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Table of Contents

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*The trial studied patients who had received prior trastuzumab, pertuzumab, and T-DM1 in the neoadjuvant, adjuvant, or metastatic setting.[13]

HER = human epidermal growth factor receptor; MBC = metastatic breast cancer; T-DM1 = trastuzumab emtansine.

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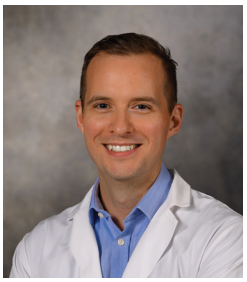

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The Evolution of PARP Inhibitors in Prostate Cancer

Michael P. Kolinsky, MD, FRCPC

Introduction

Poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors induce cell death in cancers by exploiting synthetic lethality, in which the combination of two defective cellular processes are lethal; however, either defect alone is not lethal.[1] PARP inhibitors impair the base excision repair pathway, which functions to repair single strand DNA breaks. Thus PARP inhibitors result in unrepaired single strand breaks, which are converted to double strand breaks during cellular replication. In a normally functioning cell, these double strand breaks are of little consequence, as the homologous recombination repair (HRR) pathway functions to repair these breaks efficiently and accurately. However, in the cellular background of defective HRR, classically through loss of *BRCA1* or *BRCA2* (*BRCA1/2*) protein function, the accumulation of these double strand breaks results in severe genomic stress and ultimately cell death.[2]

An extensive analysis of the early phase clinical trials of PARP inhibitors is beyond the scope of this review. However, it is worth noting the phase II TOPARP studies, were the first published trials investigating a PARP inhibitor in advanced prostate cancer. While the phase I studies of all clinically relevant PARP inhibitors were conducted in populations enriched for patients with mutations in *BRCA1/2*[3–6]; the key innovation of TOPARP was the demonstration of efficacy of the PARP inhibitor olaparib in metastatic castration-resistant prostate cancer (mCRPC) patients with defects in HRR genes other than *BRCA1* or *BRCA2*. The initial TOPARP-A study treated patients with mCRPC with olaparib in a single arm phase II design. The study's findings showed that patients with defects in a diverse range of genes, including *BRCA1, BRCA2, ATM, FANCA, CHEK2, PALB2, HDAC2, RAD51, MLH3, ERCC3, MRE11,* and *NBN,* had responses to treatment.[7] The larger TOPARP-B validation study enrolled 98 patients with mCRPC and pathogenic or likely pathogenic alterations in at least one of the following genes: *BRCA2, ATM, CDK12, PALB2, WRN, CHEK2, FANCA, FANCF, FANCM, ARID1A, ATRX, CHEK1, FANCG, FANCI, NBN,* or *RAD50*. Responses to treatment with olaparib were observed in 43 of the 98 enrolled patients. Response rates reported by gene subgroup analysis were *BRCA1/2*, 83.3%; *ATM*, 36.8%; *CDK12*, 25.0%; *PALB2*, 57.1%; and other, 20.0%. The median radiographic progression free survival in the intention to treat population was 5.5 months,

though this varied by gene subgroup as indicated: *BRCA1/2*, 8.3 months; *ATM*, 5.8 months; *CDK12*, 2.9 months; *PALB2*, 5.3 months; other, 2.8 months.[2] These results suggest a benefit of PARP inhibitors in a broader patient population beyond just patients with *BRCA1/2* alterations. Furthermore, the TOPARP trials have had a significant impact on the design of subsequent trials of PARP inhibitors in advanced prostate cancer.

Single agent PARP inhibitor trials:

Two phase III trials have been published that have evaluated the PARP inihibitors olaparib and rucaparib in patients with mCRPC.

The PROfound clinical trial compared olaparib to the investigators choice of either abiraterone acetate and prednisone (AAP) or enzalutamide in patients with mCPRC who were previously treated with AAP or enzalutamide, with prior taxane chemotherapy allowed. Patients in this trial must have had qualifying alterations in at least one gene of a 15 gene panel including *BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*, based on pre-screening tumour next generation sequencing (NGS). Patients with *BRCA1, BRCA2,* or *ATM* alterations were assigned to cohort A, and those with alterations in one of the other 12 genes were assigned to cohort B. The primary endpoint of this study was imaging-based progression free survival (ibPFS) in cohort A, and secondary endpoints included ibPFS in the overall population, response rates, and overall survival. Importantly, this trial allowed cross over to olaparib for patients with disease progression in the control arm. The PROfound trial met its primary endpoint by demonstrating an improved ibPFS in cohort A, with a median of 7.4 months for olaparib vs. 3.6 months for control (hazard ratio [HR], 0.34; 95% confidence interval [CI], 0.25 to 0.47; P<0.001).[8] A significant improvement in overall survival (OS) was also demonstrated in the cohort A population, with a median OS of 19.1 months for olaparib vs. 14.7 months for control (HR, 0.69; 95% CI, 0.50 to 0.97; P = 0.02),[9] despite 67% of cohort A patients in the control arm crossing over to receive olaparib. Results in cohort B were more modest, with a trend toward improvements in ibPFS and OS, with a median ibPFS of 4.8 months for olaparib vs. 3.3 months for control (HR 0.88, p value not reported), and a median OS of 14.1 months for olaparib vs. 11.5 months for control (HR 0.96, 95% CI 0.63 to 1.49, p value not reported). An exploratory gene-by-gene analysis of the PROfound trial has been published, and while limited by a small number of patients with alterations in many of the genes of interest, it is clear that the greatest benefit of olaparib is observed in patients with *BRCA2* alterations, with a modest if any benefit seen in patients with *ATM* alterations. The PROfound trial has led to the approval of olaparib by Health Canada for patients with mCRPC and alterations in *BRCA1, BRCA2,* and *ATM* genes based on findings from the cohort A population; whereas the FDA has approved olaparib in a broader population based on findings from the cohort A and B populations, except for patients with *PPP2R2A* alterations, who did not derive benefit from olaparib treatment.

The TRITON3 clinical trial[10] investigated rucaparib vs. a control arm of investigator's choice of therapy and was in many ways similar in design to the PROfound trial. Both trials investigated the use of a single agent PARP inhibitor compared to a control arm of standard therapies, in a previously treated mCRPC population. In both trials, patients underwent biomarker pre-screening for alterations in DNA repair genes. The primary end point of both trials was ibPFS. However, there were some key differences between the two trials. In the TRITON3 trial, the qualifying genetic alterations were limited to those in *BRCA1, BRCA2,* and *ATM* genes; eligible patients were those who received one line of prior androgen receptor pathway inhibitor (ARPI) and no prior taxane chemotherapy for mCRPC; and options in the control arm were AAP and enzalutamide, similar to the PROfound trial, but also included docetaxel. This final point is important to highlight, as a key criticism of the PROfound trial has been the choice of a relatively ineffective treatment as the control arm.[11] Indeed, in the TRITON3 trial, 56% of patients in the control arm were selected to receive docetaxel. In the overall population, rucaparib demonstrated a superior ibPFS with a median of 10.2 months for rucaparib vs. 6.4 months for control (HR, 0.61 95% CI, 0.47–0.80, p<0.001); with similar results observed in the *BRCA* subgroup, with a respective median ibPFS of 10.2 months for rucaparib vs. 6.4 months for control (HR,-0.50 95% CI 0.36–0.69, p<0.001). Similar to the PROfound trial, patients with *ATM* alterations were found to derive less benefit than that of those with *BRCA*, with a median ibPFS of 8.1 months for *BRCA* vs. 6.8 months for *ATM* (HR, 0.95, 95% CI, 0.59–1.52). Importantly,

the benefit of rucaparib was consistent when compared with either docetaxel or ARPI. The interim OS analysis has shown a trend toward improvement with a median OS of 23.6 months vs. 20.9 months (HR, 0.94, 95%.CI, 0.72–1.23) for rucaparib vs. control, respectively, in the overall population. Rucaparib had previously received FDA accelerated approval in mCRPC patients with *BRCA* alterations based on the phase II TRITON2 study, with the TRITON3 study supporting that approval. At the time of publication, rucaparib has not received Health Canada approval in this indication.

PARP inhibitor and ARPI combinations trials:

A number of trials have evaluated PARP inhibitors in combination with, as opposed to progression after, first line ARPIs. In contrast to the single agent trials however, these trials tested PARP inhibitors in a broader "all-comers" population, with biomarker stratification as opposed to selection. This approach was supported by pre-clinical evidence suggesting that ARPI therapy may induce a homologous recombination (HR) deficient state, which sensitizes cancers without genomic HRR defects to PARP inhibitors.[12,13] This hypothesis was further supported by the phase II Study 08, in which ARPI naive mCRPC patients were treated with AAP with either placebo or olaparib.[14] The study population did not undergo biomarker pre-screening. However, tumour and germline NGS was performed, and biomarker status (presence or absence of a pathogenic HRR gene alteration) was used in an exploratory analysis. The study demonstrated that the experimental treatment improved rPFS, with a median of 13.8 months for the experimental treatment arm vs. 8.2 months for the control arm (HR 0.65, 95% CI 0.44–0.97, p=0.034) with a consistent benefit across HRR biomarker status.

Following the findings of Study 08, three phase III trials have been published using a similar therapeutic strategy, though with slightly different designs.

PROpel, essentially the phase III extension of Study 08, evaluated the combination of AAP with either placebo or olaparib. The drugs were administered at standard doses for single agent use in mCPRC patients without prior exposure to ARPI or docetaxel for mCRPC.[15] While ARPI use other than AAP in earlier disease states was allowed, only one patient in the experimental arm received a prior ARPI, therefore this population should be considered ARPI naive. The primary end point of the trial was investigator-assessed ibPFS in the intention-to-treat population. The biomarker status was determined after enrolment (i.e. was not used as a prospective stratification factor). The biomarker status was determined using tumour tissue, ctDNA, and whole blood NGS. Patients were categorized by *BRCA* mutational status, as well as HRR mutational status, based on a 14 gene panel. Among the 399 patients who were randomized, ibPFS was significantly improved, with a median of 24.8 months for the experimental arm vs. 16.6 months for the control arm (HR, 0.66, 95% CI 0.54–0.81, p<0.001). This finding was consistent across all subgroups, though a greater benefit was apparent in the HRRm subgroup (median ibPFS not reached in the experimental arm vs. 13.9 months in the control arm; HR, 0.50 95% CI 0.34–0.73) vs the non-HRRm subgroup (median ibPFS of 24.1 months in the experimental arm vs 19.0 months in the control arm; HR, 0.76, 95% CI 0.60–0.97). The updated final OS analysis demonstrated a trend toward OS benefit, with a median OS of 42.1 months vs 34.7 months for the experimental and control arms, respectively. While this is an important numerical difference, it failed to reach statistical significance.[16] It is important to note that this study was conducted when access to standard of care PARP inhibitors was limited; and only 1% of patients in each arm subsequently received a PARP inhibitor.

