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1 **The Role of Site-Specific Therapy for Cancers of Unknown of Primary:**
2 **A Meta-Analysis**

3 **Short title:** Site-Specific Therapy for Cancers of Unknown of Primary

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19 **Highlights**

20 This paper is a meta-analysis of the trials evaluating site-specific treatments in CUP.

21 No significant survival benefit with site-specific versus empiric chemotherapy.

22 There was significant heterogeneity across the prospective studies.

23 Current evidence is insufficient to recommend site-specific therapy in CUP.

24 However, certain patients with CUP may still benefit from tailored treatments.

25

26

27 **Abstract**

28 Cancers of unknown primary (CUP) are among the most common causes of death due to
29 cancer, are associated with a poor prognosis, and have few therapeutic options available.
30 Molecularly-guided site specific treatments were explored based on the assumption that
31 CUP are similar in their response to treatment to predicted primary tumors. Given the
32 discordant results between these studies, a meta-analysis using a random-effects model and
33 the inverse variance method was performed. MEDLINE and conference abstracts of
34 American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology
35 (ESMO) meetings were searched from inception until November 2019. A trend towards
36 improved OS was found with site-specific versus empiric treatment for CUP (HR = 0.73; 95%
37 CI 0.52-1.02). There was significant heterogeneity across the 4 studies ($I^2= 79\%$; $p=0.002$) but
38 no significant difference between the treatment effect in the two subgroups (randomized vs.
39 non-randomized; $p=0.07$). The test for overall effect for PFS, which had only been reported
40 for the two randomized studies, was not statistically significant (HR = 0.93; 95% CI 0.74-
41 1.17), with little heterogeneity between studies ($I^2= 0\%$; $p=0.77$). The results of this meta-
42 analysis highlight the significant heterogeneity between the prospective studies comparing
43 molecularly tailored to empiric therapy for CUP and the need for other randomized studies
44 including only primary tumors with available effective therapies.

45 **Keywords**

46 Cancer of unknown primary; Tailored therapy; Site-specific; Empiric

47

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51

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53

54 **Current Perspectives**

55 Cancers of unknown primary (CUP) are a heterogeneous group of metastatic tumors, for
56 which a primary site origin cannot be identified despite a standardized diagnostic work-up ¹.
57 It accounts for 1-2% of all malignancies and ranks as the seventh cause of mortality in
58 patients with cancer ². Largely, two subsets of patients can be identified based on
59 clinicopathologic criteria ³. The first encloses a minority of patients (15-20%) that is
60 chemosensitive and has an overall favorable prognosis ³. The second subset includes the
61 larger category of patients (80-85%) that cannot be assigned to a primary tumor and
62 commonly present a dismal prognosis with empiric CUP chemotherapy regimens ⁴. The
63 efficacy of site-specific treatments in the favorable subsets of patients with CUP makes
64 compelling evidence to assess tailored therapy in patients within the unfavorable subsets ⁵.
65 Moreover, case reports and series had suggested that the use of tailored therapies in the
66 unfavorable subset leads to favorable clinical outcomes ^{6,7}.

67

68 Two prospective studies have reported on the outcomes of site-specific therapy in patients
69 with CUP. The largest is a subset of 194 patients that had both sufficient tumor material for
70 the assay and received assay-directed therapy. This subset was compared to a retrospective
71 cohort from the same consortium that had been treated by empiric chemotherapy, and
72 were found to have significantly improved overall survival (OS; hazard ratio of 0.63 [95% CI
73 0.60-0.66]; hazard ratio unpublished - obtained from authors) ⁸. In another study of 216
74 patients with CUP, 188 (87%) had had their primary tumors identified using a microarray-
75 based DNA methylation signatures ⁹. Patients treated with tailored therapy (n = 31) achieved
76 an OS benefit in comparison to those treated with empiric CUP regimens (n = 61) with a
77 hazard ratio (HR) of 0.31 (95% CI 0.14-0.70) ⁹.

78

79 The efficacy of site-specific therapy was further addressed in two randomized controlled
80 trials enrolling patients with CUP into tailored therapy or empiric CUP regimen arms. The
81 first is a phase II study comparing molecularly-driven site-specific therapy and the
82 combination of paclitaxel plus carboplatin ¹⁰. The two treatment arms showed similar OS (HR
83 = 1.03; 95% CI 0.68-1.56) and progression free survival (PFS; HR = 0.88; 95% CI 0.59-1.33) ¹⁰.
84 The second study is a phase III trial that randomized 243 patients into tailored therapy or the
85 combination of cisplatin plus gemcitabine ¹¹. No statistically significant differences in PFS (HR
86 = 0.95; 95% CI 0.72-1.25) or OS (HR = 0.92; 95% CI 0.69-1.23) were found between the two
87 treatments arms ¹¹. Given these discordant results, we performed a meta-analysis of these
88 studies while taking into account the inherent heterogeneity of the included studies.

