survival is rare, and most patients eventually develop distant metastases, often involving the central nervous system.

The ADRIATIC trial is a Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy of durvalumab, with or without tremelimumab, as consolidation therapy in patients with LS-SCLC who did not progress following concurrent CRT.[9] Patients included had received chemotherapy treatment consisting of cisplatin/carboplatin with etoposide, and radiation protocols included a standard once-daily schedule of 60–66 Gy over 6 weeks or hyperfractionated radiotherapy twice-daily at 45 Gy over 3 weeks. Patients were allowed to start the trial treatment 1–42 days after the completion of radiotherapy. Maintenance durvalumab (or placebo) was administered every 4 weeks until disease progression, unacceptable toxicity, or up to 24 months.

At an interim analysis in 2024, consolidation therapy with durvalumab was found to significantly improve overall survival compared to placebo. The median overall survival (mOS) was 55.9 months (durvalumab) vs. 33.4 months (placebo); (HR: 0.73; 95% confidence interval [CI]: 0.57–0.93). The median progression-free survival (mPFS) was 16.6 months (durvalumab) vs. 9.2 months (placebo); (HR: 0.76; 95% CI: 0.61–0.95). The treatment assessed in the ADRIATIC trial is the first treatment shown to improve survival since the introduction of CRT and has now emerged as a new standard of care for patients with LS-SCLC who did not progress after concurrent CRT. No new safety concerns were reported, and durvalumab has been approved in many jurisdictions for this indication.

Treatment Guidelines for Extensive-Stage SCLC (ES-SCLC)

The standard first-line treatment for ES-SCLC involves a combination of chemotherapy and immunotherapy. Doublet platinum with etoposide is the chemotherapy regimen of choice, but yields limited survival benefits, with prognosis rarely surpassing a year. The introduction of immunotherapy in the form of immune checkpoint inhibitors (ICI) has changed the treatment landscape, and the combination of chemotherapy and immunotherapy is now considered the standard of care.[3,4]

Immunotherapy

Two trials (Phase III, randomized, double-blind, placebo-controlled studies: IMpower 133 and CASPIAN) justify the addition of immunotherapy to treatment regimens for ES-SCLC.[10,11] In both trials, patients received immunotherapy (anti-programmed cell death ligand 1 [PD-L1] ICI) in combination with doublet platinum chemotherapy for 4 cycles, if they had a good performance status and no contraindications to the use of immunotherapy. In patients without documented disease progression after this regimen, ICI treatment could be continued as maintenance therapy.

IMpower133 compared atezolizumab + carboplatin + etoposide vs. placebo + chemotherapy (both: 4 cycles).[10] The addition of ICI improved mOS to 12.3 months (atezolizumab) vs. 10.3 months for placebo (HR: 0.70; 95% CI: 0.54–0.91). The CASPIAN trial compared durvalumab + cisplatin/carboplatin + etoposide (4 cycles) vs. placebo + chemotherapy (4–6 cycles).[11] The addition of ICI in this study also improved mOS to 12.9 months compared to 10 months in the placebo group (HR: 0.71; 95% CI: 0.62–0.91). The study also included a third arm with durvalumab + tremelimumab + chemotherapy that did not add any benefit.

Long-term survivors were observed in both studies, with some patients maintaining durable responses beyond 3 years. No significant increase in toxicity was reported with the addition of immunotherapy compared to chemotherapy alone.[10,11] Both trials reinforce immunotherapy with a platinum doublet as a standard of care in ES-SLCLC.[3,4]

Maintenance with Lurbinectedin

Even with the addition of immunotherapy, patient outcomes remain poor and other strategies are being studied to improve survival. One of the strategies is adding a new agent to the maintenance phase. Before immunotherapy became standard in first-line treatment, it was assessed in the maintenance phase, with no success. Recently, primary data from the IMforte trial were presented. This study is a Phase III, randomized clinical study that evaluates the efficacy of lurbinectedin, a synthetic alkaloid chemotherapy, in combination with atezolizumab as maintenance therapy in patients with ES-SCLC who have not progressed after first-line induction therapy.