TALAPRO-2 was a phase III trial that evaluated the combination of enzalutamide 160 mg daily with either placebo or talazoparib 0.5 mg daily, (whereas the standard single agent dose of talazoparib is 1 mg daily) in mCRPC patients with no prior mCRPC therapy, though prior docetaxel, abiraterone, or orteronel therapies were allowed in the mCSPC setting. In contrast to the PROpel trial, the biomarker status was defined prospectively during the trial screening procedures and was used as a stratification factor. Patients underwent tumour tissue and ctDNA analysis to classify their HRR mutational status based on a 12 gene panel. The primary endpoint of the study was rPFS that was assessed by a blinded independent central review. This study randomized 805 patients, of which only 50 were previously treated with an ARPI. The results of the TALAPRO-2 study were consistent with those from the PROpel trial, with a significant improvement in rPFS in the intention-to-treat population, with a median

rPFS not reached for the experimental arm vs. 21.9 months for the control arm (HR, 0.63, 95% CI 0.51–0.78, p<0.0001). Similar to the PROpel trial, a benefit was observed irrespective of biomarker status, with the greatest benefit observed in the BRCAm subgroup (HR, 0.23, 95%CI 0.10–0.53, p=0.0002), followed by the non-BRCA HRRm subgroup (HR, 0.66; 0.39–1.12, p=0.12), with the non-HRRm or unknown subgroups showing the least benefit (HR 0.70, 95%CI 0.54–0.89, p=0.0039). Overall survival data is not yet mature.

The MAGNITUDE trial, which investigated AAP at standard dosing with either placebo or niraparib 200 mg daily (standard single agent dose of niraparib is 300 mg, or 200 mg in patients <77 kg or baseline platelet count <150,000/uL) included design elements that were distinct from the other combination trials. Similar to the TALAPRO-2 trial, patients underwent prospective biomarker analysis prior to randomization, using tumour tissue, ctDNA, and whole blood to determine HRR gene mutation status, though in this trial a 9 gene panel was used. Unlike the other trials, however, patients were allocated to and analyzed in two distinct cohorts. The HRR+ cohort included patients who had at least one pathogenic alteration in at least one gene, and the HRR- cohort included patients with no pathogenic alterations. An additional unique aspect of this trial was that up to 4 months of AAP treatment for mCPRC was allowed prior to randomization to allow time for HRR biomarker testing, which 23% of patients on the trial had received. The primary endpoint of this trial for both cohorts was rPFS assessed by a blinded independent central review. In the HRR+ cohort that included 212 randomized patients, rPFS was significantly prolonged, with a median of 16.6 months in the experimental arm vs. 10.9 months in the control arm (HR, 0.53, 95% CI 0.36–0.79). However, on subgroup analysis, this finding was largely driven by the patients with *BRCA* mutations (HR 0.55, 95% CI 0.38–0.81), and patients with other non-BRCA HRR mutations demonstrating minimal if any benefit (HR, 0.99, 95% CI 0.68–1.45). Outcomes in the secondary endpoints all favoured the experimental arm. In the HRR- cohort, a futility analysis was performed after 233 patients were randomized. This analysis used both the time to PSA progression and rPFS as individual endpoints. In addition, these two measures were also used together as a composite endpoint. Futility was declared for this cohort ,with the composite endpoint showing no benefit of niraparib (HR, 1.09, 95%, 95% CI 0.75–1.57, p=0.66).

The reasons why the MAGNITUDE trial failed to demonstrate an rPFS benefit of adding niraparib to AAP in patients without *BRCA* alterations are not known but may include the following: The drug itself, which seems unlikely given that niraparib has demonstrated comparable efficacy to other PARP inhibitors as a single agent in both prostate and ovarian cancer. The reduced dose of niraparib, again this is unlikely given that the 200 mg starting dose has been used in ovarian cancer trials in patients with a baseline weight of <77 kg or a platelet count of <150,000 uL and that this dose has shown a similar efficacy to the 300 mg dose; [17,18] or the different design of the trial itself. In contrast, the consistent results demonstrated in the PROpel and TALAPRO-2 trials leaves little doubt that the benefits of these therapies exist across patient subgroups. The controversy associated with these trials is rather whether the benefit observed in the non-BRCA patient population can translate into a meaningful clinical benefit. At present, this remains an academic question, as both olaparib and niraparib have only been approved by Health Canada for use in combination with a first line AAP in patients with mCRPC and pathogenic *BRCA1/2* alterations.

Approach to patients:

Most Canadian jurisdictions now have access to tumour and/or germline NGS for *BRCA1, BRCA2,* and *ATM* at a minimum, with many using broader gene panels. I believe that, where available, all patients with mCRPC should undergo NGS testing, as well as those in earlier disease states that are likely to progress to mCRPC, such as mCSPC and nmCRPC.

A key distinction is whether patients have previously been treated with an ARPI in an earlier disease state. While prior ARPI therapy was allowed in the combination trials, the vast majority of patients on these trials were ARPI naive and therefore the results of these trials should only be applied to this population.

ARPI naive patients:

Let us first consider a patient with mCRPC with a pathogenic or likely pathogenic (also referred to as Tier I or Tier II) alteration in *BRCA1* or *BRCA2* identified on tumour or germline NGS who has not yet received an ARPI. First line mCRPC options for this patient would include

ARPI monotherapy, ARPI plus PARP inhibitor combination therapy, or docetaxel. The first consideration is that patients with *BRCA* alterations have worse outcomes on ARPI therapy compared to patients with *BRCA* wildtype. This has been conclusively demonstrated in the PROpel and TALAPRO-2 studies in which rPFS was significantly shorter for patients with HRR+ compared to HRR- patients treated on the control arms of these trials. The combination trials definitively show improved efficacy of combination therapy as measured by rPFS, as well as a number of other secondary endpoints, including response rate, time to subsequent therapy, and PFS2. However, some authors debate whether this benefit can justify exposing patients to the significantly increased cost and toxicity associated with PARP inhibitors.[19] For instance, PARP inhibitors are associated with increased toxicity, particularly hematologic toxicity, and nausea. These adverse effects are generally manageable with supportive treatment, treatment interruptions, and/or dose reduction, as evidenced by only modestly increased rates of treatment discontinuation in the combination trials. Reassuringly, combination therapy did not have a negative impact on patients' reported quality of life outcomes as described in the PROpel and MAGNITUDE trials. Undoubtedly the financial cost of combination therapy is significantly higher than that of sequential monotherapy use. While AAP is now available as a generic medication, significantly reducing its cost, the cost of olaparib for a 28-day cycle is $7380CAD,[20] with a median duration of exposure to olaparib of 17.5 months in the PROpel trial and 7.4 months in the PROfound trial. Additionally, OS benefit has not been demonstrated in any of the trials conducted thus far. And because so few patients received PARP inhibitors after progression (approximately 2% in both PROpel and TALAPRO-2 trials, and in the MAGNITUDE trial, 1% in the experimental arm, and 20% in the control arm), even a survival advantage would not address the question of whether combination therapy is superior to sequential monotherapies. On the other hand, delaying progression is an important goal for both clinicians and patients, and the magnitude of benefit observed in these trials is clinically meaningful. Therefore, in my opinion, all eligible patients should be considered for combination ARPI and PARP inhibitor therapy when it is available in the first line mCRPC setting if no prior ARPI has been received in earlier disease states. Moreover, a balanced discussion of the risks and benefits should take place to facilitate a shared decision-making process between the patient and clinician. However, for patients who are not willing to undergo the additional monitoring required for these combination therapies, for those who desire a decreased pill or side effect burden, or in situations in which financial cost is a limiting factor, sequential monotherapies with ARPI followed by a PARP inhibitor remains a reasonable therapeutic strategy.

There is no available data that compares the efficacy of first line ARPI and PARP inhibitor combinations to docetaxel for mCRPC patients; however, the TRITON3 trial demonstrated that rucaparib was superior to docetaxel in a cohort of patients with *BRCA* or *ATM* alterations after progression on ARPI. Therefore, I think it is a reasonable extrapolation that combination therapy is likely preferable to docetaxel in the ARPI naive setting. However, there are some clinical settings in which docetaxel may remain a treatment option, such as patients with a very low PSA relative to the burden of metastatic disease, in such cases ARPI therapies tend to have limited efficacy.

APRI pre-treated patients:

Patients with mCRPC previously exposed to an ARPI should be considered for PARP inhibitor monotherapy, especially considering that this was the population studied in the PROfound and TRITON3 clinical trials. Both trials primarily studied patients with pathogenic alterations in *BRCA1, BRCA2,* or *ATM*; at present, olaparib is approved by Health Canada for this indication, and rucaparib is not approved.

In my opinion, the choice of when to use olaparib depends on the gene alteration present, what other therapies are available, and patient factors, including their preferences. For patients with *BRCA* alterations, I preferentially use olaparib over other therapies based on the PROfound and TRITON3 trials that demonstrated benefit over second line ARPI, and the TRITON3 trial, which showed benefit over docetaxel. While there is no direct comparison, the objective response rate of 44% and the PSA50% response rate of 62%, respectively, that were observed in the PROfound trial[8] in *BRCA* patients compare favourably with findings that have been demonstrated in the registration trials for radium 223,[21] cabazitaxel,[22] and Lu-177-PSMA-617.[23] Additionally, most patients value an oral therapy for its convenience over intravenous therapies.

My approach to patients with *ATM* alterations follows a similar logic as noted above, but given the very modest efficacy demonstrated in the PROfound trial for this subgroup, with an objective response rate of 10% and a PSA 50% response rate of 13%,[8] with similar results noted in the TRITON3 trial, I generally recommend other agents, such as taxane chemotherapy, prior to olaparib. However, I consider using olaparib in patients who may not be fit for, or those who chose to avoid or delay, cytotoxic chemotherapy as long as they are asymptomatic or minimally symptomatic with a relatively low disease burden, such that if disease progression occurs it is not likely to cause significant clinical deterioration.

Conclusions

The introduction of PARP inhibitors in the management of advanced prostate cancer has been a significant breakthrough that offers benefits to patients. With numerous active and ongoing trials, this is a rapidly evolving field and we can anticipate further shifts in treatment approaches. As with other therapeutic agents, we may witness the introduction of PARP inhibitors into earlier disease states, such as metastatic castration sensitive prostate cancer. As always, when making treatment decisions in collaboration with patients, it is important to balance the efficacy of these treatments with their side effect burden and financial cost.