89

90 MEDLINE and conference abstracts of American Society of Clinical Oncology (ASCO) and
91 European Society of Medical Oncology (ESMO) meetings were searched from inception until
92 November 2019 for studies evaluating molecularly tailored therapies for CUP. All prospective
93 studies comparing molecularly tailored to empiric therapies for CUP were included. All data
94 were abstracted by two authors independently (ER and ZB). The meta-analysis was
95 performed using a random-effects model and the inverse variance method in order to
96 account for possible heterogeneity in treatment effect due to differences in the molecular
97 tests used, study design, and the included patient populations in the four studies. A
98 subgroup analysis by study design (randomized vs. non-randomized) was performed in order
99 to better account for this factor. The primary comparison was that of tailored versus empiric
100 therapies for CUP. The primary endpoint was OS and the secondary endpoint was PFS. All
101 analyses were done using the Review Manager software, version 5.3 (The Nordic Cochrane

102 Center, The Cochrane Collaboration, Copenhagen, Denmark). The threshold for statistical
103 significance for the tests of overall effect and subgroup comparison was 0.05 and that for
104 the tests of heterogeneity was 0.10. The I^2 coefficient was used to quantify the degree of
105 heterogeneity within and between subgroups. All hypothesis tests were tests were
106 formulated prior to data collection.

107
108 The pooled analysis included 628 patients treated empirically and 398 treated by tailored
109 therapies. For the primary outcome, a non-statistically significant trend towards improved
110 OS was found with tailored versus empiric treatment for CUP (Figure 1; HR = 0.73; 95% CI
111 0.52-1.02). Within the non-randomized subgroup (N= 225 tailored and 457 empiric), the
112 effect was statistically significant (HR = 0.56; 95% CI 0.26-0.96) but there was significant
113 heterogeneity between the two included studies ($I^2= 65\%$; $p=0.09$). Within the randomized
114 controlled trials subgroup (N= 173 tailored and 171 empiric), the effect was not statistically
115 significant (HR = 0.95; 95% CI 0.75-1.21). There was also significant heterogeneity across the
116 4 studies ($I^2= 79\%$; $p=0.002$) but no significant difference between the treatment effect in
117 the two subgroups (randomized vs. non-randomized; $p=0.07$). The test for overall effect for
118 PFS, which had only been reported for the two randomized studies, was not statistically
119 significant (HR = 0.93; 95% CI 0.74-1.17), with little heterogeneity between studies ($I^2= 0\%$;
120 $p=0.77$).

121
122 The results of this meta-analysis highlight the significant heterogeneity between the
123 prospective studies comparing molecularly tailored to empiric therapy for CUP. The possible
124 sources of heterogeneity between studies include the study design (randomized vs. non-
125 randomized), the type of molecular testing performed to identify the primary site of origin

126 (methylation vs. RNA-based), the types of systemic therapies included in the tailored and
127 empiric therapy arms, and the breakdown of expected primary sites (and how sensitive to
128 tailored and empiric therapies they are expected to be) ⁸⁻¹¹. While no overall statistically
129 significant effect in favor of tailored therapies was found in this study, certain selected
130 subgroups of patients may still benefit from this approach. The study by Moran et al. had the
131 lowest point estimate of the HR among all the included studies ⁹. One of the main
132 differences between this study and the other included studies was that the assay used to
133 infer the primary tumor type was DNA methylation-based (as opposed to the others which
134 were all RNA-based) ⁹. Another potential difference between this study and the three other
135 studies was the breakdown of the predicted primary tumors, whereby the most frequent
136 predicted primary was breast carcinoma in the study by Moran et al. as opposed to
137 pancreaticobiliary carcinoma which is generally associated with a poor prognosis in each of
138 the three other studies ⁸⁻¹¹. Moreover, certain patient subgroups did not receive the
139 therapies that constituted the standard of care at the time of enrollment of these studies
140 such as immune checkpoint inhibitors and novel targeted therapies for kidney cancer,
141 melanoma, and non-small cell lung cancer. Yet, the GEFCAPI04 trial showed that the
142 subgroup of predicted primary tumors that are known to be unresponsive to empiric CUP
143 regimens (such as kidney cancer, melanoma, and colorectal carcinoma) had a trend towards
144 improved OS with tailored therapies (2-year estimate of 24.3% vs. 10.4% and HR= 0.74; 95%
145 CI 0.36-1.51), although the study had been underpowered to detect such an effect ¹¹. Finally,
146 the population of CUP patients enrolled into clinical trials and diagnosed in clinical practice
147 has changed substantially in recent years due to improved immunohistochemistry-based
148 diagnostics. This has restricted the definition of CUP to more select cancer types, for which
149 specific protein markers are not readily available (such as squamous cell and pancreato-

150 biliary tumors) and limits the applicability of the data generated from the earlier periods of
151 enrollment of all the included trials.