The combination of lurbinectedin and atezolizumab demonstrated statistically significant improvements in both mPFS at 5.4 months vs. 2.1 months (HR: 0.54; 95% CI: 0.43–0.67) and mOS (13.2 months vs. 10.6 months; HR: 0.73; 95% CI: 0.57–0.95) compared to atezolizumab alone. The addition of lurbinectedin is therefore a new treatment option, but comes with more adverse events, mostly cytopenias and febrile neutropenia. Other immunotherapy maintenance strategies are under study, such as strategies that include the addition of T-cell engagers and vaccines.

Radiotherapy

As discussed previously, the main treatment modality for ES-SCLC is chemotherapy with immunotherapy, but radiotherapy can be considered in specific circumstances.

Thoracic radiotherapy (TRT) was studied in the CREST trial in patients with ES-SCLC who had responded to initial chemotherapy.[13] The trial did not meet its primary endpoint of improving 1-year

overall survival, but had a signal of improved 2-year survival. However, it reduced the risk of intrathoracic recurrence, particularly in patients with low residual tumour burden, very good response to chemotherapy, and persistent thoracic disease. TRT was excluded from the IMpower133 and CASPIAN trials. Data justifying its routine use and robust safety data are lacking. Therefore, it can be considered on a case-by-case basis, after careful discussion, ideally in a multidisciplinary tumour board.[3,4]

PCI was studied in the EORTC 2007 trial, in which patients were randomized between PCI and observation.[14] In this study, PCI reduced the incidence of symptomatic brain metastases with a mOS of 6.7 vs. 5.4 months for the observation group. A limitation of this trial was the absence of a mandatory brain MRI prior to PCI. A Japanese Phase III trial in 2017 similarly compared PCI with observation, but included brain MRI.[15] This study found no OS benefit, which led to the conclusion that routine PCI is not necessary if MRI surveillance is available. The treatment guidelines note that PCI may be considered in patients with ES-SCLC who have had a good response to chemotherapy and no brain metastases. However, in practice, most clinicians seem to favour surveillance with brain MRI as PCI may not improve survival but might result in toxicities, including neurotoxicity and cognitive effects.[3,4]

Emerging Therapies

The most commonly used second-line treatment for ES-SCLC is topotecan, with a small benefit observed compared to supportive care[16] and similar efficacy to the CAV regimen (cyclophosphamide, doxorubicin, and vincristine).[17] The mOS achieved by this treatment was estimated to be 25 weeks. However, in 2025, the DeLLphi-304 trial, a Phase III, randomized, open-label study, showed improved survival with tarlatamab compared to topotecan.[18] Tarlatamab is a T-cell engager (TCE) targeting delta-like ligand 3 (DLL3). It has shown interesting activity in third-line or further lines of treatment in the DeLLphi-301 study, resulting in a mPFS of 4.9 months and mOS of 14.3 months.[19] In the second line in the DeLLphi-304 trial, tarlatamab was compared to standard chemotherapy in patients who progressed after one prior platinum-based chemotherapy (with immunotherapy if applicable). The mOS improved to 13.6 months with tarlatamab vs. 8.3 months with chemotherapy (HR: 0.60; 95% CI: 0.47 to 0.77). These data have resulted in it becoming a new standard of care in the second-line setting. Tarlatamab's toxicity profile is different from chemotherapy, as cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) have been reported, though most were grades 1–2.[18]

Conclusion

The treatment of SCLC has changed in the last few years. In LS-SCLC, the backbone remains chemoradiotherapy, administered concurrently if possible. The addition of durvalumab as a consolidation treatment has significantly increased survival and has become the new standard of care. In ES-SCLC, the combination of immunotherapy (atezolizumab or durvalumab) with a platinum doublet chemotherapy is routinely used. Radiotherapy with TRT or PCI can be considered on a case-by-case basis. New emerging strategies have also been shown to improve survival, and include the addition of lurbinectedin in the maintenance phase or the modification of second-line treatment or beyond with TCEs, such as tarlatamab. Supportive and multidisciplinary care remain crucial in SCLC to improve outcomes and help maintain patients' quality of life.

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