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KRAS Inhibitors in Lung Cancer: Current Strategies and Future Approaches

Kenneth G Samala, MD
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Introduction

RAS (rat sarcoma viral oncogene homolog) proteins were among the earliest identified proteins that regulate cell growth, differentiation, and survival.[1,2] The seminal work of Harvey and Kirsten in the 1960s paved the way for discovering these proteins that are encoded by retroviral oncogenes initially observed in rat sarcoma viruses.[3,4] Among the different RAS proteins discovered to date, the *KRAS* (Kirsten Rat Sarcoma viral oncogene) isoform is the most frequently mutated in human cancers, occurring in 75% to 80% of cancers, followed by neuroblastoma RAS (*NRAS*), occurring in 12%, and Harvey RAS (HRAS), occurring in 3% of RAS cancers.[1,5,6] *KRAS*, together with Epidermal Growth Factor (*EGFR*) and Anaplastic Lymphoma Kinase (*ALK*), are the most commonly identified oncoproteins, with known mutations in non-small cell lung cancer (NSCLC), and have been the focus of many research studies over the years.[7,8] Despite significant success in targeting both *EGFR* and *ALK* mutations in NSCLC, more progress has yet to be made in developing therapies for *KRAS* mutations.[9]

Geographic variations have been observed in NSCLC patients harbouring *KRAS* mutations. The highest incidence has been observed in the Western hemisphere, particularly in Europe and North America (20–25% prevalence among Caucasians) and a lower prevalence has been observed in East Asian regions and India, with a range of (10–15%).[5,6,10,11] *KRAS* mutations are frequently detected in lung adenocarcinoma (32%) and are rarely identified in squamous cell carcinoma.[5,12,13] *KRAS*-mutant lung cancers are more common among smokers [14–17], and those with high programmed death-ligand 1 (PD-L1) expression,[18] causing increased immune invasion hypothesized to be due to chronic exposure to particulate matter from smoking.[19,20] The use of immunotherapy in *KRAS*-driven lung cancer remains unclear as co-mutations such as *STK11* and *KEAP1* may diminish the benefit of immunotherapy, especially among those with *KRAS* mutant NSCLC.[21,22] Therefore, developing *KRAS*-specific drugs is essential to improve the treatment outcomes of this patient population. There are several subtypes of *KRAS*, with most point mutations occurring at exons 2 and 3, representing hotspots at codons G12, G13, and Q61.[5,23,24] *KRAS* G12C is the most frequent subtype at 41–43% among NSCLC patients, making it a reasonable target for drug development.[25,26] Moreover, NSCLC patients with G12C mutations tend to have a poorer prognosis and usually present with metastatic disease upon diagnosis compared to other *KRAS* subtypes or patients with *KRAS* wild-type.[13,27].

Two small-molecule inhibitors are currently approved by the FDA for NSCLC patients harbouring *KRAS* G12C mutations, namely sotorasib[27,28] and adagrasib.[29] A few molecules that target *KRAS* G12C, in addition to other *KRAS* mutations, are also in early to mid-clinical development. In this review, we will focus on *KRAS* G12C inhibitors.

KRAS Mutations in Lung Cancer

RAS proteins function as finely regulated molecular switches in the cell membrane that cycle between an activated GTP (guanosine triphosphate)-bound and an inactivated GDP (guanosine diphosphate)-bound state. Two regulatory proteins govern the switching process to the active and inactive state: **1)** guanine nucleotide exchange factor (GEF), which helps GTP to bind to RAS, leading to its activation, while **2)** GTPase activating protein (GAP) leads the hydrolysis of GTP to GDP, causing RAS inactivation. Mutations in *KRAS*

impair the hydrolysis of GTP to GDP; thus, *KRAS* remains in its active state, leading to unregulated activation of several downstream intracellular pathways, including the RAF-MEK-ERK pathway, PI3K-AKT-mTOR pathway, and ral guanine nucleotide dissociation stimulator (RALGDS) which are responsible for cellular proliferation, differentiation, cell migration, and survival.[30,31]

In addition to their effects on the downstream signalling pathways, it has also been established that *KRAS* mutations have a role in immune system modulation through their interaction with the tumour microenvironment (TME), which can influence tumour progression and anti-tumour response.[2,32]

Strategies for *KRAS* G12C inhibition

The FDA granted approval to two targeted agents for *KRAS* G12 mutated NSCLC, which are sotorasib and adagrasib, while Health Canada has only granted approval of sotorasib. Both agents are covalent allosteric inhibitors of *KRAS* G12C, which prevents the release of GDP and subsequent binding of GTP, locking the mutant *KRAS* in an inactive state by wedging into a cleft around the Switch II domain.

Sotorasib is the first *KRAS* G12C inhibitor to enter a clinical trial. The phase 2 CodeBreaK 100 trial demonstrated a clinical benefit of sotorasib in patients who had received at least one prior systemic therapy. The results showed an objective response rate (ORR) of 37.1%, a median progression-free survival (PFS) of 6.8 months, a median duration of response (DOR) of 11.1 months, and a median overall survival (OS) of 12.5 months.[27] The clinical benefit was further supported by the subsequent phase 3 study, CodeBreak 200, which compared the *KRAS* G12C inhibitor to docetaxel in NSCLC patients who had progressed on platinum-based chemotherapy and checkpoint inhibitor therapy. The median PFS and ORR were superior, with the PFS for sotorasib at 5.6 months vs 4.5 months with docetaxel, and an ORR of 28.1% for sotorasib vs 13.2% for docetaxel. There was no difference in OS between the treatment arms.[33] Docetaxel-treated patients reported more severe symptoms and more significant negative impact from toxicity than sotorasib-treated patients. The quality-of-life as measured by the EQ5D visual analog scale started to deteriorate within 5 days after docetaxel was initiated and continued to deteriorate over time; with sotorasib, QOL was preserved over time.[34]

Adagrasib is the second irreversible and selective *KRAS* G12C inhibitor approved for use among NSCLC patients harbouring this mutation who were previously treated with chemotherapy and immunotherapy. Adagrasib has also demonstrated clinical efficacy with an ORR of 42.9%, a median PFS of 6.5 months, a median DOR of 8.5 months and a median OS of 12.6 months.[28] The phase 3 study (NCT04685135) comparing adagrasib and docetaxel in patients with *KRAS* G12C mutation-positive NSCLC who had received prior platinum-based chemotherapy and immunotherapy has finished enrolment, and the results are pending.

Since the availability of these two molecules, clinicians are now concerned about the most appropriate drug for their patients. As noted previously, sotorasib and adagrasib have a similar PFS and OS. In contrast, adagrasib has shown a numerically higher ORR along with higher drug-related adverse events and, consequently, a higher treatment discontinuation rate (although caution must be exercised when performing cross-trial comparisons). Both molecules cause substantial gastrointestinal side effects including diarrhea, nausea or vomiting, and elevations in liver enzymes (**Table 1**).[26,28,35]

One preclinical study reported a high concentration of adagrasib in the cerebrospinal fluid, which is comparable to other targeted therapies for other oncogenic mutations that have good activity against brain metastasis (osimertinib, alectinib, lorlatinib).[36–40] Moreover, in the phase II KRYSTAL-1 study, the use of adagrasib showed an intracranial (IC) ORR and disease control rate (DCR) of 33% and 85%, respectively. The IC PFS was 5.4 months, supporting the utility of adagrasib in NSCLC patients with brain metastases.[29] Conversely, sotorasib has limited data on central nervous system (CNS) activity. A posthoc analysis of the CodeBreak 100 trial, including 16 patients with stable brain metastases, demonstrated an IC DCR of 88%[39]. In the subgroup analysis of patients who presented with brain metastases at the time of enrollment in CodeBreak 200, those treated with sotorasib had a decrease in the risk of progression and a trend to delay in the development of new brain metastases.[40]

The presence of co-mutations and their potential impact on efficacy was also explored. CodeBreak 100 and KRYSTAL-1 showed a higher ORR and PFS for those with *STK11* alone and those with *STK11* and/or *KEAP1* and *TP53* mutations.[41,42] However, CodeBreak 200 did not show any

Event	Any Grade *number of patients (%)*	Grade ≥ 3 *number of patients (%)*
Sotorasib (N=126)[28]		
Diarrhea	40 (31.7)	5 (4.0)
Nausea	24 (19.0)	0
Alanine aminotransferase (ALT) increase	19 (15.1)	8 (6.3)
Aspartate aminotransferase (AST) increase	19 (15.1)	7 (5.6)
Fatigue	14 (11.1)	0
Vomiting	10 (7.9)	0
Adagrasib (N=116)[29]		
Diarrhea	82 (70.7)	1 (0.9)
Nausea	81 (69.8)	5 (4.3)
Fatigue	69 (59.5)	8 (6.9)
Vomiting	66 (56.9)	1 (0.9)
Anemia	41 (36.2)	17 (14.7)
Dyspnea	41 (35.3)	12 (10.3)
Alanine aminotransferase (ALT) increase	33 (28.4)	6 (5.2)
Aspartate aminotransferase (AST) increase	31 (26.7)	6 (5.2)

Table 1. Adverse Events Reported during Treatment with Sotorasib and Adagrasib; *courtesy of Kenneth Samala, MD and Qunicy S-C Chu, MD.*

difference in benefit for those with *STK11*, *KEAP1*, and *TP53* but showed less benefit for those with other co-mutations.[33] More studies in predictive biomarkers are warranted.

Several molecules targeting *KRAS* G12C mutations are currently being developed and studied. Most have shown promising preliminary clinical activity and tolerable side effects and are summarized in **Table 2**.

Challenges in managing *KRAS* mutated NSCLC

KRAS and *CNS* metastases

The lifetime incidence of brain metastases in NSCLC patients with *KRAS* G12C mutations is approximately 40%. Hence, effective treatment options for CNS disease are a significant unmet need in this population.[35] Although data have demonstrated the preliminary IC activities of both sotorasib and adagrasib in patients with *KRAS* G12C mutant NSCLC,[29,39,40] further studies on patients with known brain metastases are needed.

Resistance mechanisms

One of the significant challenges in targeted therapies is the invariable development of acquired resistance. The lower ORR for both sotorasib and adagrasib (compared to other drugs against EGFR and ALK mutations)[46–48] may be explained by the intrinsic mechanisms of resistance to *KRAS* G12C inhibitors, including an adaptive RAS-MEK pathway feedback reactivation.[28,29,50,51] There are three main acquired mechanisms of resistance, namely **1)** on-target mechanisms,[52,53] **2)** bypass mechanisms,[53,54] and **3)** lineage plasticity and epithelial-to-mesenchymal transition (**Table 3**).[53] Undiscovered mechanisms could still exist, which supports the need for and importance of investigating resistance mechanisms to develop tolerable combination strategies with superior outcomes compared to the *KRAS* G12C inhibitor alone.