152

153 This meta-analysis highlights the difficulty of evaluating the role of tailored therapies in
154 patients with CUP. While the overall effect of tailored compared to empiric therapies was
155 negative, subgroup analyses of the primary studies and the results of this analysis suggest
156 that selected patients may benefit from such an approach, site-specific therapy for all
157 comers cannot be recommended at this time. The differences in design of the studies and
158 the small sample sizes limit the conclusions of the present analysis. Future randomized
159 controlled trials that use standardized diagnostic tests and the contemporaneous standard
160 of care for patients with identified primaries, particularly in the more responsive cancer
161 types, are highly needed to accurately address the question of tailored therapies for CUP.

162 **Conflicts of interest**

163 ER, ZB, NP: None declared

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175 Research to Practice, L-path, Kidney Cancer Journal, Clinical Care Options, Platform Q,
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186 Steering Committee); Patents, royalties or other intellectual properties: International Patent
187 Application No. PCT/US2018/12209, entitled "PBRM1 Biomarkers Predictive of Anti-Immune
188 Checkpoint Response," filed January 3, 2018, claiming priority to U.S. Provisional Patent
189 Application No. 62/445,094, filed January 11, 2017 and International Patent Application No.
190 PCT/US2018/058430, entitled "Biomarkers of Clinical Response and Benefit to Immune
191 Checkpoint Inhibitor Therapy," filed October 31, 2018, claiming priority to U.S. Provisional
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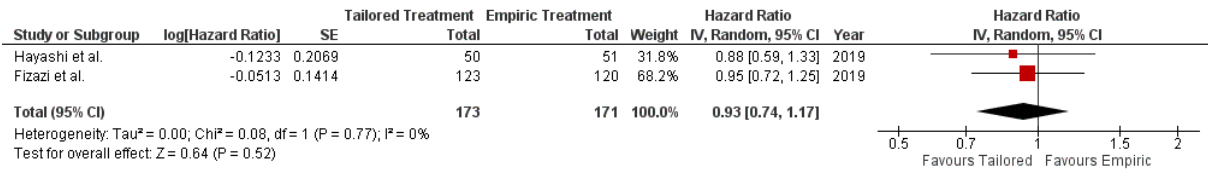
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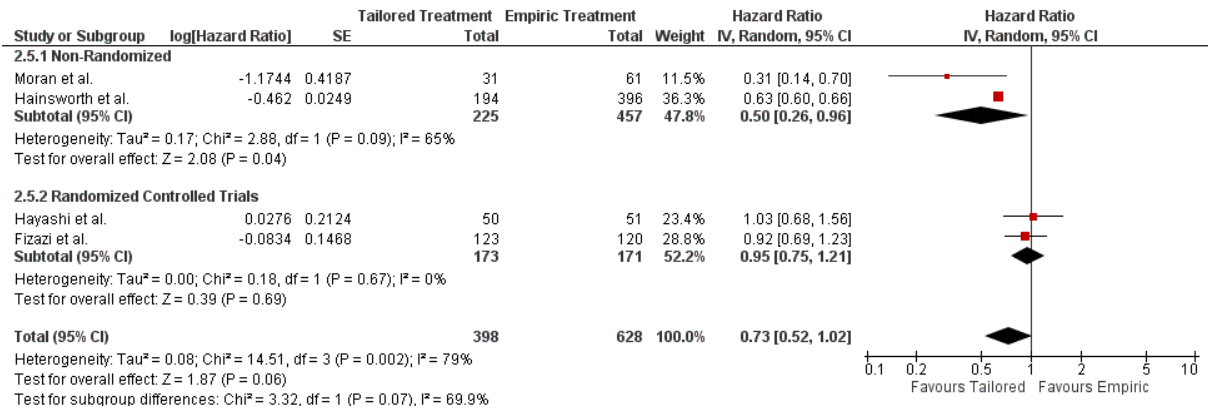
251 **Figure 1A:** Hazard ratio for PFS (95% CI) in CUP trials comparing tailored and empiric chemotherapy
 252 regimens



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254

255 **Figure 1B:** Hazard ratio for OS (95% CI) in CUP trials comparing tailored and empiric chemotherapy
 256 regimens



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