Development of *KRAS* G12C combinations can be challenging, such as the combination with PD(L)1. Li et al. reported 30–50% of secondline and beyond *KRAS* G12C positive metastatic NSCLC patients who received either sequential or concurrent sotorasib at 120–960 mg daily and pembrolizumab or atezolizumab, developed >grade 3 hepatotoxicity with the majority occurring beyond the first 30 days of therapy, which resolved with corticosteroid treatment. The phase II study of adagrasib at 400 mg BID in combination with pembrolizumab at 200 mg intravenously Q3W in treatment-naïve, advanced *KRAS* G12C mutation positive NSCLC still reported 16% of patients experiencing >grade 3 hepatotoxicity and 6.7% required corticosteroid treatment.[55] Dose reductions and interruptions were reported in 46% and 59% of patients, respectively. Treatment-related adverse event discontinuation of adagrasib, pembrolizumab and both agents were 6%, 11% and 4%, respectively.[56] The preliminary results of the phase I dose expansion of MK-1084 at 400 mg daily and pembrolizumab, reported hepatoxicity in up to 13% of treatmentnaïve *KRAS* G12C mutation positive, advanced NSCLC patients.[43]

A retrospective analysis by Chour et al. reported that patients treated with PD(L)1 immediately followed by sotorasib experienced more >grade 3 toxicity (50% versus 13%), especially hepatoxicity (33% versus 11%), than those who were not treated with this regimen. There were no fatal events. The majority of the hepatoxicity occurred within 30 days after initiation of sotorasib.[57]

Future approaches

Advances in drug development for *KRAS* mutations in the last few years has led to the approval of two selective *KRAS* G12C inhibitors, and recently, other inhibitors specific for G12D, G12S, and G12R have been identified.[58–60] Although this progress is promising, *KRAS*-mutated cancers have many other subtypes. Developing a specific drug for each one may be impractical, since nearly 20% of *KRAS* mutations occur at frequencies of, at most, 2%.

A way to resolve this issue is to develop a pan-KRAS-selective inhibitor that targets all *KRAS* subtypes while sparing RAS signalling in normal cells. Currently, two pan-*KRAS*-selective inhibitors are in preclinical development. BI-2865 and its close analogue, BI-2493, have shown activity against *KRAS* mutants and wild-type *KRAS* in cells and in animals, respectively. Both drugs spare the inhibition of NRAS and HRAS proteins.[53]

In opposition to the current inhibitors that are directed to the inactivated "*KRAS*-off" molecule, targeting *KRAS* in its GTP-bound activated "*KRAS*-on" state, may lead to further advances. For example, RMC 6236, which binds to

Molecule (Company)	Phase	Eligibility	Prior G12C Therapy?	Safety (All Grades) *(%)*	Clinical Activity	Recommended Dose
JDQ443 (Novartis)[43] n=68	Ib/II	advanced, *KRAS* G12C-mutated solid tumours (including 38 NSCLC patients); previous standard-of-care treatment; aged ≥18 years; and ECOG PS 0–1	Prior treatment with a *KRAS* G12C inhibitor may be allowed for dose escalations of combinations and a subset of groups in dose expansion; not allowed in the monotherapy arm	Fatigue (16.2) Nausea (17.6) Diarrhea (13.2) Edema (11.8) Vomiting (11.8) Grade ≥3: Neutropenia (2.9)	ORR of 41.27% (for response evaluable NSCLC patients); ORR of 54.5%	200 mg BID
Divarasib (Roche) [44] n=59 (NSCLC patients only)	I	*KRAS* G12C-mutated solid tumours (including 60 NSCLC patients) who had progressed after at least one available standard therapy; aged ≥18 years; and ECOG PS 0 or 1	Not allowed	Nausea (76.3) Diarrhea (61) Vomiting (54.2) Grade ≥3: Diarrhea (3.4) Increased ALT (6.8) Increased AST (5.1)	Response rate of 53.4% and median PFS of 13.1 months for NSCLC patients; confirmed response rate of 56.4% and median PFS of 13.7 months	400 mg OD
LY3537982 (Eli Lilly)[45] n=56	I	Locally advanced, unresectable and /or metastatic solid tumour with KRAS G12C mutation (including 16 NSCLC patients); aged ≥18 years; and ECOG PS 0 or 1	Prior G12C therapy allowed in other groups	Diarrhea (38) Constipation (16) Fatigue (16) Peripheral edema (13) Nausea (11) Grade ≥3: Neutropenia (2)	ORR of 38% in patients with *KRAS* G12C inhibitor-naïve NSCLC and ORR of 7% in NSCLC patients with prior exposure to *KRAS* G12C inhibitors.	100 mg BID
MK-1084 (Merck Sharp & Dohme)[46] n=24 (Arm 2 in combination with Pembrolizumab in patients with untreated NSCLC with PD-L1 TPS ≥1%)	I	Locally advanced unresectable or metastatic solid tumours with a *KRAS* G12C mutation and ≥1 line of prior therapy (Arm 1), or previously untreated metastatic NSCLC with PD-L1 TPS ≥1% (Arm 2); aged ≥18 years; and ECOG PS 0 or 1	No information provided	Increased ALT (79) Increased AST (33) Pruritus (29) Diarrhea (17) Fatigue (13) Grade ≥3: Increased ALT (13) Increased AST (8)	ORR of 19% in Arm 1 (including 4 NSCLC patients) and 47% in Arm 2	800 mg OD monotherapy and 400 mg with Pembrolizumab

Table 2. Current *KRAS* G12 C Molecules Undergoing Early Clinical Trials; *courtesy of Kenneth Samala, MD and Qunicy S-C Chu, MD.*
Abbreviations: ALT: alanine amino transferase; **AST:** aspartate aminotransferase; **BID:** dosing regimen of twice a day; **ECOG:** Eastern Cooperative Oncology Group; **NSCLC**: non-small cell lung cancer; **OD:** dosing regimen of once daily; **ORR**: overall response rate; **PD-L1**: programmed cell death ligand 1; **PFS**: progression-free survival; **TPS:** tumour proportion score

Mechanism	Details
On-target mechanisms[52,53]	Through secondary mutations affecting *KRAS* (via nucleotide exchange or changing GTPase activity): Example: • Sotorasib – G13D, R68M, A59S, A59T • Adagrasib – Q99L, Y96D, R68S0
Bypass mechanisms[53,54]	Via activation of RTK-RAS-MPK signalling pathways, including mutations in *NRAS*, *BRAF*, *MEK*, and *FGFR3*, to name a few
Lineage plasticity and epithelial-to-mesenchymal transition[53]	Through histological transformation from adenocarcinoma to squamous cell carcinoma and activation of the PI3K pathway

Table 3. Summary of Known Acquired Mechanisms of *KRAS* Resistance; *courtesy of Kenneth Samala, MD and Qunicy S-C Chu, MD*.

Abbreviations: BRAF: v-raf murine sarcoma viral oncogene homolog B1, **FGFR:** fibroblast growth factor receptor, **MEK:** mitogen-activated protein kinase, **NRAS:** neuroblastoma; RAS, **PI3K:** phosphoinositide 3-kinase, **RTK:** receptor tyrosine kinase

cyclophilin A, which, in turn, binds to RAS, which then leads to steric hindrance for RAF binding and activation.[61] In the near future, single-agent molecules that can potentially target almost all *KRAS* mutations will enter clinical trials, and their impact in the treatment landscape of *KRAS* mutated cancers is highly anticipated. One possible significant advantage of targeting several mutations is the prevention of secondary on-target mutations in *KRAS*.

Lastly, the outcomes for patients with CNS metastases are poor. Further investigation on the CNS penetration ability of the new targeted therapies and the development of better strategies for treating brain metastases of *KRAS* mutations in NSCLC patients are warranted to further improve their outcomes.

Conclusion

For many years, tumours harbouring *KRAS* mutations were deemed not targetable. However, recent developments in the understanding of *KRAS*-directed therapies and the approval of two drugs against *KRAS* G12C are steps in the right direction, yet more research is still needed. Admittedly, several challenges still loom in the development of an ideal drug against *KRAS* mutations—one that has good efficacy data (including CNS penetration), a tolerable side effect profile, and the ability to target several *KRAS* mutations simultaneously (hence, reducing the chance of on-target acquired resistance). Ongoing studies are being conducted to further determine the proper treatment approaches, such as the appropriate sequences or therapy combinations (including chemotherapy or immunotherapy), to improve the outcomes for patients with this elusive mutation. Overall, the progress made in the last decade is encouraging, and a highly effective treatment against *KRAS*-mutated NSCLC may be within reach in the next few years.

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About the Author

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Early Age Onset Colorectal Cancer: A Canadian Perspective

Michael J. Raphael, MD, FRCPC

Background

In Canada, 92% of colorectal cancer cases occur in patients over 50 years of age.[1] Accordingly, most colorectal cancer research and early-detection efforts have traditionally focused on older Canadians. However, the epidemiology of colorectal cancer in Canada is changing. Over the past three decades there has been a substantial decrease in the incidence of colorectal cancer among patients over age 50 but an alarming increase in the incidence among patients under 50.[2] It is estimated that by 2040 colorectal cancer will be the leading cause of cancer-related death for individuals aged 20–49.[3] This paper will provide a broad overview of the unique characteristics and care needs affecting patients with early age onset colorectal cancer (EAOCRC) from a Canadian perspective. Unless otherwise specified, EAOCRC will refer to individuals diagnosed with colorectal cancer under age 50.

Epidemiology of Early Onset Colorectal Cancer

Colorectal cancer is the third most common cancer and the second leading cause of cancer-related deaths in Canada.[1] In positive news, colorectal cancer incidence is declining faster than that of any other cancer in Canada. Between 1984 and 2019, the age-standardized incidence rate of colorectal cancer decreased by 4.0% and 3.1% per year among males and females, respectively.[1] However, this overall decline is being driven by a decrease in the incidence of colorectal cancer among adults aged 50 and over and has been largely attributed to uptake of organized colorectal cancer screening programs that detect and remove pre-cancerous polyps.[4,5]

In contrast, the incidence of EAOCRC has risen dramatically in Canada. A recent analysis using national Canadian cancer registries found a mean annual percentage increase in the incidence of colorectal cancer of 3.47% and 4.45% among males and females under age 50, respectively.[2] This analysis also identified a strong birth cohort effect, with the

more recently born young adults having higher rates of EAOCRC compared to those born earlier. Canadian men and women born in 1986 have double the risk of EAOCRC compared to those born in 1936.

Importantly, the data shows there is an alarming increase in the incidence of EAOCRC among very young Canadians. Among patients under age 50, the largest annual increase in incidence for colon and rectal cancer was noted in patients aged 20–29 and 30–39, respectively.

Risk Factors for Early Age Onset Colorectal Cancer

The reason for a rise in the incidence of EAOCRC is not known. Most likely, the reason is multi-factorial and includes a complex interplay of lifestyle, environmental and genetic factors. While studies have sometimes reported conflicting results, the most consistently reported risk factors for EAOCRC include family history, sedentary lifestyle, obesity and Westernized diet.[6] Multiple pathobiological mechanisms have been proposed, including alterations to the gut microbiome,[7] fat-tissue associated dysregulation of insulin signalling, and inflammatory and hormonal response pathways.[8]

Family History – Lynch Syndrome is the most common cause of hereditary colorectal cancer, accounting for approximately 8% of EAOCRC.[9] Although patients with EAOCRC are more likely to have an underlying genetic condition compared to older adults, nearly 85% of EAOCRC is sporadic.[9] Accordingly, a negative family history is often falsely reassuring and should not materially alter a clinician's suspicion for a diagnosis of EAOCRC. In Canada, the rate of colorectal cancer is highest in Newfoundland;[1] this has been attributed to the fact that Newfoundland has one of the highest rates of familial colorectal cancer in the world.[10]

Lifestyle – A population-based, case-control study in Ontario investigated the association between medical, lifestyle and dietary factors and EAOCRC.[11] Compared to sex- and age-matched controls, patients aged 20–49 diagnosed with colorectal cancer self-reported having a more sedentary lifestyle (≥ 10 vs < 5 hours of exercise per day, OR, 1.93; 95% CI, 1.02–3.65); greater consumption of sugary drinks (≥ 7 vs < 1 drinks/week, OR, 2.99; 95% CI, 1.56–5.68); and a more Westernized diet (quartile 4 vs. 1, OR, 1.92; 95% CI, 1.01–3.66).

Obesity - Obesity has consistently been identified as a risk factor for the development of EAOCRC,[12] particularly among women.[13] In the Nurses Health Study II, a prospective cohort study of U.S. female nurses aged 24–52 at study enrollment (1989), BMI at 18 years of age and weight gain since 18 years of age were associated with the development of EAOCRC. For every 5-unit increase in BMI, the relative risk of EAOCRC increased by 20%.[13]

Early Life Exposures – Given the noted birth cohort effect of accelerating incidence of EAOCRC among more recently born individuals, the most rapid rise in incidence affecting patients aged 20–39, and the typical long-latency period for development of colorectal cancer, it has been postulated that novel early life exposures may be important factors in the rising incidence of EAOCRC.[14] Multiple possible factors have been identified, including pre-natal (e.g. maternal stress[15]), peri-natal (e.g. cesarean delivery[16]) and early-life (e.g. antibiotic use[17], breastfeeding[18]), although no prospective studies have yet been able to establish causation.

Screening for Early Age Onset Colorectal Cancer

In Canada there are organized colorectal cancer screening programs in nine provinces and two territories, with Quebec and Nunavut being the outliers.[19] None of the organized screening programs include patients under age 50 and none recommend colonoscopy as the modality of choice for average-risk individuals. All screening programs recommend screening with a fecal immunochemical test (FIT) every 1–2 years.

In 2021, the United States Preventative Services Task Force updated their colorectal cancer screening guidelines and added a recommendation to start screening at age 45–49.[20] This recommendation was made after a modelling study showed screening for colorectal cancer with stool tests, endoscopic tests or CT colonography starting at age 45 years provides an efficient balance of "colonoscopy burden and life-years gained".[21]

In 2023, a microsimulation modelling study estimated the association of lowering the age of colorectal cancer screening using biennial FIT on colorectal cancer incidence, mortality and healthcare system costs in Canada.[22] This analysis found that screening initiation at age 45 resulted in 12,188 fewer colorectal cancer cases

and 5,261 fewer colorectal cancer deaths, and added 92,112 quality adjusted life years. Although the costs associated with screening at a younger age and the associated ensuing investigations increased, the overall healthcare system cost of managing colorectal cancer *decreased*.

In light of the rising incidence of EAOCRC, lowering the age for screening in Canada is passionately advocated for by patients, families and many clinicians.[23] Just recently, in December 2023, the Canadian Agency for Drugs and Technology in Health (CADTH) commissioned a health technology review of screening for colorectal cancer in individuals younger than age 50,[24] which many healthcare professionals anticipate may lead to a recommendation to lower the screening age.

Presentation and Diagnosis of Early Age Onset Colorectal Cancer

The diagnosis of EAOCRC is challenging because several more common conditions present with similar symptoms.[25] Therefore, a high index of suspicion is required and a diagnosis of colorectal cancer should be considered in any patient presenting with bright red blood per rectum or change in bowel habits, regardless of age, or the presence of hemorrhoids/fissures.

A population-based study from British Columbia of 1,992 patients with EAOCRC identified the most common presenting symptoms as: hematochezia (61%); abdominal pain (52%); change in bowel habits (27%); weight loss (20%); constipation (15%); anemia (14%); and diarrhea (12%).[26] The authors also found that EAOCRC patients had a significantly longer median time from symptom onset to diagnosis compared to older patients (median, 143 vs 95 days; P <0.0001).

A population-based study from Ontario evaluated time from healthcare contact, rather than symptom onset, for colorectal cancer-related signs or symptoms to diagnosis and treatment.[27] After healthcare contact, the median diagnostic interval (78 vs 85 days, P <0.001) and time to treatment interval (23 vs 27 days, P<001) were similar in early age onset vs older age onset. This study suggests that among patients who are ultimately diagnosed with colorectal cancer, once healthcare contact is made, the workup for younger and older patients occurs at a similar pace.

In part related to delays to diagnosis,[28] but also related to a lack of organized screening programs and a more aggressive tumor biology, patients diagnosed with EAOCRC present with more advanced tumors at the time of diagnosis.[29] A population-based study from Ontario of 6,775 patients identified that patients with EAOCRC are more likely to have left-sided tumors (50% vs 44%, P <0.001), lympho-vascular invasion (35% vs 27%, P=0.005), T3/T4 tumors (88% vs 79%, P=0.005), and lymph node positive disease (58% vs 41%; P <0.001).[30] Another population-based study from Ontario identified that one in five patients with EAOCRC present with metastatic disease.[27] Similarly, an analysis of 8,748 patients with colorectal cancer in Alberta identified that early-onset patients were more likely to be diagnosed with tumors in the distal colon and rectum, and have Stage 3 or 4 disease at diagnosis.[31]

Treatment of Early Age Onset Colorectal Cancer

Colon Cancer, Localized Disease - The standard upfront treatment for localized colon cancer is an oncological resection and sampling of at least 12 lymph nodes.

For most patients with Stage 2 colon cancer, adjuvant chemotherapy is not routinely recommended given the modest survival benefits.[32] Chemotherapy is selectively recommended to those with the highest-risk features, such as those patients with mismatch-repair (MMR) proficient tumors that are T4 or with less than 12 lymph nodes sampled.[32,33] A population-based study from Alberta identified that patients <40 years old were more likely to be treated with chemotherapy for Stage II colon cancer (OR, 3.41, 95%CI, 1.75-6.47), but this did not translate into better survival than for older patients.[31]

For patients with Stage 3 colon cancer, adjuvant chemotherapy is recommended in most cases. Three months of CAPOX chemotherapy is now the recommended standard of care for most patients.[34] The IDEA collaboration showed that 6 vs 3 months of oxaliplatin-based chemotherapy improved survival by 0.4% but was associated with a tripled risk of Grade 2 or higher neurotoxicity (15% vs 46%).[34]

Young age is a negative prognostic factor in Stage 3 colorectal cancer. In a retrospective analysis of the IDEA collaboration, early-onset patients had lower three-year relapse-free survival (54% vs 65%, HR 1.33; 95% CI, 1.14–1.55) and a higher five-year cancer-specific mortality rate

(24% vs 20%, HR 1.21; 95% CI, 1.00–1.47).[35] These poorer outcomes occurred despite the fact that early-onset patients had better performance status and were more likely to complete the planned treatment duration (76% completion of six months of CAPOX vs 65% in an older population, P<0.001). In an exploratory analysis of 3 vs 6 months of adjuvant therapy by age of cancer onset, EAOCRC patients with "low-risk" Stage 3 disease had lower three-year disease-free survival (DFS) with 3 months of treatment (81 vs 87%; HR, 1.49; 95% CI, 1.00–2.20). In the high-risk Stage 3 subset, there was no difference in DFS with 3 vs 6 months of treatment (57% vs 56%, HR 0.97; 95% CI, 0.73–1.29).[35]

There is no uniformly agreed upon duration of adjuvant therapy for EAOCRC with resected Stage 3 disease. Given the poorer cancer outcomes seen in EAOCRC patients, and concerns of the non-inferiority of 3 vs 6 months of adjuvant therapy particularly for low-risk Stage 3 disease in the IDEA collaboration, some experts advocate that three months of chemotherapy should not be the standard in this cohort of patients.[35] One option for early-onset patients that balances the risks of neurotoxicity and potential benefits of longer therapy is to provide three months of oxaliplatin and six months of a fluoropyrimidine. A combined review of the ACCENT/IDEA databases showed among patients planned for six months of adjuvant therapy, early discontinuation of all treatment (fluoropyrimidine and oxaliplatin) was associated with poorer oncological outcomes; however, discontinuation of the oxaliplatin component alone after the first three months was not.[36] Specifically among patients with EAOCRC (n=1312), early discontinuation of all treatment was associated with worse three-year DFS (64% vs 77%; HR, 1.89; 95% CI, 1.45–2.46) but early discontinuation of oxaliplatin was not (73% vs 78%; HR, 1.23; 95% CI, 0.87-0.74).

Rectal Cancer, Localized Disease – In 2024, there are a number of accepted standard of care treatment options for localized rectal cancer. These include: neoadjuvant chemoradiation or short course radiation followed by surgery with or without adjuvant chemotherapy; neoadjuvant chemotherapy alone followed by surgery; upfront surgery followed by adjuvant chemotherapy; and total neoadjuvant chemotherapy with or without surgery.[37] There is also increasing evidence for neoadjuvant immunotherapy for MSI-H rectal cancer.[38-40] There is often no evidence-based way to choose between these multiple treatment options as most have never been compared directly and the individual aspects of each patient's case and their values and preferences need to determine the treatment approach.

Colorectal Cancer, Metastatic - The mainstay of treatment for metastatic colorectal cancer is sequential use of systemic therapy, and at present the age of patient does not influence the treatment approach. A pooled analysis of 6,284 patients from nine first-line Phase 3 clinical trials for advanced colorectal cancer showed that the relative benefits of chemotherapy were similar regardless of age. Age was minimally prognostic for progression-free survival (<50 vs >50, median 6.0 vs 7.5 months, HR 1.10; P=0.02), and not at all for response rate (RR) (<50 vs >50, 42% vs 43%, OR, 1.02; P=0.84) or overall survival (<50 vs >50, 15.8 v 16.6 months; HR, 1.03).[41]

Considerations In Early-Age Onset Colorectal Cancer Patients

There are several considerations particularly relevant to the care of EAOCRC patients. Importantly, the treatment, including the time invested to undergo treatment, and side effects, may have particularly pronounced effects on the financial, physical and emotional well-being of EAOCRC patients. (**Figure 1**.)[23]

Fertility Preservation - All chemotherapy poses some risk of infertility in both male and female patients. Thus, early referral for fertility counselling and preservation measures is essential for all patients diagnosed with EAOCRC. Fluoropyrimidines are the backbone of most therapies for colorectal cancer. While fluoropyrimidines have been shown to be gonadotoxic, pre-clinical studies suggest they are unlikely to cause permanent infertility.[42] The impact of oxaliplatin on gonadal function was assessed in a small clinical study of 11 female patients under the age of 43 and eight male patients under the age of 45 who were treated with six months of folinic acid, fluorouracil and oxaliplatin (FOLFOX) chemotherapy.[43] All female patients continued menstruation through treatment or resumed post-treatment. All male patients demonstrated laboratory evidence of reduced spermatogenesis; however, they retained intact function of Leydig cells. Similarly, a small clinical study from five hospitals in Nordic countries of 20 males aged <55 and 16 females aged <40 who received FOLFOX chemotherapy showed no male patients developed hypogonadism post-treatment

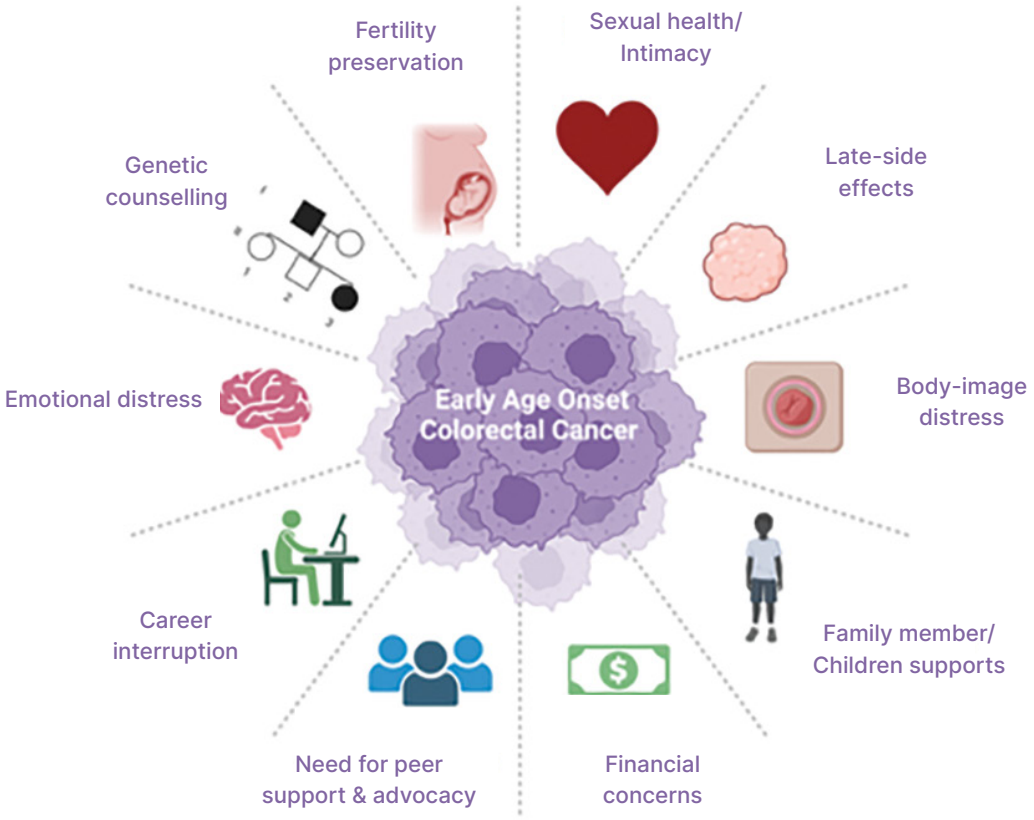

Figure 1. Important considerations in the care and survivorship of EAOCRC; *created with BioRender.com.*

and no female patient experienced alterations in sex hormones or treatment-induced menopause.[44]

Temporary ovarian suppression through use of gonadotrophin-releasing hormone agonists (GnRHa) to prevent chemotherapy-induced premature ovarian insufficiency has shown conflicting results in clinical studies.[45] The majority of the evidence for the use of this therapy comes from studies evaluating patients with breast cancer. A systematic review and meta-analysis of 12 randomized clinical trials (RCTs) including 1,231 breast cancer patients found that temporary ovarian suppression during chemotherapy reduced the rate of chemotherapy-induced premature ovarian insufficiency and increased the subsequent pregnancy rate.[46]

Radiation for rectal cancer may cause infertility and premature ovarian insufficiency. Ovarian tissue is known to be very sensitive to the effects of radiation, with 2 Gray being the estimated dose that will destroy 50% of the oocyte population.[47] If the decision is made that including radiation is part of the best treatment plan for a young female patient, for those considering future childbearing, options to consider include surgical transposition of the ovaries out of the radiation field and cryopreservation (embryo, oocyte or ovarian).[48] For young male patients, sperm cryopreservation is recommended. For female patients requiring radiation, even if fertility preservation measures are taken, it is important to recognize that the effect of radiation on the uterus can make future successful pregnancy challenging.[49]

Secondary Malignancies - A modelling study evaluated patients treated with radiation for rectal cancer and estimated that the overall lifetime attributable risk of a secondary cancer was approximately 2% for a patient aged 69, but up to 10% for a patient aged 30 years at treatment onset; secondary cancer risk increased exponentially with decreasing age at exposure to radiation.[50]

Career Interruption – In addition to the time needed to receive treatment and recover, long-lasting symptoms may impair the ability to return to work in the prior capacity. Following sphincter-sparing rectal surgery, almost all patients[51] will suffer from some symptoms of Low Anterior Resection Syndrome (LARS), which may include some or all of fecal incontinence, urgency, frequency, soiling, and difficulty with compete evacuation. A systemic review and meta-analysis of 50 studies identified the incidence of major LARS to be 44% (95% CI, 40%-48%).[52] Long-term follow-up studies have shown that bowel changes may be permanent and over 50% of patients report ongoing symptoms at 10 years.[53] LARS can be particularly problematic for younger adults, who are more likely to still be working. A study from Montreal of 154 survivors of rectal cancer found that among patients experiencing major LARS, 53% reported financial stress; 71% of those who were working pre-operatively reported that their bowel function impaired their ability to work, delayed their return to work, resulting in them needing to change work schedules and roles; and 15% reported needing long-term disability.[54]

Body-Image Distress – The need for an ostomy following rectal cancer surgery can be associated with body-image distress, intimacy concerns and financial toxicity. For some patients, avoidance of a stoma has been rated as a higher priority than prolongation of DFS. In a survey study of 98 patients with locally advanced rectal cancer, avoiding surgery with a permanent stoma was rated as the most important goal, with a relative importance (RI) of 24.4 (95% CI, 21.88-26.87) and prolongation of DFS was related as least important (RI, 5.6; 95% CI, 4.9-6.2).[55] A pan-Canadian cross-sectional survey of 467 patients living with an ostomy identified that ostomies can impose a significant financial burden.[56] Approximately 75% of respondents reported having to choose between purchasing ostomy supplies or other items such as food, medications or travel; 76% reported spending more than $1,000 dollars per year on supplies.

Sexual dysfunction and Intimacy Concerns – Treatment for EAOCRC may result in emotional, hormonal or physical changes that affect sexual function. A prospective, longitudinal survey was conducted among patients with rectal cancer at four high-volume academic centres in Ontario.[57] Among 45 patients who completed the survey, sexual dysfunction was reported in both male and female patients that continued to increase from baseline up to one year post-surgery. In qualitative interviews, patients noted that sexual function was an important topic to discuss and felt it was the responsibility of the care team to initiate these conversations. In the multinational Never Too Young Survey among patients with EAOCRC, 48% of patients reported sexual dysfunction that put a strain on their relationship; 47% worried "they are not enough for their intimate partner"; and 33% reported not feeling as a "complete person due to sexual dysfunction".[58]

Conclusion

"Children are not just small adults" is a common adage learned in medical school to highlight the unique pathophysiology and care needs of the pediatric population. Similarly, it is increasingly apparent that patients with EAOCRC have a unique epidemiology, disease biology, treatment and survivorship experience compared to older adults with colorectal cancer. Accordingly, Canada needs to appropriately invest in early detection, research and more comprehensive supportive care resources for patients and families affected by EAOCRC. For further details on the diagnosis, management and supportive care measures for patients and families affected by EAOCRC, International Management Guidelines have recently been released.[59]

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Revolutionizing Breast Imaging: Artificial Intelligence's Role in Precisely Differentiating Benign from Malignant Lesions

Vivianne Freitas, MD, MSc.
Renata Pinto, MD, MSc.

Introduction

Recent advancements in artificial intelligence (AI) have leveraged computer science with large datasets to improve predictive and classification capabilities, which are crucial for problem-solving in radiology.[1] Machine Learning (ML), the driving force behind AI's effectiveness, harnesses computational models and algorithms to analyze raw data for classification and prediction tasks.[2] AI utilizes a multi-layered network of interconnected nodes emulating the intricate neuronal structure of the human brain. These include an input layer that initially receives data, a hidden layer that discerns data patterns, and an output layer that presents the results of the processed data.[2]

The evolution of AI has propelled us from a reliance on manually intensive ML techniques to the more autonomous realms of deep learning (DL). This shift has reduced our dependence on extensive engineering knowledge and domain-specific expertise, particularly in extracting features from raw data.[3] This progression has proved pivotal in managing large-scale datasets, enhancing results, and augmenting performance with increased data exposure. Within the spectrum of DL methodologies, convolutional neural networks have emerged to transform image analysis and have particularly revolutionized the use of AI applications in radiology. The advancements of AI in the domain of clinical radiology are notably evident, with breast imaging emerging as a key beneficiary of this technological progress.[4,5]

The application of AI in breast imaging presents a range of clinical uses, from improving breast cancer screening and risk stratification,[6–8] to aiding in making treatment decisions by predicting axillary involvement,[9] neoadjuvant therapy responses,[10] and recurrence risks.[11] A significant breakthrough in the application of AI in breast imaging lies in its potential to boost the specificity of breast imaging tests, enabling accurate discrimination between benign and malignant breast lesions.

A recent systematic review and meta-analysis looked at radiomic analyses of preoperative diagnostic imaging of the breast. Data from 31 studies was analyzed,[12] with 17 studies contributing to the meta-analysis. The study included 8,773 patients, with a cohort comprised of 56.2% malignant breast cancers and 43.8% benign breast lesions. The findings showed that nine of the included studies reported the value of radiomic properties from MRI to differentiate malignant and benign breast cancer, with a sensitivity of 0.91 (95% CI: 0.89–0.92) and a specificity of 0.84 (95% CI: 0.82–0.86). In the four studies that included mammography, the sensitivity was 0.79 (95% CI: 0.76–0.82) with a specificity of 0.81 (95% CI: 0.79–0.84), and in the three studies that included ultrasound, the sensitivity was 0.92 (95% CI: 0.90–0.94) with a specificity of 0.85 (95% CI: 0.83–0.88) in differentiating between malignant and benign lesions.

Additionally, in a validation study, Lee et al.[13] compared the effectiveness of commercial AI software, assessing its performance and reading time against the proficiency of both breast and general radiologists. The AI model surpassed the diagnostic accuracy of radiologists across all levels of expertise, with an area under the curve (AUC) of AI alone, breast radiologist, and general radiologist groups of 0.915 (95% CI:

0.876-0.954), 0.813 (95% CI: 0.756–0.870), and 0.684 (95% CI: 0.616–0.752), respectively. Further, the use of AI assistance notably reduced the reading time for breast radiologists from 82.73 seconds to 73.04 seconds, $p < 0.001$, while it increased the reading time for general radiologists from 35.44 seconds to 42.52 seconds, $p < 0.001$.

Moreover, a multicentric study which included 144,231 screening mammograms from 85,580 U.S. women and 166,578 screening mammograms from 68,008 Swedish women, revealed that AI algorithms combined with a radiologist's review showed an AUC of 0.942 with a significantly improved specificity of 92.0% and an unchanged sensitivity.[14] This study demonstrates the potential of AI as an adjunctive tool in interpreting mammographic screenings. Furthermore, AI's efficacy in breast cancer detection extends to modalities beyond digital mammography, including digital breast tomosynthesis, ultrasound, and MRI.[14]

In fact, within AI-based computer-aided systems, two distinct classifications have emerged: computer-aided detection (CADe), which identifies lesions, and computer-aided diagnosis (CADx), which classifies the identified lesions as benign or malignant.[15] Radiologists can utilize these tools to assess if abnormalities detected by CADe or CADx require further investigation. Therefore, CADx can increase specificity by distinguishing lesion types, and CADe can improve sensitivity in mammography screenings, acting as a triage tool to highlight suspicious cases and confirm cancer-free diagnoses, thereby streamlining workflows.[15]

This shift from traditional mammography to CAD systems, which have often led to increases in unnecessary follow-ups without better cancer detection,[15–17] to more effective AI-CAD systems that equal or even exceed the diagnostic performance of radiologists is a significant development.[17,18] These CAD systems can both address the global shortage of radiologists skilled in breast imaging, minimize the dependence on specialized radiologists to interpret breast images, while potentially reducing unnecessary biopsies and treatments, which represents a movement toward precision medicine. For patients, the use of AI in radiology could alleviate the psychological impact and anxiety associated with false-positive results.[19,20] Operationally, these AI models, designed to process extensive imaging data efficiently, can ease the workload of radiologists and promote cost-effective healthcare resource allocation. This efficiency could lead to significant cost savings, potentially re-allocating funds to improve other aspects of patient care and medical research.

Although we have been slowly incorporating AI into clinical practice, and some AI algorithms have received FDA approval,[21] numerous challenges remain when applying these developments effectively in clinical practice. These challenges include the generalizability and transferability of AI research, which may be hampered by a limited number of multicentric studies and a lack of diverse population demographics.[22] Transparency issues, notably the "black box" nature of AI neural networks, hinder the acceptance of AI systems, which necessitate the development of methodologies for rigorous peer review and validation.[23] Moreover, the focus of AI studies on diagnostic metrics needs a shift toward tangible clinical outcomes, such as mortality rates or surrogates, to provide concrete evidence of AI's benefits.[24] Also, from a liability standpoint, different legal responsibilities have been raised during the integration of AI into clinical practice. Regarding liability in cases where AI can replace the radiologist, especially considering that the algorithm development process usually involves many steps with different experts, it is critical to define who should be held responsible for the results in situations where AI misinterpretation could potentially cause patient harm.[2] Governance also emerges as a critical barrier, with regulatory bodies such as Health Canada[25] and the FDA[26] demanding clear guidelines and stringent testing for AI medical devices, to ensure their safety and efficacy before clinical adoption. These challenges underscore the complexity of integrating AI into healthcare and the need for careful consideration to maintain patient trust and the integrity of medical services.

Conclusion

In conclusion, the integration of AI in breast imaging is set to refine the workflow and efficiency of breast radiologists and help to manage the growing caseload without overwhelming the professionals. While AI assists in diagnostic tasks, it is important to keep in mind that it will not supplant radiologists due to their role in decision-making and other complex tasks; rather, the synergy between human expertise and AI promises to enhance patient care and diagnostic accuracy. This integration represents a significant

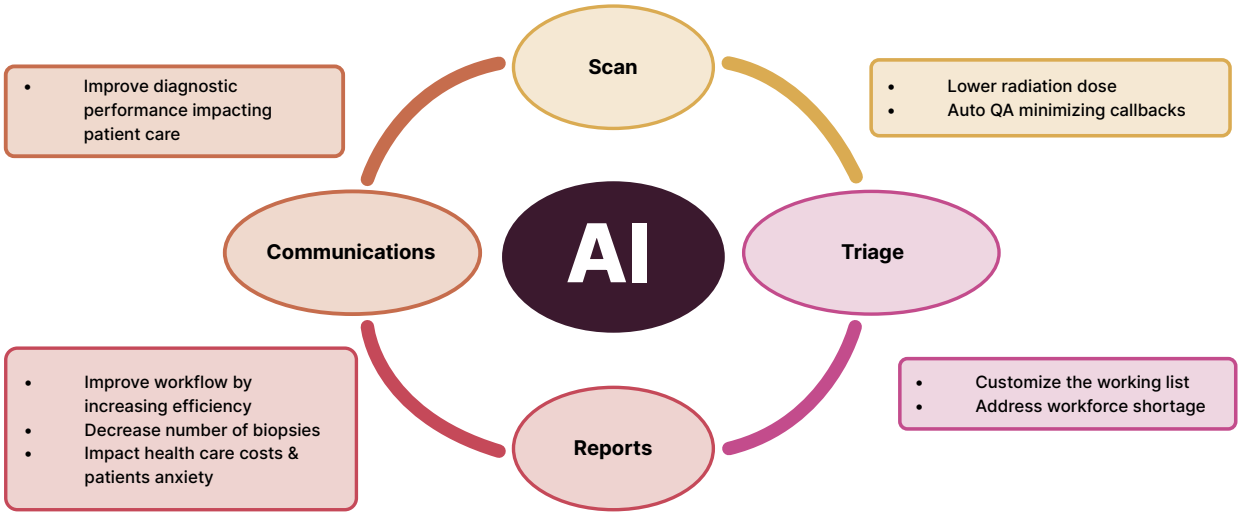

Figure 1. Impact of AI in the Breast Imaging Lifecycle; *image courtesy of Vivanne Freitas, MD, MSc. and Renata Pinto, MD, MSc.*

advancement in imaging, potentially impacting the entire breast imaging lifecycle. (**Figure 1**.) Addressing the challenges of integrating AI into clinical practice is essential to leverage its full potential for enhancing patient care.

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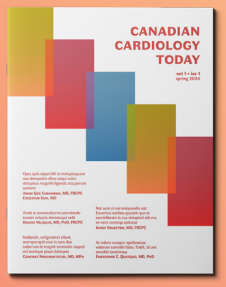

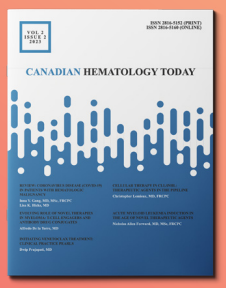

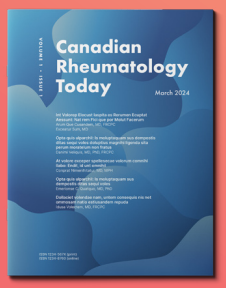

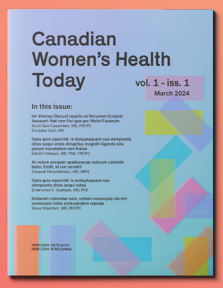

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A Review of EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC) in 2024

Florence Levesque, MD
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Introduction

Twenty years ago, our understanding of non-small cell lung cancer (NSCLC) treatment was revolutionized by the demonstration of a strong relationship between activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) and the response to tyrosine kinase inhibitors such as gefitinib. These experiments, among many others, have paved the way for two decades of exponential therapeutic growth that we have witnessed.

EGFR-mutant lung cancers account for as much as 23% of NSCLC cases diagnosed in Canada,[1] with significant variations based on geography and ethnicity including a higher prevalence in regions where the Asian population is more important. Therefore, the latest data discussed in this article have the potential to improve outcomes for a large number of patients.

Perioperative approach

Adjuvant osimertinib is approved in Canada for completely resected, stage IB to IIIA EGFR-mutant NSCLC. It is administered until the patient experiences either unacceptable toxicity or disease progression, with a maximum duration of up to three years. This approach has demonstrated a clear benefit in the ADAURA trial, first published in 2020.[2] The trial showed that disease-free survival (DFS) was significantly longer with adjuvant osimertinib compared to placebo at 48 months (70% versus 29% respectively, with a hazard ratio [HR] of 0.23).[3] Highlighting the high central nervous system (CNS) activity of osimertinib, 92% in the osimertinib group did not experience a CNS relapse at 48 months versus 81% in the placebo group, with an HR of 0.36. The substantial benefits of osimertinib are even more pronounced in the stage II to IIIA subgroup of NSCLC patients. The 5-year overall survival (OS) was recently published, confirming a clinically and statistically significant benefit (88% survival rate in the osimertinib group at 5 years versus 78% survival rate in the placebo group, with an HR of 0.49).[4] Currently, consideration for adjuvant chemotherapy in NSCLC is not dependent on the genotype and thus can be offered to patients prior to the initiation of osimertinib treatment. However, if there is a contraindication to cytotoxic chemotherapy, adjuvant osimertinib still offers benefits. This was demonstrated in the subgroup of patients who did not receive chemotherapy first (40% of the study population with a similar HR for OS of 0.47). Despite recent advances in perioperative immunotherapy, this approach is not recommended for EGFR-mutant lung cancer. This is because activity in EGFR-mutant lung cancer is typically inferior to that in wild-type counterparts in the metastatic and locally advanced setting.[5] Furthermore, limited data from the AEGEAN trial support the absence of benefit of adding perioperative durvalumab to chemotherapy for the EGFR-mutant subgroup of NSCLC patients.[6] There is also evidence suggesting that toxicity can be exacerbated when patients receive an immediate sequential use of immunotherapy and a tyrosine kinase inhibitor (TKI),[7] with some experts recommending waiting at least 3 months before initiating osimertinib treatment when this is clinically feasible.[7]

The optimal approach for managing relapse after adjuvant osimertinib needs to be investigated. Confirming histological findings and the persistence of an EGFR mutation with a new biopsy, and then retrying a course of osimertinib if the progression did not occur while on adjuvant treatment, can be considered. However, the benefit of this approach has not been clearly evaluated in clinical trials. If the relapse happens during adjuvant osimertinib, the disease should be treated as a metastatic EGFR-mutant lung cancer progressing

on targeted therapy, with some specific strategies described below.

The NeoADAURA (NCT04351555)[8] and LAURA (NCT03521154)[9] trials are currently investigating the potential benefits of neoadjuvant osimertinib before surgery and adjuvant osimertinib after chemoradiation for patients with stage III unresectable EGFR-mutant NSCLC, respectively, and could potentially provide further improvements in outcomes in the curative setting. Furthermore, very interesting data suggest that the detection of circulating tumour DNA (ctDNA) before or after resection is associated with a poorer DFS.[10] In the future, the ability to detect ctDNA could help us identify the patients who are at a high risk of relapse and who would be likely to derive greater benefit from adjuvant treatment.

Metastatic disease

Although tissue biopsies are typically used to detect EGFR mutations, studies also support the use of liquid biopsies at diagnosis. Liquid biopsy techniques usually have high specificity, especially in advanced disease. Since sensitivity is imperfect, if negative, a next generation sequencing panel should be conducted on a tissue biopsy to identify a biomarker positive subset of NSCLC, including EGFR alterations.[11]

Osimertinib, a third-generation EGFR TKI, was specifically developed to overcome the T790M resistance mutation. This mutation is found in approximately 50–60% of tumours after progression on first- and second-generation TKIs. A key benefit of osimertinib is that it improves CNS penetrance and spares wild-type EGFR which contributes to its increased tolerability.[12] Osimertinib is currently the preferred first-line choice for EGFR exon 19 deletions and exon 21 *L858R* mutations, which represent approximately 80% to 90% of all EGFR mutations.[13] The phase 3 FLAURA trial showed a statistically significant improvement in PFS (18.9 months for osimertinib versus 10.2 months for first-generation TKIs, HR 0.46) and updated OS (38.6 months for osimertinib versus 31 months for first-generation TKIs, HR 0.80).[14] Patients in the study had locally advanced or metastatic NSCLC harbouring an EGFR exon 19 deletion or an *L858R* mutation.[15] In patients with known or treated CNS metastases, the trial shows a consistent benefit of PFS in favour of osimertinib (15.2 months versus 9.6 months, HR 0.47), and an objective response rate (ORR) of 76% with a 13.8 month median duration of response.[15] These findings are notable, considering that 25%[16] of patients harbouring an EGFR mutation have CNS metastases at initial diagnosis and up to 70%[17] eventually develop brain metastases during the course of their illness.

More recently, the phase 3 study FLAURA2 evaluated the addition of platinum-pemetrexed chemotherapy to osimertinib in the first-line treatment of metastatic EFGR-mutated NSCLC. According to investigator assessment, median PFS was improved by 8.8 months with osimertinib and chemotherapy compared to osimertinib monotherapy (25.5 months versus 16.7 months, HR 0.62), respectively. The ORR was 83% for osimertinib and chemotherapy versus 76% for osimertinib monotherapy.[18] The subgroup of patients with measurable and non-measurable CNS brain metastases at baseline derived a significant benefit from the combination therapy (PFS 24.9 months versus 13.8 months, HR 0.47). In addition, the trial showed a complete intracranial response of 59% for combination therapy compared to 43% with osimertinib monotherapy. The safety profiles were as expected for each treatment, with the combination therapy arm demonstrating increased toxicity.[18] Identifying which patients require treatment intensification is a matter of ongoing debate in the medical community. Studies such as SHEDDER (NCT04410796) and PACE-LUNG (NCT05281406), might provide more clarity on this issue by evaluating the addition of chemotherapy to first-line osimertinib in patients who demonstrate ctDNA positivity after a few weeks of osimertinib.

Another intensification strategy is found in the MARIPOSA phase III study, which showed an improved PFS (23.7 months versus 16.6 months, HR 0.70) with the combination of amivantamab, an EGFR and MET bispecific receptor antibody, and lazertinib, a third generation TKI, compared to osimertinib monotherapy.[19] Combination therapy demonstrated a consistent benefit in patients with or without brain metastases. The combination therapy had higher rates of grades 1 and 2 EGFR- and MET- related adverse events, such as rash, diarrhea, and peripheral edema, as well as a significant rate of infusion reactions, mostly limited to the first infusion of amivantamab. Notably, there was also an increased signal for venous thromboembolism occurring in 37% of patients in the combination arm.[19] Prophylactic dose anticoagulation is now recommended for the first 4 months of treatment when this combination is used, further increasing the therapeutic burden

compared with a single-agent oral drug such as osimertinib.

Beyond limitations in drug access and coverage, the intensification strategy for patients with metastatic disease in first line treatment should be individualized based on the patient characteristics, preferences, and the toxicity profile of the combination treatment. Until OS data become mature for both trials, the approaches in the FLAURA2 or MARIPOSA trials should not be considered as new, broadly applicable standards of care for EGFR-mutant advanced NSCLC.

For patients harbouring atypical EGFR mutations (such as *S768I*, *L861Q*, *G719X*), updated guidelines from the NCCN recommend first-line use of osimertinib or afatinib. Clinical data for afatinib come in part from the LUX-Lung studies that allowed inclusion of atypical mutations. A post-hoc analysis showed clinical activity, particularly in patients harbouring uncommon EGFR mutations such as *G719X*, *L861Q*, and *S768I*.[21] Similarly, a randomized phase 3 study evaluating afatinib compared to chemotherapy in treatment-naïve patients with sensitizing uncommon mutations showed an ORR of 61.4% with afatinib and a PFS of 10.6 months.[22] The efficacy of osimertinib in uncommon EGFR mutations was demonstrated in UNICORN, a multicenter retrospective case series. The findings showed that osimertinib had a systemic ORR of 60% and a brain ORR of 46% in those with evaluable brain metastases.[23] The final OS data of the prospective phase 2 study KCSG-LU15-09 demonstrated a median OS of 27 months and an ORR of 51% with osimertinib.[24] The heterogeneity of atypical EGFR mutations emphasizes the importance of individualizing treatment for each patient.

Despite high initial response rates and prolonged progression-free survival, disease progression is expected to occur in all patients. Various molecular mechanisms of resistance to osimertinib have been described and can be classified into three categories, which include secondary and tertiary mutations in EGFR, activation of alternative parallel signalling pathways, and histologic transformation in small cell lung carcinoma and squamous cell carcinoma. When feasible, performing a biopsy of a site where the disease is progressing is recommended to determine if a mutation that can be targeted with therapy is present, and to exclude histologic transformation, which can help guide the choice of second-line therapy. Where available, use of liquid biopsies can also help identify resistance mutations, although they cannot rule out histologic transformation.

MET amplification is observed in 10 to 15% of NSCLC patients with EGFR mutations who are progressing on first line osimertinib, and is often considered the most frequent resistance mechanism in this setting.[25] MET amplification leads to the persistent activation of several common downstream pathway effectors, independent of EGFR signalling. These signalling pathways include mitogen-activated protein kinases, signal transducer and activator of transcription (STAT), and phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT).[26] The phase II study INSIGHT 2 (NCT03940703) evaluated tepotinib in combination with osimertinib in patients with EGFR-mutant NSCLC with MET amplification previously treated with osimertinib. The study's findings showed an ORR of 50% when amplification was detected by fluorescent in situ hybridization (FISH) and an ORR of 54.8% when detected by liquid biopsy. The median duration of response for detection by FISH or liquid biopsy was 8.5 months and 5.7 months, respectively.[27] Although found more frequently after second-line use of osimertinib, the exon 20 *C797S* mutation is the most frequent tertiary resistance mechanism to first-line osimertinib. Oncogenic fusions have also been recognized in 1% to 8% of cases of acquired resistance to first-line osimertinib. For example, combining osimertinib with selpercatinib, a RET-TKI, showed a clinical benefit in patients with an acquired RET fusion on first-line osimertinib, and led to a median duration of treatment of 7.4 months (range, 0.6–6.7 months).[28] In addition, acquired cell cycle gene alterations have been reported to occur in 10% of cases.[25]

If no underlying resistance mechanism is identified, a chemotherapy regimen, such as a combination of platinum and pemetrexed, is recommended as the standard next line therapy. The phase 2 study MARIPOSA-2 was the first to report that amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy combinations showed improvement in PFS versus chemotherapy alone for patients with EGFR-mutant advanced NSCLC who had disease progression on osimertinib, with a reduction in the risk of progression or death of 52% for amivantamab-chemotherapy and 56% for amivantamab-lazertinib-chemotherapy.[29] However, in another phase III trial, the addition of pembrolizumab to chemotherapy in the post-TKI setting did not show a clinical benefit.[20]

It is anticipated that future trials will aim to more accurately characterize the optimal sequencing strategies for treating metastatic EGFR-mutant NSCLC.

Exon 20 EGFR mutations

Insertions in exon 20 of EGFR account for approximately 2% to 12% of all EGFR-mutations in NSCLC.[30] These mutations are less sensitive to currently approved EGFR TKIs and the response rates to these therapies are typically quite low.[13,31]Amivantamab is currently approved after chemotherapy for second-line use in tumours harbouring these mutations. However, the recently published phase III PAPILLON study showed a significant PFS benefit in this population with a first-line treatment that included the addition of amivantamab to chemotherapy compared to chemotherapy alone (11.4 months versus 6.7 months with an HR of 0.4).[32] At 18 months, 31% of patients in the amivantamab-chemotherapy group were still progression-free, compared to 3% in the chemotherapy group. The response rate was also significantly higher (73% in the amivantamab-chemotherapy group versus 47% in the chemotherapy group). These are promising results for this subset of patients; however, OS data remains immature. While the current standard of care typically includes a first-line platinum doublet followed by second-line amivantamab, in jurisdictions where it is covered, the significant benefits reported in the PAPILLON study could justify pursuing the combination therapy as a first-line treatment.[33]

Conclusion

In conclusion, recent therapeutic advances in EGFR-mutant NSCLC have significantly improved the prognosis of the subset of patients with these types of tumours. These developments have also raised new questions regarding the optimal sequencing of treatments and the appropriate use of treatment intensification. This represents a major step forward in the field. Ongoing investigations are expected to provide additional insights, and it will be interesting to closely follow these developments.

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